National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from the School of Health & Related Research Sheffield (ScHARR) to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 6pm, **10 February 2011** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Subcutaneous administration

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 8. However, many patients who were identified by the submission as unsuited to subcutaneous pharmacotherapy would in fact be able to receive subcutaneous therapy administered by nursing personnel in the home.	In current practice patients who were identified by the submission as unsuited to subcutaneous pharmacotherapy would be able to receive infliximab administered intravenously or subcutaneous therapy administered by nursing personnel in the home.	The ERG report states on page 17 that for patients for whom subcutaneous self injection is inappropriate there is the offer of either; infliximab or a subcutaneous agent administered by the service provider. It is clear that there is a group of patients whose first biologic agent administered intravenously. The reasons behind this appear to be made on an individual patient basis We accept this as an area of uncertainty that there is a need for further clarification on this aspect from both clinicians and patients.	This is not a factual error. The point made in the ERG report was that many patients identified in the manufacturer's submission as unsuited to subcutaneous pharmacotherapy would in fact be able to receive such therapy.

Issue 2 Treatment paradigm

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 8. The manufacturer did not present an analysis of abatacept compared with a sequence of biologic treatments nor was there an analysis of a sequence involving both abatacept and infliximab compared with conventional DMARDs in the	Include TA195 and state that the use of a second biologic agent has been examined and recommendations published. Therefore the examining a second biologic is out of the scope of this appraisal.	The decision problem for this appraisal was to examine the use of a first biologic after the failure of 2 DMARDs not to examine sequences of biological agents. The use of a second biologic agent	This is not a factual error.

population of patients who could not have a subcutaneous injection. It is unclear whether this limitation was stipulated in the scope, which could be perceived as ambiguous.		has already been examined and recommendations published in TA195 in 2010.	

Issue 3 Infliximab vial sharing

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12: Based on previous evaluations of treatments for RA (where in 63% of cases infliximab was assumed to be vial-shared)	Consider revising exploring the validity of the 63% value.	The research from which the 63% originates is not available and so BMS are unable to comment on the quality or content of this study. There is no published evidence round vial sharing of infliximab and this lack of data as been recognised in previous appraisals. Some RA units do not permit vial sharing, and sharing appears to be dependant on protocols and facilities within pharmacies. The figure of 63% is likely to be very high and should not be utilised as a robust measurement.	This is not a factual error. The ERG has provided approximations of the ICER assuming both 0% vial sharing and 100% vial sharing and will provide ICERs to the Appraisal Committee using different values for vial sharing as requested.

Issue 4 Infliximab and dose escalation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17: The ERG's clinical advisors indicate that, in the past, dose	The ERG's clinical advisors indicate that, in the past, dose escalation or increased	The need for dose escalation with infliximab due to loss of efficacy is well documented and a recognised issue. (Blom et al 2010; van Vollenhoven et al 2004) Approximately 35% of	This is not a factual error. Moreover, the niche market referred to in the ERG

escalation or increased frequency of dosing would be used under such circumstances. However, current practice for patients with RA who do not fall within the niche market outlined in the manufacturer's submission would generally be to change to another therapeutic agent if the standard dose of infliximab was not effective.	frequency of dosing would be used under such circumstances. ~~However, current practice for patients with RA who do not fall within the niche market outlined in the manufacturer's submission would generally be to change to another therapeutic agent if the standard dose of infliximab was not effective~~.	patients will require dose escalation; if they are not dose escalated they may be switched onto their second biologic as highlighted by the ERG and in line with TA195. Abatacept therefore presents an alternative IV treatment with proven efficacy, safety and no association with dose escalation. Efficacy data show maintained response over time (7 year data reported in BMS submission). Conversely response to infliximab reduces over time (Blom et al 2010). Therefore it is more likely that patients will maintain a sustained response for longer periods on abatacept therefore removing the need to move to a second biologic. Moving a second biologic ultimately moves patients closer to the end of the list of potential therapeutic options for a chronic disease. The patient population outlined in the BMS submission is <u>all</u> patients receiving an IV first biologic. Therefore this submission does not aim to examine a niche of infliximab patients, but the whole patient population receiving infliximab as a first biologic.	report is not a niche of infliximab patients, as suggested in the justification for amendment, but the niche of RA patients for whom intravenous therapy is used.

