Abbott's response to the Appraisal Consultation Document (ACD) of adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the appraisal of adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after failure of a TNF inhibitor for efficacy reasons. Following the Executive summary, Abbott's detailed comments are set out under section headings containing the questions NICE asks consultees to comment on for the ACD.

Executive Summary

Abbott understands from the ACD document that the Committee has found it difficult to recommend adalimumab, etanercept or infliximab in RA patients who have failed a TNF inhibitor for two main reasons:

- Perceived lack of robust clinical evidence for TNF inhibitors in RA patients who have failed a first TNF inhibitor.
- Lack of evidence for the cost effectiveness of TNF inhibitors vs. rituximab in this population.

This lack of certainty is engendered by an Assessment Report that has some important errors, internal contradictions and a flawed cost effectiveness analysis. Based on the information provided in this document, Abbott contests the rationale behind the above assumptions used in arriving at the Committee's conclusions and asks that the Committee revisit them.

The first assumption, that the evidence base available for the sequential use of biological DMARDs does not currently allow for a robust analysis of the relative treatment effect, is flawed. The Abbott Mixed Treatment Comparison (MTC) provides reliable estimates of relative treatment effect by drawing on a larger body of evidence and statistically controlling for heterogeneity, using an approach recommended by NICE's methods guide and supported by experts in this field of research. Abbott argues that the concern about methodology is significantly more applicable to the estimates of effectiveness included in the Birmingham Rheumatoid Arthritis Model (BRAM) set out in the Assessment Report which ignore any differences between the study populations or designs of the trials and are much less robust than the estimates derived from the mixed treatment comparison included in the Abbott economic model.

The second assumption, that rituximab is the only or most cost-effective use of NHS resources, is based on an inappropriate use of the data in the cost-effectiveness modelling. The Committee acknowledge that the cost-effectiveness estimates are very sensitive to the re-treatment window applied to rituximab and the conclusions drawn state that, so long as re-treatment occurs less frequently than every 6 months, rituximab is a cost-effective use of NHS resources. However, the BRAM used a re-treatment window of 8.7 months but applied 6 month HAQ changes from REFLEX. Since the evidence submission in August 2009, data from the SUNRISE trial and change to the FDA labelling for rituximab indicate that a re-treatment window of 6 months would have been more appropriate in the Abbott base case analysis. Revised estimates with more frequent re-treatment with rituximab shows that TNFs inhibitors are cost effective both vs. DMARDs and vs. rituximab.

Abbott argues that there are two ways of treating a patient with rituximab and therefore two ways in which it can be modelled. Either patients are re-treated when their disease flares and thus the modelling should take into account likely higher HAQ progression as a result of losing efficacy; or patients are re-treated to maintain tight disease control, which necessitates using a 6 month re-treatment window. Abbott considers that if an 8.7 month re-treatment window is assumed in the BRAM, the base case analysis for the model should be re-run with a greater HAQ progression for rituximab than for TNF inhibitors to incorporate the impact of loss of disease control with re-treatment every 8.7 months. It does not seem clinically appropriate to let patients' disease flare, therefore, Abbott suggests that the BRAM base case analysis should apply a 6 month re-treatment window and use the QALY gain derived from the 24 week HAQ improvements from REFLEX. When this scenario is assumed, the ICERs for adalimumab and rituximab vs. conventional DMARDs in the BRAM model are similar (£34,300 and £32,600/QALY gained respectively; Table 19 of the Addendum report). Furthermore, had the BRAM included a stopping rule for the TNF inhibitors, as it should have done,

then one-way sensitivity analysis using the BRAM model shows that the ICER for adalimumab vs. conventional DMARDs would be £22,200/QALY gained (Addendum report). Both these assumptions, when taken together, indicate that TNF inhibitors are likely to be cost effective versus DMARDs and versus rituximab, and demonstrate that to conclude only in favour of rituximab is unsound.

In the same vein, Abbott contends that its original base case assumption of 9 monthly re-treatment with rituximab is no longer appropriate in light of recent trial evidence showing 6-monthly re-treatment is necessary to maintain disease control. Results of a revised base case analysis using the Abbott model assuming a 6 month re-treatment with rituximab demonstrates comparable and stable cost effectiveness ratios (around £16,000/ QALY) for TNF inhibitors and rituximab vs. DMARDs with a probability for the TNF inhibitors to be cost effective over 50% of the time. In addition, TNF inhibitors are also cost effective vs. rituximab (around £17,000/ QALY) and estimates are fairly stable under various scenarios tested in the sensitivity analyses.

Therefore, Abbott concludes that its mixed treatment comparison provides reliable and methodologically sound evidence of relative efficacy in the patient population of interest, and its economic model provides reliable assessment of the cost-effectiveness of anti-TNFs – both vs conventional DMARDs and vs rituximab.

Given uncertainties regarding the effectiveness of rituximab in rheumatoid factor negative patients, the safety of biologic treatment after rituximab and the similar cost-effectiveness of TNF inhibitors and rituximab when rituximab re-treatment is given every 6 months, as necessary to maintain disease control, Abbott considers it inappropriate to recommend rituximab as the only biologic option for patients failing a TNF inhibitor who have severely impaired quality of life.

1. Do you consider that all of the relevant evidence has been taken into account?

Abbott does not consider that all the relevant evidence was been taken into account when the Committee was making its preliminary recommendations.

1.1 Importance of non randomised controlled trial (RCT) derived effectiveness data

In paragraph 4.3.6 of the ACD, it states that "*The Committee concluded that, although the studies suggest that a second TNF inhibitor is effective after the failure of a first, the absence of any rigorously controlled data meant that it could not quantify the relative effect of a second TNF inhibitor in comparison with either conventional DMARDs or alternative biological DMARDs.*" Abbott recognises that there is a paucity of randomised controlled trials evaluating the TNF inhibitors in RA patients who have failed a first TNF inhibitor. However, the Committee's reliance solely on RCT data and subsequent dismissal of the effectiveness data from a large and growing body of observational studies and registry datasets ignores a valid and useful source of evidence.

In a recent talk given by Professor Sir Michael Rawlins to the Royal College of Physicians[1] Professor Rawlins argued that a new approach was needed to analyse clinical evidence: *"Randomised controlled trials (RCTs), long regarded at the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of "hierarchies" of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base*." As outlined by Professor Rawlins, there are several limitations with RCTs, and observational studies are a useful source of information that with care in the interpretation of the results, can provide an important source of evidence about both the benefits and harms of therapeutic interventions not captured by RCTs. Professor Rawlins comments that, "*RCTs are often carried out on specific types of patients for a relatively short period of time, whereas in clinical practice the treatment will be used on a much greater variety of patients - often suffering from other medical conditions - and for much longer*." Therefore, it follows that registry data and observational studies evaluating the effectiveness and safety of interventions in routine clinical practice also have important information value in capturing the effectiveness of an intervention in the patient population in which its use is intended. As such, data from the ReAct study evaluating the effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice, and data from country specific registries like the British Society for Rheumatology biologics Register (BSRBR), should be given due weight in the Committee's consideration of the evidence.

Furthermore, in section 3.2.8 of the NICE guide to the methods of technology appraisal it states that non-RCT data is required, "*Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available.*" The methods guide notes that there is a greater problem of confounding and bias in non-RCT data and section 3.2.9 of the guide therefore states: "*When possible, the use of more than one independent source of such evidence needs to be examined to gain some assurance of the validity of any conclusions drawn.*"

Abbott submitted 32 data sources providing evidence for the effectiveness of the anti-TNFs in over 3,000 RA patients who have failed a first TNF inhbitor (Appendix 1 - Table 2.1.1 of the Abbott submission), including recent data from country specific registries like the BSRBR, the South Swedish Arthritis Treatment Group (SSATG) data, the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry data and the large observational study, ReAct. Therefore, although the evidence base for the effectiveness of a 2nd anti-TNF agent is comprised mostly of observational studies and registry datasets, there is a large quantity of these studies providing assurance of the validity of the conclusion that a 2nd TNF inhibitor is clinically effective following failure of a first.

In summary, the NICE methods guide to technology appraisals stresses the importance of evidence outside of RCT data, for which consultees have provided data on a large number of non-RCT studies in over 3,000 RA patients showing that a 2nd anti-TNF agent is clinically effective following failure of a first. Abbott asks that this evidence is given proper consideration in this appraisal. Furthermore, as the

RCT evidence for all biologic options is only available for the biologic versus placebo (including methotrexate in some patients) rather than versus conventional DMARDs, it is necessary to apply a mixed treatment comparison approach for all biologic options adjusting for differences in the patient populations under consideration in order to gain an estimate of the effect size.

1.2 The use of alternative sources of evidence other than the Assessment Group's analysis to aid the Committee's decision making

1.2.1 Relative effectiveness of the interventions being appraised

In section 4.3.14 it states, "The *Committee heard from the Assessment Group that it had modelled the rates of effectiveness for biological and conventional DMARDs as absolute rather than relative changes, even if from placebo-controlled randomised trials, because they considered that evidence did not allow them to complete a mixed treatment or indirect comparison. The Committee considered that the use of non-randomised comparisons could affect the robustness of the results. However, it accepted that the evidence base available for the sequential use of biological DMARDs did not currently allow for a robust analysis of the relative treatment effect."* The Assessment Group's methodology to elicit the relative effectiveness of the interventions is not in line with NICE's reference case which stipulates that in the absence of head to head trials, a mixed treatment comparison (MTC) or indirect comparison (IC) should be performed. Contrary to the Assessment Group and Committee's belief that the evidence base does not currently allow for a robust analysis of treatment effect, Abbott argues that a MTC/IC can be performed in this patient population. This is why Abbott and the other four manufacturer submissions performed either an IC or MTC. Furthermore, using absolute rather than relative changes for the interventions, particularly when placebo-controlled data were available, ignores any differences between the study populations or differences in the design of the trials (e.g. RCT vs. observational). Abbott contends that this methodology is much less robust then the mixed treatment comparison included in the Abbott economic model.

