NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Royal College of Pathologists	The Royal College of Pathologists have no comments to make (on the above ACD and evaluation report of the above appraisal) at this stage of the development.	Comment noted. No actions required.
Royal College of Nursing	**Has the relevant evidence been taken into account ?** We recognise the challenges the Appraisal Committee has had to face in gaining evidence to undertake a robust and realistic evaluation of the true benefits (to the patient and the health economy) particularly when wider social costs cannot be considered. However, given this limitation, we feel the scope has considered the evidence available.	Comment noted. No actions required.
Royal College of Nursing	We note the Committee's comments in Paragraph 2.5 – With respect to missing data and the time frame taken for work disability to occur, there are no data for socio economic costs, including patients who reduce working hours / change work for sometimes lower paid employment. This can have a significant effect on patient's quality of life and their contribution to the wider economy.	Comment noted. Section 2.5 is part of background information to the condition and current management. This section does not reflect the considerations of the Committee. The Committee recognised the impact of rheumatoid arthritis on patients and its impact on employment (see FAD section 4.3.2).
Royal College of Nursing	Patient's quality of life is also largely affected by other aspects of rheumatoid arthritis such as pain, fatigue, and sleep disturbance which the report recognises in paragraph 4.3.15 as not being incorporated in the HAQ score. Failure to treat these aspects have the potential to affect a patient's function, and increase the individual's use of primary care services, and clinical nurse specialist facilities such as advice-lines and urgent appointments.	Comment noted. The Committee understood the importance of pain, fatigue and sleep disturbance with regards to their impact on quality of life. The Committee was aware that such aspects may not be captured by the HAQ score. The Committee concluded that patients may derive benefits from treatment that are not reflected in HAQ. (see FAD section 4.3.17)
Royal College of Nursing	We would agree with the paragraph 4.3.10 that treatment effects for conventional DMARD's after failure of Anti TNF therapy would be limited, given that in order to meet the criteria for the use of TNF initially include failure to respond to conventional DMARD therapy.	Comment noted. The Committee considered the clinical effectiveness of conventional DMARDs and concluded that their effect in people for whom a TNF inhibitor had failed was likely to be small (see FAD sections 4.3.12 and 4.3.23).

Consultee	Comment	Response
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** The Appraisal Committee themselves have highlighted mainly limitations to the cost effectiveness and interpretations made. We are concerned that despite attempts by all involved to input into the economic model that we still fail to capture the potential benefits to an individual rather than the group effect. Yet in reality we as clinicians are providing care to individuals who may actually benefit significantly and have a strong individual need for an effective treatment pathway. As we are making significant decisions based upon the group not the potential individual benefits of sequential use - we are significantly compromising some individuals' ability to benefit from subsequent treatments e.g. sequential use of a TNF inhibitor following failure of Rituximab. Particularly as yet it is difficult to identify the most appropriate pathway for an individual patient as research is not yet available to support the use of one or another Anti TNF therapy as a first option.	Comment noted. The Committee understood that rheumatoid arthritis is heterogeneous, that different people can respond differently to the same treatment. It also recognised that currently it is difficult to predict whose disease will respond to a given treatment (see FAD section 4.3.3). However, the Committee is asked to make recommendations for populations of individuals. Within this it may consider subgroups for whom treatment may be more clinically or cost effective. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28).
sRoyal College of Nursing	Where in the patient treatment pathway will Certolizumab pegol be placed?	Comment noted. Certolizumab pegol was subject to its own single technology appraisal (see NICE technology appraisal guidance 186). Certolizumab pegol is recommended as an option for the treatment of people with rheumatoid arthritis in the same way as the other tumour necrosis factor (TNF) inhibitor treatments in NICE technology appraisal guidance 130 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis'. The guidance for certolizumab pegol does not include recommendations for sequential use (see FAD section 4.3.5).

Consultee	Comment	Response
Royal College of Nursing	In paragraph 4.1.6, the summary notes that 51% of patients only respond with an ACR 20 with Rituximab, whereas, paragraph 4.1.8 notes a 50% ACR 20 response to Abatacept. There is no evidence to support the summarisation that the 50 % of patients who responded to Rituximab would have also responded to Abatacept or vice versa. Therefore 50% of patients who fail to respond to the first choice of anti TNF Therapy and Rituximab have no further treatment options available, despite there being the potential that they may respond to Abatacept given its different mode of action.	Comment noted. The Committee understood that some people may not be able to receive treatment with rituximab or methotrexate because of intolerance or contraindications. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28).
Royal College of Nursing	Treatment options for patients who are sero- negative remain limited (para 4.3.3).	Comment noted. The Committee considered the specific subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Consultee	Comment	Response
Royal College of Nursing	**Point 4.3.20** The Appraisal Committee state in paragraph 4.3.20 that the current guidance on stopping treatment is not fully implemented in clinical practice, therefore, the response criterion had not been incorporated into the BRAM model. We are not clear what implication this has for the economic model. It does however highlight an issue that is likely to change as PCTs robustly monitor biologics use as their knowledge and understanding of the treatment and use of biologics improve and competencies of PCTs improve. It is hoped that this modelling did not compromise the overall cost effectiveness calculations to the detriment of the patient. This also means that the NHS resources are being more effectively used. In addition, if there are implications for the reality of delivering a range of treatment options to the patient, the challenge clinicians experience on the ground is that much of the time is taken up with paper work and negotiations with PCTs when patients fall outside the current criteria. It is likely that the greatest benefit would be that patients who have failed to gain sufficient benefit can be relatively easily identified.	Comment noted. The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22).
	We do not know whether the issues related exception reporting (requests for patients to be funded/ endorsed by the PCT for further treatment when they fall outside current NICE guidance recommendations) will be increased or reduced applying the proposed recommendations. The key issue is that the patient should continue to have their disease controlled and the pathway ensures that there are robust treatment criteria and clear rationale and monitoring of those failing to receive benefit progressing to the next effective treatment option. Anecdotally we suggest that it is likely that patients would prefer to progress to a further treatment at the cost of having ineffective treatment stopped. Was this considered in patient reports for this ACD?	Comment noted. The Committee recognised the impact of rheumatoid arthritis on patients (see FAD section 4.3.2).The Committee must make recommendations that take account of both the clinical and cost effectiveness of an intervention (Social Value Judgements – Principle for development of NICE guidance, principle 3).
	If patients on biologics fail one treatment the same patient population will be moving onto a further treatment. The Committee in line with evidence suggest that 15% of RA patients will have aggressive disease – this is likely to be the population who will continue to require biologic therapies with the current high disease activity score criteria. Is it the case that these cost savings in relation to stopping ineffective treatment are then transferred to benefit when patients transfers to an effective treatment?	Comment noted. The economic model includes a population of individuals for whom a first TNF inhibitor has failed to control disease. The model starts at the point at which the second biological treatment is introduced. When a patient stops a given treatment, the costs of that treatment simultaneously stop. When a patient switches to a new treatment, the benefits and costs of that new treatment then start to be counted.

Consultee	Comment	Response
Royal College of Nursing	**Point 4.2.27:** We understand that costs for hospitalisation and joint replacement were estimated using a cost per unit HAQ score but are unclear where the rationale/evidence for this approach has been validated?	Comment noted. All the models submitted included a cost of hospitalisation and joint replacement. The sources of the data varied but included the BSRBR and NOAR. The Assessment group included an assumed cost per unit HAQ score rather than one based on these data sources. However, this was tested in sensitivity analyses where it was found that the model was not very sensitive to this parameter (see FAD section 4.3.15).
Royal College of Nursing	We welcome the attempt to explore more fully the limitations of the HAQ score and considering evidence in relation to the EQ5D. A paper presented at ACR in 2009 (Neovius et al) shows that there are significant heterogeneity and that there are large subgroup differences that are likely to be important when using the EQ5D. They identify four distinct patient clusters first group consisting of patients with low pre-treatment utility who experienced major improvement, the second and third group consisting of patients with high or low pre-treatment utility changed little on average with a small fourth group with high utility as baseline deteriorated. We note the comments by the Appraisal Committee that the results of using HAQ and EQ-5D scores were subject to considerable uncertainty. How did this impact upon the modelling decisions?	Comment noted. The NICE reference case specifies that economic models should use directly-elicited health-related quality of life (HRQoL) data. In addition, for adults there is a preference that this is from EQ-5D (section 5.4.1 of the guide to the methods of technology appraisal). None of the economic models included directly elicited HRQoL data using a generic measure (such as the EQ-5D) and all relied on mapping in some way to get from a disease specific measure (such as DAS score or HAQ score) to a generic measure. The Committee heard from the Assessment Group that the use of alternate mapping functions did not significantly change the estimated ICERs. The Committee considered that mapping had shortcomings, but in the absence of directly-elicited generic HRQoL data, it was an acceptable way to derive estimates of utility (see FAD section 4.3.20). The methods guide states that the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented (see methods guide section 6.2.23).

Consultee	Comment	Response
Royal College of Nursing	The National Audit Office Report (2009) reviewed the cost effectiveness of biologic therapies in the context of wider implications and costs to the NHS. They also produced an additional paper on health economics of their findings (NAO 2009). This evidence demonstrated that improved management including biologic therapies were cost effective if the analysis was considered over a five year period. Has the Appraisal Committee been aware of the modelling approach used by NAO and compared these with the current approach with BRAM?	Comment noted. The model in the National Audit Office (NAO) report focused on the treatment of early rheumatoid arthritis, incorporating published NICE guidance for TNF inhibitors to reflect treatment for established disease. The current appraisal starts at the point a TNF inhibitor has failed. Therefore the NAO analysis and the current appraisal respond to different questions. The time horizon in this appraisal was life time and not 5 years, reflecting that the benefits and costs (including cost savings) of treatment for rheumatoid arthritis can accrue for the lifetime of the patient.
Royal College of Nursing	We are unclear as to how important factors related to shortened life expectancy and increased poor outcomes related to cardiovascular disease have been considered in the model. We presume a short life expectancy is cost effective? Patients may not die but face an additional health care burden such as cardiovascular disease or osteoporosis with its potential risk of fracture.	Comment noted. The economic models assume a shorter life expectancy for people with rheumatoid arthritis than for the general population. In addition, the models include a cost of hospitalisation. These factors are associated with HAQ score to the extent that people with higher (worse) HAQ scores have a greater number of associated costs and a shorter life expectancy. Although fewer costs may be accrued over a shortened life expectancy, so will fewer quality-adjusted life years. As a result, it is not the case that a shorter life expectancy will result in cost effective treatment.
Royal College of Nursing	We would welcome clarity about the changing patterns of RA management as set out in the NICE RA management guidelines (2009) and how this approach would have been considered in the model. If as is hoped patients will be eligible for treatment with biologic therapies much earlier in their disease with less joint damage (however, they will as currently set out still have to achieve a high level of disease activity at a DAS ≥5.1).	Comment noted. The Committee understood that changes are occurring in the management of rheumatoid arthritis The Committee was mindful of this during its deliberations (see FAD section 4.3.4). The appraisal considers a specific position in the care pathway, that is after the failure of a TNF inhibitor. Different patient populations can be considered at this point in the pathway such as people with lower disease activity. However, consideration of subgroups is dependent on availability and submission of data for the subgroup and demonstration that the subgroup itself is robust.

Consultee	Comment	Response
Royal College of Nursing	**Point 4.3.13:** Was the potential to avoid long term joint damage considered in the sense of previous models and future models considered?	Comment noted. All the models submitted included costs of hospitalisation and joint replacement (see FAD sections 4.2.5, 4.2.9, 4.2.13, 4.2.17, 4.2.21, 4.2.25). The Assessment group included an assumed cost per unit HAQ score. People with higher (worse) HAQ scores were modelled as having greater associated costs of hospitalisation and joint replacement. The potential to avoid long term damage was considered such that patients with lowered (improved) HAQ scores resulting from treatment did not accrue the costs associated with such damage to the extent that they would have had they not received treatment.
Royal College of Nursing	It is also stated in this paragraph (4.3.13) that a variety of analyses were undertaken and demonstrated that the ICERs were not very sensitive to changes in cost but more sensitive to changes in assumptions about natural history of disease (including DAS below 5.1?) and stopping treatment early (see Point 4.3.20). Would pressure to ensure treatment is stopped when ineffective be a good approach with a greater option for new therapies being offered?	Comment noted. The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22).
Royal College of Nursing	**Views on whether the resource impact and implications for the NHS are appropriate** See our response to paragraph 4.3.20 (above), and implications for PCTs and clinicians.	Comment noted. Please see the above response.

Consultee	Comment	Response
Royal College of Nursing	The additional workload for nurses will be as a result of spending more time with highly complex patients who have no effective treatment option, there will be psychological support particularly with respect to withdrawal of treatments, additional support for flare and poor disease control. The impact of this is likely to be an increase in the use of telephone advice line for support and liaison and an increase in the use of inpatient facilities for urgent access for inpatient beds (e.g. for intravenous methylprednisolone infusions). The long term consequences (>5 years) will be difficult to quantify depending upon future decisions but potentially a small group of patients will require high level nursing support related to symptom management, increased co-morbidities and surgery. For example, multiple joint replacements, fusion of the neck to resolve instability due to erosion of odontoid peg, tissue viability issues such as managing patients requiring long term treatment for vasculitis and leg ulcers, pinch grafts and cardiovascular /osteoporosis management and associated fractures. This may be translated in the future into increased community nursing support and use of day care and or nursing home facilities. The ongoing audit and data collection together with completion of specific reports to PCTs remain an important but additional workload for nurses.	Comment noted. The models submitted by Bristol-Myers Squibb and by Roche included costs of palliative care. The Assessment Group's model also included the costs of palliative care. This cost estimate was subject to sensitivity analyses where it was identified that the estimates of cost effectiveness were not very sensitive to this factor (see FAD sections 4.2.5, 4.2.9, 4.2.13, 4.2.17, 4.2.21, 4.2.25, 4.3.15).

Consultee	Comment	Response
Royal College of Nursing	**Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance top the NHS?** We recognise the challenges in undertaking such complex modelling. However, we still perceive the evidence and the crafting within the models weighs rather heavily on the cost effectiveness components that are easily measurable and fails to balance these within the model of the wider healthcare and societal costs that we recognise remain a challenge with the NHS. Despite the challenges, we still feel it is important that these are given fair and detailed consideration before the final determination is made. We hope the modelling considerations in the NAO report and the focus on extending the model to a 5 year approach would be helpful.	Comment noted. As per the NICE reference case (see sections 5.2.7 to 5.2.10 of the NICE methods guide), costs incurred outside the NHS or PSS were not incorporated. The model in the National Audit Office (NAO) report focused on the treatment of early rheumatoid arthritis, incorporating published NICE guidance for TNF inhibitors to reflect treatment for established disease. The current appraisal starts at the point a TNF inhibitor has failed. Therefore the NAO analysis and the current appraisal respond to different questions. The time horizon in this appraisal was life time and not 5 years, reflecting that the benefits and costs (including cost savings) of treatment for rheumatoid arthritis can accrue for the lifetime of the patient.
Royal College of Nursing	**Are there any equality related issues that need special consideration that are not covered in the ACD?** The HAQ and the ACR 20, 50, 70 criteria are tools used to measure the group response and have not been used to evaluate within those groups the numbers of people who would have had an individual and significant benefit to treatment. This has true significance when social and wider health care perspectives fail to be adequately considered. Some patients will be affected by this ACD more than others but there are no specific issues otherwise to be considered.	Comment noted. The Committee makes recommendations for the population of people identified in the scope. Within this, it may consider subgroups of people for whom treatment may be more clinically or cost effective. When considering subgroups, these should be clearly defined and preferably be identified on the basis of a priori expectation of known differential clinical or cost effectiveness due to known biologically plausible mechanisms, social characteristics or other clearly justified factors (methods guide section 5.10.1). The Committee has considered the subgroups identified by consultees and included in the scope. The subgroups identified were based on reason for previous withdrawal of treatment and test of seronegativity (FAD section 4.3.10, 4.3.11).

Consultee	Comment	Response
Royal College of Nursing	We also consider that to only approve the use of a second TNF inhibitor in the context of research may be discriminatory. Although clinical trials endeavour to make stringent efforts to include persons from minority populations, the design of studies if they require good command of written English to complete questionnaires may exclude certain ethnic groups. Access to research studies may also be dependent on the patient's locality, as research is often restricted to certain centres; therefore access to participate in research is not universal.	Comment noted. The FAD no longer includes an only in research recommendation (see section 1).

Consultee	Comment	Response
British Society for Rheumatology	**Over estimation of response to DMARDS after TNF failure** In 4.3.10 the committee concluded; *"That, 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".* In the Addendum Report, from the West Midlands Health Technology Assessment Collaboration the assessment group concluded on p77 that; "t*he results were fairly sensitive to the assumptions on efficacy of conventional DMARDs given after biologic therapy. The differences between the reference case results in the BRAM and those produced by Abbott and Schering-Plough can be explained by changing a small number of parameters in the model."* We broadly agree with these conclusions. As we discussed at the Appraisal Committee meeting, we would particularly support the poor late DMARDs scenario, as there is evidence to support poor benefits from conventional DMARDs after the failure of anti-TNF. Analysis of the BeSt trial suggested that if patients fail on methotrexate in any of the conventional treatment arms, there is only a 15% chance that they will respond to subsequent conventional DMARDs (van der Kooij SM et al. Ann Rheum Dis 2007;66:1356-62). Furthermore, this was in patients not exposed to anti-TNF, which would suggest that in patients failing on anti-TNF, the success rate on subsequent DMARDs would be even lower. We wish to emphasise that the expected response in patients with established RA is anticipated to be even worse than that seen in the BeSt study. We feel that an estimate of 0% improvement on conventional DMARDs after the failure of anti-TNF is likely to be much closer to reality than the 50% improvement quoted in previous BRAM models. Table 21 on page 76 of the Addendum Report shows, under a variety of different scenarios, changing from adalimumab to infliximab achieves ICERs close to £20,000. We would suggest that Table 21 supports the cost effectiveness of infliximab following the failure of adalimumab, and that this should be an alternative strategy to rituximab. We would like to seek clarification on why other approaches such as IFX-ETN and IFX-ADA are not included in the Table? We therefore broadly agree with the committee's conclusions in 4.3.16; *"that the Assessment Group may have overestimated the efficacy of conventional DMARDs",* and urge the committee to consider the ICERs described in the addendum report by the assessment group.	Comment noted. The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations. Please note that the Addendum Report is considered a product solely of the Assessment Group. As a result, NICE cannot comment on what tables included within that report do or do not include. The column referred to in Table 21 does not compare changing from adalimumab to infliximab. This column shows the ICERs for the comparison of infliximab and adalimumab. The ICERs in table 21 have to be considered alongside those in comparison with conventional DMARDs and also those in comparison with rituximab.

Consultee	Comment	Response
British Society for Rheumatology	**Inappropriate use of HAQ multiplier** We would also wish to agree with the conclusion in 4.3.15; "t*he Committee concluded that patients may derive benefits from the treatment that are not reflected in HAQ score because of irreversible joint damage".* However, we wish to express concern that this has not been taken into account in the assessment report. Aletaha et al (Arthritis & Rheum 2006; 54: 2784-2792) were able to quantify the reduced response of the HAQ to treatment in established disease. They found that among the 295 patients in whom clinical remission was achieved, the average HAQ scores despite clinical remission increased progressively with the duration of RA, from 0.19 (<2 years of RA) to 0.36 (2-<5 years) to 0.38 (5-<10 years) to 0.55 (≥10 years) ($P < 0.001$). In addition they found that the reversibility of HAQ scores decreased with the duration of RA (median 100%, 83.3%, 81.9%, and 66.7%, respectively; $P < 0.001$). We consider that these observations should have been taken into account with the assessment group modelling and would identify a greater improvement in utility from treatment. We also consider that this data suggests the use of the HAQ multiplier to be inappropriate. The Committee considered in 4.3.16; "*that the use of such a multiplier to model changes in HAQ meant that absolute changes in the upper range of the HAQ scores were larger than those in the lower range, and that therefore people with more severe disease would have larger HAQ improvements than if the HAQ scores from the clinical studies were used directly. Bearing in mind these considerations, the Committee accepted the use of a HAQ multiplier as a reasonable way to model changes in HAQ score".* This approach would be relevant in patients without irreversible disability but is likely to underestimate the benefits of treatment in patients with late disease who have established joint damage and would hope the assessment group would be able to model the health economic analysis to take these data into account.	Comment noted. As indicated in section 4.3.15 of the ACD (section 4.3.17 of the FAD), the Committee was mindful of the limitations of HAQ score, including that it may be subject to 'ceiling effects', and that it does not incorporate symptoms such as pain, fatigue and sleep disturbance. The Committee bore these limitations in mind during it deliberations. Similarly, the Committee considered the limitations of the HAQ multiplier in its deliberations (see FAD section 4.3.20).The use of a multiplier to represent improvement (reduction) in HAQ score owing to treatment gives a greater reduction to higher (worse) HAQ scores. As a result, a multiplier may over estimate the benefits of treatment in patients with established rheumatoid arthritis who tend to have higher HAQ scores because where there is irreversible damage, it would be expected that the benefits of treatment would be smaller.

Consultee	Comment	Response
British Society for Rheumatology	**Failure to incorporate stopping rules** We are concerned that the health economic analysis by the assessment group does not take into account stopping rules as expressed in the NICE guidance and BSR guidelines. In 4.3.20 it is stated that; “the Committee heard from the clinical specialists that data from the British Society for Rheumatology Biologics Register indicate that a number of people will continue treatment with a TNF inhibitor even in the absence of such a response, indicating that the use of stopping rules does not reflect current clinical practice. It further heard from the Assessment Group that for this reason stopping rules based on a response criterion had not been incorporated into the Birmingham Rheumatoid Arthritis Model base-case analysis. The Committee understood that the Birmingham Rheumatoid Arthritis Model was not designed in a way which could incorporate stopping rules based on a response criterion. The Committee noted, however, that a scenario analysis which included the proportions of people stopping treatment early that were used in the manufacturers’ response-based models lowered the ICERs for the TNF inhibitors and abatacept by approximately £10,000 per QALY gained. 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. In addition, the Committee questioned if the application of such response criteria would be reflective of clinical practice”. It is our view that health economic evaluation must include stopping rules as this is adopted by responsible prescribers and that NICE guidance should be based on best treatment and clinical excellence and not a pragmatic approach by some rheumatologists. In addition we are aware that health commissioners are increasingly likely to ‘police’ the stopping rules of patients. We consider that it is inappropriate not to incorporate stopping rules in the analysis while issuing guidance that patients should stop treatment if there is inadequate response.	Comment noted. The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22).

Consultee	Comment	Response
British Society for Rheumatology	**Conclusion** We are grateful to the assessment group for undertaking additional analysis that indicates the reduction in ICERs when modelling for a poor response from DMARDs after TNF failure. We consider these results to be closer to real life experience. In addition we consider that if the response to HAQ in point 2 and the stopping rules in point 3 were included, the analysis would demonstrate all treatments to be cost effective after TNF failure. In addition the scope stated that certolizumab pegol would also be included as a comparator. Now that this has been accepted as cost-effective under a Patient Access Scheme, we would ask that this be included in analyses with the risk sharing strategy included in models	Comment noted. See FAD section 1 regarding the recommended technologies. The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations. The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22). Certolizumab pegol was subject to its own single technology appraisal (see NICE technology appraisal guidance 186) and was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5). It was included as a comparator in the scope of this appraisal, but the Committee is unable to make recommendations about comparators.
British Health Professionals in Rheumatology	**Do you consider all relevant evidence has been taken into account?** There are some challenges when considering the evidence for this appraisal and this is apparent as the social and care costs are not included in the evidence.	Comment noted. As per the NICE reference case (see sections 5.2.7 to 5.2.10 of the NICE methods guide), costs incurred outside the NHS or PSS (such as those owing to time away from work) were not incorporated.