Issue 5 Decision Problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 21. The manufacturer's statement of the decision problem further limits the population defined in the final scope to patients for whom self-administration of subcutaneously-injected biological agents is	The manufacturer's statement of the decision problem further limits the population defined in the final scope to patients for whom self-administration of subcutaneously-injected biological agents is inappropriate. The clinical	The abatacept clinical trials did not attempt to pre-identify those patients in whom self-administration of subcutaneously injected biological agents was inappropriate. Similarly, other comparator clinical trials in RA	This is not a factual error.

inappropriate. The clinical evidence submitted by the manufacturer matches the final scope in that it is limited to studies in patients with RA who have had an inadequate response to one or more conventional DMARDs, including methotrexate; it is not further restricted to patients for whom self-administration of subcutaneously-injected biological agents is inappropriate.	evidence submitted by the manufacturer matches the final scope in that it is limited to studies in patients with RA who have had an inadequate response to one or more conventional DMARDs, including methotrexate; it is not further restricted to patients for whom self-administration of subcutaneously-injected biological agents is inappropriate however these data are unavailable within both the abatacept clinical trials and comparator clinical trials.	also have not attempted such subpopulation identification. Such sub-classification of the trial population is not feasible.	

Issue 6 Patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 16. The manufacturer's submission claims that patients with a DAS28 ≥3.2 are estimated to form 30% of the total population with RA, and that therefore, according to the BSR/BHPR guidelines, 103,907 patients in the UK would be eligible for biological therapy. The estimate that 30% of patients with RA have a DAS28 ≥3.2 rests on personal communications from RA specialists;[2] if it is correct, its application to the NAO estimate would suggest that approximately 174,600 people in England alone would be eligible for a biological agent on the	The manufacturer's submission claims that patients with a DAS28 ≥3.2 are estimated to form 30% of the total population with RA, and that therefore, according to the BSR/BHPR guidelines, 103,907 patients in the UK would be eligible for biological therapy. The estimate that 30% of patients with RA have a DAS28 ≥3.2 rests on personal communications from RA specialists;[2] if it is correct, its application to the NAO estimate would suggest that approximately 174,600 people in England alone would be eligible for a biological agent on the basis of their	It is estimated that 10% of total eligible patients with severe RA receive a first biologic agent (as stated in TA195 costing template) which incorporates the consideration that patients have previously failed on 2 DMARDs. In order to estimate the increase in patients receiving their first biologic agent if moderate and severe patients were considered clinical opinion was sought from several experts. The estimate of 30% does consider the failure of two previous	The ERG report's comment that "the manufacturer's estimates appear to be based solely on the DAS28 score, and do not take into account the eligibility criterion relating to the previous failure of two DMARDs" related to the manufacturer's claim that only 10% of the estimated eligible population receive an IV biological agent, and not to their claim that patients with a DAS28 ≥3.2

basis of their DAS28 score. The manufacturer's submission claims that, currently, only 10% of the estimated eligible population receive an IV biological agent; again, this estimate rests on personal communications from RA specialists.[2] Two factors should be borne in mind when interpreting this claim: • the manufacturer's estimates appear to be based solely on the DAS28 score, and do not take into account the eligibility criterion relating to the previous failure of two DMARDs • no data are presented relating to the proportion of the estimated eligible population who receive a biological agent which is administered subcutaneously	DAS28 score. The manufacturer's submission claims that, currently, only 10% of the estimated eligible population receive an IV biological agent; again, this estimate rests on personal communications from RA specialists.[2] ~~Two factors should be borne in mind when interpreting this claim:~~ • ~~the manufacturer's estimates appear to be based solely on the DAS28 score, and do not take into account the eligibility criterion relating to the previous failure of two DMARDs~~ • ~~no data are presented relating to the proportion of the estimated eligible population who receive a biological agent which is administered subcutaneously~~	DMARDs. Data on market share of all comparators is presented in Section 7 of the BMS submission. This presents the estimated eligible population who receive a biologic agent administered subcutaneously.	form 30% of the total population with RA. It was not clear from the submission (page 33, penultimate paragraph) that this figure of 30% took into account data relating to the failure of 2 previous DMARDs, as stated in the amendment. The claim on page 33 of the manufacturer's submission that only 10% of the estimated eligible population receive an IV biological agent is not supported by any evidence at that point; a reference to the relevant data on page 299 would have been useful to the reader.