In section 4.3.14 of the ACD, the Appraisal Committee discussed the different sources of estimates of clinical effectiveness for the biological DMARDs that had been used in the economic modelling. It noted that, "*Some models had included RCT data from populations outside of the scope of the appraisal, or uncontrolled observational studies or registry data. The Committee was aware that no head-to-head evidence existed that compared all the biological DMARDs, and as a result some models derived relative treatment effect from indirect comparisons. The Committee noted that these had included evidence from studies in which participants had not previously been treated with a TNF inhibitor. The Assessment Group reported that it considered that the use of data from populations beyond the scope of the appraisal to complete an indirect comparison was inappropriate because of the variability of the studies from which the data were taken.*" However, the Assessment Group themselves subsequently estimated the effectiveness of traditional DMARDs in patients who have failed a TNF inhibitor as an (arbitrary) 50% reduction in efficacy estimated from data on an early RA population who had not been previously treated with a TNF inhibitor. This is no more, and arguably less, defensible than the Abbott approach the Assessment Group has criticised.

Abbott is in agreement with the Assessment Group that the key premise in undertaking a mixed treatment comparison is the assumption of exchangeability of relative treatment effects between the trials included in the analysis. The Abbott MTC included trials outside of the scope, uncontrolled observational studies and registry data; therefore it is understandable that the Assessment Group thought that the exchangeability of relative treatment effects between the included studies could not be assumed and thus the validity of the results was questionable. However, the Assessment Group may have misunderstood the methodology behind the MTC. This is explored further below.

While heterogeneity is clearly of concern, it is not a concern unique to meta-analysis. Indeed, meta-analysis is essentially observational in nature – the context in which each datum is generated and the process by which that datum is observed and reported is inherently complex and heterogeneous. When estimating treatment effects in epidemiology or the social sciences, one would rarely have the luxury of unconditional exchangeability between individuals in treatment and control groups. Hence the wide use of regression analysis. By casting a relatively wide evidentiary net, it is possible to include observations from a variety of contexts and then use that variability together with a statistical model to identify and at least partially control for heterogeneity. To do otherwise would be to throw away data relevant to the decision-maker. Such is the published view of academic experts on

evidence synthesis for cost-effectiveness modelling, including individuals who have played important roles in developing NICE methodology for appraisal[2,3]:

> *"A second issue about the evidence base for CE analysis is that there are always likely to be multiple sources of evidence on particular parameters, particularly on relative effectiveness. It is very rarely the case, for example, that a single RCT represents the entirety of information about effectiveness. In reality, there are likely to be several trials and probably some observational evidence. However these different sources are not likely to relate to identical patient groups or clinical practice – in other words, they exhibit heterogeneity. Such evidence may be indirect in various ways, but it is clearly relevant and therefore cannot be excluded. To assess CE, all available data should be incorporated into an analysis with explicit methods used to reflect the heterogeneity and uncertainty in the evidence."*[2]

This has been the approach taken in the Abbott MTC. By adopting a broad set of inclusion criteria, it is possible to borrow strength from a larger body of evidence when RCT data strictly on the comparative efficacy of 2nd line biologics in the treatment of RA are extremely limited. Variation in study settings and design allows for the exploration of several specific potential sources of heterogeneity through the use of "mixed effects" meta-regression modelling in an approach similar to an MTC meta-regression on RA treatment published by Nixon and colleagues[4]. Furthermore, this approach uses a single complete evidentiary network for estimation of all treatment effects relevant to the appraisal. Contrary to approaches where treatment effects are estimated in separate analyses, this approach also obtains meaningful 'cross-parameter' correlation of treatment effects, which can be of critical importance to the inference obtained from probabilistic sensitivity analysis:

> *"Firstly, cost-effectiveness analyses need to be based on all the available evidence, not a selected subset, and the uncertainties in the data need to be propagated through the model in order to provide a correct analysis of the uncertainties in the decision. In many--perhaps most--cases the evidence structure requires a statistical analysis that inevitably induces correlations between parameters."*

All non-randomised studies included in the MTC had control arms. This allowed Abbott to model relative treatment effects rather than treatment response levels, thus preserving randomisation in those studies in which randomisation was used. Abbott suggests that it is possible that the use of mixed-effect modelling to formally account for heterogeneity was missed in the Assessment Group's critique. Such would explain the factually incorrect statement on page 23 of the Addendum report that: "*Statistical heterogeneity between included studies were either not assessed or (where assessed) only dealt with by using random effects model [sic] without further exploration of potential source of heterogeneity*." To the contrary, potential sources of heterogeneity were explicitly modelled. The Addendum further states: "*Due to the broad inclusion criteria beyond the scope of the appraisal, substantial clinical and statistical heterogeneity exists between the RCTs included in the MTCs. The basic requirement for indirect comparisons/MTCs regarding the exchangeability of relative treatment effects between the included studies could not be assumed and thus the validity of the results was questionable*." Whilst Abbott agrees that exchangeability is a basic requirement, it need not be unconditional. In the mixed effect model, exchangeability is assumed conditional on the value of several study-arm level covariates thought to underlie the heterogeneity between studies, including: baseline HAQ, duration of study follow-up, mean duration of RA and whether the treatment assigned was subsequent to the failure of a first-line TNF inhibitor.

For example, the log odds ratio of ACR20 response in arm j of study i was modelled as a linear function of a study-level baseline response, μ_i , adjusted by the proportion of individuals in the study arm who previously failed anti-TNF-α therapy, X^F_{ij} the proportion who received methotrexate, X^M_i and a treatment effect of biologic relative to non-biologic therapy, Δ_{ij} multiplied by an indicator function that equals one when the assigned treatment is biologic.

$$\text{logit}(p20_{ij}) = \mu_i + \beta_1 X^M_{ij} + \beta_2 X^F_{ij} + 1(t_{ij} > 1) \cdot \Delta_{ij}$$

To maximally account for inter-study heterogeneity, "unconstrained" baselines have been assumed (see, e.g., Lu and Ades 2004[5]), where each μ_i is treated as an independent nuisance parameter.

This specification does not require baselines to be drawn from a common distribution. Relative treatment effects are modelled using a mixed effect specification. Specifically, treatment effects are drawn from a distribution with study-arm specific mean δ_{ij} and common variance σ_{Δ}^2.

$$\Delta_{ij} \sim N(\delta_{ij}, \sigma_{\Delta}^2)$$

The mean of the random treatment effect δ_{ij} is modelled as the effect of assigned treatment $d(t_{ij})$ minus the effect of the assigned control, $d(c_{ij})$ and is adjusted by study-arm level covariates: X^D_{ij} the mean duration of rheumatoid arthritis (in years divided by 12); X^H_{ij} the mean baseline HAQ score (divided by 3); X^L_{ij} the length of follow-up assessment (in months divided by 6, 6 chosen as the most common follow-up time); X^F_{ij} the proportion who received methotrexate; and X^{SB}_{ij} the proportion of individuals in the arm for whom the treatment assigned was a subsequent biologic (i.e., a biologic treatment given after failure of a previous biologic treatment).

$$\delta_{ij} = d(t_{ij}) - d(c_{ij}) + \gamma_1 X^D_{ij} + \gamma_2 X^H_{ij} + \gamma_3 X^L_{ij} + \gamma_4 X^F_{ij} + \gamma_5 X^{SB}_{ij}$$

Minimally informative priors were assigned, N(0, 1.0E-6) to the relative (placebo) treatment effects for the five modelled treatments, $d(t=2, \ldots 6)$. Note that by convention, $d(t=1) = 0$, since the relative effect of placebo compared to itself is zero. Therefore, the assumption of exchangeability of relative treatment effects d is conditional on the values of X for each study arm. Estimates of the marginal effects of these potential sources of heterogeneity on the log-odds scale (parameters β for baseline heterogeneity and γ treatment effect heterogeneity) were provided in Figures 9 and 10 of Appendix 1 (UBC report) in Abbott's evidence submission.

In addition to formally modelling potential sources of heterogeneity using mixed-effects, heterogeneity was also assessed through the examination of level-1 standardised residuals (Lu and Ades, 2004), treating each ACR outcome as a binomial process:

$$\varepsilon N_{ij} = \frac{rN_{ij} - n_{ij}\, pN_{ij}}{\sqrt{n_{ij}\, pN_{ij}\,(1 - pN_{ij})}}$$

Under the mixed model specification, level-1 residuals should be approximately normally distributed. Level-1 residual plots and normal QQ-plots for ACR20, 50 and 70 demonstrating the reasonability of our assumptions were provided in Appendix B to submission Appendix 1 (UBC report), Figures B 1 through to B 6.

The main criticism from the Assessment Group was the inclusion of trials outside of the population defined in the scope. As a result, Abbott has conducted two revised versions of the MTC to test the effects of changing inclusion criteria of studies. In one analysis (37 studies), two studies were deleted: STAR/Furst(2003) since it was a safety study and Maini (2006); and 5 new studies were added: Combe (2006), RAPID2/Smolen (2008), FAST4WARD/Fleischman (2008), Moreland (1997), and LITHE/Kremer (2008), representing data which were not available/ included / or in the DSU's evidence review based on inclusion criteria used in that analysis. In a second analysis, the following early RA studies of the biologics were removed from this list of 37 studies: ERA (2000), ASPIRE (2004), PREMIER (2006), COMET (2008), and GO-BEFORE (2008). Observational data were retained in the MTC, mainly because they contribute important relevant information especially for TNF inhbitors (ReACT) where RCT data in the population of interest are extremely limited. Results of these new analyses are presented in Table 1.2.1.1 below:

Table 1.2.1.1: Abbott MTC estimates of relative treatment effect using different study inclusion criteria

34 Studies (Original Submission)	Placebo/None +MTX	anti-TNF +MTX	Anakinra +MTX	Abatacept +MTX	Rituximab +MTX	Tocilizumab +MTX
ACR20	25.2%	64.4%	52.7%	54.9%	61.8%	64.0%
ACR50	10.4%	40.2%	29.4%	31.3%	38.4%	39.9%
ACR70	4.1%	20.6%	13.8%	14.9%	19.8%	20.4%

37 Studies	Placebo/None+ MTX	anti-TNF+MTX	Anakinra+ MTX	Abatacept+ MTX	Rituximab+ MTX	Tocilizumab +MTX
ACR20	27.4%	66.5%	49.9%	54.3%	64.1%	66.6%
ACR50	12.0%	43.1%	27.7%	31.4%	41.5%	43.4%
ACR70	4.8%	22.9%	13.0%	15.2%	22.3%	23.2%

32 Studies (Excluding Early RA)	Placebo/None+ MTX	anti-TNF+MTX	Anakinra+ MTX	Abatacept+ MTX	Rituximab+ MTX	Tocilizumab +MTX
ACR20	25.6%	63.7%	44.1%	50.3%	62.3%	63.1%
ACR50	10.2%	39.3%	22.6%	27.3%	38.9%	38.9%
ACR70	3.4%	19.6%	9.8%	12.3%	19.8%	19.4%

As is evident, changing the selection of studies included in the MTC has a relatively negligible impact on both the overall relative effectiveness of different therapies, as well as, the absolute magnitude of the differences in all levels of ACR response. As such, these additional analyses demonstrate the robustness of the Abbott MTC methodology.