Consultee	Comment	Response
British Health Professionals in Rheumatology	**Do you consider that the summaries of clinical effectiveness and cost effectiveness are reasonable interpretations of the evidence?** There appear to be some inconsistency regarding interpretation of QALY's - abatacept now appears to have the same QALY as etanercept yet etanercept is recommended and abatacept is not – we would appreciate clarification on this point.	Comment noted. Following the consultation on the preliminary guidance the recommendations have changed. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
British Health Professionals in Rheumatology	There are now NICE guidelines for the management of RA and we wondered whether these had been taken into account during the BRAM analysis	Comment noted. The Committee understood that changes are occurring in the management of rheumatoid arthritis The Committee was mindful of this during its deliberations (see FAD section 4.3.4). The appraisal considers a specific position in the care pathway, that is after the failure of a TNF inhibitor. The clinical guideline incorporated the existing guidance for rituximab (TA126) and abatacept (TA141) which are currently being reviewed in this appraisal.
British Health Professionals in Rheumatology	It is becoming more apparent that RA will become divided into different subtypes and depending on the heterogeneity of the patient we will be able to use the best drug for those patients most likely to derive benefit. However, as the NHS is restricting the use of biologic therapies the rheumatology world will be unable to pursue this line of treatment in the future as UK patients won't have been exposed to the same therapies as the rest of Europe. This is likely to decrease innovation and investment in UK based clinical research and reduces the amount and quality of UK based cost effectiveness data.	Comment noted. The Committee recognised that at present there are difficulties in targeting treatment to people most likely to benefit. NICE recommends the use of the TNF inhibitors after the failure of two conventional DMARDs (TA130, TA186), and the guidance in this appraisal recommends the use of rituximab after the failure of a TNF inhibitor. Abatacept is recommended along with the TNF inhibitors in situations where rituximab or methotrexate is contraindicated or withdrawn because of an adverse event (see FAD section 1).
British Health Professionals in Rheumatology	Has the committee taken into account the length of time between rituximab infusions - the consensus of opinion suggests that these should be given 6 monthly.	Comment noted. The Committee discussed the length of time between rituximab treatments. It concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
British Health Professionals in Rheumatology	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Has the effectiveness of DMARDs been addressed for those patients that fail one TNF and don't go onto rituximab (sero negative) or fail rituximab due to adverse event?	Comment noted. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The Committee considered the specific subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).
British Health Professionals in Rheumatology	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation religion or belief?** This guidance does not recognise patients as individuals but reflects a class effect of the drugs. Patients who have a sero negative arthritis are unlikely to respond to rituximab and therefore have nowhere else to go in their patient pathway. Would this be classed as discrimination for these patients?	Comment noted. The Committee considered the specific subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Consultee	Comment	Response
Wyeth (Pfizer)	Wyeth (Pfizer) welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) and Evaluation Report for the above mentioned appraisal. In summary, Wyeth is concerned that not all of the relevant evidence has been taken into account appropriately and that the summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence. As a consequence, the clinical effectiveness of etanercept has been underestimated whilst that of rituximab overestimated. Furthermore the frequency of dosing and therefore the cost associated with rituximab treatment have been underestimated. Wyeth concur with the Appraisal Committee that the Assessment Group's analysis, based on the current construct of the BRAM model, is inappropriate for decision making.	Comment noted. Please see the responses below to each individual comment.
Wyeth (Pfizer)	In reporting improvements in HAQ of up to 0.35 compared with pre-treatment values, the clinical summary of etanercept (ACD section 4.1.3) omits the Haraoui study in which the mean HAQ improvement was 0.45. This omission is significant given the impact of HAQ change on the estimates of QALYs gained on a particular treatment.	Comment noted. The FAD (section 4.1.3) has been amended to reflect this.

Consultee	Comment	Response
Wyeth (Pfizer)	Results from the SUNRISE trial cast doubt on the assumption that initial HAQ improvements are maintained over the long term with repeat dosing of rituximab. The mean reduction in HAQ score at 48 weeks, despite re-dosing after 24 weeks was 0.27 (18% reduction in baseline HAQ of 1.5), compared with the 0.40 reduction at 24 weeks observed in the REFLEX study. Wyeth's assertion that HAQ improvements with etanercept remain constant on treatment is based on direct RCT observation coupled with evidence that etanercept halts radiographic progression of disease for at least 3 years. Whilst rituximab significantly lowers the rate of joint damage in a similar patient population, the failure to halt progression together with the lack of long-term HAQ data brings into question the base-case assumption that HAQ score remains constant irrespective of the biological DMARD used. The recent publication of the SUNRISE trial, sponsored by the manufacturer, noted that retreatment with rituximab typically occurred 30 to 40 weeks apart, depending on the trial. This resulted in worsening disease activity on average between retreatment courses. Worsening of most components of the ACR response criteria were first observed 28 – 32 weeks after initial dosing. The paper concludes 'Because the goals of retreatment include maintenance of efficacy and prevention of flare, retreatment should occur prior to worsening, and therefore Week 24 appeared to be an appropriate time to retreat in most patients'. Thus the Assessment Group's reference case analysis, which assumes repeat dosing of rituximab every 8.7 months (38 weeks), both over estimates the efficacy and underestimates the costs associated with rituximab treatment. It would therefore be more appropriate for the Appraisal Committee to consider the scenario analysis which assumed a time to retreatment of 6 months to be the most plausible estimate of the incremental cost effectiveness of rituximab at £32,600 per QALY gained. Whilst we acknowledge that the SUNRISE data was not available to the Appraisal Committee at the time they developed the ACD, given the large contribution the study makes to the evidence base for rituximab treatment, incorporation of the findings from this study into the FAD would ensure the robustness of the final guidance.	Comment noted. The Committee discussed the results of the SUNRISE trial (see FAD section 4.1.7). It concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Wyeth (Pfizer)	We note the additional analysis undertaken by the Assessment Group to assess the impact of differences between the models submitted to inform this appraisal (section 6 of the Technology Assessment Addendum Report). This analysis confirms the impact of accounting for 'continuation rules' in the economic modelling of sequential rheumatoid arthritis treatment. The best practice of assessing the response to treatment of rheumatoid arthritis after 6 months and only continuing treatment in those patients who have responded is enshrined in all authoritative guidelines (BSR, NICE, EULAR etc.) Given the Institute's focus on maximising health gain from limited resources and the requirement within the NICE Guide to the Methods of Technology Appraisal to analyse the impact of continuation rules as separate scenarios, Wyeth concur with the Appraisal Committee's conclusion that the Assessment Group's analysis cannot be used as a basis for decision making because it did not fully incorporate response criteria. Consideration should be given to modifying the BRAM to incorporate stopping rules based on response criteria before it is used to inform subsequent appraisals.	Comment noted. The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. It concluded that the modelling of stopping rules should be considered as it examined the estimates of cost effectiveness (see FAD section 4.3.22).
Wyeth (Pfizer)	In addition the BRAM utilises mean changes in HAQ from all treated patients to estimate the QALYs gained on each treatment. However HAQ changes vary with clinical response, with greater HAQ improvements observed in patients with a good clinical response than in patients who fail to respond to a particular treatment. As only patients who respond remain on treatment the BRAM systematically underestimates the QALYs gained over the time a patient remains on treatment. A more representative estimate of QALYs gained would be derived from the change in HAQ observed in treatment responders. We thank the Appraisal Committee for their consideration of these comments and those contained in the table below.	Comment noted. The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22).

Consultee	Comment	Response
Wyeth (Pfizer)	Section 1.1: Propose combining the bullets to read: 'who have had an inadequate response to or are intolerant of other DMARDs, including treatment with at least one TNF inhibitor' to ensure clarity and consistency with MA and previous guidance (TA 126).	Comment noted. These bullets have been combined to more closely reflect the licensed indication. (see FAD section 1.1)
Wyeth (Pfizer)	Section 1.2 The guidance fails to identify at what time point following initiation of therapy the assessment of response should be made. Should be 6 months	Comments noted. Because rituximab is given as needed (that is, not at some specified dosing interval). It is, therefore, not appropriate to specify that treatment of response should be measured at 6 months. However, the guidance has been amended to reflect that treatment should only be continued if an adequate response is achieved after the initiation of therapy and if an adequate response can be maintained after re-treatment using a dosing schedule no more frequently than once every six months (see FAD sections 1.2, 4.3.24).
Wyeth (Pfizer)	Section 3.14 Contraindications refer to the use of rituximab rather than abatacept	Comment noted. The contraindications are for abatacept. However, the text incorrectly refers to rituximab. This has been amended in the FAD.
Wyeth (Pfizer)	Section 4.3.19 The Appraisal Committee's assumption that treatment with rituximab would occur, on average, less frequently than every 6 months should be revisited in the light of evidence from the SUNRISE study.	Comment noted. The Committee discussed the results of the SUNRISE trial (see FAD section 4.1.7). It considered the length of time between rituximab treatments in its deliberations. It concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Wyeth (Pfizer)	Section 4.3.23 Given the underestimation of the cost per QALY associated with rituximab treatment (see above) and the revised BRAM analysis accounting for the change in HAQ increase and the short term quit rate on TNF inhibitors it seems implausible that rituximab would now dominate TNF inhibitor treatment in the majority of models.	Comment noted. The Committee did not consider that everyone would require retreatment with rituximab every 6 months (see FAD section 4.3.21). Although, the application of stopping rules reduces the ICERs for the TNF inhibitors and abatacept, it also reduces the total costs and the benefits. It is therefore not the case that the application of stopping rules necessarily means that rituximab becomes a less favourable option.
Bristol-Myers Squibb	Bristol-Myers Squibb (BMS) welcomes the opportunity to review and comment on the Appraisal Consultation Document (ACD) relating to the ongoing appraisal of abatacept, adalimumab, etanercept, infliximab and rituximab for the treatment of rheumatoid arthritis (RA) after the failure of a TNF-□ inhibitor (anti-TNF). BMS disagrees with the preliminary recommendation of the ACD not to recommend abatacept. ***References included, but not reproduced here***	Comment noted. Please see response to individual comments listed in subsequent rows of this table.

Consultee	Comment	Response
Bristol-Myers Squibb	1. The Birmingham Rheumatoid Arthritis Model (BRAM) uses rituximab as a comparator for abatacept and the anti-TNFs. Rituximab is an inaccurate and inappropriate comparator in the BRAM because patients with rheumatoid factor (RF) negative RA are less likely to respond to rituximab. The AG justifies the use of rituximab as a comparator with the argument that they were not able to identify differences in the effectiveness of rituximab in patients with RF negative or positive RA. The ACD acknowledges (section 4.1.12) that in the REFLEX trial, absolute response rates were lower in both the rituximab and the placebo groups for people who were RF negative compared with those who were RF positive. It further acknowledges that when participants were stratified according to both RF and anti-cyclic citrullinated peptide antibody (anti-CCP) status, data suggest a greater treatment response in people who were RF positive than in those who were RF negative. However, the AG noted that this retrospective analysis should be treated with caution. BMS believes that these data highlight that rituximab is not an optimal treatment option for patients who have RF negative RA. The BMS position is further supported by the findings of the trials studying rituximab for the treatment of RA after the failure of conventional disease modifying anti-rheumatic drugs (DMARDs) (i.e. MIRROR, SERENE) (1). In a combined analysis of these studies, RF positive patients were 2–3 times more likely to achieve ACR (American College of Rheumatology) responses compared with patients negative for both autoantibodies (1). This is further supported by clinical opinion (2). ***Comments continued on next page***	Comment noted. The model by the Assessment Group makes comparisons with conventional DMARDs and also with the biologics in comparison with each other. This is in line with the scope for the appraisal. It does not only use rituximab as a comparator for abatacept and the TNF inhibitors. The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance, the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Consultee	Comment	Response
Bristol-Myers Squibb	BMS acknowledges that the available data from randomised clinical trials (RCTs) for rituximab in anti-TNF failure patients may not be sufficient to be used in the BRAM, but asks the AC to acknowledge the large degree of uncertainty regarding the effectiveness of rituximab for these patients. In addition, recent data from the United Kingdom (UK) suggests, that B-cell depletion with rituximab is linked with the development of psoriasis (3). As a consequence, the use of rituximab for some patients may also harm. Therefore, BMS asks the AC to accept that rituximab should not be used as a comparator in the BRAM. Instead conventional DMARDs should be used as the appropriate comparator.	Comment noted. The model by the Assessment Groups makes comparisons with conventional DMARDs and also with the biologics in comparison with each other. This is in line with the scope for the appraisal. The Committee considered the analyses where the comparator was rituximab. It also considered the analyses where the comparator was conventional DMARDs for those patients for whom rituximab was contraindicated or not tolerated (see FAD sections 4.3.26, 4.3.27).
Bristol-Myers Squibb	2. The BRAM (in the reference case) assumes no Health Assessment Questionnaire (HAQ) score deterioration whilst on treatment for all biologic DMARDs irrespective of their mechanism of action. However, rituximab is associated with radiographic deterioration whilst on treatment, which is not what is observed with abatacept or the anti-TNFs. In one scenario analysis the AG incorrectly assumes a worsening of the HAQ score whilst being treated with abatacept although this scenario is not supported by the available evidence. Therefore BMS asks the AG to use a worsening of the HAQ score in the BRAM whilst on treatment with rituximab, but not for abatacept.	Comment noted. A variety of data were submitted from each of the manufacturers about the progression of disease while on the different biological treatments. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered progression of disease more so than the other biological treatments. The Committee agreed to consider the estimates of cost effectiveness which assumed no deterioration in HAQ while on treatment with a biological treatment. (See FAD section 4.3.19).

Consultee	Comment	Response
Bristol-Myers Squibb	3. The BRAM insists on using a treatment interval of 8.7 months for rituximab based on historical data. In the current clinical environment in the UK this is too long for rituximab. Recent market research showed an average re-treatment interval with rituximab of 5.9 months (4). This is supported by clinical opinion (2), which states that although longer treatment intervals were common historically, physicians now use shorter 6 month re-treatment intervals to prevent unnecessary flaring of the disease, and this has become recognised as the optimal treatment paradigm with rituximab (2). Therefore BMS ask the AG to use a re-treatment interval for rituximab of not more than 6 months in the BRAM.	Comment noted. The Committee considered the length of time between rituximab treatments in its deliberations. It heard from clinical specialists that they would aim to treat disease before it flared and that time to re-treatment varied considerable. The Committee concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Bristol-Myers Squibb	4. The ACD recommends the use of the anti-TNF switching in the context of research only, but not abatacept. The AC explains this by citing the lack of clinical effectiveness data for the anti-TNFs at this stage in the treatment pathway, and the resulting uncertainty in the ICERs (Incremental Cost Effectiveness Ratio). However, they acknowledge the robustness of the available data for abatacept. BMS believes that this is a discriminatory recommendation for abatacept and is also a disincentive for research and innovation. Therefore, BMS asks the AC to recommend abatacept for treatment of RA, without the restriction on use in the context of research. Furthermore, the BRAM generates similar ICERs for abatacept and the anti-TNFs, all of which are in areas where the anti-TNFs, adalimumab and infliximab have been recommended in earlier appraisals (TA130). In addition, recent data from the golimumab (another anti-TNF) GO-AFTER study indicates that the effectiveness of the use of a second anti-TNF may be reduced.	Comments noted. The final recommendations for abatacept differ from the preliminary recommendations. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
	Therefore BMS asks the AC to recommend abatacept for patients with RA after anti-TNF failure in line with new, evidence based European treatment guidelines from EULAR to be published in Annals Rheumatic Diseases in April 2010.	

Consultee	Comment	Response
Bristol-Myers Squibb	5. The BRAM insists on using a clinical effectiveness that is too high for conventional DMARDs (in both, the reference case and its scenario analyses) when used after the failure of an anti-TNF. This is in contrast to the findings of the British Society for Rheumatology Biologics Register (BSRBR), who report that conventional DMARDs produce no further HAQ score improvements (5). The AG may argue that these data come from a non-randomised dataset. However, BMS considers that non-randomised and observational data are able to produce a robust analysis, if there is a lack of randomised data. Furthermore, as pointed out by Professor Rawlins in his Harveian Oration delivered at the Royal College of Physicians of London: *'RCTs, long regarded as 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'.*	Comment noted. The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations.
	Therefore BMS ask the AC to accept the BSRBR as an appropriate data source, and the AG to use a 0-HAQ-multiplyer for conventional DMARDs in the BRAM.	
	In conclusion BMS asks the AC to reconsider its draft recommendation and to recommend abatacept for patients with RA.	

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 1.1: The second bullet point is not in line with the scope of this appraisal. In addition it is outside of the license for rituximab (6). Furthermore BMS believe that only recommending rituximab will leave the substantial number of patients who do not respond adequately to a tumour necrosis factor alpha inhibitor (anti-TNF) treatment (approximately 50% [7]) without further treatment options. Rituximab is known to be inadequate therapy for patients who are rheumatoid factor (RF) negative (1).	Comment noted. The recommendation has been reworded to more accurately reflect the marketing authorisation for rituximab. Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance, the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).
Bristol-Myers Squibb	ACD Section 1.4: Abatacept has extensive clinical data proving efficacy in this population, with robust RCT data, and the analyses demonstrating similar cost-effectiveness results to the anti-TNFs. Furthermore, the anti-TNFs have been shown to be associated with dose escalation, something which is not seen with abatacept (21). Despite this, abatacept has not been recommended. BMS requests the Appraisal Committee (AC) reviews this decision. BMS considers recommending anti-TNFs under the restriction of 'research purposes' to be a bizarre disincentive for innovation.	Comments noted. The final recommendations for abatacept differ from the preliminary recommendations. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 2.8: BSR draft guidelines recommend anti-TNF treatment as an option for patients with active RA who have a disease activity score (DAS28) > 3.2 (8).	Comment noted. It is recognised that NICE guidance may differ from that of other organisations because of different criteria used for decision making. The use of TNF inhibitors is discussed within the context of NICE guidance (see FAD section 2.9).
Bristol-Myers Squibb	ACD Section 3.11: Rituximab is associated with an increased risk of developing progressive multifocal leukoencephalopathy (PML) and there are currently 60 reported cases (9-11,18).	Comment noted. The FAD is not meant to reflect all the possible undesirable effects associated with a technology. Section 3 of the FAD lists the contraindications to each of the technologies. The summary of product characteristics provides further details of adverse events. No changes made to the FAD.
Bristol-Myers Squibb	ACD Section 4.1.10: The BRAM showed that abatacept produced more QALYs in comparison to rituximab; it can therefore be assumed that abatacept is more effective than rituximab (12). Because RA is a long-term disease, the long-term implications and the chronic nature of the disease need to be taken into account. Rituximab is associated with radiographic deterioration whilst on treatment. This has not been shown with either abatacept or the anti-TNFs. Such radiographic deterioration can be translated into a worsening of the HAQ score and should therefore be included in the economic modelling.	Comment noted. A variety of data were submitted from each of the manufacturers about the progression of disease while on the different biological treatments. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered progression of disease more so than the other biological treatments. The Committee agreed to consider the estimates of cost effectiveness which assumed no deterioration in HAQ while on treatment with a biological treatment. (See FAD section 4.3.19).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.1.12: The lower absolute response rates seen in RF negative patients in the REFLEX trial supports the evidence from observational studies and clinical opinion that rituximab is less effective in RF negative patients than in RF positive patients (1,13). In addition, the recently updated Consensus Statement on biological agents (which reviewed evidence from two RA patient populations) concluded that more robust ACR responses were seen with rituximab in RF/anti-CCP positive patients who were DMARD non responders, and in TNF non responders (14). Therefore, the cost-effectiveness analyses for these patients should use conventional DMARDs as the comparator of choice, not rituximab.	Comment noted. The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).
Bristol-Myers Squibb	ACD Section 4.2.20: The improvement in HAQ score whilst on treatment with abatacept is based on data from the ATTAIN trial (15). In contrast, rituximab is associated with a radiographic deterioration (6). This deterioration can be translated into a worsening of the HAQ score (16,22-24). Therefore BMS ask the Assessment Group (AG) to incorporate this into their economic modelling.	Comment noted. A variety of data were submitted from each of the manufacturers about the progression of disease while on the different biological treatments. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered progression of disease more so than the other biological treatments. The Committee agreed to consider the estimates of cost effectiveness which assumed no deterioration in HAQ while on treatment with a biological treatment. (See FAD section 4.3.19).
Bristol-Myers Squibb	ACD Section 4.2.22: There is no HAQ deterioration associated with abatacept, whilst there is with rituximab (6,15,16,22-24). BMS therefore ask the AG to incorporate this in their economic modelling.	Comment noted. A variety of data were submitted from each of the manufacturers about the progression of disease while on the different biological treatments. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered progression of disease more so than the other biological treatments. The Committee agreed to consider the estimates of cost effectiveness which assumed no deterioration in HAQ while on treatment with a biological treatment. (See FAD section 4.3.19).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.2.24: There is no HAQ score deterioration associated with abatacept, whilst there is with rituximab (6,15,16,22-24). BMS ask the AG to incorporate this in their economic modelling.	Comment noted. A variety of data were submitted from each of the manufacturers about the progression of disease while on the different biological treatments. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered progression of disease more so than the other biological treatments. The Committee agreed to consider the estimates of cost effectiveness which assumed no deterioration in HAQ while on treatment with a biological treatment. (See FAD section 4.3.19).
Bristol-Myers Squibb	ACD Section 4.2.25: The re-treatment interval with rituximab has been shown to be 6 months (4). Any re-treatment interval which is < 6 month would need to be accounted for in the economic model with a rebound effect on the HAQ score (20) (in addition to accounting for the underlying radiographic progression). An analysis of responses to a single course of rituximab treatment over 6 months shows maximal efficacy on HAQ-DI at week 16 with a subsequent reduction in efficacy after this (20). BMS asks the Assessment Group to account for this in their economic model.	Comment noted. The Committee considered the length of time between rituximab treatments in its deliberations. It heard from clinical specialists that they would aim to treat disease before it flared and that time to re-treatment varied considerable. The Committee concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.2.26: The reference case in the BRAM model underestimated the true cost of rituximab because it used a hypothetical re-treatment interval of 8.7 months, whereas 6 months would be more reflective of clinical practice (4). Furthermore, rituximab is associated with an underlying disease progression whilst on treatment (6,16,22-24). A comparison of abatacept, or the anti-TNFs, with rituximab is only acceptable in patients who are RF positive, as it has been shown that rituximab is less effective in RF negative patients (1,13). For the analysis of the cost-effectiveness of abatacept in the RF negative population, comparison to conventional DMARDs should be used (instead of rituximab). BMS ask the AG to incorporate this into their modelling.	Comment noted. The Committee considered the length of time between rituximab treatments in its deliberations. It concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21). A variety of data were submitted from each of the manufacturers about the progression of disease while on the different biological treatments. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered progression of disease more so than the other biological treatments. The Committee agreed to consider the estimates of cost effectiveness which assumed no deterioration in HAQ while on treatment with a biological treatment. (See FAD section 4.3.19). The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.2.27: These sensitivity analyses explored only the impact of single assumptions, not their combined impact. BMS asks the AG to present revised sensitivity analyses to the AC.	Comment noted. In their considerations the Committee took into account multiple factors including the efficacy of conventional DMARDs, the re-treatment interval and the application of stopping rules (see FAD section 4.3.12, 4.3.21, 4.3.22 and 4.3.23).
Bristol-Myers Squibb	ACD Section 4.2.28: There is no HAQ progression associated with abatacept, whilst there is with rituximab (6,15,16,22-24). BMS ask the AG to use this data in their economic modelling. Conventional DMARDs used after an inadequate response to methotrexate and an anti-TNF have been shown not to lead to any further improvement in HAQ score (5,17). Therefore BMS ask the AG to use a 0-HAQ-multiplyer for conventional DMARDs in the BRAM.	Comment noted. A variety of data were submitted from each of the manufacturers about the progression of disease while on the different biological treatments. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered progression of disease more so than the other biological treatments. The Committee agreed to consider the estimates of cost effectiveness which assumed no deterioration in HAQ while on treatment with a biological treatment. (See FAD section 4.3.19). The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations.

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.3.2: RA is a complex disease which requires a differentiated and individualised treatment approach. Currently there are only very few therapeutic options available for patients who have failed a series of treatments, including at least two conventional DMARDs and one anti-TNF. The current ACD will further limit the already scarce treatment options available. Furthermore, the only fully recommended treatment option (rituximab) is associated with uncertain treatment outcomes in RF negative patients, as well as with the risk of developing (9-11,18). BMS ask the AC to recommend abatacept.	Comment noted. The final recommendations for adalimumab, etanercept, infliximab and abatacept differ from the preliminary recommendations. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
Bristol-Myers Squibb	ACD Section 4.3.3: The lower absolute response rates seen in RF negative patients on rituximab in the REFLEX trial reinforces evidence from observational studies and clinical opinion that rituximab is not as effective in RF negative patients than in RF positive patients (1,2,13). Therefore, cost-effectiveness analyses for these patients should use conventional DMARDs as the comparator of choice, not rituximab.	Comment noted. The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).
Bristol-Myers Squibb	ACD Section 4.3.4: The treatment paradigm for RA has indeed changed in recent years towards a more aggressive and earlier therapy. However, in the absence of better data sources, the British Society for Rheumatology Biologics Register (BSRBR) should be used to inform any economic analyses.	Comment noted. The Committee considered the efficacy data from the BSRBR. In doing so it understood that the changes in management of rheumatoid arthritis (in line with recent NICE guidelines) limited the generalisability of data from the British Society for Rheumatology Biologics Register. Data for rituximab and abatacept are not available from the BSRBR, and therefore data for these treatments have to be obtained from other sources. The appropriateness of using the BSRBR as an estimate of effectiveness for the TNF inhibitors has to be considered in the context of the data sources available for abatacept and rituximab (see FAD section 4.3.4, 4.37, 4.3.8).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.3.6: Conventional DMARDs used after an inadequate response to methotrexate and an anti-TNF have not been demonstrated to lead to any further improvement in HAQ score (5,17). Therefore BMS ask the AG to use a 0-HAQ-multiplyer for conventional DMARDs in the BRAM.	Comment noted. The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations.
Bristol-Myers Squibb	ACD Section 4.3.7: Rituximab is associated with a radiographic deterioration (6). This deterioration can be translated into a worsening of the HAQ score (16,22-24). The BRAM shows that abatacept produces more QALYs in comparison to rituximab, therefore it can be assumed that abatacept is more effective than rituximab (12).	Comment noted. A variety of data were submitted from each of the manufacturers about the progression of disease while on the different biological treatments. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered progression of disease more so than the other biological treatments. The Committee agreed to consider the estimates of cost effectiveness which assumed no deterioration in HAQ while on treatment with a biological treatment. (See FAD section 4.3.19). The Committee makes recommendations to the NHS based on both clinical and cost effectiveness. To that end, the Committee takes into account both QALYs and costs in its deliberations.