Issue 7 Patient population receiving IV administered biologic

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 18. The ERG's clinical advisors recognise that there is a subgroup of	The ERG's clinical advisors recognise that there is a subgroup of patients with	Clinical opinion was sought from several clinical experts who advised	This is not a factual error.

patients with RA who, because they are unable to inject subcutaneous drugs, are candidates for treatment with biological agents which are delivered by intravenous infusion (infliximab, rituximab or abatacept); however, from clinical experience, they would not expect this proportion to be as high as 10%.	RA who, because they are unable to inject subcutaneous drugs, are candidates for treatment with biological agents which are delivered by intravenous infusion (infliximab, rituximab or abatacept); ~~however, from clinical experience, they would not expect this proportion to be as high as 10%.~~	10% of the eligible population currently receive an IV biologic. This has been reconfirmed since receipt of this ERG report. Although there may be some variation across the country, 10% is the overall estimate.	

Issue 8 Interpretation of clinical evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9. Relative to placebo, abatacept also appeared to be associated with improved physical function, as measured using the HAD-DI or MHAQ, at 6 months and 1 year, and with less joint damage at one year; however, the clinical significance of these results was not clear	Relative to placebo, abatacept also appeared to be associated with improved physical function, as measured using the HAD-DI or MHAQ, at 6 months and 1 year, and with less joint damage at one year; ~~however, the clinical significance of these results was not clear~~	The significance of HAD-DI at 1 year has been shown to be a predictor of long-term outcomes in patients (Jansen LM et al. 2000. An Rheum Dis. 59(3):223-6), as well as a predictor of mortality (Wolfe F et al. 2003. Arth Rheum 48(6):1530-1542).	This is not a factual error. The ERG were using the term 'clinical significance' in the sense of a change in physical function perceptible to the patient at the time when the outcome was measured, rather than in the sense of predicting long-term outcomes.
Page 10. Moreover, the submission indicated an 80% discontinuation rate from the two-year LTE of the ATTEST study, and no explanation was provided for this.	In the LTE only 46% of patients discontinued the study prior to the CSR cut-off date. In fact, 254 (68%) patients completed the OL period prior to the CSR cut-off. The 76 patients stated were	This proposed amendment describes that the majority of patients (at least 68%) completed the open-label period, rather than just the 20% stated in the report.	The ERG accept this amendment.

	ongoing at the time of the CSR cut-off.		
Page 12; The populations of the included studies had a shorter duration of RA, 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 two populations is such that less benefit may be gained abatacept in UK clinical practice than in the study populations.	The populations of the included studies had a shorter duration of RA, 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 two populations is such that less benefit may be gained abatacept in UK clinical practice than in the study populations.~~	The population investigated in the abatacept clinical studies are reflective of those patients who have previously failed MTX, are no different from those investigated in other anti-TNF Phase III studies. The assumption made is also open to question. What is the basis of the conclusion that the population in the abatacept studies causes a difference in benefit to abatacept compared to other agents studied in Phase III RA trials.	We have no evidence that the population in the abatacept studies causes a difference in benefit compared with other agents studied in Phase III RA trials, nor did we wish to suggest this. Our statement was meant to suggest that it may overestimate the benefit compared with no treatment.
Page 26. The manufacturer's submission states that the minimum clinically relevant difference is an improvement of ≥ 3 units in the SF-36;[6] it is not clear whether this relates specifically to the physical and mental component summary measures or to any aspect of the SF-36.	The manufacturer's submission states that the minimum clinically relevant difference is an improvement of ≥ 3 units in the SF-36;[6] ~~it is not clear whether this relates specifically to the physical and mental component summary measures or to any aspect of the SF-36~~	The improvement of ≥ 3 units used in these trials relates to both the physical and mental component summaries as well as the 8 subscales of the SF-36.	This is not a factual error.
Page 46. The Kremer Phase 2b study was considered by the Cochrane reviewers to be at high risk of bias because the drop-out rate at 12 months exceeded 20%, and the resulting incomplete data were not felt to be	The Kremer Phase 2b study was considered by the Cochrane reviewers to be at high risk of bias because the drop-out rate at 12 months exceeded 20%, ~~and the resulting incomplete data were not felt to be addressed adequately for~~	Phase IIb trial is not a pivotal trial and aimed to assess dose-response. Primary analysis used imputation for missing data as described above. However, as stated in the paper, a secondary analysis was pre-	This is not a factual error.