Abbott considers that the comparison of MTC evidence synthesis to single trials (GO-AFTER, REFLEX and ATTAIN) in the addendum report (Table 3, pp. 29-30) is misleading. Firstly, the summarised evidence included a broad set of data, including ReAct – not just the smaller set of in-scope trials. Therefore, whereas an IC based only on those 3 studies should produce estimates that are close to the results from the single trials, the broader evidence base used in the Abbott MTC might well produce a different outcome because it contains significantly more information. As the model adjusts for study level characteristics, the response predictions are specific to the particular starting HAQ of 2.0 and disease duration of 11 years; whereas the trial referred to as the comparator contained patients with a mean HAQ score of 1.8 (1.3-2.1) and disease duration of 9.8 (4.9-17.64).

1.2.3 Use of response criteria to stop treatment

In section 4.3.20 of the ACD, it states that, "*The Committee did not consider that the Assessment Group's analysis could be used as a basis for decision making because it did not fully incorporate response criteria*." Given that the Committee feels it cannot make a decision based on the Assessment Group's analysis, Abbott considers it is appropriate for the Committee to use the Abbott economic model for its decision making. The model submitted by Abbott in common with all of the manufacturers' models incorporates response criteria. In the Abbott model, patients only continue treatment if they achieve at least an ACR50 response at 24 weeks. Sensitivity analyses were also presented using ACR20 response at 24 weeks for assessment of response.

1.3 Consultees were not given the opportunity to respond to the Assessment Group's critique of the economic models so that the Committee were not in possession of all the evidence at the first meeting

The Assessment Group report, sent to consultees and commentators on 30 November 2009, included a section entitled "Critique of manufacturers' submissions". This section was in fact a brief overview of the manufacturer models, with no mention of the evidence synthesis and did not provide a detailed critique of the model structures or their inputs. Abbott submitted comments on the Assessment Group report on the 12 January 2010 in accordance with the timelines stipulated by NICE.

On release of the ACD and the accompanying evaluation report on 24th February 2010, Abbott became aware that the Assessment Group had produced an Addendum report dated 28th January 2010 which was available to committee members at the Committee meeting on the 4th February 2010. This Addendum report contained a critique of the manufacturers' indirect comparisons and mixed treatment comparisons, as well as a section entitled "further critique of manufacturers' models" which stated that the supposed critique of manufacturers' submissions in the Assessment Report was in fact "*a description of the models included in each of the manufacturers' submissions, and a summary of results from this modelling*". Abbott therefore considers it is reasonable to conclude that the Assessment Group accepts that the Assessment Report did not include a critique of the manufacturer submissions. Abbott considers it unfair that the manufacturers were provided with no opportunity to address the critique of their submissions, particularly when this critique was made available to the Committee members prior to the Committee meeting.

Furthermore, section 3.4.9 of the NICE Methods Guide states that: "*After comments are received and considered, the Assessment Group may need to perform additional analysis before the Appraisal Committee meets to develop the ACD. NICE incorporates any additional analysis produced into the evaluation report for distribution to consultees and commentators with the ACD*." However, the methods guide does not state that it is acceptable for the Assessment Group to include a critique of the manufacturer submissions after comments are received and considered which appears to be the approach taken in this instance.

As a result, section 4.3.14 of the ACD discusses the manufacturers' evidence syntheses, including the Assessment Group's critique, without any explanation or clarification from the manufacturers. Moreover, based on the Assessment Group's comments, the Committee subsequently dismissed the manufacturers' evidence syntheses as a source of relative treatment effect and relied on the Assessment Group's estimates, even though the Committee recognised the methodology was defective. Abbott contends that had manufacturers been given an opportunity to respond to the critique made by the Assessment Group prior to the Committee Meeting, the evidence syntheses developed by the manufacturers may have been given more weight in the consideration of the evidence, and as a result, the preliminary recommendations may have been different.

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?

Abbott does not consider that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence nor that the preliminary views on the resource impact and implications for the NHS are appropriate.

2.1 Cost-effectiveness of anti-TNFs vs. conventional DMARDs

2.1.1 Implication of the presumed effectiveness of conventional DMARDs on the cost-effectiveness estimates

In section 4.3.6 and 4.3.21 of the ACD, the Committee noted that the BRAM assumed that conventional DMARDs used after the failure of a TNF inhibitor were 50% as effective as when used in

early rheumatoid arthritis. The Committee considered that in light of the clinical experts' testimony regarding the poor efficacy of conventional DMARDs at this point in the treatment pathway, the Assessment Group may have overestimated the efficacy of conventional DMARDs and as a result overestimated the ICERs in the base case analysis.

In the Assessment Group's addendum, scenario analysis using efficacy estimates for DMARDs comparable to placebo shows that the ICER for adalimumab vs. conventional DMARDs would be about £28,100/QALY gained. Whilst the Committee concluded that an analysis that assumed the effect of conventional DMARDs to be no more than that of placebo was not plausible, it should be noted that the placebo analysis is derived from RA patients from the REFLEX or ATTAIN randomised controlled trials who have failed a TNF inhibitor and who were receiving a DMARD - methotrexate. It is therefore not unreasonable to assume that conventional DMARDs would be about as effective as 'placebo' at this stage in the treatment pathway, in line with data from the BSRBR for patients stopping TNF inhibitor therapy (0 HAQ improvement for patients stopping a TNF inhibitor and going back onto conventional DMARDs). In the 'poor DMARD response' scenario, the probability that adalimumab would be a cost-effective treatment option at a willingness to pay threshold of £30,000/QALY would increase from 30% in the Assessment Group's base case to 57%.

In section 4.3.10 of the ACD, the Committee concluded that, "*Overall, on the basis of clinical opinion, the effect of conventional DMARDs in people for whom a TNF inhibitor had failed was likely to be small, but the relative effect in comparison with biological treatments was not currently quantifiable*."

As has been extensively discussed in previous correspondence on this issue, there is a paucity of evidence available for the effectiveness of conventional DMARDs in a TNF inhibitor failure population. This data gap is not only wide for patients failing a TNF inhibitor, it also exists for patients failing two prior DMARDs as no randomised controlled trials have considered the effectiveness of conventional DMARDs after failure of two DMARDs in patients with established/ late RA with many years of disease duration. One of the consequences of the lack of data on the effectiveness of conventional DMARDs in later lines of therapy is that it is difficult to precisely quantify the cost effectiveness of all biologic therapies versus conventional DMARDs. The outcome of this uncertainty could be the restriction of biologic therapies leading to use of conventional DMARDs in anti-TNF failure populations with minimal effect. As one option, given the absence of appropriate clinical trial data for conventional DMARDs, it may be instructive to assess their effectiveness using observational data. The limited observational data from the BROSG and BSRBR studies indicate that sequential use of conventional DMARDs after methotrexate failure in late RA does not significantly improve HAQ scores in either the short term or long term.

Although the populations in the above studies do not adequately reflect the anti-TNF failure population, given that sequences of conventional DMARDs have not been able to reduce HAQ scores in studies of late RA it is highly unlikely that this would be possible in the more severe anti-TNF failure population (who have failed two or more DMARDs prior to failing their first TNF inhibitor). Therefore, cost-effectiveness estimates used in the Committee's decision making should be based on the limited clinical effect of DMARDs in this patient group as the most plausible estimates, and not on the Assessment Group's arbitrary 50% reduction in effectiveness from an early RA study.

2.1.2 Impact on the cost-effectiveness estimates when response criteria are included in the economic modelling

In section 4.3.20 of the ACD, the Committee noted that the Assessment Group's analysis could not be used as a basis for decision making because it did not fully incorporate response criteria. However, in the Addendum report, the Assessment Group did conduct a scenario analysis in which a proportion of patients stopped treatment due to non-response after 6 months of therapy based on the Abbott model stopping rule of an ACR50 response. This analysis reduced the ICER for adalimumab vs. conventional DMARDs to £22,200/QALY gained. Unfortunately the Assessment Group did not present the probability that each drug would be cost-effective at various thresholds for this scenario analysis.

The Assessment Group's reason for not including a stopping rule based on response criteria stemmed from BSRBR data indicating that a number of people continue treatment with a TNF inhibitor even in the absence of such a response. Abbott agrees with the Committee that this is not an

appropriate assumption to make. NICE guidance TA130 has a clear stopping rule based on an improvement of at least 1.2 in DAS28 response at six months, which is why all of the other submitted models included a stopping rule based on response criteria.