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.3.9: The ACD acknowledges (section 4.1.12) that, in the REFLEX trial, absolute response rates were lower in both the rituximab and the placebo groups for patients who were RF negative compared to those who were RF positive. The ACD also acknowledges that when participants were stratified according to both RF and anti-CCP status, the data suggest a greater treatment response in those who were RF or anti-CCP positive than in those who were negative for RF and anti-CCP. However, the AG noted that this retrospective analysis should be treated with caution. BMS believes, these data highlight that rituximab is not an optimal treatment option for patients who have seronegative RA. This is further supported by the findings of the trials studying rituximab for the treatment of RA after the failure of conventional DMARDs (i.e. MIRROR, SERENE) (1). In a combined analysis of these studies, seropositive patients were 2–3 times more likely to achieve ACR responses compared with patients seronegative for both auto-antibodies. In the DANCER study, rituximab was even less effective than placebo when administered to patients who have seronegative RA. These data are further supported by clinical opinion (2). BMS acknowledges that there may not be sufficient data available from randomised clinical trials (RCTs) for rituximab in TNF- inhibitor failure patients to be used in the BRAM, but asks the AC to acknowledge the high degree of uncertainty regarding the effectiveness of rituximab in seronegative RA.	Comment noted. The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.3.10: Conventional DMARDs used after an inadequate response to methotrexate and an anti-TNF have been shown not to lead to any further improvement in HAQ score (5,17). BMS asks the AG to use a 0-HAQ-multiplyer for conventional DMARDs in the BRAM. In the absence of better data sources, the British Society for Rheumatology Biologics Register (BSRBR) should be used to inform any economic analyses.	Comment noted. The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations. The Committee considered the efficacy data from the BSRBR. In doing so it understood that the changes in management of rheumatoid arthritis (in line with recent NICE guidelines) limited the generalisability of data from the British Society for Rheumatology Biologics Register. Data for rituximab and abatacept are not available from the BSRBR, and therefore data for these treatments have to be obtained from other sources. The appropriateness of using the BSRBR as an estimate of effectiveness for the TNF inhibitors has to be considered in the context of the data sources available for abatacept and rituximab (see FAD sections 4.3.4, 4.3.7, 4.3.8).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.3.11: The ACD recommends the use of anti-TNFs for research only, but not abatacept. The BRAM generates similar ICERs for abatacept and the anti-TNFs versus conventional DMARDs. The AC explains this with the lack of clinical effectiveness data for the anti-TNFs at this stage in the treatment pathway, and the resulting uncertainty in the ICERs, whilst they acknowledge the robustness of the available data for abatacept. BMS believes that this is a differential recommendation for abatacept and disincentives research and innovation. In addition, recent data from the golimumab (a further anti-TNF) GO-AFTER study indicates that the effectiveness of the use of a second anti-TNF maybe lower.	Comment noted. The FAD no longer includes an only in research recommendation. Please see section 1 for the final recommendations. The Committee considered the results of the GO-AFTER study and the application of data for golimumab to the other TNF inhibitors (see FAD section 4.3.7).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.3.14: In the absence of better data sources, the BSRBR should be used to inform any economic analyses. BMS considers that the use of non-randomised and observational data are able to produce a robust analysis when there is a lack of randomised data. Furthermore, Professor Rawlins stated in his Harveian Oration delivered at the Royal College of Physicians of London (19) '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' A consistent use of non-randomised data should be used for all comparators. For example, currently the BRAM model assumes efficacy for DMARDs post anti-TNF failure, but is reluctant to use effectiveness data from non-randomised studies on abatacept that suggest maintenance/improvement in HAQ score over time. BMS ask the AC to consider the quality of the non-randomised data provided and that non-randomised data are used consistently across comparators.	Comment noted. The Committee considered the efficacy data from the BSRBR. In doing so it understood that the changes in management of rheumatoid arthritis (in line with recent NICE guidelines) limited the generalisability of data from the British Society for Rheumatology Biologics Register. Data for rituximab and abatacept are not available from the BSRBR, and therefore data for these treatments have to be obtained from other sources. The appropriateness of using the BSRBR as an estimate of effectiveness for the TNF inhibitors has to be considered in the context of the data sources available for abatacept and rituximab (see FAD section 4.3.4, 4.3.7, 4.3.8). The Committee considered the range of evidence submitted. The acceptance of any evidence is dependent on its internal and external validity and fitness for purpose. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered long-term progression of disease more so than the other biological treatments. (See FAD section 4.3.19).
Bristol-Myers Squibb	ACD Section 4.3.17: The improvement of the HAQ score whilst on treatment with abatacept is based on data from the ATTAIN trial (15). In contrast, rituximab is associated with a radiographic deterioration (6). This deterioration can be translated into a worsening of the HAQ score (16, 22-24). Therefore BMS ask the Assessment Group (AG) to use these data in their economic modelling.	Comment noted. A variety of data were submitted from each of the manufacturers about the progression of disease while on the different biological treatments. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered progression of disease more so than the other biological treatments. (See FAD section 4.3.19).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.3.19: The BRAM still uses a treatment interval of 8.7 months - this is too long for rituximab. Recent market research showed an average re-treatment interval with rituximab of 5.9 months (4). This is supported by clinical opinion (2), which states that although longer treatment intervals were common historically, physicians now use shorter 6 month re-treatment intervals to prevent unnecessary flaring of the disease, and this has become recognised as the optimal treatment paradigm with rituximab (2). Therefore BMS ask the AG to use a re-treatment interval for rituximab of not more than 6 months in the BRAM.	Comment noted. The Committee considered the length of time between rituximab treatments in its deliberations. It concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21).
Bristol-Myers Squibb	ACD Section 4.3.21: Conventional DMARDs used after an inadequate response to methotrexate and an anti-TNF have been shown not to lead to any further improvement in HAQ score (5,17). Therefore BMS ask the AG to use a 0-HAQ-multiplyer for conventional DMARDs in the BRAM.	Comment noted. The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations.
Bristol-Myers Squibb	ACD Section 4.3.22: The BRAM still uses a treatment interval of 8.7 months - this is too long for rituximab. Recent market research showed an average re-treatment interval with rituximab of 5.9 months (4). This is supported by clinical opinion (2), which states that although longer treatment intervals were common historically, physicians now use shorter 6 month re-treatment intervals to prevent unnecessary flaring of the disease, and this has become recognised as the optimal treatment paradigm with rituximab (2). Therefore BMS ask the AG to use a re-treatment interval for rituximab of not more than 6 months in the BRAM.	Comment noted. The Committee considered the length of time between rituximab treatments in its deliberations. It concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Bristol-Myers Squibb	ACD Section 4.3.24: The BRAM shows that abatacept produces more QALYs in comparison to rituximab, and so it can be assumed that abatacept is more effective than rituximab (12).Therefore the statement that rituximab is more effective than abatacept is not true. The improvement in HAQ score whilst on treatment with abatacept is based on data from the ATTAIN trial. In contrast rituximab is associated with a radiographic deterioration. This deterioration can be translated into a worsening of the HAQ score. Therefore BMS ask the AG to use this data in their economic modelling, and that the AC base their decision on the revised analyses.	Comment noted. The Committee makes recommendations to the NHS based on both clinical and cost effectiveness. Section 4.3.24 relates to the Committee's considerations of the cost-effectiveness of rituximab, not of its clinical effectiveness relative to that of rituximab. A variety of data were submitted from each of the manufacturers about the progression of disease while on the different biological treatments. The Committee was not persuaded that the evidence was sufficient to support an assumption that abatacept differentially altered progression of disease more so than the other biological treatments. (See FAD section 4.3.19).
Bristol-Myers Squibb	ACD Section 4.3.26: Abatacept has extensive clinical data proving efficacy in this population, with robust RCT data. The analyses demonstrate similar cost-effectiveness results to the anti-TNFs. Furthermore, unlike abatacept, anti-TNFs have been shown to be associated with dose escalation (21). Despite this, abatacept has not been recommended. BMS requests the AC reviews this decision. Recommending anti-TNFs under the restriction of 'research purposes', would seem to be a disincentive for innovation.	Comment noted. The FAD no longer includes an only in research recommendation. Please see section 1 for the final recommendations.

Consultee	Comment	Response
Arthritis Care	**Arthritis and Arthritis Care** 1. Arthritis is the biggest cause of physical disability in the UK, affecting up to 10 million people, including 12,000 children, and accounting for 30% of GP visits. It carries a huge economic as well as human and social cost, estimated at £7 billion annually in terms of lost labour in 2007. 2. Arthritis Care is the UK's leading organisation working with and for people with all forms of arthritis. We offer people with arthritis the information and support they need to make informed choices about managing their arthritis, to reach their potential in society and to fully participate in their communities. 3. We believe that people with arthritis are entitled to receive the best available treatment and medication, and to have their voice heard in decisions affecting their health – as enshrined in the NHS Constitution.	Comments noted. No actions required.

Consultee	Comment	Response
Arthritis Care	**Rheumatoid arthritis** Rheumatoid arthritis (RA) is a lifelong, progressive, musculoskeletal condition that causes severe pain, swelling and inflammation of the joints, and can lead to reduced joint function and disability. Approximately 10% of people with RA have the condition in a particularly severe form, manifesting itself as relentless pain and swelling, often in multiple joints. This causes severe disability and loss of function, meaning that simple daily tasks, including self-care, can become impossible without assistance. Severe RA is extremely serious. 30% of people with untreated severe RA will die within 5 years, a figure comparable with triple vessel Coronary Heart Disease or stage III Hodgkin's Disease. While someone with RA can expect to live 5 years less than someone without it on average, much of this is accounted for by the massively reduced life expectancy of the population with severe RA. A recent report by the National Audit Office (NAO) on services for people with RA revealed that the number of people with RA is much higher than previously thought, estimated at 580,000 people in England alone, with 26,000 new cases diagnosed each year. It also found that RA has annual healthcare costs of £560 million to the NHS, with costs to the economy of £1.8 billion in sick leave and work-related disability.	Comments noted. The Committee was aware of the impact of rheumatoid arthritis on quality of life and employment (see FAD section 4.3.2)

Consultee	Comment	Response
Arthritis Care	The NAO report clearly emphasised the importance of aggressively treating RA within three months from the onset of symptoms, as this can stop the development of the condition in its tracks and lead to remission. After the first three months, the impact of any treatment or medication is vastly reduced. The report also found an enormous variation in spending across PCTs in England, amounting to a postcode lottery. Those that do receive treatment for RA often do not receive sufficiently high-quality treatment. The Public Accounts Committee released a report in February this year reaffirming the findings and endorsing the recommendations of the NAO report. What these findings demonstrate is that very large numbers of people are living in often severe and debilitating pain because they are not getting the services and the treatment they need. Central to this is prompt access to the best available medication, including anti-TNFs. NICE's position regarding the availability of anti-TNF medication and the ability of clinicians to prescribe more than one particular anti-TNF for sequential treatment, based on the patient's responsiveness to it, should therefore be viewed with this context, and these findings, firmly in mind.	Comments noted. The Committee recognised the importance placed on the availability of a variety of medications (see FAD section 4.3.2).
Arthritis Care	Arthritis Care is extremely disappointed with the preliminary findings of this consultation, which do not reflect the majority of medical opinion on anti-TNF treatment for RA and which do not seem to take any account of either the real experience or indeed the wishes of people with RA, whom these treatments are intended to serve. The preliminary findings appear to entirely ignore the patient dimension of RA, and sit decidedly at odds with the growing consensus on the importance of a more patient-centred health service, patient involvement in decisions affecting their health and patient choice – all of which are enshrined in numerous and varied high-profile documents, from the NHS Constitution to High Quality Care for All to the World Class Commissioning Framework.	Comment noted. The Committee consider all of the evidence submitted, which includes statements from clinical specialists and patient experts (see FAD sections 4.3.2 – 4.3.4). For both legal and bioethical reasons, those undertaking technology appraisals must take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).

Consultee	Comment	Response
Arthritis Care	NICE's own guideline on the management of RA in adults, issued in February 2009, emphasises the importance of person-centred care: "Treatment and care should take into account peoples' needs and preferences. People with RA should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals." (p.6) The preliminary findings, however, appear to negate this, as they unduly restrict the options available to both clinicians and people with RA, and therefore the real choice available to people with RA with respect to their health needs.	Comment noted. The Committee recognised the importance placed on the availability of a variety of medications. The Committee heard from clinical specialists that the pathway of care following the failure of treatment with a TNF inhibitor depends on the individual persons' responses to therapies, the clinical experience of the physician and the person's preference (see FAD section 4.3.2). Although NICE accepts that individual NHS users will expect to receive treatments to which their conditions may respond, this does not impose a requirement on the Committee to recommend technologies that are not cost effective enough to provide the best value to users of the NHS as a whole (see 'Social Value Judgement – Principles for the development of NICE guidance; principle 5). Please see section 1 for the final recommendations.
Arthritis Care	Far from helping to provide a more efficient or better quality service to the over half a million people with RA in England, these findings, if implemented, will impact severely on the health and quality of life of many thousands of people, and the overall effect will be entirely counterproductive in terms of the long-term or indeed short-term gains, economic or otherwise.	Comment noted. For both legal and bioethical reasons, those undertaking technology appraisals must take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).
Arthritis Care	There is abundant evidence, including a very large number of firsthand testimonies from clinicians and people with RA, who are best placed to know how any specific treatment is or is not helping them, which demonstrates that different anti-TNFs work differently for different people, and it is only by being able to try different treatments that many people are able to find the one that actually works for them. This for them is not a whim; it is a need.	Comment noted. The Committee considered all of the evidence submitted, which included statements from clinical specialists and patient experts. The Committee recognised that different people may respond differently to any given treatment (see FAD sections 4.3.2 – 4.3.4).

Consultee	Comment	Response
Arthritis Care	Additionally, there is no clinical, anecdotal or practical evidence to support the decision to allow the use of rituximab in combination with methotrexate but not anti-TNFs for sequential use. Each anti-TNF is different and will work for some people but not others. For many, rituximab simply does not work.	Comment noted. The directions from the Secretary of State for Health requests the Institute to make recommendations to the NHS based on both clinical and cost effectiveness. The appraisal considers the cost effectiveness of a treatment which incorporates both the costs and benefits. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1, see methods guide section 6.1.3). The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28).
Arthritis Care	Lord Darzi made it clear that quality is the unifying principle behind the NHS. Surely, therefore, any decision on the availability and sequential use of anti-TNFs must be taken with the best interests of the population at heart, and should only consider cost issues in this light, i.e. where they do not impact negatively on the overall quality of service for the people the NHS is there to serve.	Comment noted. The directions from the Secretary of State for Health requests the Institute to make recommendations to the NHS based on both clinical and cost effectiveness. The appraisal considers the cost effectiveness of a treatment which incorporates both the costs and benefits (see Guide to the methods of technology appraisal, section 6.1.3).
Arthritis Care	Arthritis Care therefore urges NICE to review its preliminary findings, taking account of the clinical evidence which exists on the real use and impact of anti-TNF treatment, and which clearly demonstrates the importance of a wide range of options for sequential anti-TNF treatment. We also urge NICE to consider this evidence in light of the fundamental importance of person-centred care and of ensuring the best possible outcomes for people with RA, based on their needs and their wishes.	Comment noted. The final recommendations for adalimumab, etanercept, infliximab and abatacept differ from the preliminary recommendations. For people who are contraindicated to rituximab or methotrexate or who require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).

Consultee	Comment	Response
Arthritis Care	**Background to the current consultation** The current NICE consultation on anti-TNF treatments is the latest in a long line of deliberations on the issue of anti-TNFs. Most recently, NICE announced its intention to restrict the sequential use of anti-TNFs 2008, in much the same way as at present. At the time, the Arthritis and Musculoskeletal Alliance (ARMA), also speaking on behalf of Arthritis Care, described NICE's proposal as a "prescription for pain," on the grounds that it withdrew available treatment options and condemned many people with RA to a life of debilitating pain. ARMA also made a detailed submission to Dr. Carole Longson, Director of the Centre for Health Technology Evaluation, regarding NICE's proposals, the substance of which is still equally valid in relation to the current preliminary findings. We are attaching a copy of this submission, for your reference and information.	Comments noted. The Committee has considered all the evidence submitted. The Committee was aware of the impact of rheumatoid arthritis on quality of life, employment and the importance placed on the availability of a variety of medications (see FAD sections 4.3.2 – 4.3.3).
Arthritis Care	**The importance of sequential use of anti-TNFs** Between 20,000 and 40,000 people in England and Wales are taking an anti-TNF at any one time, and 50% have needed to switch treatments at least once. In order for people with RA to receive the treatment that actually works for them, and clinicians need access to the widest possible range of treatments in order to provide the best possible care for patients. The British Society for Rheumatology Biologics Register shows that 70% of patients who switch anti-TNFs derive a benefit from the second one, and this has been established good practice in the UK for some years. These therapies are already available for clinicians to use sequentially across Europe, and it is perverse that they should not be available in the UK.	Comment noted. The Committee considered evidence from the British Society for Rheumatology Biologics Register (see FAD section 4.3.8). With regards to the access to these technologies across Europe, funding decisions for drugs are each country's individual responsibility. Funding decisions can differ across countries because of the different criteria applied.

Consultee	Comment	Response
Arthritis Care	Clinicians themselves stress the importance of being able to try different anti-TNF treatments for individual patients. Professor Rob Moots, a clinician and Professor of Rheumatology at the University of Liverpool, for example, has said that "it's almost impossible to know which anti-TNF will work for a patient at the outset." He has described NICE proposals to restrict the options for anti-TNF treatment available to clinicians, as "flying in the face of clinical judgement", stating that "many patients will be left in astonishing pain", while clinicians will be left knowing that they haven't explored all the options for them.	Comment noted. The Committee considered all of the evidence submitted, which included statements from clinical specialists and patient experts. The Committee recognised that currently there are difficulties in targeting treatments to people most likely to respond (see FAD sections 4.3.2 – 4.3.4).
Arthritis Care	The importance of this is illustrated very clearly and very powerfully by the firsthand testimonies of people with RA themselves, many of whom have had to try a number of different anti-TNFs before they could find one that worked for them, and many of whom have yet to find the one that does because they have been unable to try more treatments so far. In some cases, certain anti-TNFs have worked initially but then ceased to work, and in other cases certain anti-TNFs which did not work originally seemed to work better only after the person had gone on to try another. In almost all cases, however, the difference which finding the right anti-TNF treatment has made to that person's life has been transformational. Very often, this has made the difference between having a good-quality life and being able to live independently and remain in or return to work, and living in chronic, debilitating pain and being reliant on others and the health sector for basic needs.	Comment noted. The Committee considered all of the evidence submitted, which included statements from clinical specialists and patient experts about the impact of rheumatoid arthritis and its management (see FAD sections 4.3.2 – 4.3.4). The Committee considered the subgroups of people whose disease may not have responded to treatment with a TNF inhibitor, and the group for whom response may reduce over time (See FAD section 4.3.10). The Institute must take into account both the clinical and cost effectiveness of treatment when making recommendations.
Arthritis Care	Arthritis Care has collated a number of personal testimonies from people with RA in the attached Appendix. We urge NICE to read these testimonies to gain an accurate picture of the real experiences – and the real needs - of people with RA, and what this means for the regulation of anti-TNF treatment. **Appendix received but not reproduced here.**	Comments noted. The Committee has considered all the evidence submitted. The Committee was aware of the impact of rheumatoid arthritis on quality of life, employment and the importance placed on the availability of a variety of medications. This guidance relates only to rheumatoid arthritis and not to other forms of arthritis, such as juvenile idiopathic arthritis and psoriatic arthritis (see FAD sections 4.3.2 – 4.3.3).

Consultee	Comment	Response
Arthritis Care	The fact that the side effects of anti-TNF treatment can also be quite significant is another reason why people with RA should be allowed to try more than one – this is in fact the basis on which many PCTs operate.	Comment noted. Following the consultation on the preliminary guidance the recommendations have changed. For people who are contraindicated to either rituximab or methotrexate or require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
Arthritis Care	The decision to allow rituximab but not anti-TNFs for sequential use is not based on good evidence and appears to have been made without due consideration of the context and effect on patient pathways. Given the current lack of clarity around patient access to a second anti-TNF therapy, this decision is flawed.	Comment noted. Following the consultation on the preliminary guidance the recommendations have changed. For people who are contraindicated to either rituximab or methotrexate or require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
Arthritis Care	Under the preliminary findings, the only way patients would be able to try more than one anti-TNF would be by entering into a clinical trial, which clearly would be available only to a tiny fraction of people with RA. This would also lead to people choosing to enter into clinical trials for the wrong reasons.	Comment noted. Following the consultation on the preliminary guidance the recommendations have changed. For people who are contraindicated to either rituximab or methotrexate or require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).The guidance no longer includes an “only in research” recommendation.
Arthritis Care	**Cost effectiveness** The figures mentioned above demonstrate that any cost saving achieved by a restrictive - and short-sighted - approach to the sequential use of anti-TNFs will be very quickly and very clearly outweighed by the numerous negative implications which this decision would have, not only for people with RA but for the NHS and the UK economy.	Comment noted. The directions from the Secretary of State for Health requests the Institute to make recommendations to the NHS based on both clinical and cost effectiveness. The appraisal has been completed in accordance with the published guide to the methods of technology appraisal including a perspective of the NHS and PSS (see methods guide sections 5.5, 6.1.3).

Consultee	Comment	Response
Arthritis Care	People denied clinically effective anti-TNF treatments will not cease requiring treatment or accessing NHS services. On the contrary, if denied a treatment which could slow the progress of the disease, many people will inevitably rely much more heavily on NHS resources, including, for example, cases where lack of appropriate treatment leads people with RA to require expensive – and preventable – joint surgery, and greater use of palliative care.	Comment noted. Models considered by the Committee included costs associated with palliative care and joint replacement surgery. The model by the Assessment Group suggests that the estimates of cost effectiveness were not very sensitive to changing cost assumptions about hospitalisation and joint replacement and palliative care (see FAD section 4.3.15).
Arthritis Care	It is important to take a broad view of the costs involved, beyond the financial costs to secondary care. The NAO has clearly highlighted that non-biological treatment of RA carries significant costs to primary and secondary care, in addition to the person with RA. On the other hand, recent evidence compiled by the NAO shows that biological treatment of RA saves money, e.g. in terms of reduced emergency admissions and less reliance on the health sector generally. The NAO has also developed an economic model in connection to its aforementioned report on services for people with RA. This model states that the analyses conducted "have provided clear evidence that better value for money could be achieved by providing more rapid treatment for people with early onset rheumatoid arthritis," improving patients' quality of life and delivering productivity gains for the economy. The document goes on to say that "although it could increase the cost to the NHS in the short-term, it would be cost effective, and could be cost saving in the longer term". Finally, it states that "the analyses also confirm the NICE conclusion that intensive early treatment with step-down strategy is more cost effective than current routine practice in terms of sequential DMARD treatment (which is dominated by mono switch treatment strategy), and suggest that potential cost savings to the NHS could be realised in the medium to long-term."	Comments noted. The National Audit Office (NAO) analysis focused on the cost effectiveness of providing earlier treatment and diagnosis of rheumatoid arthritis, incorporating published NICE guidance for TNF inhibitors to reflect the treatment pathway for established disease. The current appraisal starts at the point after the failure of a TNF inhibitor. Therefore these two analyses respond to different questions and their conclusions may differ.