addressed adequately for either efficacy or safety outcomes. The method used was imputation of missing data using the last observation carried forward: patients who discontinued the study because of worsening disease were considered to have had no response, while for those who discontinued the study for other reasons the values for the last efficacy observation were carried forward.28 This use of two separate criteria for imputing data was considered potentially inappropriate: the Cochrane reviewers noted that, for example, if a participant did not tell investigators that the reason for no longer attending follow-up visits was worsening disease, the last observation would be carried forward, whereas in fact the patient should have been considered to have had no response. In addition, the method did not allow for the possibility that some patients might have multiple reasons for withdrawal, and might or might not share all of these with study staff.	~~either efficacy or safety outcomes. The method used was imputation of missing data using the last observation carried forward: patients who discontinued the study because of worsening disease were considered to have had no response, while for those who discontinued the study for other reasons the values for the last efficacy observation were carried forward.28 This use of two separate criteria for imputing data was considered potentially inappropriate: the Cochrane reviewers noted that, for example, if a participant did not tell investigators that the reason for no longer attending follow-up visits was worsening disease, the last observation would be carried forward, whereas in fact the patient should have been considered to have had no response. In addition, the method did not allow for the possibility that some patients might have multiple reasons for withdrawal, and might or might not share all of these with study staff.~~	specified to assess robustness of results of the primary analysis. In this secondary analysis, imputation of missing data was the following: all patients who discontinued the study for any reason were considered as "non responder". Note that this is the convention used in the other abatacept trials (AIM and ATTEST especially). The results of the Phase IIb study are consistent with the primary analysis and with results in other trials. In addition, the imputation convention rule in the primary analysis did not lead to an overestimation of the treatment effect of abatacept 10 mg vs. placebo.	
Page 47. All four studies were said to be double-blind, but none undertook an assessment of the success of the blinding.	In all four studies (Ph IIb, AIM, ATTEST, IM101-119), because of the largely subjective nature of the outcome measures, the blinding of patients,	Please see Cochrane paper (Maxwell and Singh 2009) • pages 14 and 16 • page 25 related to blinding:	This is not a factual error. The manufacturer has misunderstood what is meant by an assessment of

	clinical staff, and outcome assessors to treatment allocation is crucial. ~~All four studies were said to be double-blind, but none undertook an assessment of the success of the blinding~~.	"Additional information was also obtained regarding clarification on blinding of study participants, investigators, and outcomes assessors. After this information was obtained, all included studies were deemed to be adequately blinded for patients assessed and physician assessed outcomes". • details on blinding procedures were detailed by study : Phase IIB page 333; AIM page 35-36; ATTEST page 39-40 For the assessment of the blinding procedures: • The "randomization schedules were generated and kept by the randomization Group within Drug Supply Management of BMS" (section Treatment Group assignment in the protocol of each study). Corresponding appendixes are the randomization schedule and code and the	the success of the blinding, namely a specific assessment, after study conclusion, of the extent to which patients, clinicians, and outcome assessors had been aware of treatment allocation despite the use of blinding.