When a stopping rule is included in the BRAM, the ICER for adalimumab vs. conventional DMARDs decreases from £34,300 to £22,200/QALY gained (table S10, page 84, of the addendum report using Abbott model short-term quit rates). When the effectiveness of conventional DMARDs is amended to reflect the testimonies of the clinical experts, the ICER for adalimumab vs. conventional DMARDs decreases from £34,300 to £28,100/QALY gained, and the probability of adalimumab being cost-effective at a willingness-to-pay threshold of £30,000 increases to 57%. Abbott requests that the BRAM model be re-run with these combined assumptions. Furthermore, given that the probability of adalimumab being cost-effective at a willingness-to-pay threshold of £30,000 was 57% just based on the change in efficacy for conventional DMARDs, it is highly likely that when the stopping rule is also included that the probability of TNF inhibitors being cost-effective is very high. In the ACD, the Committee accepts the fact that the effect of conventional DMARDs in people for whom a TNF inhibitor had failed is likely to be small, and that a stopping rule based on response criteria should be used to determine whether patients should continue treatment. Therefore, Abbott considers that it would be appropriate for the Committee to recognise the impact these two assumptions have on the cost-effectiveness estimates, which show that the TNF inhibitors are a cost effective use of NHS resources vs. conventional DMARDs in patients who have failed a TNF inhibitor. This can be demonstrated using either the BRAM or Abbott model as the basis for decision making.

2.2 Interpretation of the evidence for the cost-effectiveness of rituximab

In section 4.3.19 of the ACD, the Committee noted that, "*The BRAM modelled time to repeat treatment as 8.7 months in the base case, basing this estimate on Roche's submission. It noted that similar time to re-treatment had been assumed in a number of the other manufacturers' submissions. On the basis of the clinical specialists' advice, the Committee assumed that treatment with rituximab would occur, on average, less frequently than every 6 months.*" It states elsewhere in the ACD that the cost-effectiveness estimates are very sensitive to the re-treatment window applied to rituximab; and the conclusions from this statement imply that as re-treatment occurs less frequently than every 6 months, rituximab is a cost-effective use of NHS resources. However, the BRAM used a re-treatment window of 8.7 months but applied 6 month HAQ changes from REFLEX. The only other model to use an 8.7 month re-treatment window was the Abbott model but this included the following caveat: "The results represent an optimistic estimate of the cost-effectiveness of rituximab with regards to assumptions around the re-dosing interval". Since the evidence submission in August 2009, data from the SUNRISE trial[6] and the change to the FDA labelling for rituximab indicate that a re-treatment window of 6 months would have been more appropriate in the Abbott base case analysis.

There is an increasing body of evidence (discussed in 2.2.1 below) which shows that if patients are re-treated on average every 8.7 months then it is highly likely that they will lose efficacy and return to near baseline disease activity, which is associated with commensurately lower QALY gains as patients losing response would suffer a reduction in their quality of life until re-treated. An additional concern with this rituximab dosing regimen is that it is not yet clear what the implications of losing tight disease control will have on radiographic progression in the future. Abbott argues that there are two ways of treating a patient with rituximab and therefore two ways in which it can be modelled. Either patients are re-treated when their disease flares and thus the modelling should include a higher HAQ progression rate for rituximab; or patients are re-treated to maintain tight disease control, which necessitates using a 6 month re-treatment window. What cannot be done is use 6 month efficacy data for an 8.7 month re-treatment window, as this considerably over-estimates the cost-effectiveness of rituximab by simultaneously applying costs based on an 8.7-month re-treatment interval with effectiveness based on the initial 6-month HAQ improvements.

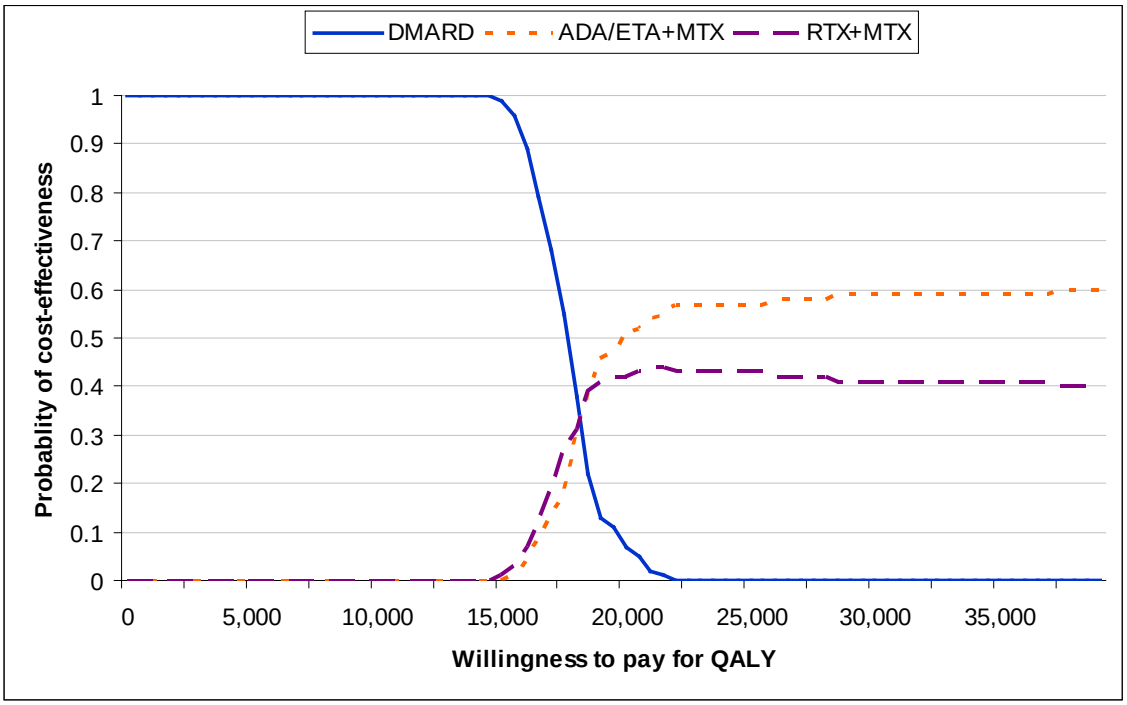
Abbott asks that if a 8.7 month re-treatment window is assumed in the BRAM base case analysis that the model is re-run with a greater HAQ progression for rituximab than for TNF inhibitors to incorporate the impact of loss of disease control with re-treatment every 8.7 months. Given that it does not seem clinically appropriate to let patients' disease flare, Abbott suggests that the base case analysis assumes a 6-month re-treatment window and uses the QALY gain derived from the 24 week HAQ improvements from REFLEX. When this scenario was assumed, the ICERs for adalimumab and rituximab vs. conventional DMARDs in the BRAM model are similar (£34,300 and £32,600/QALY

gained respectively; as shown in Table 19 of the Addendum report). Furthermore, had a stopping rule been included in the BRAM for the anti-TNFs, as it should have done (section 2.1.2), then the ICER for adalimumab vs. conventional DMARDs would be lower than rituximab vs conventional DMARDs at £22,200/QALY gained. Abbott requests that probabilistic sensitivity analysis be run by the assessment group to highlight the combined impact of these changes for the ICER estimates.

The model submitted by Abbott indicates that when a 6-month re-treatment interval is applied for rituximab, the ICER estimates for TNF inhibitors versus rituximab are low. The TNF inhibitors are more costly but also more effective than rituximab and the ICER in the base case for adalimumab/ etanercept versus rituximab is £17,517/QALY.

Using probabilistic sensitivity analysis, the cost-effectiveness acceptability curve illustrates the point that beyond an ICER threshold level of about £18,000 both TNF inhibitors and rituximab could be cost-effective options with probabilities close to 40%. However, the TNF inhibitors gain higher probabilities up to the 60% range around the level of £30,000, but rituximab remains at 40%. As such, limiting use of TNF inhibitors only in the context of research may risk excluding a treatment option that is cost-effective over 50% of the time.

Figure 2.2.1. Probabilistic sensitivity analysis results for the Abbott model (6-monthly re-treatment with rituximab, ACR 50 response criteria)



Appendix 2 contains a number of one-way sensitivity analyses using the Abbott model which confirm that compared to rituximab, TNF inhibitors represent a cost-effective treatment option under various scenarios when a 6-monthly dosing assumption for rituximab is applied.

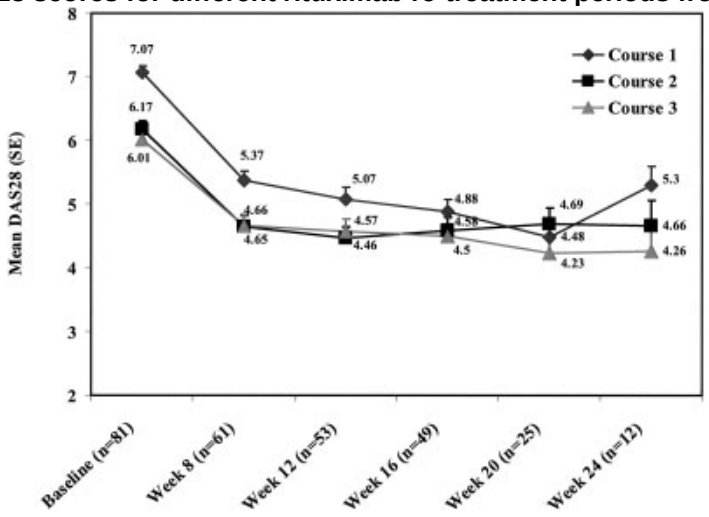
2.2.1 Evidence supporting loss of efficacy for rituximab when > 6 month re-treatment interval is used

The current EMA marketing authorisation for rituximab does not give any guidance as to the time period between treatments for rheumatoid arthritis, simply the minimum time between re-treatment (16 weeks). However, in June 2009 the manufacturer of rituximab filed a variation to the EMA seeking approval for first line biologic use of rituximab in RA patients who have failed conventional DMARD therapy. The data supporting this variation are based on the MIRROR and SERENE trials which all specified re-treatment with rituximab starting at 24 weeks for patients with a DAS28 score ≥ 2.6. Given that the patients in these trials had not failed a prior TNF inhibitor, then this suggests that re-treatment with rituximab in a more refractory patient population who have failed a TNF inhibitor is

likely to be at least every 24 weeks to ensure maintenance of response. Furthermore, in February 2010 the US FDA label for the use of rituximab in RA patients who have failed a TNF inhibitor was amended to the following based on newly available clinical evidence: "Subsequent courses of rituximab should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks."