Consultee	Comment	Response
Arthritis Care	**Conclusion** Arthritis Care feels strongly that the preliminary findings do not reflect the existing medical evidence, expert clinical opinion and patient views, and are not at all in the best interests of people with RA. Where a clinically effective treatment is available, it is unacceptable – and medically pointless - to deny people with RA this option, forcing them to return to treatments which they and their health professionals know to be ineffective. Crucially, being able to access the best treatments – and find the anti-TNF treatment which works for each individual person with RA – helps to keep people independent, allows them to remain in or return to work, and ultimately saves the NHS and the UK economy vast sums of money. The outcome of this long and difficult appraisal process must not be another "prescription for pain". This would be perverse, counterproductive and self-defeating. On the contrary, it must be an outcome which has the best interests of people with RA at heart. We therefore urge NICE to review its preliminary findings in light of the information in this document, taking much greater account of not only the existing clinical evidence for the need for a wide availability of anti-TNF treatment, but also of patient experience and patient choice as a fundamental and essential driver of decisions regarding people's health. Key to the above is to base any decision on anti-TNF treatment on a genuine, open and honest discussion with a wide range of key stakeholders, including clinicians, people with RA and user-led organisations.	Comment noted. The directions from the Secretary of State for Health requests the Institute to make recommendations to the NHS based on both clinical and cost effectiveness. The Committee considered all of the evidence submitted, which included statements from clinical specialists and patient experts about the impact of rheumatoid arthritis and the importance of the availability of medications (see FAD sections 4.3.2 – 4.3.4). Following the consultation on the preliminary guidance the recommendations have changed. For people who are contraindicated to either rituximab or methotrexate or require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).

Consultee	Comment	Response
National Rheumatoid Arthritis Society	**Has all the relevant evidence been taken into account?** We agree that relevant evidence has been taken into account, however, we have considerable and real concerns about the fact that the NICE Appraisal Committee (AC) have made an interim decision which has been based on: In 4.2.27 Scenario analyses indicated that the results are subject to considerable uncertainty.	Comments noted. The Committee recognised the uncertainty in the estimate of cost effectiveness. The NICE guide to the methods of technology appraisals states that the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented (see methods guide section 6.2.23)
National Rheumatoid Arthritis Society	In 4.3.4 the AC acknowledged that the profile of current patients differs from that used in analysis of the BSRBR data.	Comments noted. The Committee discussed these data and recognised that the BSRBR data may not be generalisable to the current UK patient population (see FAD section 4.3.4).
National Rheumatoid Arthritis Society	In 4.3.5 the AC acknowledge that it is inappropriate to assume a class effect for TNFs.	Comments noted. The Committee discussed whether it would be appropriate to assume a differential effect of the TNF inhibitors (see FAD section 4.3.6).
National Rheumatoid Arthritis Society	In 4.3.6 the AC acknowledge the absence of rigorously controlled data on the clinical effectiveness of the sequential use of TNFs and in 4.3.14 agree that the evidence base available for sequential use does not currently allow for a robust analysis of the relative treatment effect.	Comments noted. The Committee discussed the currently available evidence base and recognised this uncertainty (see FAD section 4.3.7).
National Rheumatoid Arthritis Society	In 4.3.9 it was stated that there was insufficient evidence to make differential recommendations for sub-groups. We disagree with this and in fact, even Roche themselves are now recommending/marketing Rituximab for patients who are sero-positive because they acknowledge that treatments are more successful when they can be targeted in this way.	Comments noted. The Committee considered the specific subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Consultee	Comment	Response
National Rheumatoid Arthritis Society	In 4.3.10, we agree with the AC that that the effect of DMARDs post TNF failure is likely to be very small and certainly less than the 50% on which the economic modeling has been based.	Comments noted. The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations.
National Rheumatoid Arthritis Society	In 4.3.15 The AC accepts that HAQ does not incorporate some aspects of RA such as pain, fatigue and sleep disturbance all of which lead to a significant reduction in QoL and that patients may also derive benefits from treatment which are not reflected in HAQ. We have stated previously that we believe costs of the treatment of RA have been under-estimated (including cost of palliative care).	Comments noted. The Committee recognised that factors such as pain, fatigue and sleep disturbance may not be adequately recognised in HAQ score (see FAD section 4.3.17). The economic models submitted included costs of palliative care. Sensitivity analyses by the Assessment Group showed that in their model the estimates of cost effectiveness were not very sensitive to changes in the costs of palliative care (see FAD 4.3.15).
National Rheumatoid Arthritis Society	Following on from the above point, we do not agree that it is 'reasonable' to assume that the shortcomings and inaccuracies in HAQ modeling (4.3.16) mean that this is a 'reasonable' way to model changes in HAQ score.	Comment noted. The Committee considered that mapping had shortcomings. However, in the absence of directly-elicited generic HRQoL data, it was an acceptable way to derive estimates of utility (see FAD section 4.3.20).
National Rheumatoid Arthritis Society	The AC said that all models used included EQ5D data derived from HAQ and yet this was subject to considerable uncertainty.	Comments noted. The Committee discussed the methods used in the economic modelling including the derivation of EQ5D data. (see FAD section 4.3.20)

Consultee	Comment	Response
National Rheumatoid Arthritis Society	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** The AC have themselves pointed out and agreed that there are significant limitations in the robustness of data available.	Comments noted. The Committee recognised these uncertainties. The methods guide states that the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented (see methods guide section 6.2.23)
National Rheumatoid Arthritis Society	I do not believe that the totality of the patient pathway and the impact on individual lives has been sufficiently considered in this Appraisal. We should be including certolizumab pegol, abatacept and tocilizumab in the treatment pathway as this is what would happen in clinical practice if there were no restraints on use of biologic therapy. Certolizumab Pegol has been passed by NICE for use in the NHS, yet how will it be sequenced, given the complications outlined in the ACD?	Comments noted. Certolizumab pegol was subject to its own single technology appraisal (see NICE technology appraisal guidance 186). This guidance recommended its use in the same way as the other TNF inhibitors in technology appraisal guidance TA130. Certolizumab pegol was not subject to appraisal by the Committee in this instance (see FAD section 4.3.5). It was included as a comparator in the scope of this appraisal, but the Committee is unable to make recommendations about comparators.

Consultee	Comment	Response
National Rheumatoid Arthritis Society	In paragraph 4.1.6 and 4.1.8 patients responded to Rituximab and abatacept equally in respect of ACR20 response and yet sero-negative sub group have no further treatment options should they fail TNF/Rituximab in spite of an effective treatment option with abatacept. We believe that under such circumstances abatacept is a viable option.	Comment noted. Following the consultation on the preliminary guidance the recommendations have changed. For people who are contraindicated to either rituximab or methotrexate or require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The Committee considered the specific subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11). The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28).

Consultee	Comment	Response
National Rheumatoid Arthritis Society	From a patient and health professional perspective, the evidence that sequential use of TNF, particularly in secondary non-responders is effective for the majority of patients is clear and the AC have now acknowledged that all the TNFs work differently and it is therefore inappropriate to assume a 'class effect', (4.3.5). We would therefore argue that for secondary non-responders, a second TNF should be allowed, but agree that primary non-responders would be better at that stage to try a biologic with a different mechanism of action and this is supported by clause 4.1.9.	Comments noted. The Committee considered that although it may not be appropriate to assume that the TNF inhibitors form a homogenous group with regards to clinical effectiveness, the current evidence does not allow for the TNF inhibitors to be distinguished from one another in terms of clinical effectiveness (see FAD section 4.3.7). Additionally, the Committee discussed the evidence for a specific subgroup based on reason for withdrawal of the first TNF inhibitor. It considered there to be insufficient evidence to use reason for withdrawal from the first TNF inhibitor (that is, whether treatment was withdrawn because of a primary or secondary failure) as a basis for decision making. The data identified by the Assessment Group demonstrate in some instances reduced response, similar response and greater response for primary non response in comparison with secondary non-response (see FAD section 4.3.10).

Consultee	Comment	Response
National Rheumatoid Arthritis Society	We are extremely concerned about the resource impact and implications for the NHS in respect of patients who, having failed one TNF and RTX, are then expected to go back onto DMARDS which have already failed or are likely to have little or no effect, which leaves the option of long term use of steroids, something which the AC agree will increase possibility of recurrent infections and is not recommended in the NICE RA Guidelines. We have in our previous submission highlighted that the costs of palliative care, we believe, are significantly under-estimated by NICE and the burden that these patients will put on already stretched health professionals, particularly specialist nurses, is considerable. This can be very powerfully demonstrated by the story of one of our young volunteers, Justine, appended hereto. **Appendix received but not reproduced here.**	Comments noted. The economic models submitted included costs of palliative care, hospitalisation and joint replacement. Sensitivity analyses by the Assessment Group showed that in their model the estimates of cost effectiveness were not very sensitive to changes in the costs of palliative care (see FAD 4.3.11). The Committee has considered all the evidence submitted. The Committee was aware of the impact of rheumatoid arthritis on quality of life, employment and the importance placed on the availability of a variety of medications (see FAD sections 4.3.2 – 4.3.3). Following the consultation on the preliminary guidance, the recommendations have changed. For people who are contraindicated to either rituximab or methotrexate or require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28).

Consultee	Comment	Response
National Rheumatoid Arthritis Society	In previous submissions, I believe both we and the RCN have drawn attention to the huge number of beds which have now gone from rheumatology due to better and more effective treatment. This represents a major saving to the NHS yet I do not believe that these types of savings have ever been reflected in the economic modelling. I am concerned that if we are not allowed effective use of a variety of biologic treatments in a patient's pathway that gradually we will start to see a pool of very ill patients (we are already seeing this reflected in calls to our helpline) who will require substantial resource and represent a high cost to the NHS. I think the point made in the RCN submission regarding psychological counselling for those not allowed to go onto another biologic option, when they are aware that there are effective drugs available elsewhere in the world, including Scotland (!), is a very valid one. Unfortunately we know how difficult it is to access such services in the NHS. This is reflected in the NAO report.	Comment noted. All the models submitted included a cost of hospitalisation and joint replacement. The sources of the data varied but included the BSRBR and NOAR. The Assessment group included an assumed cost per unit HAQ score rather than one based on these data sources. However, this was tested in sensitivity analyses where it was found that the model was not sensitive to this parameter (see FAD section 4.3.15).
National Rheumatoid Arthritis Society	We would appreciate understanding what access to research means in the context of this ACD and a second TNF. Does this include patients who may go onto the BSRBR? Given that the 3 TNF cohorts are now closed, we are concerned that whilst this may appear to be a research option, negotiation of additional TNF data collection for new patients as well as additional biologic agents is a very lengthy process for the BSR to arrange and we seek clarification on this matter	Comment noted. The guidance no longer includes an "only in research" recommendation (see FAD section 1).
National Rheumatoid Arthritis Society	**Are the provisional recommendations of the AC sound and do they constitute a suitable basis for the preparation of guidance to the NHS?** The cost to individuals, their families and carers and to the wider society of uncontrolled disease cannot be over-estimated. We shall be publishing a report on the 'Economic Burden of RA' at the end of March which will show that previous figures of total costs being in the £3 – 4 Billion, fall well short of the reality.	Comment noted. The appraisal has been completed in accordance with the published NICE methods guide. As per the NICE reference case (see sections 5.2.7 to 5.2.10 of the NICE methods guide), costs incurred outside the NHS or PSS (such as those owing to time away from work) were not incorporated.

Consultee	Comment	Response
National Rheumatoid Arthritis Society	We have just completed a survey of the impact of RA on individuals with RA across Scotland. This is a repeat of the work survey we undertook on a UK wide basis in 2007. The figures are very comparable, with 57% (nearly 30% in the UK wide survey) of people who have lost their job due to their RA, losing it within 1 year of diagnosis and 80% losing their job within 6 years of diagnosis (59% in respect of the UK wide survey). 80% of people in the recent Scotland survey said that fatigue was the biggest barrier to remain in work and yet this is not adequately reflected in HAQ. >65% said that pain was the biggest barrier to remaining in work and this, equally, is not adequately reflected in HAQ. It is no longer a supportable position to take for NICE to simply say that these costs are 'not within their remit'. NICE should be lobbying government to change their remit to reflect wider societal costs in their economic modelling. The figures in the economic modelling contained in the NAO report and the work of Dame Carol Black support this.	Comment noted. The framework for this appraisal is the NICE 2008 methods guide. The appraisal has been completed in accordance with this. As per the NICE reference case (see sections 5.2.7 to 5.2.10 of the NICE methods guide), costs incurred outside the NHS or PSS (such as those owing to time away from work) were not incorporated. The Committee recognised that factors such as pain may not be adequately recognised in HAQ score (see FAD section 4.3.17). The model in the National Audit Office (NAO) report focused on the treatment of early rheumatoid arthritis, incorporating published NICE guidance for TNF inhibitors to reflect treatment for established disease. The current appraisal starts at the point a TNF inhibitor has failed. Therefore the NAO analysis and the current appraisal respond to different questions.
National Rheumatoid Arthritis Society	In the light of the above and the substantial lack of robust evidence which has informed the economic modelling on which the above ACD has made its interim recommendations, together with inadequate reflection of pain, fatigue and other symptoms which dramatically affect people's lives, would lead me to the obvious answer to this question – 'NO'!	Comment noted. The Committee recognised the impact of symptoms on the lives of people with rheumatoid arthritis (see FAD sections 2.3 and 4.3.2). The methods guide states that the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented (see methods guide section 6.2.23) Following the consultation on the preliminary guidance the recommendations have changed. For people who are contraindicated to either rituximab or methotrexate or require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).

Consultee	Comment	Response
National Rheumatoid Arthritis Society	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** I believe that the clinical experts explained at some length in the meeting on 4th Feb. the heterogeneity of RA and we believe that whilst the matter of the sero-negative sub group has been discussed in the ACD, we believe that the conclusions drawn are totally discriminatory. Approximately 25-30% of the RA population are sero-negative and to deny them a second anti-TNF (secondary non-responders) or access to a biologic with a different mode of action (tocilizumab or abatacept) is an infringement of their human rights and, as far as dedicated rheumatology health professionals are concerned, unethical.	The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11). Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5). It was included as a comparator in the scope of this appraisal, but the Committee is unable to make recommendations about comparators.
National Rheumatoid Arthritis Society	I believe that there is sufficient evidence to support use of a second TNF in secondary non-responders. Many people have successfully switched to a second TNF which has allowed them to enjoy a good quality of life and enabled them to remain working and contributing to their family and society. Primary non-responders are more likely to respond to a drug with a different mode of action and access only to Rituximab, whilst an effective option, is inadequate.	The Committee discussed the evidence for a specific subgroup based on reason for withdrawal of the first TNF inhibitor. It considered there to be insufficient evidence to use reason for withdrawal from the first TNF inhibitor (that is, whether treatment was withdrawn because of a primary or secondary non response) as a basis for decision making The data identified by the Assessment Group demonstrate in some instances reduced response, similar response and greater response for primary non response in comparison with secondary non-response (see FAD section 4.3.10).

Consultee	Comment	Response
National Rheumatoid Arthritis Society	If we are not allowed to use the available biologic treatments, how are we to ever to reach the reality of 'personalised medicine'? In my last submission I highlighted the disconnect between the aims of the Office of Life Sciences and the restriction NICE is placing on best clinical practice and UK research and we are already seeing the impact of this in reduction of UK based clinical trials. Not being able to use clinically effective treatments like abatacept which is freely available elsewhere in Europe is damaging UK PLC	These recommendations are based on the Committee's considerations of the evidence regarding both the clinical and cost effectiveness of the technologies. Although NICE accepts that individual NHS users will expect to receive treatments to which their conditions may respond, this does not impose a requirement on the Committee to recommend technologies that are not cost effective enough to provide the best value to users of the NHS as a whole (see 'Social Value Judgement – Principles for the development of NICE guidance; principle 5). With regards to the access to these technologies across Europe, funding decisions for drugs are each country's individual responsibility. NICE recognises that funding decisions can differ across countries, because of different criteria applied.
National Rheumatoid Arthritis Society	The most valuable development in treating RA will be 'biomarkers' to help diagnose it early, identify those with more severe disease, and indicate the most appropriate therapy for each person. Biomarkers may even help to decide the best time to step down therapy. There is a huge amount of research taking place worldwide into RA, which reflects the excellent relationship between rheumatology health care professionals and people with RA. Patients are actively participating in research, to help scientists reach answers more quickly. The last thing we want is that this process is damaged in the UK because it is only by being able to target therapy in this way that this will, in time, change RA from a chronic, disabling disease to an acute condition that is potentially curable. We would urge NICE to reconsider their interim guidance and allow greater flexibility in the sequencing of biologic therapies.	Comment noted. Following the consultation on the preliminary guidance the recommendations have changed. For people who require rituximab treatment be withdrawn because of an adverse event or for whom rituximab or methotrexate is contraindicated, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).

Consultee	Comment	Response
Roche Products	**1. Has all of the relevant evidence been taken into account?** Roche is not aware of any other data that would assist the Committee in addressing the decision problem for this appraisal. Roche believe that high quality RCT data should be used to appropriately guide clinical practice.	Comment noted. No changes required.
Roche Products	**2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Roche believe that the summaries of clinical and cost effectiveness data pertaining to rituximab are accurate in this patient population.	Comment noted. No changes required.

Consultee	Comment	Response
Roche Products	**3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Roche consider that one area of clarification is needed. This relates to section 1.4: "1.4 The TNF inhibitors adalimumab, etanercept, and infliximab are recommended for the treatment of rheumatoid arthritis after the failure of a previous TNF inhibitor only in the context of research. Such research (including but not limited to clinical trials) should be designed to evaluate the clinical effectiveness of adalimumab, etanercept and infliximab when used sequentially after the failure of a previous TNF inhibitor, in comparison with management strategies that do not include the use of TNF inhibitors." Roche agree with the need for randomised, controlled clinical trials demonstrating efficacy of a second anti-TNF, as systematic reviews have consistently identified gaps in the hierarchy of evidence. This has been a clear area of concern in that establishing the magnitude of treatment effect of the 2nd aTNF was not possible and therefore a recommendation could not be given. According to the NICE guide to methods hierarchy of evidence it is clear that only robustly designed RCTs, or prospective, comparative high quality studies, with efficacy as a primary end point should be used for cross trial comparisons and mixed treatment comparisons. Otherwise there would be little or no improvement on the existing evidence base and the fundamental question would remain unanswered. In addition, clarification on the extent of the mandatory funding directive in the context of future research would be helpful, given the current wording of this recommendation.	Comment noted. Following the consultation on the preliminary guidance the recommendations have changed. For people who are contraindicated to either rituximab or methotrexate or require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).The guidance no longer includes an "only in research" recommendation.
Roche Products	**4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** None	Comment noted. No changes required.

Consultee	Comment	Response
Abbott Laboratories	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.	Comment noted. See the responses to individual comments below.
Abbott Laboratories	**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.	Comments noted. See responses to individual points below.

Consultee	Comment	Response
Abbott Laboratories	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.	Comments noted. The Committee's considerations are not limited to the results presented in the Assessment Report; the Committee considers all of the evidence submitted in its deliberations. The Committee specifically considered the Assessment Group's use of non randomised comparisons and their rationale for not completing a mixed treatment or indirect comparison (see FAD section 4.3.16). The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.25).
Abbott Laboratories	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. **Comment continued on next page**	The Committee considered the length of time between rituximab treatments in its deliberations. It concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months. The guidance for rituximab includes a stopping rule that rituximab is withdrawn in people requiring infusions more frequently than every six months (see FAD section 4.3.21). The technologies' marketing authorisations from other countries does not influence the Committee recommendation. However, the evidence that leads to these changes may be considered by Committee where it is submitted.

Consultee	Comment	Response
Abbott Laboratories	**Comment continued from previous page** 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.	The Committee considered the length of time between rituximab treatments in its deliberations. It heard from clinical specialists that they would aim to treat patients before disease flared, and disease control was lost. However, there was wide variation in time required between infusions. The Committee concluded that while 8.7 months between treatments may be an over estimate of the average re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months. Even taking into account the provision of treatment before disease flared, the Committee did not accept that the treatment schedule would be 6 monthly. The guidance for rituximab includes a stopping rule that rituximab is withdrawn in people requiring infusions more frequently than every six months (see FAD section 4.3.21).

Consultee	Comment	Response
Abbott Laboratories	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.	Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
Abbott Laboratories	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.	Comment noted. See the responses to individual comments below.
Abbott Laboratories	**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. **Comment continued on next page**	The Committee considered the non-randomised evidence identified by the Assessment Group and submitted by consultees. The Committee accepted that the data available suggested that a second TNF inhibitor was effective. It did not dismiss the non randomised data. However, the Committee considered that it could not quantify with certainty the relative effect of adalimumab, etanercept and infliximab in comparison with conventional or biologic DMARDs (see FAD sections 4.3.7, 4.3.8). **Response continued on next page**

Consultee	Comment	Response
Abbott Laboratories	In a recent talk given by Professor Sir Michael Rawlins to the Royal College of Physicians 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.” **Comment continued on next page**	As indicated in the comment, the NICE guide to the methods of technology appraisal recognises that evidence from RCTs is not always available and acknowledges that non-randomised data may be required to supplement RCT data. However, the methods guide also states that RCTs are considered to provide the most valid evidence of relative effectiveness and that inference drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence (sections 3.2.5, 3.2.9). The Committee considered the non-randomised evidence identified by the Assessment Group and submitted by consultees. The Committee accepted that the data available suggested that a second TNF inhibitor was effective. However, it considered that it could not quantify with certainty the relative effect of adalimumab, etanercept and infliximab in comparison with conventional or biologic DMARDs (see FAD sections 4.3.7, 4.3.8).

Consultee	Comment	Response
Abbott Laboratories	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 inhibitor (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.	The Committee considered the non-randomised evidence identified by the Assessment Group and submitted by consultees. The Committee accepted that the data available suggested that a second TNF inhibitor was effective. It did not dismiss the non randomised data. However, the Committee considered that it could not quantify with certainty the relative effect of adalimumab, etanercept and infliximab in comparison with conventional or biologic DMARDs (see FAD sections 4.3.7, 4.3.8). Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).

Consultee	Comment	Response
Abbott Laboratories	**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. **Comment continued on next page**	The NICE guide to the methods of technology appraisal states that in the absence of head-to-head RCTs indirect comparison methods may be used. However, these should follow the principles of good practice for standard meta-analyses. The Committee specifically considered the Assessment Group's use of non randomised comparisons and their rationale for not completing a mixed treatment or indirect comparison. The Committee recognised that the use of non-randomised comparisons may affect the robustness of the Assessment Group's analyses. (See FAD section 4.3.16). The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.25). Not all manufacturers performed mixed treatment comparisons that linked all treatments. One manufacturer did not include an indirect or mixed treatment comparison in their submission. Another included in their cost effectiveness analysis an MTC of only abatacept and rituximab, and finally another completed two separate analyses one of TNF inhibitors and one of abatacept and rituximab.

Consultee	Comment	Response
Abbott Laboratories	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. **Comment continued on next page**	The Committee specifically considered the Assessment Group's use of non randomised comparisons and their rationale for not completing a mixed treatment or indirect comparison. The Committee recognised that the use of non-randomised comparisons may affect the robustness analyses. The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.16, 4.3.25). NICE does not respond directly to comments on the Assessment Group's reports and analyses. These are completed independently.

Consultee	Comment	Response
Abbott Laboratories	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 , : *"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] **Comment continued on next page**	Comments noted. The Committee considered the use of relative and absolute treatment effects in the economic models. It agreed that alternative approaches to that of the Assessment Group should not necessarily be discounted. The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25).

Consultee	Comment	Response
Abbott Laboratories	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 . 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."* [3] **Comment continued on next page**	Comments noted. The Committee considered the use of relative and absolute treatment effects in the economic models. It agreed that alternative approaches to that of the Assessment Group should not necessarily be discounted. The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25).

Consultee	Comment	Response
Abbott Laboratories	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. $$\text{logit}(p20_{ij}) = \mu_i + \beta_1 X^M_{ij} + \beta_2 X^F_{ij} + 1(t_{ij} > 1) \cdot \Delta_{ij}$$ **Comment continued on next page**	Comments noted. The Committee considered the use of relative and absolute treatment effects in the economic models. It agreed that alternative approaches to that of the Assessment Group should not necessarily be discounted. The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25). NICE does not respond directly to comments on the Assessment Group's reports and analyses. These are completed independently.

Consultee	Comment	Response
Abbott Laboratories	To maximally account for inter-study heterogeneity, "unconstrained" baselines have been assumed (see, e.g., Lu and Ades 2004[i]), 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). $$\delta_{ij} = d(t_{ij}) - d(c_{ij}) + \gamma_1 X^D_{ij} + \gamma_2 X^H_{ij} + \gamma_3 X^L_{ij} + \gamma_4 X^F_{ij} + \gamma_5 X^{SB}_{ij}$$ **Comment continued on next page**	Comments noted. The Committee considered the use of relative and absolute treatment effects in the economic models. It agreed that alternative approaches to that of the Assessment Group should not necessarily be discounted. The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25). NICE does not respond directly to comments on the Assessment Group's reports and analyses. These are completed independently.