		listing of batch number by subject. • It is stated "the clinical assessor must remain blinded to treatment assignment by having a qualified staff member perform the study medication infusion " (section 6.2.2.1 in Phase IIB, AIM ,ATTEST and section 5.5.1.1 in IM101-119 protocol). • A sample of sites in 3 studies (Phase IIB, AIM, ATTEST) underwent an audit from the regulatory compliance department. Number of sites are provided in appendix 7.2 of the CSR for Phase IIB, AIM, ATTEST	
Page 58. The published data from the AIM study[4] relating to the number of participants with DAS28 scores indicating low disease activity (DAS28 ≤3.2) or remission (DAS28 <2.6) differ considerably from those presented in the manufacturer's submission (see Table 10). The reason for these differences is not clear,	The published data from the AIM study[4] relating to the number of participants with DAS28 scores indicating low disease activity (DAS28 ≤3.2) or remission (DAS28 <2.6) differ considerably from those presented in the manufacturer's submission (see Table 10). ~~The reason~~	The data used in the submission was taken from the AIM CSR and not from the published data. In the publication results on DAS28 were based on CRP. In contrast, in the CSR, DAS28 results were based	This is not a factual error.

	~~for these differences is not clear,~~	on ESR.	
Page 81. This omission is particularly unfortunate in relation to the LTE of the ATTEST study: despite the fact that only 76 of the 372 patients (20%) who had entered the LTE were still ongoing at the end of the two years, reasons for discontinuation are provided for only 43 of the 296 patients who discontinued (see Table 28), and no further explanation is provided	In the LTE only 46% of patients discontinued the study prior to the CSR cut-off date. In fact, 254 (68%) patients completed the OL period prior to the CSR cut-off. The 76 patients stated were ongoing at the time of the CSR cut-off.	This proposed amendment describes that the majority of patients (at least 68%) completed the open-label period, rather than just the 20% stated in the ERG report.	The ERG accept this amendment, and note that reasons for discontinuation are provided for all 43 patients who discontinued early.
Page 84. The manufacturer's submission states that 113 abatacept-treated patients (51.6%) reported adverse events… As Table B 63 in that submission also states that 113 abatacept-treated patients (51.6%) reported serious adverse events, it is not clear which figure is correct; depending upon which is appropriate, the study had either a substantially lower proportion of patients than the AIM and ATTEST LTEs who reported any AE, or a higher proportion who reported an SAE.	The manufacturer's submission states that 210 abatacept-treated patients (~~51.6~~ 95.9%) reported adverse events… ~~As Table B 63 in that submission also states that~~ 113 abatacept-treated patients (51.6%) reported serious adverse events, ~~it is not clear which figure is correct; depending upon which is appropriate,~~ the study had ~~either a substantially lower~~ the same proportion of patients ~~than~~ as the AIM and ATTEST LTEs who reported any AE, ~~or~~ and a higher proportion who reported an SAE. **Table 29: Adverse events reported during the open-label LTEs (data from the manufacturer's submission[6])**	Error in original submission. Correct data in Phase IIb CSR.	This was a factual error in the manufacturer's submission. The Phase IIb CSR is not in the public domain.

	Phase 2b LTE (N=219)	**(N=539)**	**LTE (N=372)**
Duration of open-label phase	**6 years**	**59 months**	**12 months**
Total patients with AE	210 (95.9%)	517 (95.9%)	348 (93.5%)
Patients with AE considered related to study drug	NR	NR	163 (43.8%)
Total patients discontinuing treatment due to AE	42 (10.0%)	54 (10.0%)	9 (2.4%)
Total patients with SAE	113 (51.6%)	211 (39.1%)	82 (22%)

Issue 9 The conceptual model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
PRIORITY **Page 112.** The costs of joint replacement appear to be double counted. The mathematical model states that the costs of joint replacements were contained in the underlying disease costs that were sourced from Kobelt *et al*.[20] As such, having an additional calculation to estimate the specific costs of joint replacement will lead to overestimated	Please remove statement	The joint replacement costs were incorrectly documented in the input sheet in the economic model. However the data were not used in the analyses. The analysis performed and reported in the NICE submission did not include "double counting".	Having revisited the model used by the manufacturer to generate the presented results the ERG confirms that the costs of joint replacement were not included twice. However, the costs used within the model were not deemed appropriate as detailed in