Keystone *et al* assessed the DAS28 score of patients prior to re-treatment with rituximab[7]. In this open-label extension study, patients were enrolled from three rituximab phase II and III trials in patients previously treated with TNF inhibitors. They were eligible for repeated courses of rituximab based on certain criteria: a <20% reduction in tender and swollen joint count from baseline, with associated active disease defined as >8 tender and swollen joints present. Clinical efficacy, as measured by DAS28, was analysed at 24 weeks (see Figure 2.2.1.1) but the median time between courses of re-treatment was 38 weeks (course 1 to 2) and 42 weeks (course 2 to 3). In the period between 24 weeks and re-treatment with the next course, the DAS28 demonstrates a poor clinical response with return to near baseline values. The mean DAS28 just prior to course 1 was 7.01 and just prior to course 2 re-treatment was 6.17, or a reduction of 0.84, showing that patients are not maintaining clinical response.

Figure 2.2.1.1: DAS28 scores for different rituximab re-treatment periods from Keystone *et al.*

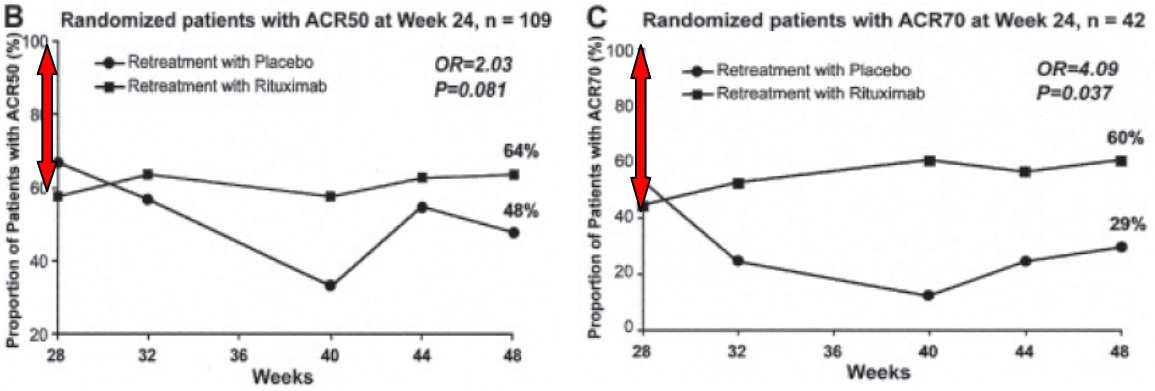


This has clear implications for optimal disease management and the cost-effectiveness estimates for rituximab. The loss of efficacy between 24 and 38 weeks would suggest more frequent dosing (i.e. every 16-24 weeks) is required to maintain disease control and keep the DAS28 improvement greater than the 1.2 reduction required for re-treatment under NICE guidelines for adalimumab, etanercept and infliximab (TA130).

Mease *et al.* recently published results from the SUNRISE trial, which examined the safety and efficacy of 1 versus 2 course of rituximab over 48 weeks in patients with RA who have previously failed treatment with anti-TNF agents. In this 559 patient trial, all patients were given rituximab at week 0; at week 24 those patients not in remission (DAS28 $\leq$ 2.6) were then randomised in a 2:1 ratio to receive a second course of rituximab or placebo. Approximately 85% of patients were not in DAS28 remission at week 24 and were randomised; although it is not clear whether the 15% of patients not randomised were actually in remission or whether they were lost to follow-up as the paper does not report how missing data were handled. The authors then assessed clinical response at week 24 using ACR response criteria and for those patients in response at week 24, they then examined response for both the rituximab group and the placebo group over time until week 48. Therefore this analysis is only following week 24 responders who have achieved either an ACR20, ACR50 or ACR70 response over time. Figure 4 in the paper shows the maintenance of response over time from week 28 until week 48. When considering the ACR50 and ACR70 graphs, it is apparent that from week 24 to week 28 over 40% of patients lose their ACR50 response and approximately 55% of patients have lost their ACR70 response (Figure 2.2.1.2). This suggests that a large proportion of patients are losing response between weeks 24 and 28, and are not regaining it *i.e*. there does not seem to be as much benefit from a 2nd course of rituximab for the group who lose response between weeks 24 and 28. The authors of this study concluded that because the goals of re-treatment include

maintenance of efficacy and prevention of flare, re-treatment should occur prior to worsening, and therefore Week 24 appeared to be an appropriate time to re-treat in most patients.

Figure 2.2.1.2: Maintenance of ACR 50 and ACR70 for patients receiving rituximab or placebo from the SUNRISE trial



Finally, post-hoc analyses of re-treatment with rituximab in anti-TNF naïve patients indicated that re-treatment to maintain a DAS28 score ≤ 2.6 gives better disease control than re-treatment without regard to specific disease activity levels[8]. Furthermore, when the re-treatment protocol was to maintain a DAS28 ≤ 2.6, the median time to re-treat was a 25-week interval. Patients receiving rituximab re-treatment without regard to keeping DAS28 score ≤ 2.6 had high DAS scores at time of re-treatment (DAS28 scores were 5.9 to 6.2 at time of re-treatment depending on which course of re-treatment was assessed, i.e. close to baseline DAS28 levels). This loss of response would have led to withdrawal of therapy if a TNF inhibitor were being used, in line with the guidance given in TA130. The worsening of DAS28 score was also associated with higher levels of withdrawals due to disease flares. The impact of this lower level of control will need to be assessed in long term follow up of radiographic progression and functional impairment in observational studies.

In summary, the modelling of rituximab costs should not be independent of treatment effect, that is to say, either rituximab re-treatment should occur more frequently than the currently applied mean of 8.7 months (i.e. every 6 months[7,9]) or the loss of efficacy observed prior to re-treatment at 8.7 months and potential for longer term functional impairment via HAQ progression needs to be included in the cost effectiveness analyses.

2.3 Additional Issues regarding the clinical effectiveness and safety of treatment with rituximab

2.3.1 Effectiveness of TNF inhibitors and rituximab for Rheumatoid Factor negative patients

Section 4.3.9 of the ACD discusses the impact of the presence of auto-antibodies on the clinical effectiveness of rituximab. The Committee noted that, "*the REFLEX trial showed no statistically significant differences in relative effectiveness between subgroups defined by auto-antibody status. Furthermore, the analyses by both rheumatoid factor and anti-CCP status were post hoc*." Abbott contends that there is a notable difference in clinical effectiveness for rituximab dependent on RF status. In contrast, data available for the TNF inhibitors indicate that TNF inhibitors show comparable efficacy in both RF+ and RF- patients[10].

Radiographic progression is one of the key outcome measures used in RA; furthermore it is one of the most objective measures available. Analysis of the REFLEX clinical trial data show that patients seronegative for Rheumatoid Factor (RF-) and/or anti-CCP negative have no significant difference in radiographic progression at week 56 when compared with placebo (Figure 2.3.1)[11]. Although the Committee have concluded that the REFLEX trial does not show any statistically significant differences in ACR response criteria by RF status, the data do show a trend to a lower rate of response for the RF seronegative group (Figure 2.3.2). Furthermore, where rituximab may give some benefit for the signs and symptoms of RA in RF negative patients, the radiographic data indicate that the disease is not adequately controlled in this sub-group of patients.

Figure 2.3.1: Radiographic Progression data by auto-antibody status from the REFLEX trial

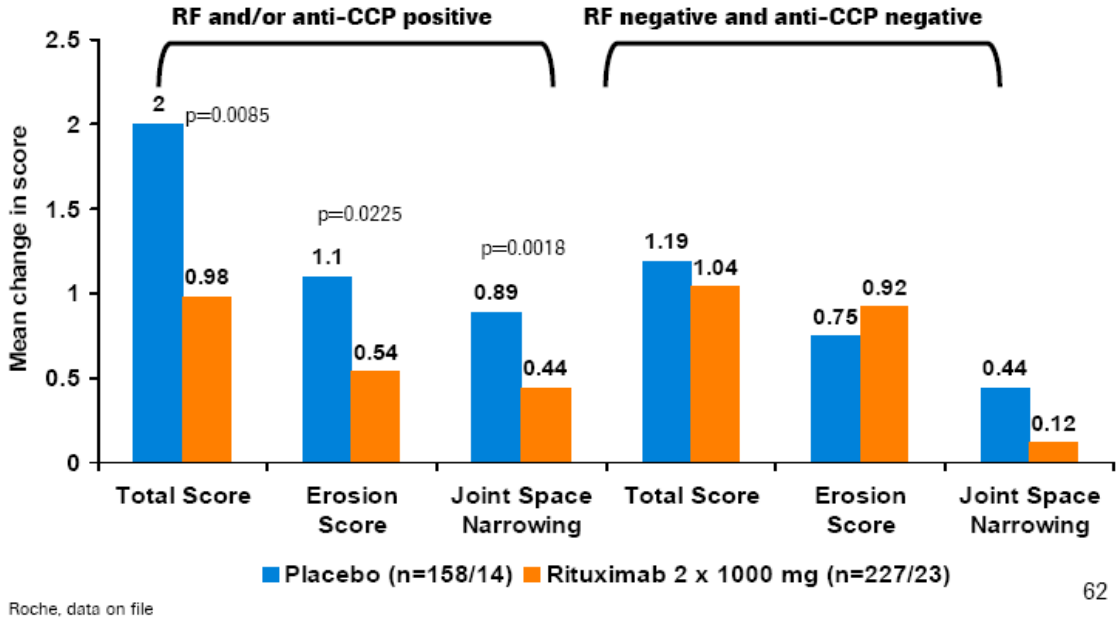
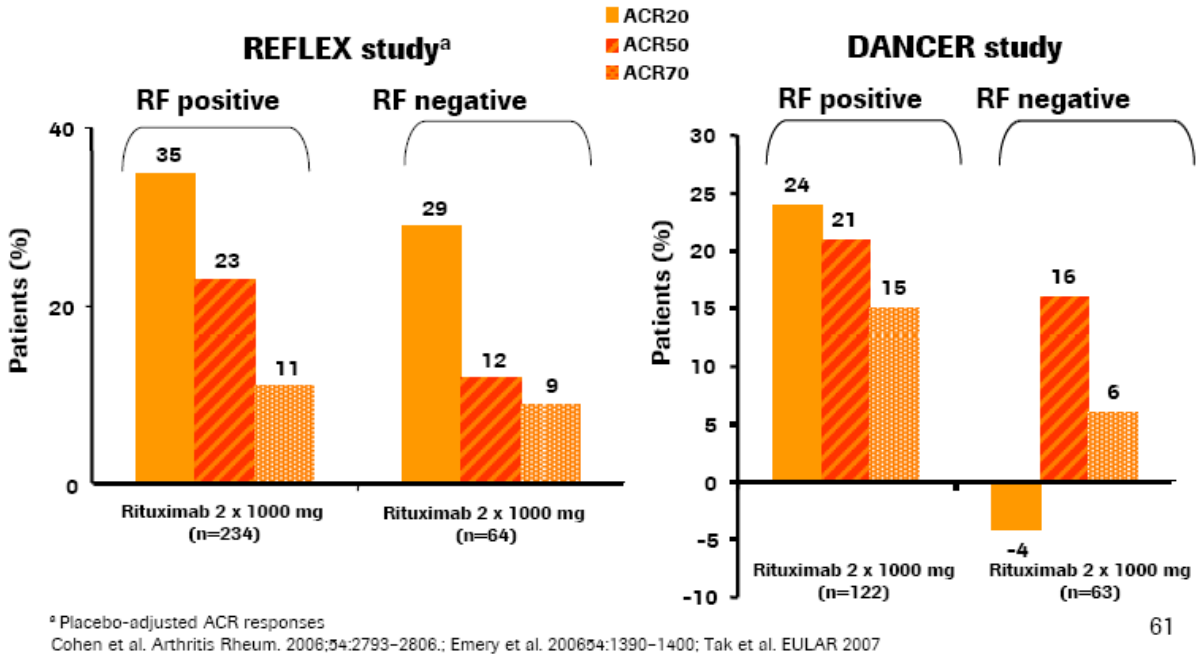