Consultee	Comment	Response
Abbott Laboratories	Minimally informative priors were assigned, N(0, 1.0E-6) to the relative (placebo) treatment effects for the five modelled treatments, d(t=2, … 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.	Comments noted. The Committee considered the use of relative and absolute treatment effects in the economic models. It agreed that alternative approaches to that of the Assessment Group should not necessarily be discounted. The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25). NICE does not respond directly to comments on the Assessment Group's reports and analyses. These are completed independently.

Consultee	Comment	Response
Abbott Laboratories	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 inhibitors (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 included, but not reproduced here** **Comment continued on next page**	Comments noted. The Committee considered the use of relative and absolute treatment effects in the economic models. It agreed that alternative approaches to that of the Assessment Group should not necessarily be discounted. The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25). NICE does not respond directly to comments on the Assessment Group's reports and analyses. These are completed independently.

Consultee	Comment	Response
Abbott Laboratories	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).	Comments noted. The Committee considered the use of relative and absolute treatment effects in the economic models. It agreed that alternative approaches to that of the Assessment Group should not necessarily be discounted. The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25). NICE does not respond directly to comments on the Assessment Group's reports and analyses. These are completed independently.
Abbott Laboratories	**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.	The Committee heard from specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. It concluded that the modelling of stopping rules should be considered as it examined the estimates of cost effectiveness. The Committee considered the full range of models submitted while considering the estimates of cost effectiveness presented (see FAD section 4.3.22).

Consultee	Comment	Response
Abbott Laboratories	**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. **Comment continued on next page**	The NICE guide to the methods of technology appraisals 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" (section 3.4.9). A number of consultees commented on the economic analysis in the Assessment Report. NICE therefore requested further work from the Assessment Group. The addendum report was circulated with the ACD and consultees had an opportunity to comment on the addendum as part of the consultation. These comments were seen and circulated to the Committee for discussion at the second Committee meeting. Manufacturer representatives were present at the second Committee meeting and had the opportunity to respond to further clarifications from Committee members.

Consultee	Comment	Response
Abbott Laboratories	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.	Please see the response above. The NICE Guide to the methods of technology appraisals does not define what additional analyses may or may not be acceptable to complete following consultation. The Committee considered the use of relative and absolute treatment effects in the economic models. It agreed that alternative approaches to that of the Assessment Group should not necessarily be discounted. The Committee considered the methods through which the clinical effectiveness data had been calculated and incorporated into the submitted economic analyses. It considered the range of estimates of cost effectiveness and identified where the models could lead to different conclusions about the cost effectiveness of the treatments under appraisal. The Committee did not consider that the different methods of analysis of the clinical effectiveness data altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25). Preliminary recommendations are draft recommendations and are subject to change following the consultation on the ACD, and second Committee meeting. Preliminary recommendations do not constitute recommendations to the NHS. The recommendations have changed following the second Committee meeting (see FAD section 1).
Abbott Laboratories	**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.	See responses to individual comments below.

Consultee	Comment	Response
Abbott Laboratories	**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."* **Comment continued on next page**	The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations. Both the REFLEX and ATTAIN trials are placebo controlled trials in which rituximab or abatacept are added to background methotrexate or conventional DMARDs. Conventional DMARDs had to be given at a stable dose prior to randomisation. These studies demonstrate the effect of rituximab and abatacept in comparison to placebo rather than the effect of treatment with a conventional DMARD.

Consultee	Comment	Response
Abbott Laboratories	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.	The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations.

Consultee	Comment	Response
Abbott Laboratories	**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. **Comment continued on next page**	The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22).

Consultee	Comment	Response
Abbott Laboratories	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.	In its considerations the Committee took into account multiple factors including the efficacy of conventional DMARDs, the re-treatment interval and the application of stopping rules. Additionally the Committee was mindful of the uncertainty in the estimates of efficacy particularly for the three TNF inhibitors. The Committee was not persuaded that adalimumab, etanercept, infliximab and abatacept had been demonstrated to be cost effective in comparison with rituximab. (see FAD sections 4.3.12, 4.3.21, 4.3.22 and 4.3.23, 4.3.26, 4.3.27). Following the consultation on the preliminary guidance the recommendations have changed. The Committee was persuaded that where the appropriate comparator was conventional DMARDs, namely where people are contraindicated to either rituximab or methotrexate or require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept could be considered a cost effective use of NHS resources (see FAD section 1).

Consultee	Comment	Response
Abbott Laboratories	**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 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. **Comment continued on next page**	The Committee considered the length of time between rituximab treatments in its deliberations. It heard from clinical specialists that they would aim to treat patients before disease flared, and disease control was lost. However, there was wide variation in time required between infusions. The Committee concluded that while 8.7 months between treatments may be an over estimate of the average re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months. Even taking into account the provision of treatment before disease flared, the Committee did not accept that the treatment schedule would be 6 monthly. The guidance for rituximab includes a rule that rituximab is only continued if an adequate response can be maintained following retreatment with a dosing interval of at least 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Abbott	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. **Comment continued on next page**	The Committee considered the length of time between rituximab treatments in its deliberations. It heard from clinical specialists that they would aim to treat patients before disease flared, and disease control was lost. However, there was wide variation in time required between infusions. The Committee concluded that while 8.7 months between treatments may be an over estimate of the average re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months. Even taking into account the provision of treatment before disease flared, the Committee did not accept that the treatment schedule would be 6 monthly for every person. The guidance for rituximab includes a rule that rituximab is only continued if an adequate response can be maintained following retreatment with a dosing interval of at least 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Abbott Laboratories	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 included, but not reproduced here**	In its considerations the Committee took into account multiple factors including the efficacy of conventional DMARDs, the re-treatment interval and the application of stopping rules. Additionally the Committee was mindful of the uncertainty in the estimates of efficacy particularly for the three TNF inhibitors. The Committee was not persuaded that adalimumab, etanercept, infliximab and abatacept had been demonstrated to be cost effective in comparison with rituximab. (see FAD sections 4.3.12, 4.3.21, 4.3.22 and 4.3.23, 4.3.26, 4.3.27). The Committee specifically considered the length of time between rituximab treatments in its deliberations. It heard from clinical specialists that they would aim to treat patients before disease flared, and before disease control was lost. However, there was wide variation in time required between infusions. The Committee concluded that while 8.7 months between treatments may be an over estimate of the average re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months. Even taking into account the provision of treatment before disease flared, the Committee did not accept that the treatment schedule would be 6 monthly for every person. The guidance for rituximab includes a rule that rituximab is only continued if an adequate response can be maintained following retreatment with a dosing interval of at least 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Abbott Laboratories	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.	The Committee considered the length of time between rituximab treatments in its deliberations. It heard from clinical specialists that they would aim to treat patients before disease flared, and disease control was lost. However, there was wide variation in time required between infusions. The Committee concluded that while 8.7 months between treatments may be an over estimate of the average re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months. Even taking into account the provision of treatment before disease flared, the Committee did not accept that the treatment schedule would be 6 monthly. The guidance for rituximab includes a rule that rituximab is continued only if an adequate response can be maintained following retreatment with a dosing interval of at least 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Abbott Laboratories	**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 . 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 included, but not reproduced here** **Comment continued on next page**	The current marketing authorisation for rituximab does not specify a re-treatment interval. It is the current marketing authorisation which forms the basis for consideration of rituximab. NICE recognises that different regulatory agencies may specify different marketing authorisations. However, labels from other regulatory agencies do not inform the appraisal, although the evidence leading to the amendment may do so if submitted. The Committee considered the length of time between rituximab treatments in its deliberations. It concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Abbott Laboratories	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 agents7. In this 559 patient trial, all patients were given rituximab at week 0; at week 24 those patients not in remission (DAS28 < 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.	The Committee recommended a stopping rule whereby treatment with rituximab is stopped if treatment is required more frequently than every 6 months. The Committee heard from clinicians that they would aim to re-treat disease before the condition flared. The Committee concluded that while 8.7 months between treatments may be an over estimate of the interval for re-treatment, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Abbott Laboratories	**Figure included, but not reproduced here** 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 . 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) 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.	The Committee considered the length of time between rituximab treatments in its deliberations. It heard from clinical specialists that they would aim to treat patients before disease flared, and disease control was lost. However, there was wide variation in time required between infusions. The Committee concluded that while 8.7 months between treatments may be an over estimate of the average re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months. Even taking into account the provision of treatment before disease flared, the Committee did not accept that the treatment schedule would be 6 monthly. The guidance for rituximab includes a rule that rituximab is only continued if an adequate response can be maintained following retreatment with a dosing interval of at least 6 months (see FAD section 4.3.21).

Consultee	Comment	Response
Abbott Laboratories	**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 . 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) . 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. **Figures included, but not reproduced here.** **Comment continued on next page**	The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Consultee	Comment	Response
Abbott Laboratories	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 . 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. **Comment continued on next page**	The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Consultee	Comment	Response
Abbott Laboratories	Finally, data on response by RF status are also available in an observational cohort of patients on rituximab from European registries (n=1,372). 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*) 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 included, but not reproduced here.** As can be seen in Table 2.3.2, this finding is also supported by data from the large observational ReACT study. **Table included, but not reproduced here.** 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.	The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Consultee	Comment	Response
Abbott Laboratories	**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 . 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) . 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 , . 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 . 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 . 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. **Comment continued on next page**	The Committee understood the adverse effects of each of the technologies. The Committee does not make decisions solely on the basis of adverse events. The balance of benefits and harms of a treatment are for the consideration of the regulatory agencies.

Consultee	Comment	Response
Abbott Laboratories	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 . 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 . 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) 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 analysis24. **Comment continued on next page**	The Committee understood the adverse effects of each of the technologies. The Committee does not make decisions solely on the basis of adverse events. The balance of benefits and harms of a treatment are for the consideration of the regulatory agencies.

Consultee	Comment	Response
Abbott Laboratories	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.	The Committee understood the adverse effects of each of the technologies. The Committee does not make decisions solely on the basis of adverse events. The balance of benefits and harms of a treatment are for the consideration of the regulatory agencies.
Abbott Laboratories	**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.	Comment noted. In making recommendations the Committee did not differentially prefer infliximab over the other TNF inhibitors.

Consultee	Comment	Response
Abbott Laboratories	**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 and 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.	The Committee specifically considered the subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11). The Committee considered the length of time between rituximab treatments in its deliberations. It concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21). Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
Abbott Laboratories	**4. Are there any equality related issues that may need special consideration?** None that Abbott is aware of. **Appendices included but not reproduced here**	Comment noted. No action required.

Consultee	Comment	Response
Schering-Plough	Schering-Plough welcomes the opportunity to comment on the ACD which sets out the Appraisal Committee's ("the Committee") recommendations on adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis ("RA"). In addition to our ACD response, we have included a response to the Assessment Group's critique of the manufacturer submissions (the "Addendum Report") which was received by consultees after the first Technology Appraisal Committee Meeting on 4 February 2010. Prior to detailing our comments on the ACD, we wish to make a number of procedural points regarding this appraisal as follows:	Comment noted. Please see the responses below to each individual comment.
Schering-Plough	**Lack of transparency** Schering-Plough is particularly disappointed not to have had an opportunity to review and/or provide its responses to the Addendum Report prior to the first Committee meeting. Unlike members of the Committee who had the benefit of reading the Addendum Report prior to the meeting, Schering-Plough was unable to engage fairly in a balanced discussion with members of the Committee during that meeting. Had Schering-Plough received a copy of the Addendum Report, we believe that we could successfully have challenged the outputs of that report before the Committee. The failure to provide Schering-Plough and other consultees with a copy of the Addendum Report unfairly prejudices infliximab, particularly in the context of this appraisal where there has been a documented lack of transparency throughout. Schering-Plough has not received a fully executable version of the model. We refer to our comments in our letter to you dated 12 January 2010, where we state that we have not been able to validate the model given the near complete lack of explanation of the 2,000 lines of source code in the model. Until Schering-Plough has been given a fully executable version of the model, we are unable to scrutinise and validate it appropriately and therefore unable to engage effectively in consultation on the model or the ACD.	The NICE guide to the methods of technology appraisals 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" (section 3.4.9). A number of consultees commented on the economic analysis in the Assessment Report. NICE therefore requested further work from the Assessment Group. The addendum report was circulated with the ACD and consultees had an opportunity to comment on the addendum as part of the consultation. These comments were seen and circulated to the Committee for discussion at the second Committee meeting. Manufacturer representatives were present at the second Committee meeting and had the opportunity to respond to further clarifications from Committee members. Consultees were provided with an executable version of the model. Separately consultees were also provided with the source code for the model. Neither the source code nor a description of it, are required for the model to be executable.

Consultee	Comment	Response
Schering-Plough	**Failure to re-model and consider key evidence** Schering-Plough recognises the history of this appraisal since its inception within TA 130 over 5 years ago and aims to provide clinical and economic clarification of the evidence to assist the Committee in making its recommendations. It is highly regrettable that notwithstanding the recommendations of the Appeal Panel on the sequential use of adalimumab, etanercept and infliximab for RA, the Committee has yet to be presented with a comprehensive review of the available evidence, including relevant randomised controlled trial ("RCT") data and has failed to demand a re-modelling of the data. The Appeal Panel on sequential use said: *"The appeal panel considered that the topic should be re-scoped and that the Institute's normal procedures and methods, for a multi-technology assessment, should then follow. This should include invitations to consultees for submission of evidence,* ***re-modelling*** *if necessary and the development of new draft guidance for consultation." (Emphasis added.)* Further, we are nonplussed by the failure to include key RCT data on tocilizumab, golimumab, and certolizumab pegol as these are comparators specifically referred to in the Final Scope of the appraisal. Failure to include such evidence, particularly as evidence incorporating the key trials was submitted by Schering-Plough and other consultees, is therefore outside the final scope of this appraisal and unfairly prejudices infliximab. We note the final protocol for this appraisal proposed a discretionary deadline for considering evidence relating to the above technologies, however, Schering-Plough considers that imposing such a deadline is itself unfair given that it restricts the agreed terms of the appraisal and that the manufacturers, who are ideally placed to inform NICE of likely marketing authorisation dates, were not consulted on this restriction. In any event, the deadline proposed was discretionary and given the relevance of the studies, the discretion should have been exercised in favour of including the studies in the modelling.	As a result of the appeal, a new appraisal was started with new invitations and new evidence submissions. The evidence before the Committee is not that submitted as part of TA130 or the subsequent work on sequential use of TNF inhibitors completed after this. The BRAM used in this appraisal was updated from versions used in previous appraisals, in line with the appeal decision that states re-modelling if necessary. The Assessment Group's are not chosen by NICE, but are commissioned by the National Coordinating Centre for Health Technology Assessment (section 4.1.1 of the methods guide). The definition of a comparator for an appraisal is a therapy routinely used in the NHS, including technologies regarded as current best practice (Methods Guide table 5.1). The scope defines the appropriate comparators, but it is not necessarily the case that these have to be included in an appraisal. People who submit evidence to an appraisal can argue that a comparator isn't valid, if for example they can provide evidence that it is not in use in current UK clinical practice. The Committee considered that golimumab, tocilizumab and certolizumab pegol were not yet in routine clinical use at the time of the Committee meeting, and therefore the Assessment Group's exclusion of it from their report was appropriate (see FAD section 4.3.5, 4.3.7).

Consultee	Comment	Response
Schering Plough	We urge the Committee to reconsider its preliminary recommendations in light of substantial clinical evidence and the alternative economic approaches submitted by Schering-Plough that reflect clinical practice in the UK, unlike the approach presented within the West Midlands Technology Assessment Report that does not reflect UK clinical practice. We hope that following a review of our response, along with those of the other consultees, the Committee will re-model the data as recommended by the Appeal Panel above using a different Assessment Group that has not been involved in the review of tumour necrosis factor ("TNF") inhibitors for rheumatoid arthritis. Failing that, the Committee should require a re-evaluation of the approach and assumptions applied within the Birmingham Rheumatoid Arthritis Model ("BRAM") and support a recommendation for the use of biological disease modifying anti-rheumatic drugs ("biologics"), including TNF inhibitors in the treatment of rheumatoid arthritis following an inadequate response on a first TNF inhibitor.	The Committee's considerations are not limited to the results presented in the Assessment Report; the Committee considers all of the evidence submitted in its deliberations (section 4.1.6 of the methods guide). The Committee considered the economic model submitted by Schering Plough as well as those of the other manufacturer's. The Committee did not consider that the results of the other economic models altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25). Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).

Consultee	Comment	Response
Schering-Plough	Schering-Plough has identified the following key points to inform the Committee that further assessment is required before proceeding beyond preliminary recommendations. • **Substantial clinical evidence has not informed the appraisal** o Overly restrictive search criteria unfairly led to the exclusion of nearly 70% (113) of identified studies. o A detailed clinical write-up of GO-AFTER, the first RCT assessing the efficacy and safety of a TNFα inhibitor after an inadequate response to a first TNFα inhibitor has not been fairly or appropriately assessed by the Assessment Group and not given adequate consideration by the Committee. o Additional published or unpublished data (e.g., individual patient level data from the GO-AFTER trial) has not been requested from Schering-Plough by the Assessment Group or the Committee despite the clear need for such information. Analyses based upon GO-AFTER were misinterpreted within the Addendum Report and thus incorrectly questioned the validity of the submitted evidence.	Systematic reviews usually perform broad searches which lead to the exclusion of a number of studies from the final review. The Assessment Report contains an appendix of the studies excluded and the reason for exclusion. If consultees considered that a study had been inappropriately excluded, then these may be identified and commented on. The Committee considered the results of the GO-AFTER RCT in its deliberations. Clinical specialists and patient experts advised that the TNF inhibitors should be considered separately. The Committee considered whether the results for golimumab from this study could be applied to the TNF inhibitors included as interventions in this appraisal. The Committee did not consider that data for a technology not in the appraisal should be used to reflect the effect of treatments in the appraisal. However, it accepted that the GO-AFTER trial could be considered as supporting a benefit for TNF inhibitors when used after the failure of a first TNF inhibitor (see FAD section 4.3.7). The current guide to the methods for technology appraisals does not stipulate that either the Assessment Group or the Institute request data from consultees. If a consultee has data which it feels are relevant to the appraisal, it should submit these data for consideration by the Committee via the appropriate channels.

Consultee	Comment	Response
Schering-Plough	• **The BRAM does not appropriately inform the decision problem. Alternative modelling approaches do exist which could better inform the Committee based on UK clinical practice** o Discrepancies exist between the simulated BRAM Health Assessment Questionnaire ("HAQ") multiplier and the HAQ multipliers observed from actual clinical trials. Schering-Plough has emphasised this in its response to the Assessment Report. The Assessment Group has made no attempt to validate this critical component, which is a primary determinant in the differential therapeutic effects between the biologics. o The BRAM relies on a health outcome with well-documented shortcomings, particularly the HAQ score. An alternative model submitted by Schering-Plough based on Disease Activity Score ("DAS"), which is more in line with UK clinical practice and NICE Guidelines, was unfairly dismissed purely because a small component of the model was informed by HAQ. o The BRAM does not include a treatment stopping rule based on a response criterion which is contradictory to previous appraisals (TA 130: 6 months stopping rule for TNFα inhibitors) and the current appraisal which found rituximab to be cost-effective based on the assumption that the product "is stopped if there is an inadequate response to treatment" (ACD, Section 4.3.22). The BRAM is highly sensitive to the stopping rule and Schering-Plough has a legitimate expectation that the stopping rule would be included in this appraisal.	The Committee considered the validity of the HAQ multiplier in its deliberations. The Committee was not persuaded that the use of a HAQ multiplier in itself was unreasonable. However, it agreed that alternative approaches should not be discounted and that it was appropriate to consider the cost effectiveness analyses of the manufacturers that use alternative methods (see FAD section 4.3.18). The Committee's considerations are not limited to the results presented in the Assessment Report; the Committee considers all of the evidence submitted, including those models submitted by the manufacturers, in its deliberations. The Schering Plough model was not dismissed by the Committee, the results of this model were considered. The Committee did not consider that the results of the other economic models altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25). The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22).

Consultee	Comment	Response
Schering-Plough	• **The appraisal does not take account of relevant safety information** o Preliminary recommendations have relied on the economic evaluation of rituximab and may not have fully taken into account the implications of solely recommending rituximab after an inadequate response on a TNFα inhibitor. Further to comments made in our response to the Assessment Report, Schering-Plough urges the Committee to consider the warning remarks issued by the Food and Drug Administration ("FDA") on the associated risk of treatment with rituximab and progressive multifocal leukoencephalopathy ("PML"). Detailed comments in relation to the ACD are presented below.	The Committee understood the adverse effects of each of the technologies. The Committee does not make decisions solely on the basis of adverse events. The balance of benefits and harms of a treatment are for the consideration of the regulatory agencies.

Consultee	Comment	Response
Schering-Plough	**Exclusion of relevant clinical data: GO-AFTER Randomised Controlled Trial** **GO-AFTER** "The Committee concluded that, although the studies suggest that a second TNF inhibitor is effective after the failure of the 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" (ACD, Section 4.3.6, Page 35). Indirect comparisons presented by the British Society for Rheumatology ("BSR"), two of the consultees as well as the West Midlands Assessment Group found no statistically significant difference in effect between the TNF inhibitors following an inadequate response to a first TNF inhibitor. Similarly to the previous appraisal of TNF inhibitors for sequential therapy, where evidence for a biologic not being appraised was used to inform modelling by the Assessment Group (Schering-Plough TAR Response, Section 2.3.1), Schering-Plough considers the prospective, double-blind, placebo-controlled phase III trial that investigates the sequential use of TNF inhibitors in RA patients for Golimumab to be highly relevant to the decision problem. The Addendum Report unfairly disqualified our indirect comparison since it was presumed that we had included Golimumab trials not relevant to the TNF-experienced population (i.e., methotrexate ("MTX")-naïve patients). By misrepresenting methods to the Committee, the Committee's conclusion that it was not appropriate to assume a class effect among the TNF inhibitors is misinformed (ACD, Section 4.3.5, Page 34). Schering-Plough is grateful now to have the opportunity to comment on the Addendum Report, following receipt of the document following the first Technology Appraisal Committee Meeting ("TAC") (note, however, our comments above on the lack of transparency). **Comment continued on next page**	The paragraph referred to by Schering Plough has been amended in the FAD to specify that the absence of any rigorously controlled data meant that the Committee could not quantify with certainty the relative effect of etanercept, adalimumab and infliximab, rather than for unspecified TNF inhibitors. This is to clarify that this is not a conclusion being drawn about the efficacy of golimumab in this population (FAD section 4.3.8). The Committee considered that although it may not be appropriate to assume that the TNF inhibitors form a homogenous group with regards to clinical effectiveness, the current absence of evidence does not allow for the TNF inhibitors to be distinguished from one another in terms of clinical effectiveness (see FAD section 4.3.7). The Committee's conclusion about whether it was appropriate to assume a class effect was driven by the evidence from the clinical specialists and patient experts and not by the Addendum report. This is specifically referred to in section 4.3.6 of the FAD. The Committee considered the results of the GO-AFTER RCT in its deliberations. The Committee did not consider that data for a technology not in the appraisal should be used to reflect the effect of treatments in the appraisal. However, it accepted that the GO-AFTER trial could be considered as supporting a benefit for TNF inhibitors when used after the failure of a first TNF inhibitor (see FAD section 4.3.7).

Consultee	Comment	Response
Schering-Plough	In line with NICE's method guidance, which states that baseline utilities can be derived from other populations, Schering-Plough applied RCT data from GO-BEFORE and GO-FORWARD (Golimumab RCTs in MTX-naïve and MTX-experienced populations) solely to establish the baseline utility. The relative treatment effect was directly extracted from the GO-AFTER trial. Based on the robust and systematic indirect comparison, Schering-Plough concludes that the TNF inhibitors should be viewed as a class and therefore data from the GO-AFTER trial would be relevant to the decision problem. In any event, golimumab is listed as a relevant comparator in the Final Scope and evidence regarding golimumab should have been included in the appraisal.	The definition of a comparator for an appraisal is a therapy routinely used in the NHS, including technologies regarded as current best practice (Methods Guide table 5.1). The scope defines the appropriate comparators, but it is not necessarily the case that these have to be included in an appraisal. People who submit evidence to an appraisal can argue that a comparator isn't valid, if for example they can provide evidence that it is not in use in current UK clinical practice. The Committee considered that golimumab was not yet in routine clinical use, at the time of the Committee meeting and therefore the Assessment Group's exclusion of it from their report was appropriate (see FAD section 4.3.5). However, the Committee considered the results of the GO-AFTER RCT in its deliberations. The Committee did not consider that data for a technology not in the appraisal should be used to reflect the effect of treatments in the appraisal. However, it accepted that the GO-AFTER trial could be considered as supporting a benefit for TNF inhibitors when used after the failure of a first TNF inhibitor (see FAD section 4.3.7).