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
costs.			the ERG report.
Page 113. There is a conceptual error in evaluating the utility of patients when the HAQ score at the end of the treatment period is predicted to be greater than 3. In this circumstance, the HAQ score is set to equal 3 at the end of the treatment period, with a linear increase across the treatment period. This may introduce inaccuracy where the maximum HAQ score of 3 is reached early in the treatment period, with a plateau until end of treatment. This is illustrated in Figure 8. This error is likely to have most influence when a patient reaches palliative care and may remain at a HAQ score of 3 for a considerable time	Please consider revising	The values of the HAQ are by definition between 0 and 3 and the associated utility function is bound by these values also. The question is therefore whether we allow for linearity above and below the HAQ limits. This seems not logical. The same holds with respect to costs etc. Therefore, the assumption is made that patients having a predicted HAQ above 3 are comparable with people in real practice having a HAQ of 3. The same logic applies for the lower HAQ limit. Although this is a simplification, it is a conservative approach since the HAQ efficacy source data for conventional DMARDs and infliximab are (slightly) less favourable than those of abatacept.	This is not a factual error
Page 113. It is unclear that all biologic interventions would be discontinued at an identical time if a patient neither had an adverse event nor failed to respond to treatment. The ERG has amended the code in order that the time of discontinuation is randomly sampled (from the same distribution) for each intervention for each patient.	Please add clarification provided by BMS.	Although it was unclear, the model submitted did randomly sample the time of discontinuation (from the same distribution) for each intervention for each patient.	This is not a factual error

Issue 10 Population of the model.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 113. As previously detailed, the manufacturer does not explain why the standard deviation associated with baseline HAQ has been assumed to be the standard deviation associated with patient variability in HAQ response to treatment. The assumed patient variation was depicted in Figure 3. Whilst it is unlikely that the manufacturer would have the relevant data, it is expected that the change in HAQ score will be correlated to baseline HAQ score.	Please add clarification provided by BMS.	Although the intention was to include this correlation, the decision was made to simplify the modelling approach since solid data to support the correlation was lacking.	This is not a factual error