Figure 2.3.2: Placebo adjusted percentage of patients achieving ACR20/50/70 in the REFLEX and DANCER studies of rituximab.



As noted by the Assessment Group in its report, an unusually high number of RF- placebo patients in the DANCER study had an ACR20 response, and the numbers of RF- negative patients were low. Given this uncertainty, it is worthwhile considering other studies of rituximab in RA patients. In the phase III studies MIRROR and SERENE, patients seropositive for Rheumatoid Factor (RF+) and / or anti-CCP, showed enhanced clinical responses to rituximab when compared to seronegative patients[12]. A pooled cohort of patients was analysed which included patients with active RA where RTX was added to existing methotrexate. Rituximab was given by IV infusion on days 1 and 15 at doses of 2 x 500mg or 2 x 1000mg and from Week 24 further courses of RTX were permitted according to individual study criteria. Patients positive for either or both RF / anti-CCP were compared

with those who were seronegative for both. A total of 670 patients were included (554 [82.6%] seropositive, 116 [17.4%] seronegative). Despite similar baseline demographics and characteristics, seropositivity was associated with a significantly greater proportion of patients achieving ACR20/50/70, EULAR responses and DAS28 remission versus seronegative patients. Seropositive patients were 2-3 times more likely to achieve a clinical response at week 48 versus seronegative patients - odds ratios (95% CI) for seropositive pts achieving ACR 20, 50 and 70 were 2.23 (1.38–3.58), 2.72 (1.58–4.70) and 3.3 (1.40–7.82) respectively, versus seronegative patients. These data indicate that patients who were RF negative and anti-CCP negative had lower response rates. It would be interesting to know whether patients who were RF negative alone had lower response rates, as these studies may have a sufficiently large sample size when pooled to confirm this hypothesis.

Finally, data on response by RF status are also available in an observational cohort of patients on rituximab from European registries (n=1,372)[13]. These data indicate that 14.4% of patients receiving rituximab were RF- negative. These patients were less likely to be EULAR responders in a logistic regression analysis, although it should be noted that this difference was not statistically significant (Odds Ratio for RF+ status 1.5, 95% CI 0.96-2.0). However, these data indicate that a smaller proportion of patients receiving rituximab in clinical practice are RF- compared to patients receiving TNF inhibitors. Hyrich et al. reported 28% of TNF inhibitor patients as RF- in the BSRBR.

This is in contrast to the data for the anti-TNF agents. Analysis of the DE019 study of adalimumab (Keystone *et al*[14]) versus placebo found that RF- patients had similar levels of ACR response as RF+ patients (Table 2.3.1). The impact of adalimumab on radiographic progression in DE019 (as assessed using the Total Sharp Score) was also not affected by whether patients were RF+ or RF-.

Table 2.3.1: Percentage of patients achieving ACR 20 response at week 24 in the DE019 study of adalimumab by RF status

	ACR 20 response rate at week 24 (primary endpoint)		Relative Risk
	Adalimumab 40mg every other week	Placebo	
Rheumatoid Factor positive	66%	30%	2.2
Rheumatoid Factor negative	67%	33%	2.0

As can be seen in Table 2.3.2, this finding is also supported by data from the large observational ReACT study.

Table 2.3.2: Percentage of patients achieving ACR 20/50/70 response at week 12 in the ReACT study of adalimumab by RF status (as observed)

Response type	RF + n=4811	RF - n=1788
ACR 20	69.7%	66.7%
ACR 50	41.3%	37.0%
ACR 70	18.4%	17.9%
EULAR moderate or good response	83.3%	81.3%
EULAR good response	31.9%	36.6%

Both the ReACT and BSRBR studies have very large samples of rheumatoid factor negative patients to confirm the hypothesis that patients receiving TNF inhibitors do not have lower response rates when they are RF negative.

Therefore, although the Committee concluded that, "*there was insufficient evidence to make differential recommendations for subgroups based on auto-antibody status"*, Abbott believes that the radiographic data by RF status show that RF seronegative patients' disease is not adequately controlled on rituximab and these patients may benefit from treatment with a 2nd TNF inhibitor, given that there are extremely limited therapies available at this stage in the treatment pathway.

2.3.2 Safety of treatment with rituximab in RA patients

The safety of rituximab needs to be given due consideration in this appraisal considering the increased risk of Progressive Multifocal Leukoencephaolopathy (PML) in RA patients receiving rituximab detailed in the SmPC[15]. In September 2009, Genentech and the FDA notified healthcare professionals about a case of PML in a patient receiving treatment with rituximab for rheumatoid arthritis (the patient had not previously been treated with methotrexate or a TNF inhibitor) [16]. This represents the third fatal case of PML in an RA patient receiving rituximab which now has a black box safety warning regarding the infectious demyelinating condition[17,18]. Interestingly, rituximab treatment has also been associated with the development of PML in a number of other conditions: in a recent publication 52 patients with lymphoid malignancies, 2 patients with SLE, 1 patient with rheumatoid arthritis, 1 patient with idiopathic autoimmune pancytopenia, and 1 patient with immune thrombocytopenia purpura all developed PML after rituximab treatment[19]. The case fatality rate was 90% for these patients. As of July 29, 2008, there were 76 reports in the manufacturer's global safety database of confirmed or suspected PML in patients receiving rituximab in any indication[20]. This further highlights the need for increased awareness and reporting of rituximab-associated PML cases in order to improve our understanding of the risk factors, natural course, and alternative therapeutic approaches. Overall, the reported incidence of PML in patients with RA receiving rituximab is rare (3 reports in approximately 100,000 RA patients on rituximab). However, the information to date suggests that patients with RA who are treated with rituximab have an increased risk of PML.

Overall, the level of rituximab exposure (patient-years) is low in rheumatoid arthritis compared to the TNF inhibitor class and it is important to bear this in mind when analysing the clinical efficacy and safety data. As of September 2008, pooled data from the rituximab global clinical trial programme showed a total of 3,095 patients had been treated with rituximab for rheumatoid arthritis providing 7,198 patient years of treatment[21]. However, only 750 patients (24%) remained on treatment for greater than 3 years with 2,365, 1,581, 1,038 and 497 patients receiving≥2, ≥3, ≥4 and ≥5 courses respectively. Taken together, the long-term impact of sustained CD20+ cells depletion on relevant safety concerns and immune memory functions remains unanswered for this patient population.

Furthermore, there is limited experience regarding the safety of giving TNF inhibitors after rituximab therapy[22]. Safety data are currently available for only 178 patients who have received a TNF inhibitor after rituximab, with a median follow up of 11 months (191.72 patient-years). Given that in REFLEX, treatment with rituximab was associated with a rapid and complete depletion of CD19 positive peripheral B cells, (with some recovery of cell counts beginning between weeks 16 and 20) with a non-existent median CD19+ve B cell count at week 24, poor responders to rituximab will have severely limited treatment options as the safety of further biologic therapy in patients with low or no circulating peripheral B cells is largely unknown. Preliminary data from patients who withdrew from rituximab therapy during rituximab clinical trials and then started treatment with either conventional DMARDs and/or TNF inhibitor therapies have been reported (n=153)[23] and show a near doubling of the serious infection rate in those that switched to TNF inhibitors. However, the overlapping 95% confidence intervals do not permit inference of a significant difference between rates before and after TNF inhibitor therapy in this analysis.

Given these issues around treatment options for patients who do not respond to rituximab, and the duration of disease for RA patients, it makes sense clinically to exhaust treatment options at each step of the treatment pathway before moving on to the next level. Current practice suggests that at least two DMARDs are tried before initiation of anti-TNF therapy, and the NICE clinical guidelines support this by suggesting patients diagnosed with RA are given combination DMARDs within 3 months of diagnosis. The next step after DMARD failures would be TNF inhibitor therapy. If a patient loses response to more than one member in this class, they should then move on to rituximab, as once rituximab has been given, there is currently uncertainty regarding the long term safety of alternative biologic options.