Consultee	Comment	Response
Schering-Plough	**Additional clinical evidence** Whilst RCT data is ideal, NICE's methods guide to technology appraisals states that other sources of evidence should be evaluated – particularly in light of available studies within a UK perspective. Large observational studies and registry data were dismissed but have large UK patient populations which can provide estimates of relative treatment effect. The Committee concluded that a recommendation for TNF inhibitors was not possible due to strict criteria relying ultimately on RCT data. Although relative efficacy and safety parameters from a large, observational study of adalimumab (n=899) by Bombardieri et al 2007 were presented within the Assessment Report, they appear to be dismissed in the final discussions. Nearly 70% (113) of identified studies were excluded based on stringent and potentially arbitrary criteria (≥20 patients in an arm) (TAR, Section 5.1.2, Page 45). Biologics listed as treatment comparators within the Final Scope were not included within the search strategy (certolizumab pegol, tocilizumab, golimumab) and thus published findings (including RCTs) were not identified by the Assessment Group. A cost-effectiveness analysis based solely on the BSR Biologics Registry ("BSRBR") data set was submitted to the Committee by the BSR for consideration. With a registry containing over 3,200 UK RA patients, Schering-Plough questions the reasons for dismissing this data based on perceived weaknesses in representing clinical practice. Given the absence of an alternative data set containing such large UK patient numbers and in light of an Appeal Panel Decision that suggested the appraisal "explain more fully its reasons for failing to recommend such treatment if there may be a reasonable possibility" (Appeal Panel Decision, TA130, Paragraph 141, Page 30), we would urge these data sets to be taken into account by the Committee. Our view is that there is sufficient data to form a recommendation for TNF inhibitors as a class.	The Committee considers all evidence submitted by consultees in its deliberations. The Committee considered the non-randomised evidence submitted including the Bombardieri study (n=899) see FAD section 4.1.2. The Bombardieri study is a single arm study, the Committee while accepting that these data suggested a benefit of TNF inhibitors, did not consider that these data helped quantify with certainty the relative effect of the TNF inhibitors under appraisal with current NHS standard care. A list of excluded studies are included in Appendix 10.4 of the Assessment Report, if relevant studies including equal to or less than 20 patients had been excluded these can be identified by stakeholders. The Committee did not dismiss the data from the BSRBR (see FAD section 4.3.8). However, it was highlighted that because of changing management of rheumatoid arthritis, there may be issues in generalising this data to current UK clinical practice (FAD section 4.3.4). Clinical specialists and patient experts highlighted that they considered that the TNF inhibitors should be considered separately. The Committee considered that although it may not be appropriate to assume that the TNF inhibitors form a homogenous group with regards to clinical effectiveness, the current absence of evidence does not allow for the TNF inhibitors to be distinguished from one another in terms of clinical effectiveness (see FAD section 4.3.7).
Schering-Plough	CIC information removed	Comment noted. The RESTART data were considered by the Committee (see FAD section 4.3.13)

Consultee	Comment	Response
Schering-Plough	**The BRAM contains fundamental flaws and thus does not inform the decision problem** **HAQ multiplier** "…Bearing in mind these considerations, the Committee accepted the use of a HAQ multiplier as a reasonable way to model changes in HAQ score" (ACD, Section 4.3.16, P41). Lengthy discussions in the first TAC meeting on 4 February 2010 highlighted the issues regarding the HAQ multiplier: discrepancies between the simulated and clinical HAQ multipliers, weak base case data which was arbitrarily applied across multiple biologics, and general confusion on the applicability of the HAQ multiplier to clinical practice. It is therefore of some concern that the Committee has accepted this as the most appropriate method over the numerous alternatives presented by the consultees. On 3 February 2010, Schering-Plough submitted additional evidence regarding the validation of the HAQ multiplier applied by the Assessment Group. This addendum was not included within the distributed Evaluation Report and may not have been taken into consideration by the Committee due to its late submission and thus is included again within Appendix 2. **Comment continued on next page**	The Committee considered the validity of the HAQ multiplier in its deliberations. The Committee was not persuaded that the use of a HAQ multiplier in itself was unreasonable. However, it agreed that alternative approaches should not be discounted and that it was appropriate to consider the cost effectiveness analyses of the manufacturers that use alternative methods (see FAD section 4.3.18).

Consultee	Comment	Response
Schering-Plough	As the HAQ multiplier is the primary determiner of differences in biologic treatment effects, the application of the simulated HAQ multiplier should be reflective of clinically observed outcomes. Given that Appendix 2 graphically depicts the discrepancies between observed actual trials and the BRAM simulated HAQ multiplier, it is worrying that a major input of the BRAM is fundamentally flawed and this casts substantial doubt on the credibility of the resulting analysis. Further, at the TAC meeting above, the Assessment Group responded to questions from the Committee about the failure to validate the simulated HAQ multipliers by stating that the Assessment Group had not been provided with the relevant data. Schering-Plough is willing to provide individual patient level data from appropriate trials if this would help the Assessment Group's analysis. However, the Assessment Group should have asked Schering-Plough for such data in accordance with NICE's usual procedures. To date, we have not been approached to provide further data, which is surprising given that other manufacturers in this appraisal have been asked to submit additional unpublished data. This inconsistent approach has unfairly prejudiced infliximab and led to perverse modelling.	The Committee considered the validity of the HAQ multiplier in its deliberations. The Committee was not persuaded that the use of a HAQ multiplier in itself was unreasonable. However, it agreed that alternative approaches should not be discounted and that it was appropriate to consider the cost effectiveness analyses of the manufacturers that use alternative methods (see FAD section 4.3.18). Two manufacturers were asked by the Institute (on behalf of the Assessment Group) to clarify (1) the existence of published data relating to conference abstracts identified in the literature search; and (2) the previous exposure of patients to TNF inhibitors in a number of trials identified in the literature search. No individual patient data were requested by the Assessment Group of these manufacturers. The Committee considered the results of the GO-AFTER RCT in its deliberations. The Committee did not consider that data for a technology not in the appraisal should be used to reflect the effect of treatments in the appraisal. However, it accepted that the GO-AFTER trial could be considered as supporting a benefit for TNF inhibitors when used after the failure of a first TNF inhibitor (see FAD section 4.3.7).

Consultee	Comment	Response
Schering-Plough	**HAQ vs DAS** "…The Committee was mindful that all models presented had included EQ-5D data derived from HAQ, and therefore no alternative was available...The Committee concluded that mapping HAQ to EQ5D had shortcomings, but in the absence of an alternative was an acceptable way to derive estimates of utility, and that the use of a non-linear function was not unreasonable" (ACD, Section 4.3.18, Page 42). The West Midlands Assessment Group has applied minor updates to the BRAM from the last appraisal rather than re-modelling and assessing whether an alternative approach may be better suited. The Committee notes that current clinical practice is shifting in line with NICE Guidelines and thus DAS may be a more appropriate health outcome measure than HAQ (ACD, Section 4.3.11, Page 37). Whilst the issues of HAQ within RA are documented extensively (ceiling effects, insensitivity at upper bounds for changes in quality of life and failing to fully capture treatment benefits ,), the BRAM remains built around this inappropriate health outcome (ACD, Section 4.3.15, Page 40). The Committee was informed that alternative approaches do not exist and that the manufacturers had all submitted models based on HAQ. However, this is misleading. Schering-Plough requests that the Committee considers our patient level model which only draws upon HAQ for a baseline response for conventional DMARDs, in line with NICE's recommended methodology. All relative treatment effects are driven by EULAR response (which is based on DAS). Schering-Plough recommends that the Committee requests a more robust alternative approach to explore appropriate modelling methods submitted by consultees, and which may be more in line with current NICE Guidance and therefore more suited to clinical practice.	The Committee considers all evidence submitted by consultees in its deliberations, including all models submitted by consultees. The Committee considered the Schering Plough model and understood that this model calculated EQ-5D from EULAR response (based on DAS). This has been amended in the FAD. However, the Committee understood that the algorithm used in the Schering Plough model to calculate EQ-5D from EULAR response was, in itself, developed from BSRBR data for EULAR and HAQ, with EQ-5D imputed from HAQ using a mapping exercise (Schering Plough submission page 63, FAD section 4.3.20). Therefore the Committee considered that none of the models used directly elicited EQ-5D data reflecting the preferred NICE approach (methods guide section 5.4.1).

Consultee	Comment	Response
Schering-Plough	**Stopping Rule** "…The [BRAM] was not designed in a way which could incorporate stopping rules based on response criterion…The [BRAM] is most sensitive to changes in assumptions about…the number of people stopping treatment early" (ACD, 4.3.20, Page 44; 4.3.13, Page 39) Four of the manufacturers submitted models that included a stopping rule based on treatment response. A sensitivity analysis conducted by the Assessment Group found that partial incorporation of a stopping rule based on response criterion within the BRAM lowered the ICERs by approximately £10,000 / QALY gained. The Committee found that the BRAM was not able fully to incorporate a response criterion. This coupled with a belief that the use of stopping rules does not reflect current clinical practice led to the Committee's conclusion that this component could not be the basis for decision making. Schering-Plough believes that the Committee's view set out in section 4.3.20 of the ACD is perverse for the following reasons: • Firstly, it is our understanding that the majority of Primary Care Trusts ("PCTs") will audit the use of TNF inhibitors and will require data on response. No evidence that we are aware of has been presented to substantiate the view that there is widespread refusal to stop TNF inhibitor therapy where patients have not responded. • Secondly, the Institute's own guidance as set out in TA130 requires that response to treatment is determined and non-responders are withdrawn from therapy. Modelling cost-effectiveness must therefore take this into account. • Thirdly, it is unacceptable for the Committee to dismiss the relevant cost-effectiveness estimates on the basis that response criteria are only partially incorporated – clearly the appropriate course of action is to demand that the BRAM is amended to allow for this clinically important element of therapy to be fully incorporated, particularly since it appears that cost-effectiveness estimates are likely to be sensitive to this assumption. **Comment continued on next page**	The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22).

Consultee	Comment	Response
Schering-Plough	Weaknesses within the structural aspects of the BRAM need to be addressed rather than dismissed, especially in light of cost-effectiveness arguments for the sole product recommended for sequential use, rituximab being conditional on the inclusion of a stopping rule. In line with previous and ongoing appraisals, NICE recommendations have a notable impact upon prescribing patterns. Indeed, the current appraisal noted the effect of TA 130 guidance on treatment practice based on DAS response and tailored to the specified endpoints recommended in the final guidance. Schering-Plough urges the Committee to re-evaluate the strengths and challenge the shortcomings of the BRAM whilst working to apply solutions which are representative of the clinical practice that they envisage will comprise the best use of NHS resources. This may ultimately mean that the data needs to be re-modelled in line with the Appeal Panel's recommendation above, preferably by a different Assessment Group.	The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22). Please note that the Institute is not responsible for determining the Assessment Group assigned to each appraisal. This is done by the NIHR Evaluation, Trials and Studies Coordinating Centre.
Schering-Plough	**Determining response to treatment in the Schering-Plough model** Section 4.2.12 of the ACD summarises how response to treatment is determined in Schering-Plough's model. The summary provided is somewhat misleading. The first step in the two-step process is more accurately defined as follows: baseline EULAR response data from the BSRBR (from TNF inhibitor experienced DMARD receiving patients) was converted to baseline ACR response using an algorithm derived from the GO-AFTER trial, results from the MTC on the ACR scale were then applied to generate ACR responses for each treatment, these were then converted back to EULAR response rates.	Comment noted. Section 4.2.12 has been amended.

Consultee	Comment	Response
Schering-Plough	**Sub-group analysis: contraindication or intolerance to rituximab** Section 4.3.25 of the ACD states that the Committee considered that it had not been presented with any clinical evidence regarding the use of TNF inhibitors or abatacept in patients for whom rituximab failed or in whom rituximab was contraindicated on not tolerated. However, as set out elsewhere in this response, there is a large body of evidence demonstrating the effectiveness of TNF inhibitors used sequentially. It is not clear why the Committee believes that it requires further specific evidence in relation to patients with for example a contraindication to rituximab, particularly given that it acknowledges that ICERs presented for TNF inhibitors compared with conventional DMARDs are a reasonable proxy for this sub-group analysis. Schering-Plough requests that the Committee reconsiders its assessment of this potential patient group and is more explicit about its rationale for not giving adequate consideration to the potential cost-effectiveness of TNF inhibitors used in these patients.	Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
Schering-Plough	**Subgroups based on the presence of auto-antibodies** The Committee concluded that there was insufficient evidence to make differential recommendations for subgroups based on auto-antibody status. Schering-Plough believes that the Committee has not given adequate consideration to the reduced or absent response of seronegative patients to rituximab. The Committees view appears to have been determined on the basis that there were no statistical differences observed in trials designed with seropositivity as a selection criterion and that were inadequately powered to test a hypothesis regarding this issue. Independent data showing reduced or no responses in patients who are seronegative are available. Schering-Plough believes that the Committee has failed to give adequate consideration to this patient population.	The Committee considered the specific subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).
Schering-Plough	**Relevant safety information not included** As raised and discussed in the previous TAC, concerns exist over the safety profile for rituximab. Schering-Plough urges the Committee fully to consider the risk of PML as detailed within our Assessment Report response (Schering-Plough TAR response, Section 2.1.1, Page 4).	The Committee understood the adverse effects of each of the technologies. The Committee does not make decisions solely on the basis of adverse events. The balance of benefits and harms of a treatment are for the consideration of the regulatory agencies.

Consultee	Comment	Response
Schering-Plough	**Vial Optimisation** Vial optimisation with infliximab in RA has implications on the cost-effectiveness of the technology (see comments in our letter to you dated 12 January 2010). Following the Appeal to TA130, the Committee was instructed to consider an appropriate range of doses for infliximab and to take account of vial wastage. Further, NICE's response to Schering-Plough's comments on the Draft Scope for this appraisal explicitly state that a range of doses will be taken into account. NICE stated: "All included technologies will be appraised as per their respective licensed indications, which will include the alternative dosing schedules for infliximab. No changes made to the scope." The failure to take account of vial optimisation is unfair and outside the Final Scope given the comments above. In its addendum to the Assessment Report, the Assessment Group notes that "In any case all [sic] any savings from vial sharing are dwarfed by dose escalation. In the cited systematic review 44% of patients treated with infliximab had the drug dose increased." This is apparently a justification for not accounting for vial optimisation in the economic evaluation. In relation to this, we would like to raise two fundamental issues – firstly, the evidence presented for dose escalation and the extent to which it "dwarfs" vial sharing is sourced from outside the UK – the majority of studies were from the USA and all studies were published between 1998 and 2002; secondly TA130 recommends against dose escalation and an economic evaluation to determine the effective use of NHS resources ought to reflect this. Further, a recent update to the research conducted by Schering-Plough, with a higher response rate (57%) compared to that referred to by the Assessment Group, confirms similar findings to those reported in our original submission and research – i.e. that around two thirds of patients receive infliximab which has been prepared using vial optimisation.	The boundaries of an appraisal are defined by the final scope and not by the responses to the comments on the draft scope. The response to the draft scope reflects the consideration of dose escalation (that is, a response to the comment by Schering Plough about consideration of a wider range of doses of infliximab). Guidance on vial optimisation is not reflected in the marketing authorisation. The report by the Assessment Group is not the only evidence that informs that Appraisal Committee's consideration of a technology under appraisal. The Schering Plough model assumed a proportion of vial optimisation. The Schering Plough model was considered by the Committee. The Committee did not consider that the results of the other economic models altered its conclusions about the use of the technologies in the NHS (See FAD sections 4.3.13, 4.3.18, 4.3.25).

Consultee	Comment	Response
Schering-Plough	**Conclusion** The preliminary recommendations by the Committee do not take into account all of the available evidence to inform this appraisal. Manufacturers were not given the opportunity to comment on the Addendum Report which misinterprets much of the evidence and misinforms the Committee. Sufficient clinical evidence exists for the Committee to form a recommendation for the sequential use of TNF inhibitors for the treatment of RA. Given the considerable attention that has been paid to identifying all potential sources of evidence for sequential therapy during the course of TA130 and the Appeal Hearing of 29 September 2008 regarding sequential use of TNF inhibitors, it is unfair and perverse to assess biologic DMARDs without the inclusion of all of the available evidence for potentially relevant comparators, particularly given the fundamental flaws and lack of transparency over the BRAM model. Based on the concerns raised above, Schering-Plough questions the validity of the conclusions reached by the Committee within the ACD and believes that substantial adjustments, if not a complete re-modelling, are needed by this Assessment Group or a different Assessment Group for the appraisal to reflect clinical evidence and fully inform the Committee. We are grateful for the opportunity to comment on the ACD and the Addendum Report and look forward to continued dialogue with NICE regarding the issues raised in this response. Please do not hesitate to request any additional data from us which may be of use during this appraisal. **Appendices included but not reproduced here.**	Comment noted. Please see the responses to the individual comments above.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
	No comments received.	

Comments received from commentators

Commentator	Comment	Response
UCB Pharma	***Key point summary included but not reproduced here*** **1.1 Context** NICE has produced draft guidance on using adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor in the NHS in England and Wales, in the form of an appraisal consultation document (ACD). A key conclusion in the ACD is that "The TNF inhibitors adalimumab, etanercept, and infliximab are recommended for the treatment of rheumatoid arthritis after the failure of a previous TNF inhibitor only in the context of research." This decision is driven by two key factors: 1) The lack of clinical effectiveness data for the TNF inhibitors in this stage of the treatment pathway and the resulting uncertainty in the ICERs. 2) ICERs for the TNF inhibitors compared with rituximab that were either very high or dominated by rituximab. This document serves to provide comments on the ACD, in particular a response to the question "Has all of the relevant evidence been taken into account?" While Certolizumab pegol (CERTOLIZUMAB®) is not included as an intervention in the ACD (due to licensing after the MTA scope had already been developed), it is UCB's position that the draft guidance does not take all the relevant evidence into account. Specifically, the ACD does not account for the fact that the cost-effectiveness of anti-TNFs after failure of a previous anti-TNF is greatly improved by a situation where there is no drug acquisition cost to the NHS for non-responders to the given anti-TNF, as is the case with certolizumab. When the patient access scheme (PAS) currently in place for certolizumab is accounted for, the use of certolizumab as a second-line anti-TNF is cost-effective, and furthermore eliminates the financial impact of any uncertainty around clinical effectiveness because the NHS would not pay for non-responders to treatment.	Comments noted. The Committee discussed the inclusion of certolizumab pegol as a comparator in this appraisal (see FAD section 4.3.5). Certolizumab pegol was subject to its own single technology appraisal (see NICE technology appraisal guidance 186). It was therefore not subject to appraisal by the Committee in this instance. It was included as a comparator in the scope of this appraisal, but the Committee is unable to make recommendations about comparators. The guidance in this appraisal relates only to the use of adalimumab, etanercept and infliximab and not to the TNF inhibitors more generally. TA186 for certolizumab pegol does not make recommendations about sequential use. In the absence of recommendations the use of certolizumab pegol after the failure of a first TNF inhibitor is subject to local decision making.

Commentator	Comment	Response
UCB Pharma	**1.2 NICE recommendation of certolizumab pegol** Certolizumab pegol (CERTOLIZUMAB®, CZP) was recommended for use in the NHS by NICE in February 2010 (TA 186) for the treatment of rheumatoid arthritis after inadequate response to conventional DMARDs (i.e., first-line biologic DMARD use). As an antibody against TNF-α, certolizumab is in the same therapeutic class as three of the other drugs considered in this appraisal, namely adalimumab (ADA), infliximab (IFX) and etanercept (ETA). Response to certolizumab can be determined by week 12 of treatment, at which point non-responders can be taken off certolizumab.1 A novel patient access scheme (PAS) for Certolizumab was approved by the Department of health in September 2010 and is currently in place. Under this scheme the first 12 weeks (10 vials) are provided by UCB free of charge to the NHS. Importantly, the PAS when combined with the 12 week clinical effectiveness decision time point results in non-responders to certolizumab incurring no drug acquisition cost to the NHS.	Comments noted. The Committee discussed the inclusion of certolizumab pegol as a comparator in this appraisal (see FAD section 4.3.5). Certolizumab pegol was subject to its own single technology appraisal (see NICE technology appraisal guidance 186). It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5). It was included as a comparator in the scope of this appraisal, but the Committee is unable to make recommendations about comparators. The guidance in this appraisal relates only to the use of adalimumab, etanercept and infliximab and not to the TNF inhibitors more generally. TA186 for certolizumab pegol does not make recommendations about sequential use. In the absence of recommendations the use of certolizumab pegol after the failure of a first TNF inhibitor is subject to local decision making.
UCB Pharma	**1.3 Certolizumab in second-line use - economic modelling methodology** As certolizumab was not yet licensed at the time the scope of the current MTA was developed, it was not included as an intervention in the current MTA. In order to consider the impact the inclusion of certolizumab would have on the MTA findings, UCB has evaluated the cost-effectiveness of certolizumab in the second-line setting by adapting the certolizumab model submitted to NICE as part of the single technology appraisal process (TA 186). This model has been rigorously evaluated by NICE and formed a key part of the evidence which led to the approval of certolizumab for use on the NHS; we therefore consider this an appropriate model on which to base our analysis of the cost-effectiveness of certolizumab. In the original model on which the positive NICE recommendation was based, patients discontinuing on first-line anti-TNF therapy moved on to a sequence of follow-up therapies, beginning with sulfasalazine. We have modified this model so that patients discontinuing on first-line anti-TNF therapy instead move on to a second anti-TNF.	Comments noted. The Committee discussed the inclusion of certolizumab pegol as a comparator in this appraisal (see FAD section 4.3.5). Certolizumab pegol was subject to its own single technology appraisal (see NICE technology appraisal guidance 186). It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5). It was included as a comparator in the scope of this appraisal, but the Committee is unable to make recommendations about comparators. The guidance in this appraisal relates only to the use of adalimumab, etanercept and infliximab and not to the TNF inhibitors more generally. TA186 for certolizumab pegol does not make recommendations about sequential use. In the absence of recommendations the use of certolizumab pegol after the failure of a first TNF inhibitor is subject to local decision making.

Commentator	Comment	Response
UCB Pharma	**1.4 Results of modelling certolizumab as a second-line biologic** The BRAM model evaluates a patient population in second line treatment and thus does not include consideration of first-line treatments. In contrast, the certolizumab model incorporates a choice of first-line treatments. Results of the cost-effectiveness of second-line treatment are therefore presented in four ways, each considering a different first-line anti-TNF: (etanercept (ETA), adalimumab (ADA), infliximab (IFX), and certolizumab (CZP). **Second line use of anti-TNFs vs. cDMARDs – table 1** The results in Table 1 below indicate that regardless of the first-line therapy used, in second line use the ICER for certolizumab vs cDMARDs (range: £15,500 to £16,300) is lower than the ICERs for all the other three anti-TNFs vs cDMARDs (range: £19,000 to £46,000). It should be noted that the results from the CERTOLIZUMAB model differ in magnitude from the results presented in the independent Assessment Group model, however the order and pattern of results are the same, with infliximab being the least cost-effective second-line treatment and rituximab being the most cost-effective second-line treatment. ***Table included but not reproduced here***	Comments noted. The Committee discussed the inclusion of certolizumab pegol as a comparator in this appraisal (see FAD section 4.3.5). Certolizumab pegol was subject to its own single technology appraisal (see NICE technology appraisal guidance 186). It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5). It was included as a comparator in the scope of this appraisal, but the Committee is unable to make recommendations about comparators. The guidance in this appraisal relates only to the use of adalimumab, etanercept and infliximab and not to the TNF inhibitors more generally. TA186 for certolizumab pegol does not make recommendations about sequential use. In the absence of recommendations the use of certolizumab pegol after the failure of a first TNF inhibitor is subject to local decision making.

Commentator	Comment	Response
UCB Pharma	**Second line use of anti-TNFs vs. rituximab – table 2** Similarly, the results indicate that regardless of the first-line therapy used, in second line use the ICER for CZP vs rituximab (range: £31,000 – 35,000) is lower than the ICERs for all the other three anti-TNFs vs rituximab (range: £400,000 to dominated). It should be noted that the results presented above only consider a 6-month stopping rule. If a 3-month stopping rule is employed with certolizumab rather than a 6-month stopping rule, non-responders to certolizumab would come off treatment earlier, making the results more favourable towards certolizumab than those presented above. As has been outlined, certolizumab efficacy can be assessed at 3 months (12 weeks) and so no patients would progress and then fail at 6 months. All the other TNFs have a 6-month initial review period.1, 2 These results have not been presented here as we have only modelled the PAS as a cost saving option over the first three months. This has been done to allow proper comparison between each TNF inhibitor option. If we had applied a 3-month stopping rule to certolizumab and a different 6-months stopping rule to the other TNF inhibitors, the QALY for certolizumab would improve, the cost base would reduce and the ICER for certolizumab against the other TNF inhibitors would be further improved. ***Table included but not reproduced here***	Comments noted. The Committee discussed the inclusion of certolizumab pegol as a comparator in this appraisal (see FAD section 4.3.5). Certolizumab pegol was subject to its own single technology appraisal (see NICE technology appraisal guidance 186). It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5). It was included as a comparator in the scope of this appraisal, but the Committee is unable to make recommendations about comparators. The guidance in this appraisal relates only to the use of adalimumab, etanercept and infliximab and not to the TNF inhibitors more generally. TA186 for certolizumab pegol does not make recommendations about sequential use. In the absence of recommendations the use of certolizumab pegol after the failure of a first TNF inhibitor is subject to local decision making.