Issue 11 Internal validity of the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 118. It is likely that the costs of a nurse training a patient how to administer a subcutaneous injection are strongly correlated. The model assumed that each intervention was sampled independently.		In Table 31 of the model, administration costs are presented. These are set a one-off cost for subcutaneous injections. These costs are included in the PSA by independent sampling values per treatment. A more elegant approach would indeed be to apply a single cost for all subcutaneous injections. It is unlikely that changing this sampling will only have a small impact on the ICERs.	This is not a factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		Please note that the main positioning is against infliximab, rather than subcutaneous agents for which this issue applies.	
Page 118. One of the parameters feeding into the eval2disc function is incorrect. For example, in Cell W41 of the 'Model' worksheet the evaldisc2 function the first parameter should be V41 rather than U41. The ERG has amended this error.		The eval2disc function evaluates the costs for the second half of the first 6 months of treatment. Indeed, instead of the use of the costs after the lower HAQ value is reached, the costs at start of treatment are used. The impact of the error on the ICER is marginal, as this applies to a quarter of a year only.	This is not a factual error
Page 118. The formula used to calculate the costs for biologic DMARDs that are delivered subcutaneously does not round up the dose to an integer number of vials. This will be favourable to such interventions.		This is indeed the case, but the approach biases against abatacept. Again, please note that the main positioning is against infliximab, rather than subcutaneous agents for which this issue applies.	This is not a factual error
Page 118 . The model assumes that patients have an underlying progression in HAQ whilst on conventional DMARDs (0.045 increase in HAQ score per annum). However, this progression is not applied when a patient discontinues a DMARD within 6 months for either lack of efficacy of an adverse event. This will cause some inaccuracy in that, were a conventional		The model assumes an underlying progression in HAQ for responders only. Non-responders are assumed to have the same HAQ value at the end of the 6-month period as the baseline HAQ value. Although the 0.045 increase in HAQ per annum is a rate for responders only (so effectively after an improvement in HAQ value), this rate	This is not a factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
DMARD to fail due to lack of efficacy, it would be expected that the HAQ score of the patient would have increased by 0.0225 during this period.		could have been applied to the non-responders. However, no data were found to validate the annual progression for non-responders.	
Page 118. There appears to be an error in the user-defined rxcostdisc function employed in the model as it appears that the cost of the first treatment has been omitted from this calculation. This has been amended by the ERG.	Please remove	The original model was did not contain an error here. The model was originally programmed to allow for exploratory analyses. Because of this, the formula look cumbersome, but no costs have been omitted.	This is not a factual error
Page 118. If both the PSA and rndNO flags used within the mathematical model are set to true, then the model does not calculate a valid result as a component of the utility calculation returns a '#Num!' error. It is unclear whether this would also need to be corrected were the manufacturer to correct the logic regarding the PSA that is described later.		It is indeed true, but the PSA and rndNO should not be used in combination in the model, but only subsequently. The rndNO function values are only updated once rndPSA is set to TRUE. In the model rndPSA is set to TRUE each time the source data values are sampled and directly followed by setting rndPSA to FALSE. Further computations, including those relating to PSA, are based on rndPSA = FALSE.	This is not a factual error
Page 119. As previously detailed, the novel method for adjusting the random number rather than the survival curve adds slight inaccuracy to the predicted time of death (Figure 6). The ERG	Please consider deleting statement	From a mathematical perspective both methods should give the same results.	This is not a factual error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
believes that this error will not have a marked impact on the results.			
Page 118. Inconsistency was noted in the attempted use of probabilistic sensitivity analyses for conventional DMARDs which was incorporated for leflunomide but not for the remaining conventional DMARDs		More detailed information is needed to find this inconsistency.	This is not a factual error. However, for further clarification cell E16 in the 'Time To Event' worksheet which deals with leflunomide has a different structure to cells E17:E20. The impact of this error is marginal.
Page 126 The HAQ increase required to be a responder increased to 0.5.	HAQ increase to be a responder should be 0.3.	A HAQ increase of < 0.3 is generally recognised as being of clinical significance. Wells et al (1993) state that "a clinical meaningful improvement in physical function is defined as a reduction in the base HAQ DI score of $\geq$0.3 units" Similarly, Maxwell and Singh 2009 state: "physical function as measured by changes in HAQ or modified HAQ scores, proportion achieving "minimal clinical important change" (MCID), defined as ≥ 0.22 or ≤ 0.30".	This is not a factual error

Issue 12 The probabilistic analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 118. On inspection of the logic used to perform the PSA, it became apparent that the HAQ score change associated with each treatment was not included within the analyses, with the values erroneously fixed at the midpoint values. This can be seen by inspecting the distributions that should have been used for abatacept and infliximab which are shown in Table 45 and in conjunction with the cost-effectiveness plane reported by the manufacturer comparing the two drugs (replicated in Figure 10). Since the relative efficacy of each drug is sampled independently, it would be expected that infliximab would be more efficacious reasonably often as the two confidence intervals overlap. Comparing Monte Carlo samples from the two distributions indicates that this probability is in the region of 14%, ignoring the favourable rates of discontinuation for abatacept due to fewer serious adverse events that cause discontinuation. However, the cost-effectiveness plane submitted by the manufacturer suggests that this probability is very low, and corroborates the opinion of the ERG that changes in the HAQ score were not included in the PSA undertaken by the manufacturer. This error has been corrected by the ERG. In addition, it is believed that the rates of serious adverse events were not included within the PSA. This has also been amended by the ERG.		There is a problem with the Visual Basic coding on the probabilistic analyses. More time is needed to locate the nature and exact impact of this error. Having said this, the ERG have corrected the problem, and it did not result in large differences between the deterministic and probabilistic ICERs for the majority of the evaluated scenarios. This is not a factual error	This is not a factual error

References

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