2.4 Costing errors in the BRAM

Abbott welcomes the corrections made to the cost inputs in the Addendum to the Assessment Report, however it is a concern that the model still contains errors. Table 9.1 and Table 9.2 of the Addendum states that 6 doses of infliximab are given per year, with one additional dose in the first year. The licence for infliximab states that treatment should be administered at week 0, 2 and 6 and then every 8 weeks thereafter. It is clear from the dosing assumptions for adalimumab and etanercept that the

Assessment Group assumes a 52 week year. As stated in NICE's costing template for TA130, this corresponds to 8 doses in the first year, and either 6 or 7 doses per year thereafter (i.e. 6.5 doses on average). The BRAM therefore currently underestimates the cost of infliximab by 1 dose in the first year, and 0.5 doses thereafter.

3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

Abbott considers that the provisional recommendations do not constitute a suitable basis for the preparation of guidance to the NHS because the recommendations do not take into account the need for a sequence of biologic therapy options for patients with severe RA with very low quality of life. A significant proportion of TNF failure patients have pain, fatigue and functional impairment which the general population views as so severe that they consider these states as worse than death, highlighting the severity of this patient population.

At present it is unknown which patients will respond to a particular biologic therapy and, at the individual level, patients show a significant heterogeneity of response, such that a patient responding poorly to a first TNF inhibitor could have a markedly greater response to a 2nd TNF inhibitor. If the provisional recommendations were to become guidance to the NHS, UK patients would not get the opportunity to receive a 3rd or 4th biologic treatment option, which at the individual patient level could deny the patient the chance of an improved quality of life. Abbott considers that this lottery is not justifiable on cost effectiveness grounds as the different biologic therapies are likely to have ICERs of less than £30K per QALY versus conventional DMARDs andm therefore, should be recommended as treatment options. Given uncertainties regarding the effectiveness of rituximab in rheumatoid factor negative patients, the safety of biologic treatment after rituximab and the similar cost of TNF inhibitors and rituximab when rituximab re-treatment is given every 6 months, as necessary to maintain disease control, Abbott considers it is inappropriate to recommend rituximab as the **only** biologic option for patients failing a TNF inhibitor.

4. Are there any equality related issues that may need special consideration?

None that Abbott is aware of.

Appendix 1

Table A1.1: Summary of included studies in the DSU Evaluation Report published in January 2008 that evaluate the use of a 2nd anti-TNF agent in patients with active RA who have failed treatment with a first anti-TNF agent and reasons for switching

Study (year)	Agents	Number of patients in study	Reasons for switching	Time beyond switch measurement made	Primary outcome variable	Results
Ang et al. (2003)	IFX → ETA ETA → IFX	24 5	Lack of efficacy/adverse event	Not reported	Joint count	Patients with an inadequate response to the first can respond to another
Atenzi et al. (2006)	IFX → ETA → ADA ETA → IFX → ADA	15	Non response or AEs for first switch, switch to ADA if DAS28>5.1	At time of stopping 2nd biologic and then every 6 months	HAQ, DAS	DAS 28 mean change at 26 weeks of -2.7
Bennett et al. (2005)	IFX → ADA ETA → ADA AKA → ADA	26	No response (27%) Loss of efficacy (5%) AEs (21%)	4,8,16,26,52 weeks	DAS28, HAQ, EULAR	DAS28 = -2.7 EULAR none = 19% EULAR moderate = 46% EULAR good = 35%
Bombardieri et al. (2007)	IFX → ADA or ETA → ADA	899	Mixture of no response, loss of efficacy and intolerance.	12 weeks	ACR, DAS28	**No response (n=173):** ACR20 = 52% ACR50 = 25% ACR70 = 8% DAS28 = -1.9 EULAR none = 26% EULAR moderate = 55% EULAR good = 19% HAQ = -0.44 **Loss of response (n=306):** ACR20 = 67% ACR50 = 37% ACR70 = 13% DAS28 = -2.0 EULAR none = 21% EULAR moderate = 57% EULAR good = 22% HAQ = -0.51
Brulhart et al. (2006)	Any anti-TNF → RTX Any anti-TNF → another anti-TNF	10 20	'failure' according to patient's rheumatologist	3, 6 months	DAS, HAQ	DAS28 = -1.48 DAS28 = -0.8
Buch et al (2005 a)	IFX → ETA	34	Non response, and a) never achieved 20% improvement in CRP (n=10), b) achieved a temporary improvement in CRP (n=15)	12 weeks	ACR	**Group A (n=12)** ACR20 = 66% ACR50 = 66% ACR70 = 33%

Study (year)	Agents	Number of patients in study	Reasons for switching	Time beyond switch measurement made	Primary outcome variable	Results
						Group B (n=22) ACR20 = 71% ACR50 = 57% ACR70 = 14%
Buch et al (2005 b)	IFX → ADA	59	Non response (32%) Loss of efficacy (51%) Toxicity (18%)	12 weeks	EULAR and DAS28	**Non response (n=19)** DAS28 = -1.3 EULAR none = 57% EULAR moderate = 36% EULAR good = 7% **Loss of response (n=30)** DAS28 = -1.4 EULAR none = 32% EULAR moderate = 61% EULAR good = 7%
Buch et al. (2007)	IFX → ETA	95	Non response (36%) Loss of efficacy (40%) Toxicity (24%)	12 weeks	EULAR and DAS28	ACR20 = 38% ACR50 = 24% ACR70 = 15% DAS28 = -1.47 EULAR none = 27% EULAR moderate = 61% EULAR good = 12%
Brocq et al. (2002)	IFX → ETA ETA → IFX	8 6	Miscellaneous	Not reported	Not reported	
Brocq et al. (2004)	ETA → ADA ETA → IFX → ADA	8 10	Mixed	2-8 months	Not stated	Details not reported
Cantini et al. (2005)	IFX → ETA ADA → ETA	15 7	Inefficacy (68%) AEs (32%)	Baseline, 2, 12, 24 weeks	ACR, DAS28	ACR20 = 90% ACR50 = 33% ACR70 = 10% DAS28 = -2.43
Cohen et al. (2005)	IFX → ETA ETA → IFX	24 14	Non response (76%) AEs (24%)	3 months	DAS28	DAS28 = -1.5 EULAR none = 26% EULAR moderate = 16% EULAR good = 58%
Di Poi et al. (2007)	IFX → ETA	18	Non response (61%) Loss of efficacy (39%)	2 weeks, 3 months, every 3 months until last follow-up	EULAR, DAS28	DAS28 = -2.0 EULAR none = 28% EULAR moderate = 33% EULAR good = 39%
Favelli et al. (2004)	IFX → ETA ETA → IFX	14 1	Lack of efficacy/AE Lack of efficacy	6 months	ACR20, DAS28, HAQ	DAS28 = -1.42 HAQ = -0.34
Finckh et al. (2004)	Any anti-TNF →	50	Any	3, 6 and 9 months	DAS28	DAS28 = -1.28 – 12 weeks

Study (year)	Agents	Number of patients in study	Reasons for switching	Time beyond switch measurement made	Primary outcome variable	Results
	RTX Any anti-TNF → another anti-TNF	66				DAS28 = -0.8 – 12 weeks
Furst et al. (2007)	ETA → IFX ETA → ETA	14 14	Not reported	16 weeks	ACR, DAS28, HAQ	**ETA → IFX** ACR20 = 61.5% ACR50 = 30.7% DAS28 = -2.2 **ETA → ETA** ACR20 = 29% ACR50 = 15% DAS28 = -1.3
Gomez-Puerta et al. (2004)	IFX → ETA	12	Lack of efficacy	6 months	DAS28, EULAR	DAS28 = -1.33 EULAR none = 17% EULAR moderate = 67% EULAR good = 17%
Hansen et al. (2004)	ETA → IFX	20	Lack of efficacy/ AE	Not reported	SWJ, TJC	Not reported
Haroui et al. (2004)	IFX → ETA	22	Lack of efficacy/ AE	12 weeks	ACR20, HAQ	ACR20 = 64% ACR50 = 23% ACR70 = 5% HAQ = -0.45
Hjardem et al. (2007)	IFX → Any ETA → Any ADA → Any	178 18 39	Lack of efficacy (46%) AEs (31%)	3, 6 months	DAS28, EULAR	DAS28 = -1.41 EULAR none = 28% EULAR moderate = 48% EULAR good = 24%
Kafka et al. (2005)	Any anti-TNF → another anti-TNF	191	Physician choice (46%) AEs (18%) Lack of efficacy (17%)	12 weeks	DAS	DAS28 = -0.8
Keystone et al. (2004)	IFX → ETA ETA → IFX	83 72	Lack of efficacy	6 months	HAQ	**IFX → ETA** HAQ = -0.41 **ETA → IFX** HAQ = -0.
Kristensen et al. (2006)	Any anti-TNF → ETA Any anti-TNF → ADA	239 165	Any	3,6,12,24,36 months (12 for ADA)	ACR20	**Any anti-TNF → ETA (n=239)** ACR20 = 59% **Any anti-TNF → ADA (n=165)** ACR20 = 52%
Naumann et al. (2006)	Any anti-TNF → another anti-TNF	31	Severe adverse event (7) Ineffectiveness (22) Incompliance (2)	3 yrs max	DAS	Details not reported
Nikas et al. (2006)	IFX → ADA	24	Lack of efficacy/AE	12 months	ACR, DAS28	ACR20 = 89% ACR50 = 56% ACR70 = 33%

Study (year)	Agents	Number of patients in study	Reasons for switching	Time beyond switch measurement made	Primary outcome variable	Results
						DAS28 = -2.1 EULAR moderate/good = 78%
Van der bilj et al. (2005)	IFX → ADA	37	Lack of response (35%) Loss of efficacy (51%) Toxicity (13.5%)	16 weeks	ACR, DAS28, EULAR	**Loss of efficacy (n=19)** ACR20 = 61% ACR50 = 39% DAS28 = -2.1 EULAR moderate = 74% **Lack of response (n=13)** ACR20 = 33% ACR50 = 8% DAS28 = -1.0 EULAR moderate = 46% **AEs (n=5)** ACR20 = 40% ACR50 = 20% DAS28 = -1.4 EULAR moderate = 80%
Van Vollenhoven et al. (2003)	IFX → ETA ETA → IFX	13 18	Lack of efficacy Adverse event	> 8 weeks	DAS28, ACR-N	Details not reported
Wick et al. (2005)	IFX → ADA ETA → ADA	27 9	Secondary loss of efficacy	3, 6 months	DAS28	I**FX → ADA** ACR20 = 70% DAS28 = -1.3 **ETA → ADA** ACR20 = 78% DAS28 = -1.9
Yazici et al. (2004)	ETA → IFX	21	Miscellaneous	Not reported	Not reported	Details not reported

Appendix 2. Cost effectiveness estimates using the model submitted by Abbott

As demonstrated in section 1.2, the Abbott MTC meta-regression used to derive ACR responses for the specific population in this appraisal offers reliable estimates which were incorporated in the economic model submitted by Abbott. However, to address concerns expressed by the Assessment Group and endorsed by the Appraisal Committee, a number of additional sensitivity analyses were prepared for the cost-effectiveness analysis to test the robustness of the model under varying assumptions, in line with those made in the BRAM and other manufacturer submissions.