Commentator	Comment	Response
UCB Pharma	**1.5 Conclusions** 1. There is limited clinical trial data investigating use of second-line biologic DMARD therapy after failure on first-line biologic therapy. As acknowledged within this appraisal, this lack of evidence leads to considerable uncertainty in decision-making. 2. However, as discussed by clinical specialists and acknowledged by the committee, the efficacy of follow-up conventional DMARD therapy after failure on a biologic is limited, and there is therefore an unmet need for effective therapy in this setting (4.3.10). 3. The economic evaluation performed by the Assessment Group indicated considerable uncertainty as to whether infliximab, etanercept and adalimumab were cost-effective, due to either to high ICERs, or to considerable uncertainty in the results. 4. The introduction of certolizumab with the associated patient access scheme (PAS) overcomes the concerns around cost-effectiveness of second-line usage. With the PAS, ICERs for the anti-TNFs were within recognised standards of cost-effectiveness. Furthermore, the ICERs for certolizumab were lower than those of the other anti-TNFs. 5. The PAS overcomes uncertainty in the clinical and economic data because patients who do not respond to second-line anti-TNF therapy with certolizumab by week 12 should discontinue treatment. This is included within the treatment period covered by the PAS, and means that the NHS will not pay for non-responders. The uncertainty over lack of trial data is mitigated by ensuring that failed patients have no drug acquisition cost to the NHS, allowing certolizumab to be considered a cost effective therapy as a follow on TNF inhibitor. ***Appendix included but not reproduced here***	Comments noted. The Committee discussed the inclusion of certolizumab pegol as a comparator in this appraisal (see FAD section 4.3.5). Certolizumab pegol was subject to its own single technology appraisal (see NICE technology appraisal guidance 186). It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5). It was included as a comparator in the scope of this appraisal, but the Committee is unable to make recommendations about comparators. The guidance in this appraisal relates only to the use of adalimumab, etanercept and infliximab and not to the TNF inhibitors more generally. TA186 for certolizumab pegol does not make recommendations about sequential use. In the absence of recommendations the use of certolizumab pegol after the failure of a first TNF inhibitor is subject to local decision making.
NHS Quality Improvement Scotland – Expert 1	There is a paucity of good evidence for the anti-TNF agents in this context. There is uncontrolled evidence of the efficacy or RXB in combination with other DMARDs (e.g. Valleala et al. Scand J of Rheum 2009; 38: 323-7). This evidence could be used to support the use of RXB for patients who are intolerant of MTX.	Comment noted. Rituximab is currently licensed only in combination with methotrexate. The Committee is unable to make recommendations about the use of technologies outside of their current marketing authorisation. (See section 6.1.8 of the NICE methods guide).

Commentator	Comment	Response
NHS Quality Improvement Scotland – Expert 1	*Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?* Emerging data from abstracts suggest that RXB is more effective when given at regular 6 month intervals. This would change the cost-analysis. Unfortunately this data is not yet available in peer reviewed journals as far as I am aware. *Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations*? In addition, the SPC advises that RXB can be repeated at 4 months. The recommendation is therefore illogical to restrict it to 6 months if the patient has a good initial response but then flares. Current data suggest that response improves with subsequent infusions. It should therefore be possible to repeat the RXB at 4 months for the second infusion only. Subsequent infusions could then be repeated at 6 months or later.	The Committee discussed evidence for rituximab retreatment intervals available from the SUNRISE trial. It concluded that while 8.7 months between treatments may be an over estimate of the re-treatment interval, it would not be the case that every person required rituximab re-treatment every 6 months (see FAD section 4.3.21). The Committee is able to make recommendations within the marketing authorisation that enable a cost effective use of the technology. It concluded that rituximab could be considered cost effective as long as infusions were not required more frequently than every six months. (see FAD section 4.3.21)
NHS Quality Improvement Scotland – Expert 1	*Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound?* I consider these recommendations to be unsound because they do not take into sufficient consideration the opinions of clinical specialists who are highly experienced in the management of patients with RA. It is accepted that there is an inadequate research basis on which to make this recommendation and because of this, greater weight should have been placed on best practice. In addition the recommendation is already out of date because it does not take into consideration Tocilizumab (TOC). If this recommendation is to go forward it should be with a predetermined short review date so as to be able to incorporate emerging data on the use of Rituximab in seropositive vs seronegative patients as well as the placing of TOC in the pathway.	The Committee considered all of the evidence submitted, which included statements from clinical specialists and patient experts. In addition patient exerts and clinical specialists attended the Committee meeting to provide expert advice (see FAD sections 4.3.2 – 4.3.4). Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5)..

Commentator	Comment	Response
NHS Quality Improvement Scotland – Expert 1	*Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland?* The pathways suggested in this appraisal would restrict treatment for patients in Scotland. At present it is possible to switch patients from one TNF treatment to another and all of us are very aware of the numbers of patients that benefit from the switch. Tocilizumab is also now available in Scotland and thus patients who fail one TNF are likely to be tried on either TOC or RXB. In view of the, albeit limited, suggestion that seronegative patients do not respond so well to RXB, it is likely that clinicians will try TOC instead.	Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5).
NHS Quality Improvement Scotland – Expert 1	*Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be.* The pathways would be changed for patients in Scotland. The current guidance in Scotland allows patients to receive either a second anti-TNF agent or RXB after initial failure of one TNF for whatever reason.	Comment noted. No action required.
NHS Quality Improvement Scotland – Expert 1	*Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.* This guidance would represent a backward step for patients in Scotland and my opinion should not be adopted.	Comment noted. No action required.
NHS Quality Improvement Scotland – Expert 2	*Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?* I would consider that the relevant evidence has been considered. It is noted that there are few RCTs and that the observational data do not allow conclusions to be reached with certainty	Comment noted. No action required.

Commentator	Comment	Response
NHS Quality Improvement Scotland – Expert 2	*Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations*? I agree that the main conclusion, that Rituximab is a cost effective option following anti TNF failure is a reasonable interpretation of the clinical and cost effective evidence presented. There is clearly great uncertainty regarding the magnitude of effect of a biologic agent against conventional DMARD and this uncertainty leads to the conclusion that other anti TNFs should not be used outwith a clinical trial environment. This is a fair conclusion, but a scenario based on conventional DMARD having efficacy equivalent to placebo could lead to ICERs that might be acceptable in a Scottish context. In Scottish practice the choice of "untried" conventional DMARD is likely to be largely restricted to those agents considered to be of least utility and infrequently prescribed in modern practice	The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations.
NHS Quality Improvement Scotland – Expert 2	*Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound?* The provisional recommendations are sound as basis of guidance, though it needs to be recognised that not all technologies have been included in this appraisal	Comment noted. Tocilizumab, certolizumab and golimumab are subject to their own appraisals. They were not therefore subject to appraisal by the Committee in this instance (see FAD section 4.3.5).
NHS Quality Improvement Scotland – Expert 2	*Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland?* The treatment pathways will differ in Scotland primarily due to the availability of Tocilizumab which has not been considered in this appraisal. It is currently accepted for use for DMARD failure and TNF failure, so could fit into the pathway before the first anti TNF or after. In reality, it is likely that it will be used primarily after both anti TNF and Rituximab (personal opinion). In addition the ORBIT study (starting 2010) will mean that some individuals will receive Rituximab before anti TNF, which would alter the sequence	Comment noted. Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5).

Commentator	Comment	Response
NHS Quality Improvement Scotland – Expert 2	*Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be.* At present, Scottish clinicians will often opt to use a second anti TNF agent on the grounds that the effectiveness of this approach is accepted. The implementation of this guidance would change this practice although it may be that the recent availability of Tocilizumab will already be reducing the extent to which "switching" between anti TNFs is practiced. The greater use of infusions (Rituximab and Tocilizumab) as opposed to subcutaneous agents that will likely result may be problematic for Rheumatology units in Scotland where there is often limited physical capacity and human resource	Comment noted. No changes required to the guidance document.
NHS Quality Improvement Scotland – Expert 2	*Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.* Responses to Q5 and Q6 will affect implementation	Comment noted. No action required.
NHS Quality Improvement Scotland – Expert 2	*Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment* It might be worth commenting on "stopping rules" which are discussed in the ACD. In general, stopping rules are adhered to in Scottish practice, though with varying degrees of rigour depending *inter alia* on whether viable options are available. Expert comment has indicated that there is little confidence in the use of "untried conventional DMARD" in this context. If an individual patient may only receive a maximum of 2 out of the range of biologic agents now licensed for use, it is likely that stopping rules will be less rigorously applied. Again the availability of a 3rd biologic in Scotland might mitigate this	The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22).

Commentator	Comment	Response
NHS Quality Improvement Scotland – Expert 3	*Do you consider that all the relevant evidence has been taken into account?* Yes *Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence?* I continue to have reservations about the BRAM model, particularly with respect to: • Its' failure to incorporate stopping rules into the model. Whilst there is some evidence from the BSRBR that some patients continue on treatment despite a failure to respond, these data are 1) limited by the nature of the BSRBR, which was not designed to collect disease activity or drug response data 2) of questionable relevance – the Committee questions whether the application of response criteria would be 'reflective of clinical practice' (p44). I would submit that the Committee should assess the cost effectiveness of therapy according to best practice. Experience of clinicians around the country shows that PCTs and HBs are increasingly auditing the use of anti-TNF carefully, and that drug continuation in the absence of response will be increasingly rare. • Its over-optimistic assessment of the value of DMARD therapy in patients who have failed biologic therapy. The Committee recognise that the BRAM model probably over-estimates the magnitude of response to conventional DMARDs but it has not explored the issue of treatment longevity with conventional DMARDs. The assumptions about the duration of benefit from conventional DMARDs used by the BRAM model are not credible.	Comments noted, no actions required. The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22). The Committee considered that the assumed 50% reduction in efficacy of conventional DMARDs to be an underestimate of the reduction in efficacy, when conventional DMARDs are used in established as opposed to early disease. However, it did not accept that there would be no effect at all associated with therapy (see FAD sections 4.3.12 and 4.3.23). The Committee considered the ICERs reflecting a greater reduction in conventional DMARD efficacy in their deliberations.

Commentator	Comment	Response
NHS Quality Improvement Scotland – Expert 3	*Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?* Not, in my opinion, for the following reasons: • The Committee only considered anti-TNF therapy or abatacept as alternatives to rituximab. The conclusion that rituximab is the most cost-effective option for patients who fail anti-TNF therapy is probably correct, but a significant proportion of patients will fail to respond to rituximab. Leaving such patients without an option for further biologic therapy will generate significant unmet need and this will be associated with considerable personal hardship and suffering for the patients involved. • The Committee has given insufficient attention to that sub-group of patients which responds very well to therapy. The ICER for each of the drugs changes dramatically if the stopping rules change – so for instance, if patients were required to have a larger response in order to stay on treatment (for example by achieving a DAS28<3.2) it is probable that this would represent cost effective treatment. The evidence suggests that some patients do respond very well, for example, to abatacept following failure of an anti-TNF drug and the Committee should explore a risk-sharing scheme with the companies involved such that patients would be granted a trial of therapy free of charge, with the NHS only paying for subsequent therapy in patients with a good response.	Following the consultation on the preliminary guidance the recommendations have changed. For those who are contraindicated to either rituximab or methotrexate or require rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28). The Committee heard from clinical specialists that although implementing stopping rules could be difficult, clinicians were increasingly following guidance on stopping rules. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness (see FAD section 4.3.22). It is not within the Committee's remit to engage in price negotiation (including the initiation of a patient access scheme). The manufacturer may submit a patient access scheme to the Department of Health.
NHS Quality Improvement Scotland – Expert 3	*Are the patient pathways and treatment options described in the assessment applicable to NHSScotland?* Yes, although tocilizumab is also approved for use in NHS Scotland in patients who fail anti-TNF therapy.	Comments noted. Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5).

Commentator	Comment	Response
NHS Quality Improvement Scotland – Expert 3	*Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland?* The total number of patients on anti-TNF therapy will grow less quickly if patients could not be switched from one drug to another, and the use of rituximab and tocilizumab is likely to grow correspondingly faster. *Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales?* No *Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment* No comment	Comment noted. No action requested.
NHS Quality Improvement Scotland – Expert 4	*Do you consider that all the relevant evidence has been taken into account?* Yes, although the available evidence is limited.	Comment noted. No action requested.
NHS Quality Improvement Scotland – Expert 4	*Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence?* Yes	Comment noted. No action requested.
NHS Quality Improvement Scotland – Expert 4	*Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?* The appropriate RCTs have been reviewed under the terms of reference set out by NICE.	Comment noted. No action requested.
NHS Quality Improvement Scotland – Expert 4	*Are the patient pathways and treatment options described in the assessment applicable to NHSScotland?* There is a major difference in treatment pathways available in Scotland in that the SMC has passed tocilizumab (anti-IL 6 therapy) for use after one DMARD failure in RA.	Comment noted. Please note this appraisal does not include a recommendation regarding the use of tocilizumab. Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5).

Commentator	Comment	Response
NHS Quality Improvement Scotland – Expert 4	*Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland?* Please see below.	Comment noted. No action requested.
NHS Quality Improvement Scotland – Expert 4	*Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales?* Potentially, yes. As rheumatologists in Scotland are able to use tocilizumab early in the treatment pathway for RA, the patient population of TNF failures in Scotland is likely to represent a group of patients with more resistant disease, compared to the population of patients considered in the ACD ie patients in Scotland who fail anti-TNF therapy may have already failed anti-IL 6 therapy (and thus two biologic agents), compared to the NICE population, who will only have failed anti-TNF therapy. The role of a second anti-TNF drug in patients who have already failed two biologics has not, to the best of my knowledge, been subject to rigorous study.	Comment noted. Please note this appraisal does not include a recommendation regarding the use of tocilizumab. Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5).
NHS Quality Improvement Scotland – Expert 4	*Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment.* No further comments.	Comment noted. No action required.

Commentator	Comment	Response
Arthritis Research UK	Having read this I find the health economic arguments difficult to follow. However, from the academic perspective the main comment I have is that they have not referred to the 'GO-AFTER' study or ATTEST study (both attached). GO-AFTER was an RCT in which patients who had 'failed' MTX were randomised to either placebo or one of two doses of golimumab. Although golimumab is not NICE approved, I think the results of this study could be extrapolated to other mAb TNF inhibitors. 39,19 and 11% of patients achieved ACR 20, 50 and 70 at 24 weeks compared to 17, 5 and 3% of PBO patients. Although these numbers look quite low, patients did not need to be taking MTX and acute phase response could be normal at baseline. I guess this makes the study difficult to compare to the RTX and ABA studies after anti-TNF. (Incidentally, I cannot understand how this paper made it into the Lancet). The other arguably relevant paper is the ATTEST study (also attached). This was a study of abatacept or infliximab vs PBO. It was not a head-to-head of abatacept vs infliximab but patients were randomised to either drug or PBO (3:3:2). At one year both drugs were superior to PBO. Abatacept patients fared numerically better than INF patients (across all domains, including HAQ-DI) and had fewer AEs and SAEs. Although these were MTX IRs, one could argue that the INF arm would have performed relatively worse if this had been a TNF-IR study. Thus, whilst not a head-to-head, the therapeutic ratio looked somewhat better for abatacept. Whilst neither of these papers address exactly the appropriate populations I would argue that they are of relevance to the consultation and should at least have been referred to. I hope this is helpful	Comments noted. Please note that a table which summarizes the Committee's key conclusions (including those related to health economics) is included at the end of the document. The Committee considered the results of the GO-AFTER RCT in its deliberations. It considered whether the results for golimumab from this study could be applied to the other TNF inhibitors (see FAD section 4.3.7). A key uncertainty in the appraisal relates to the efficacy of adalimumab, etanercept and infliximab after the failure of a first TNF inhibitor. The ATTEST study included patients with no history of treatment with abatacept or TNF inhibitor therapy, and for whom treatment with methotrexate had provided an inadequate response. It therefore did not represent the appropriate patient group for this appraisal.

Commentator	Comment	Response
Department of Health	Thank you for the opportunity to comment on the Appraisal Consultation Document for the above health technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted.

Comments received from members of the public

Role*	Section	Comment	Response
Patient 1	1	As a patient it is currently a lottery whether the anti-TNF you try first will be the one that helps you. In my experience there is a very different response to different anti-TNF?s and to Rituximab and there is no way to know which will be successful in advance. NICE?s decision to limit the opportunity to try more than one anti-TNF In point 4.1.makes treatment a lucky dip.	The Committee understood that rheumatoid arthritis is heterogeneous, that different people can respond differently to the same treatment and that currently it is difficult to predict whose disease will respond to a given treatment (see FAD section 4.3.3). Following the consultation on the preliminary guidance the recommendations have changed. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
Patient 1	1	Clearly there is a problem about research to justify costs of trying different anti-TNFs. Surely the information already exists in every consultant's case files. Why is it not possible to collect and analyse this existing information and to offer alternative anti-TNF?s to patients while instituting proper, uniform data collection. This would mean patients in category 1.4. would not have to suffer for another three years while waiting for someone to institute the research NICE wants.	The Committee can only consider evidence which consultees identify and submit to it. The Committee considered all of the evidence submitted, which included statements from clinical specialists and patient experts. (see FAD sections 4.3.2 – 4.3.4). Following the consultation on the preliminary guidance the recommendations have changed. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options. The guidance no longer includes an only in research recommendation (see FAD section 1).
NHS Professional 1	1	Patients with severe RA have very significant morbidity, disability, poor quality of life and increased mortality. This disease is so bad we should allow them more than one chance to improve their disease control. If NICE recommendations are followed these patients with the most severe disease will be left without any form of treatment once they have failed one anti-TNF therapy and Rituximab. This is unethical when there are available treatemts that have been proven to work. Rituximab should be available as an alternative to anti-TNF therapies in patients who have failed conventional DMARDs (without the requirement of failing an anti-TNF therapy first. The response to Rituximab is of a similar order to anti-TNF therapies, the mode of and frequency of delivery suits certain patients better than self injections or 8 weekly infusions and it is cheaper.	The Committee recognised the impact of rheumatoid arthritis on patients (see FAD sections 4.3.2). Although NICE accepts that individual NHS users will expect to receive treatments to which their conditions may respond, this does not impose a requirement on the Committee to recommend technologies that are not cost effective enough to provide the best value to users of the NHS as a whole (see 'Social Value Judgement – Principles for the development of NICE guidance; principle 5) The Committee can only appraise technologies within their licensed indications. At present, rituximab does not have a marketing authorisation for use after the failure of conventional DMARDs.

Role*	Section	Comment	Response
NHS Professional 1	2	A DAS 44 would be a better scoring system to use as the DAS 28 discriminates against patients who mainly have lower limb disease (i.e. foot, ankle and knee involvement)	The guidance states that when assessing DAS28, healthcare professionals should take account of any physical, sensory or learning disabilities, communication difficulties or disease characteristics that could adversely affect patient assessment and make any adjustment they consider appropriate. If a clinician considered that a patient had a greater burden of lower limb disease that would not be reflected in DAS28 then adjustments to the assessment tool should be made (see FAD section 1.5).
NHS Professional 1	4	The REFLEX trial should not have been excluded from review -why was a placebo controlled trial excluded?	The REFLEX trial was not excluded from review. The Committee considered the results of the REFLEX trial in its deliberations (see FAD sections 4.1.6, 4.3.16, 4.3.21)
NHS Professional 1	7	NICE appear to have moved the goal posts when assessing the use of Tocilizumab in RA (in comparison to their reviews of anti-TNF therapies). The efficacy is virtually identical to that of anti-TNF therapies, the cost is the same, SEM have approved it so why have NICE refused it? For those with the very worst RA not responsive to anti-TNF therapy it is a very good additional possible treatment and should be available. I have seen people with extremely severe RA who are unable to work and have carers because of the severity of their disease and who have failed anti-TNF therapies go into remission and go back to work having been treated with Tocilizumab. These must be individuals where interleukin 6 is driving their disease rather than TNF.	Please note this appraisal does not include a recommendation regarding the use of tocilizumab. Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5).
Patient 2	1	As a patient I was not allowed to upgrade to Rituximab without first trialing methotrexate which I then suffered side affects. The Llefnomide which was introduced at the same time as methotrexate was not taken into consideration which I have been taking since the clinical trials were processed.	Comment noted. Rituximab is licensed for use after the failure of DMARDs including a TNF inhibitor. NICE can only make recommendations for technologies within their marketing authorisation. NICE guidance recommends rituximab as an option in the context of its marketing authorisation.

Role*	Section	Comment	Response
Patient 2	2	Need more atention to the cause of flare-ups which can be brought on by pressure, physical or mental. More information to the patient to cope with arthritis involving pain and exercise	Comment noted. The section 2 of the document provides background information only. Technology appraisals guidance provides recommendations to the NHS about the clinical and cost effectiveness of technologies. It is outside of the scope of a technology appraisal to provide guidance to patients on managing rheumatoid arthritis. This is more appropriately considered as part of a clinical guideline.
Patient 2	4	Prevention is always better than cure and is also more cost effective. Suspected R.A. should be nipped in the bud at the earliest signs without a postcode lottery . This could save millions	Comment noted. This appraisal considers treatments used for established rheumatoid arthritis, after the failure of conventional DMARDs and a TNF inhibitor. The remit for this appraisal did not address the treatment of early rheumatoid arthritis.
Patient 2	5	More information should be given to the general public in laymans terms which can be passed via voluntary groups or workshops	Comment noted. When the guidance is published NICE will also publish a summary of the recommendations for patients.
Patient 2	7	As above but not everyone is pc literate	Comment noted. No actions required to the guidance document.
Patient 2	8	Autumn 2010	The current date for consideration of review (May 2013; see FAD section 8) reflects the standard length of time for guidance to remain in place prior to consideration for review. Consultees can request review prior to this date if further data that may affect the decision become available.

Role*	Section	Comment	Response
NHS Professional 2	1	I believe there is sufficient evidence to support the use of a second anti-TNF agent where one has failed. I have a number of patients with severe RA that have responded to one agent and not to another. These patients have severe disease and should be given the maximum opportunity to try available treatments. There is still a lot we dont know about disease sub-groups within RA that respond differently to different agents - it may be that in the future we are able to target treatments based on the patients pharmacogenetic profile. But until then we need to try the different agents to find one that works for an individual patient.	The Committee recognised that not everyone will respond to the same treatment (see FAD sections 4.3.2, 4.3.3) Although NICE accepts that individual NHS users will expect to receive treatments to which their conditions may respond, this does not impose a requirement on the Committee to recommend technologies that are not cost effective enough to provide the best value to users of the NHS as a whole (see 'Social Value Judgement – Principles for the development of NICE guidance; principle 5)
NHS Professional 2	1	We conducted an audit and found that 50% of patients had stopped their first anti-TNF within 6 months. This demonstrates an important need for considering options after failure of one anti-TNF. We have demonstrated that different anti-TNF agents work through different mechanisms and therefore it seems logical to at least try one other ant-TNF after failure of first anti-TNF. For patients who are rheumatoid factor this guidance means that there are no therapeutic options after failure of anti-TNF since rituximab is not generally effective in patients who are rheumatoid factor negative.	The guidance recommends the use of rituximab after the failure of a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The Committee considered the specific subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Role*	Section	Comment	Response
NHS Professional 2	1	This document would be much more useful if it included guidelines for newer drugs also: tocilixumab and certiluzumab (perhaps also golimumab) are or will be competing for this same market. What status will they have if not included?	Certolizumab pegol was subject to its own single technology appraisal (see NICE technology appraisal guidance 186). Certolizumab pegol is recommended as an option for the treatment of people with rheumatoid arthritis in the same way as the other tumour necrosis factor (TNF) inhibitor treatments in NICE technology appraisal guidance 130 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis'. Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5).