The comparisons presented here are limited to the sequences starting with ADA/ETA+MTX or RTX as the single second biologic after the failure of the 1st TNF inhibitor.

Table A2.1 Treatment sequences in the Abbott model

Treatment Line	Sequence 1	Sequence 2	Sequence 4
1	gold	ADA/ ETA+mtx	rtx+mtx
2	lef	gold	gold
3	mtx+cyc	lef	lef
4	rescue	mtx+cyc	mtx+cyc
5	rescue	rescue	rescue
6	rescue	rescue	rescue

ACR response rates from the REFLEX study for DMARDs and RTX, and from ReACT – the source of the efficacy data for the BRAM model for TNFs inhibitors were applied to generate sensitivity analyses. These response rates are shown in Table A2.2 below. A 6-monthly RTX dosing was applied as per the rationale outlined in section 2.2.1 of this response document. Results of this analysis are shown in Table B

Table A2.2 ACR response rates from Reflex (DMARD and rituximab) and ReACT (TNF inhibitors

	ACR20	ACR50	ACR70
DMARD (REFLEX):	18	5	1
Anti-TNF (ReACT):	60	33	13
Rituximab (REFLEX)	51	27	12

Table A2.3 Abbott model results using ACR response from Reflex (DMARD and rituximab) and ReACT (TNF inhibitors)

	DMARD	ADA/ETA +MTX	RTX+MTX
Discounted Results (Per Patient)			
Costs	£27,056	£47,141	£43,582
Life Years	11.71	12.18	12.10
QALYs	1.52	2.74	2.52
Net Costs		£20,085	£16,526
Net Life Years		0.468	0.386
Net QALYs		1.220	0.997
Cost per Life Year		£42,931	£42,795
Cost per QALY vs DMARD		**£16,462**	**£16,580**

Consistent with Abbott's base case results originally submitted, the ICER remains under £20,000/QALY for the ADA/ETA+MTX sequence and is in fact the least among all arms in the analysis vs DMARDs. Total costs are higher for ADA/ ETA than for the RTX sequence, but QALY gains are also higher for ADA/ETA.

A second alternative set of ACR responses were taken from REFLEX and the Roche MTC, shown in Table A2.4 below. Results of this analysis are shown in Table A2.5.

Table A2.4 ACR response rates from Reflex (DMARD and rituximab) and Roche MTC (TNF inhibitors)

	ACR20	ACR50	ACR70
DMARD (REFLEX):	18	5	1
Anti-TNF (Roche MTC):	46	31	13
RTX (REFLEX)	51	27	12

Table A2.5 Abbott model results using ACR response from Reflex (DMARD and rituximab) and Roche MTC (TNF inhibitors)

	DMARD	ADA/ETA +MTX	RTX+MTX
Discounted Results (Per Patient)			
Costs	£27,056	£46,231	£43,582
Life Years	11.71	12.15	12.10
QALYs	1.52	2.67	2.52
Net Costs		£19,175	£16,526
Net Life Years		0.439	0.386
Net QALYs		1.151	0.997
Cost per Life Year		**£43,717**	**£42,794**
Cost per QALY vs DMARD		**£16,654**	**£16,578**

Again, results do not show a large change: overall QALYs and costs are reduced, increasing the ICERs by less than £1,000. In essence, although the ACR response estimates from different sources vary, the *relative difference* between DMARD and TNF inhibitor ACR responses based on the alternative datasets are not very different from those of Abbott's original MTC. Results in general are not sensitive to ACR70 response rates – as the ACR70 response is relatively uncommon in this population. Furthermore, the difference between DMARD and biologics is relatively small for ACR70, and ACR70 does not determine withdrawal in the model.

ACR50 will have a relatively larger impact since it determines withdrawal from treatment at 6 month in the Abbott CE model. However, relative to DMARDs, the differences in ACR50 estimates are close to each other (26-30%). That explains why the alternative sets do not have an impact on the magnitude of the ICER.

The mean HAQ change associated with each level of ACR response in the current base case (MTC results with HAQ reductions from the DE019 trial's full population) leads to a higher mean reduction in HAQ than the HAQ multipliers used in the BRAM model. An alternative dataset of starting HAQ >2 patients from the adalimumab DE019 trial was tested in a sensitivity analysis included in Abbott's evidence submission[24]. However, these HAQ progression values were based on very small patient numbers and therefore were not applied in the base case. Smaller mean HAQ changes increased the ICER for ADA/ETA vs DMARDs to £20,000/QALY. Most importantly, the same trial based values are applied uniformly across all biologic treatments.

Estimates of clinical effectiveness – long term, p. 32 of the Addendum report

The Addendum Report criticises the submission and comments that "it is not credible that HAQ does not change with time in this population". In fact, Abbott's submission model did not assume 'no change'. In line with previous NICE Assessments Abbott's submission considered an annual increase of 0.03 in HAQ progression while on biologic treatment.

Discontinuation rule and treatment duration p.33 of the Addendum report

The Abbott model was criticised because the "[ACR50] response threshold appears too high compared to clinical practice". While ACR50 is a relevant and appropriate clinical standard for assessing treatment response, the impact of changing the ACR cut-off to ACR20 was also tested. As expected, patients stay on treatment longer, therefore accumulate more costs, however, they also accumulate QALYs to a greater extent. Even under the conservative assumptions of worsening of HAQ by 0.03 while on treatment, the aggregate effect changes the ICER minimally.

TableA2.6: Univariate Sensitivity Analysis – ADA/ETA+MTX vs conventional DMARDs

Scenario	DMARDs		Ada/Eta+mtx		ICER (£/QALY)	% change
	Cost (£)	QALY	Cost (£)	QALY		
Base case	26,866	1.69	50,289	3.16	15,962	
Non-responders defined by ACR 20 (withdrawal at 6 month)	26,721	1.85	60,840	3.86	16,962	6.27%

Handling of mortality

The Addendum report states that "The reported mortality advantages for patients on TNF inhibitor treatment compared with conventional DMARDs, need great care in interpretation because of selection biases involved in treating patients with a TNF inhibitor which may not be sufficiently adjusted for."

Scenario	DMARDs		Ada/Eta+mtx		ICER (£/QALY)	% change
	Cost (£)	QALY	Cost (£)	QALY		
Base case	26,866	1.69	50,289	3.16	15,962	
No mortality benefit for anti-TNF	26,868	1.69	48,493	3.05	15,899	-0.04%

As the table above shows, sensitivity analyses with an assumption of no mortality benefit for anti-TNFs shows that results are not sensitive to changes in mortality benefits.

Cost effectiveness estimates of Adalimumab/ Etanercept versus rituximab in the Abbott model

Additional sensitivity analyses were performed to assess the robustness of cost effectiveness of TNF inhibitors vs. rituximab, using the Abbott model and a 6 monthly re-treatment assumption for rituximab.

Results are stable under various assumptions of efficacy, HAQ progression and mortality. Thus, the TNF inhibitors remain cost-effective, with an ICER of around £20,000 versus rituximab in most scenarios tested.

	Rituximab + MTX		ADA/ETA+mtx			
Scenario	Cost (£)	QALY	Cost (£)	QALY	ICER (£/QALY)	% change
Basecase with 6 mthly RTX	48,661	3.06	50,289	3.16	17,517	
REFLEX and ReAct data	43,582	2.52	47,141	2.74	15,936	-9.03%
REFLEX and Roche MTC	43,582	2.52	46,231	2.67	17,144	-2.13%
Updated MTC (37 trials)*	49,987	3.22	51,638	3.31	18,085	3.24%
Updated MTC no Early Trials*	48,875	3.07	49,943	3.12	22,536	28.65%
NICE RA 75% HAQ rebound	46,938	3.90	48,540	4.00	15,463	-11.73%

NICE RA linear utilities	48,661	3.77	50,289	3.85	20,663	17.96%
ACR 20 response criteria for withdrawal	58,830	3.76	60,840	3.86	20,047	14.44%
Discount rate 6% for costs, 1.5% for utilities	40,079	3.46	41,268	3.56	11,033	-37.01%
Long term HAQ prog: 0 anti-TNF, 0.044 dmard responders, 0.132 non-responders	52,580	2.71	54,342	2.82	15,939	-9.01%
Long term HAQ prog: 0 for anti-TNF, 0.022 for dmard responders, 0.03 for non-responders	50,075	4.22	51,853	4.32	17,805	1.65%
No anti-TNF related mortality	47,084	2.97	48,493	3.05	16,595	-5.26%

*****See section 1.2 of this document for details of the updated MTC

Summary

In summary, Abbott's discrete event simulation model is a flexible tool that is designed to reflect the disease pathways for RA patients and allows testing of various scenarios easily. Abbott considers that the results that TNF inhibitors are cost effective versus DMARDs or rituximab are robust against changes in various parameters and that criticisms of the model do not undermine its usefulness for decision making in this appraisal.

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