Role*	Section	Comment	Response
Patient 3	1	I have had RA since 1979 onset at age 13. I am extremely concerned at the limitations this guidence will cause in the treatment available to manage this awful disease. I urge NICE to reconsider this devastating decison and ask that a more favourable guidence can be drawn up. I cannot understand that out of the 7 currently licensed & available biologic therapies, I and other RA patients will be allowed only one chance at a TNF. I read that possibly two chances may be available if I/we can go onto a research programme. However I also undertand that the biologics register is closed to new patients so rules out this chance and the likelihood of finding myself in an area with a research programme in reality rules out any chance of being offered a 2nd anti TNF treatment. So in effect if my one treatment fails my only chance of a therapy that may help is then Rituximab. I will have no opportunity to try any of the other available therapies that NICE will not approve. This is not and cannot be acceptable. I/We need access to more therapies such as Tocilizumab and abatacept. Why are RA pateints to be treated differently then crohns patients? I understand that 2 TNFs + maintenance dose are allowed and it is left to clinical judgement? Why is it acceptable to limit us to one try of Anti TNF but acceptable to allow another group of patients with auto immune disease the chance of a 2nd? Why are our clinicians not allowed the same freedom to exercise clinical judgement in the use of TNF therapy	Following the consultation on the preliminary guidance the recommendations have changed. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options. The guidance no longer includes an “only in research” recommendation (see FAD section 1). The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28). Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5). NICE guidance for Crohn’s disease recommends infliximab and adalimumab as alternatives. It does not make recommendations about the use of these two agents sequentially.

Role*	Section	Comment	Response
Patient 3	1	Please can you consider when deciding on these guidelines that RA is not one disease but involves different sub-groups. Mine is RF+ and is an aggressive progressive disease. I and other RA patients react differently to different therapies, and when going onto anti TNF therapy I/we cannot know, at this time, which therapy will work for us. By denying the opportunity to try the available treatments I and others like me are potentially destined to return to the use of DMARDs/steroids that have failed us.	The Committee considered two subgroups in this appraisal: subgroups based on antibody status (including rheumatoid factor), and subgroups based on reason for withdrawal of the first TNF inhibitor. The Committee recognises the severity of the disease and the need in this population (see FAD section 4.3.2 and 4.3.3). However, for both legal and bioethical reasons, those undertaking technology appraisals must additionally take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).
Patient 3	1	I have had 30 years of living with RA, the pain, the joint damage, the gradual erosion and loss of the ability to function and perform normal everday tasks and the numerous and painful joint operations. The growing expense of buying equipment, moving into suitable accommodation, having to buy automatic cars, loss of income etc. Believe me,I know all about the cost of RA. To see these new therapies and treatments being developed, but seeing them denied to RA patients is devasting. Therefore again, I urge you to reconsider this latest guidence decision.	Following the consultation on the preliminary guidance the recommendations have changed. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).

Role*	Section	Comment	Response
NHS Professional 3	2	I am dismayed to understand that our patients with RA once they have failed one Anti-TNF will not be allowed to try another except in the context of a drug trial. I was involved in the recent NICE review of Certolizumab which I think got a fair hearing. We presented all the data on why additional drugs was needed then. Thus it is discouraging that you now appear to be saying that patients will not be able to use them.	NICE recommended the use of certolizumab in the same context as it recommends the other TNF inhibitors, that is, after the failure of conventional DMARDs. The appraisal of certolizumab did not make recommendations about the use of certolizumab after the failure of a first TNF inhibitor. Following the consultation on the preliminary guidance the recommendations have changed. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).. The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28).
NHS Professional 4	1	Even though Rituximab is effective following anti TNF therapy for those patients who are RA Sero-negative this drug will be less effective. Therefore Abatacept provides a further treatment option for that group of RA patients.	The Committee considered the specific subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup (see FAD section 4.3.11).

Role*	Section	Comment	Response
Patient 4	1	My personal experience as that I first received Humira, which had no noticable effect on my RA. After several months I was given Enteracept (allowed in Scotland) which immediately gave me almost 100% relief allowing me to continue working full-time. It seems incomprehensible that a second anti-TNF is not allowed in England after the failure of a first.	Comment noted. The Committee recognises the severity of the disease and the need in this population, it also recognises that some people will respond to their second TNF inhibitor (see FAD section 4.3.2 and 4.3.3). However, for both legal and bioethical reasons, those undertaking technology appraisals must additionally take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).
Patient 4	2	This seems OK except that the DAS score does not take into account knees and feet.	The guidance states that when assessing DAS28, healthcare professionals should take account of any physical, sensory or learning disabilities, communication difficulties or disease characteristics that could adversely affect patient assessment and make any adjustment they consider appropriate. If a clinician considered that a patient had a greater burden of lower limb disease that would not be reflected in DAS28 then adjustments to the assessment tool should be made (see FAD section 1.5).
Patient 4	4	There does not seem to be enough evidence to justify denying a 2nd anti-TNF to patients following failure of a first. My own case and anecdotal evidence from other patients in Scotland who have been prescribed 2 sequentially favours the use of a 2nd.	Comment noted. The methods guide states that the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented (see methods guide section 6.2.23) The Committee recognise that some people will respond to their second TNF inhibitor (see FAD section 4.3.2 and 4.3.3). However, for both legal and bioethical reasons, those undertaking technology appraisals must additionally take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).
Patient 4	6	More randomised trials essential. Use scotland where many people have had sequential anti-TNFs	Comment noted. No actions required to the guidance document.

Role*	Section	Comment	Response
NHS Professional 5	1	It is disappointing that the original decision to prevent switch therapy has been maintained in the face of significant clinical evidence that patients may benefit it is in my view a decision underpinned by a failure to understand that the various preparations used either act in different ways on TNF, or act at a different point in the inflammatory pathway (abatacept - and tocilizumab). To consider them all as identical because of their end effect is equivalent to suggesting that a patient whose blood pressure is not controlled on a beta-blocker becomes ineligible for treatment with a calcium channel antagonist.	The Committee recognised both the heterogeneity of the disease and the different mechanisms of action of the technologies (see FAD sections 4.3.2 and 4.3.3). The Committee did not consider the TNF inhibitors identical. It concluded that although it may not be appropriate to assume that the TNF inhibitors form a homogenous group with regards to clinical effectiveness, the current evidence does not allow for the TNF inhibitors to be distinguished from one another in terms of clinical effectiveness (see FAD section 4.3.7).
NHS Professional 5	1	Whatever the assessed health costs it is also clear that England is now not only out of step with Europe, but in relation to tocilizumab is out of step with Scotland. The preconditions for use are more stringent in England than in most of the rest of the EU. This raises the question of equity of access and might be deemed an unacceptable infringement of human rights in the European Court.	With regards to the access to these technologies across Europe, funding decisions for drugs are each country's individual responsibility. NICE recognises that funding decisions can differ across countries, because of different criteria applied.
NHS Professional 5	1	I have made some detailed comments below but am unable to complete these because of a character entry limit.	Comment noted. No actions requested.
NHS Professional 5	3	There is oversimplification of the exact mode of action of the TNF blockers. They are not identical. Two work by binding to TNF the other appears to work by acting as a false substrate and binding direct to receptors	Section 3 is a summary description of the technologies, and does not reflect a detailed description of the mechanisms of action. The Committee did not consider the TNF inhibitors identical. It considered that although it may not be appropriate to assume that the TNF inhibitors form a homogenous group with regards to clinical effectiveness, the current absence of evidence does not allow for the TNF inhibitors to be distinguished from one another in terms of clinical effectiveness (see FAD section 4.3.7).
NHS Professional 5	4	Para 4.3.4. While it is true that accelerated use of standard DMARDs may hasten the time to a biologic there is some evidence that early DMARD use, particularly in high doses or in combination, is more effective and may thus reduce the need to progress	Comment noted. No action required.

Role*	Section	Comment	Response
NHS Professional 5	6	It should also be noted that some patients have severe allergic reactions to rituximab and are thus denied any further treatment should this occur. Clinicians find it very difficult to manage resistant patients who know that there are other possible treat	Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
NHS Professional 5	6	I have noted my concern about tocilizumab which has been approved in Scotland this produces an internal UK inconsistency which takes us back to postcode prescribing.	Tocilizumab is currently subject to its own single technology appraisal. It was therefore not subject to appraisal by the Committee in this instance (see FAD section 4.3.5).
Patient 5	1	As a sufferer from RA I have tried numerous Dmards with no lasting success and moved to etanercept in 2003 and am currently doing well. However these proposed guidelines would severely limit future alternative treatments should I either develop any side effects or its efficacy diminish. I have observed that no two peoples experience of RA or response to the different drugs are the same and feel that we need more alternatives and not less. I only moved on to an anti TNF drug when all dmards had been tried and either not been efficient or had had serious side effects - a return to these would not be an option and steroids have too many side effects. I am unable to imagine how it would feel to be struggling with uncontrolled RA again whilst knowing that there are actually were treatments out there but not being able to access them.	These recommendations are based on the Committee's considerations of the evidence regarding both the clinical and cost effectiveness of the technologies. The Committee understood that different people may respond to the same treatment differently (see FAD section 4.3.3). Although NICE accepts that individual NHS users will expect to receive treatments to which their conditions may respond, this does not impose a requirement on the Committee to recommend technologies that are not cost effective enough to provide the best value to users of the NHS as a whole (see 'Social Value Judgement – Principles for the development of NICE guidance; principle 5).

Role*	Section	Comment	Response
NHS Professional 6	1	Not recommending abatacept or switching of anti-TNF agents effectively limits RA patients to 2 biologic agents during their lifetime, which may be a particular problem for those patients who are RF/antiCCP negative and may therefore not respond as well to rituximab.	The Committee considered the specific subgroup of people who test seronegative. The Committee recognised that data suggested that the absolute response rates for rituximab were lower for this group than for those who were seropositive. However, it considered that the clinical data did still suggest a benefit of treatment with rituximab. This was supported by clinical opinion. On balance the Committee was not persuaded that the evidence supported differential recommendations for this subgroup. (see FAD section 4.3.11). Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
NHS Professional 6	3	The differences in duration of the infusions also impacts on units and staff. Specifically, the shorter abatacept infusions allow for more patients to be treated than the longer rituximab infusions, despite the requirement for more frequent infusions with abatacept	Comment noted. No changes to the guidance document required.

Role*	Section	Comment	Response
NHS Professional 7	3	I think cost alone should not influence decisions esp. as ACR responses are good.What is important to me as a clinician is to have available a wide choice of biologics to use in patients who have severe RA and have failed on anti TNF alpha.	Comment noted. When making its decision the Committee take account of a range of factors. The Committee recognised the importance of a choice in biologics (see FAD section 4.3.2 and 4.3.3). It also recognised that some people will respond to their second TNF inhibitor. However, for both legal and bioethical reasons, those undertaking technology appraisals must additionally take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).
Patient 6	4	Perhaps I have missed it, but I cannot see that the cost-effectiveness calculations take into account the lack of spending on the anti-tnf that is no longer being taken. In other words, the cost of eg rituximab should be calculated as the differential between the rituximab and the cost of the previous anti-tnf, since the patient is only on the rituximab because they are no longer on the failed anti-tnf. If the previous anti-tnf had not failed, the patient would still be taking it and that cost would still be being met by the health service. Therefore the cost to the health service of eg rituximab is only any extra cost above that of the previous anti-tnf. The whole cost of eg rituximab cannot be treated as a de novo cost for the health service when calculating cost effectiveness eg continuation of working life.	The economic models include a population of people for whom a first TNF inhibitor has failed to control disease. The models start at the point at which the second biological treatment is introduced. When a patient stops a treatment, the costs of that particular treatment stop being added. When a patient switches to a new treatment, the benefits and costs of that new treatment then start to be counted.

Role*	Section	Comment	Response
Patient 6	6	The research should surely take some account of the likely prognosis of the patients and the severity of their RA. There is large variation in the severity of the illness in individuals and in its progression. Some patients are likely to become severely ill without these drugs, and may suffer disproportionate hardship, such as job loss. It is also surprising that we havent got more patient numbers in the report (unless I have missed them). Cost effectiveness is different from cost. Cost is a function of the cost of the drugs times the size of the patient group. But there are no calculations that I can find in this document, which assess this. Surely we need to look at both cost effectiveness and cost? After all, if we are only talking about 100 patients a year, and these are patients with the most severe disease, we may make a different decision than if we are talking about 100,000 patients with moderate disease. So unless we see these figures, its difficult to say whether this guidance is reasonable.	Comment noted. Consideration of the severity of disease and the prognosis could be considered in the recommended research. The Committee does not base its decision on the potential budget impact of a technology. The Committee takes account of how its advice may enable the more efficient use of available healthcare resources, as represented by estimates of incremental cost effectiveness (see Guide to the Methods of Technology Appraisal, section 6.2.14).

Role*	Section	Comment	Response
Patient 7	1	I suffer from severe RA & have been taking anta TNF since 2004. I am horrified & very frightened to learn of the possible outcome of NICEs decision regarding swapping from one anti TNF to another, as I am living proof that this does work. I commenced on Etanercept in 2004 which slowly became less effective in controlling my disease & subsequentally changed to Adalimumab in 2007 which I am currently taking. Should this happen again then where would I be, as there would be no futher option other than one treatment option which may not be a suitble for me. I could & would not be able to go back to that time when I required constant care & supervision & had no quality of life. The amount of pain was unbearable & indescribable. It is unacceptable & I feel criminal that there are proven therapies which are not being made accesible to patients like myself. I would like the decision makers to have to suffer the amount of pain for just one day, & im sure their minds would be changed.	The guidance recommends the use of rituximab as a treatment option after the failure of a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28). The Committee recognise that some people will respond to their second TNF inhibitor (see FAD section 4.3.7). However, for both legal and bioethical reasons, those undertaking technology appraisals must additionally take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).
Patient 8	1	it is devastating news to me that should my TNF inhibitor Humira become less effectiove in the treatment of my RA, I would not be allowed to change drugs to another TNF inhibitor. Before using Humira (Adalimumab) I was unable to move easily.... not able to wlk, so use of my muscles was limited..... now i am able to do virtually anything. It is truely wonderful, and I want the option to be able to switch to another TNF inhibitor should Humiras effect become ineffective.	The Committee recognises the severity of the disease (see FAD section 4.3.2 and 4.3.3). However, for both legal and bioethical reasons, those undertaking technology appraisals must additionally take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).
Patient 8	5	I work and pay a lot of tax. I would not be able to do this if I did not use Humira (Adalimumab). I lead a normal fulfilled life and contribute to society.	Comment noted. The guidance refers only the use of treatments after the failure of a TNF inhibitor. It does not impact on the guidance issued in TA130, which recommended adalimumab, etanercept and infliximab after the failure of at least two conventional DMARDs.

Role*	Section	Comment	Response
Patient 9	1	Why is the supply of these drugs undertaken by commercial companies? Surely NHS supply would lessen th cost.	Comment noted. No changes to the guidance document required.
Patient 9	2	The patient suffers far more than set out in 2.4. There is no assessment of the physological damage of the diease taken into account.	Section 2 is meant to provide a summary of background information. It is not intended to provide a comprehensive description of the condition.
Patient 9	3	The cost of not allowing the drugs is far more from increased costs of ineffectively treating the disease - causing more visits to GPs, use of ancillary services such as Podiatry, occupational health. This is without the loss of tax and NI and increase in state benefits from patients unable to work.	As per the NICE reference case (see sections 5.2.7 to 5.2.10 of the NICE methods guide), costs incurred outside the NHS or PSS (such as, those owing to time away from work) were not incorporated.
Patient 9	4	Why are patients taking these drugs at present not being followed up and their results being used as part of the study? Obviously more money need to be put into studying the effect of drugs on this disease.	Comment noted. A proportion of patients on TNF inhibitors and rituximab are followed up through the British Society of Rheumatology Biologics Register. The Committee considered that more research in the area is needed (see FAD section 8).
Patient 9	6	See above re follow up of patients. Look at the dreadful cost to patients. Two years ago I had a successful business and lived a full life. Now I have lost my business and just exist in a pain filled exhausted stupor.	The Committee recognises the severity of the disease (see FAD sections 4.3.2 and 4.3.3). As per the NICE reference case (see sections 5.2.7 to 5.2.10 of the NICE methods guide), costs incurred outside the NHS or PSS (such as those owing to time away from work) were not incorporated.

Role*	Section	Comment	Response
Patient 10	Notes	I just cant understand Nices stance on the restrictions being placed on the use of Biologicals for the treatment of Rheumatoid Arthritis, from which Ive suffered since 1996. Because TNF and other biologicals were not available in 1996 (in Sheffield) I subsequently lost both of my ankle joints (left is fused with 3 metal pins, right is a total replacement) and had to retire early (aged 55) in 2004 from a high paying job in IT (£63k pa in 2004) to live on a pension of £11k + DLA. Having had all of the usual suspects as treatment initially (DMARDs like Sulphasalazine, Steroids and Methotrexate) plus many other pills I eventually got onto Entercept injections - these worked great for about 18 months and then stopped working. Subsequently I got onto a trial drug (2H7 - a MAB derivative) which has given me back my life. The trial has been running over 2 years and has been extended to 5 and is looking a definite to market drug. Once the trial is complete then under your new guidelines I will NOT be entitled to this new treatment as I have failed already on Enbrel and my health will then dive back to how it was pre-trial with numerous other joints eventually needing replacement, possible total infirmity and possible death causing a huge increase in cost and strain on precious NHS resources - I fail to understand the rationale behind your decisions if you believe it to be a cost saver then you must have very inferior project managers, statisticians and decision makers to have made this cost saving decision.	This appraisal makes recommendations only about the use of adalimumab, etanercept, infliximab, rituximab and abatacept. It does not include guidance on other biological treatments such as 2H7. In the absence of NICE guidance on the use of 2H7 this would be subject to local decision making. The guidance recommends the use of rituximab after the failure of a TNF inhibitor (such as etanercept). For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).

Role*	Section	Comment	Response
Patient 11	Notes	I would just like to say that I am very disappointed with the decision that NICE has made with regard to approval of alternative TNF inhibitors I have suffered with RA for the past 26 years and have tried almost every DEMARD that has been on the market, all of which made little or no improvement to my condition. I was also on high doses of steroids for almost 10 of those years, consequently leaving me with a low bone density, for which I take Ibandronic Acid. Four years ago I was offered Etanercept as a last ditch attempt to improve my condition. Within four weeks I was a different woman, leading an almost normal life. If this medication ceased to be effective for me what hope do I have? This type of action by NICE no doubt, reduces research funding as it gives the public the perception that if they donate to research for new drugs, the new drugs will not be authorised onto the market by NICE and therefore, what is the point !	The Committee recognises the severity of the disease (see FAD section 4.3.2 and 4.3.3). The guidance recommends the use of rituximab after the failure of a TNF inhibitor (such as etanercept). For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
Patient 12	1	Rituximab should be available to those who respond inadequately to DMARDS without any requirement to have tried a TNF inhibitor first.	NICE can only issue guidance on the use of a drug within its licensed indications. At the time of the appraisal, rituximab was not licensed for patients who had not tried a TNF inhibitor.
Patient 12	1	The sequential use of different TNF inhibitors should be available for use at any time and not only for research purposes. Patients may respond successfully to a different anti-TNF after having an unsatisfactory outcome using a previous drug. We also need the maximum possible options left open to us.	The guidance recommends the use of rituximab as a treatment option after the failure of a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1). The guidance no longer recommends the use of the technologies only in the context of research. The Committee was not presented with any evidence that enabled to it make recommendations about the use of adalimumab, etanercept, infliximab and abatacept after the failure of rituximab (see FAD section 4.3.28).

Role*	Section	Comment	Response
Patient 13	8	How many of these people who make these judgements actually have Rheumatoid Arthritis? If they had got it the outcome would be very different as they would do anything to relieve the pain and suffering it causes. I have paid my taxes for over 40 years so if I want the drugs available I should be able to have them after all I have paid for them many times over.	The Committee considered all of the evidence submitted, which included statements from clinical specialists and patient experts. In addition, clinical specialists and patient experts attended the Committee meeting to provide specialist advice (see FAD sections 4.3.2 – 4.3.4). The Committee makes recommendations to the NHS to enable the most efficient use of the limited healthcare resources available. Based on the evidence available, the Committee concluded that rituximab is a cost-effective treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
Patient 14	Notes	As a patient with moderately active RA I am currently taking Etanercept and leading a relatively normal life. However if this fails and I am not allowed to try another of the biologic drugs then I would have to give up my job and become housebound, possibly need a carer and be a burden on society. How can one part of the UK be able to have these drugs and not others. Nice need to look at the wider picture!	Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).

Role*	Section	Comment	Response
Patient 14	1	I feel that if a TNF inhibitor does not work for a patient then others should be allowed without reference to research. Keeping people mobile and as fit as possible for as long as possible not only enhances their lives but stops them becoming a burden on the NHS regarding all the extra help and medication both for physical and mental problems that they will require.	Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options. The recommendations no longer include an “only in research” component (see FAD section 1).
Patient 15	Notes	how dare you deprive thousands of RA sufferers of Biological Medicine when it works so well. I am sure your decision is purely financial SHAME ON YOU	The Committee recognises that some patients may respond to a second TNF inhibitor (see FAD section 4.3.7). It also recognizes the importance of having a variety of treatment options (see FAD section 4.3.2 and 4.3.3). However, for both legal and bioethical reasons, those undertaking technology appraisals must additionally take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).
Patient 16	1	SHAME ON YOU NICE this is so obviously a financial decision/	The Committee recognises that some patients may respond to a second TNF inhibitor (see FAD section 4.3.7). It also recognizes the importance of having a variety of treatment options (see FAD section 4.3.2 and 4.3.3). However, for both legal and bioethical reasons, those undertaking technology appraisals must additionally take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).

Role*	Section	Comment	Response
Patient 16	2	I would be unable to walk without Humira and there were far to many restrictions Before I was given biologics with the result that some of my points were damaged beyond repair.....SHAME ON YOU	This appraisal considers only the use of adalimumab, etanercept, infliximab, rituximab and abatacept after the failure of a TNF inhibitor. It does not provide recommendations for the use of a first TNF inhibitor after the failure of only conventional DMARDs. The use of TNF inhibitors in this situation is covered by recommendations in technology appraisal TA130.
Patient 16	3	The freedom from pain is worth the risk of some infections.....ITS ALL ABOUT MONEY isn,t it SHAME ON YOU	The Committee recognises that some patients may respond to a second TNF inhibitor (see FAD section 4.3.7). It also recognizes the importance of having a variety of treatment options (see FAD section 4.3.2 and 4.3.3). However, for both legal and bioethical reasons, those undertaking technology appraisals must additionally take account of economic considerations (see Social Value Judgements – Principles for the development of NICE guidance; principle 5).
Patient 16	4	Money Money Money shame on you	The directions from the Secretary of State for Health requests the Institute to make recommendations to the NHS based on both clinical and cost effectiveness. The appraisal has been completed in accordance with the published guide to the methods of technology appraisal, including a perspective of the NHS and PSS (see methods guide sections 5.5, 6.1.3).
Patient 16	5	You shouls insist on results from ALL hospitals, there seem to be many uncontrolled results.....get a grip and do your job properly, you are playing with peoples lives.....ESPECIALLY MINE	NICE is unable to issue guidance on data collection within the NHS.
Patient 16	6	make all biologics report experiences to a central body.....impartial..... no drug companie invloved, only rheumatolagists and people with RA.	NICE is unable to issue guidance on data collection within the NHS, nor on the extent to which drug companies involve themselves in data collection.

Role*	Section	Comment	Response
Patient 16	7	Your guidance is crap get into the real world and talk to doctors nurses and patients about Anti-TNF,s	The Committee consider all of the evidence submitted, which includes statements and submissions from clinical specialists and patient experts. In addition clinical specialists and patient specialists attended the Committee meeting to provide specialist advice (see FAD sections 4.3.2 – 4.3.4).
Patient 16	8	Yuo must do better SHAME ON YOU	The appraisal has been completed in accordance with the published guide to the methods of technology appraisal (see methods guide sections 5.5, 6.1.3). Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).
Patient 17	Notes	I have been injecting with HUMIRA since 2005 with 100% improvement after failing on other drugs,It has really given me my life back. I don,t want to see these antiTNF drugs withdrawn	This guidance refers only to the use of adalimumab, etanercept, infliximab, abatacept and rituximab after the failure of a TNF inhibitor. It does not make recommendations on the use of a first TNF inhibitor after the failure of conventional DMARDs.

Role*	Section	Comment	Response
Patient 18	Notes	I have been on humira for 2years now and it has transformed my life. I first started on embrel but did nothing for me, so was lucky enough to be changed. There is no doubt in my mind that I would have ended up with depression and in a wheel chair, costing the nhs far more money. Now I am able to be an active member in society, and help others.	Following the consultation on the preliminary guidance the recommendations have changed. Rituximab is recommended as a treatment option for people who do not respond adequately to a TNF inhibitor. For people who have contraindications to rituximab or methotrexate or who require that rituximab treatment be withdrawn because of an adverse event, adalimumab, etanercept, infliximab and abatacept are recommended as treatment options (see FAD section 1).