NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Sequential use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis

Response to consultee, commentator and public comments on the ACD

Source	Comment	Response
Abbott	Abbott considers that there is a strong rationale for the recommendation of sequential use of TNF inhibitors in case of inefficacy:	Please see response below
Abbott	1 Estimates from the BSRBR modelling using categorical response according to the EULAR criteria indicate a cost per QALY estimate for sequential TNF inhibitors of under £30K applying discount rates of 6% and 1.5%. This estimate of cost effectiveness supports Abbott's contention that the higher cost per QALY estimates generated in the BRAM model should not be considered as realistic estimates, as they are based on unduly pessimistic assumptions of comparative effectiveness of TNF inhibitors when used sequentially.	The BSRBR model has not been submitted to the Institute and has not been independently evaluated. The estimates are not comparable with those in the BRAM analyses because of different discounting. In the BSRBR submission the ICER for first use was £23,000 per QALY rising to £32,000 when a discount rate of 3.5% was used for both costs and benefits. The ICER for 2 TNF inhibitors in comparison with 1 TNF inhibitor is £27,000 which would rise to above £30,000 if discount rates of 3.5% were used. This is comparable with the estimates in the BRAM that use both ReACT and ATTAIN data. See FAD section 4.3.9.

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Abbott	2. In order to have a full understanding of the cost effectiveness estimates from the BRAM, Abbott would like to request an executable version of the model, with a list of the data inputs for key variables in this revised version of the BRAM modelling. It is unclear whether cost offsets are included in the latest analyses using the BRAM model. For consistency with the modelling conducted for the appraisals of rituximab and abatacept, it is appropriate that cost offsets due to lower non-drug resource utilisation are included in the current revised BRAM modelling. Abbott considers inclusion of cost offsets due to lower hospitalisation and surgery costs will further reduce the ICERs for sequential use of TNF inhibitors. It is also unclear whether the latest BRAM results reflect the use of lower starting HAQ scores from the NOAR database, or a more reflective distribution of HAQ scores for the sequential TNF inhibitor population. Given the greater effectiveness of TNF inhibitors compared to other treatment options in the latest version of BRAM model results, it is important to consider whether the results of the BRAM model are sensitive to the starting HAQ level. Abbott considers that use of a HAQ distribution for a population with higher mean HAQ than the NOAR cohort may further reduce the estimated ICERs for sequential use of TNF inhibitors.	The Institute has responded separately to your request for a fully executable model. See email communication sent 02.07.08. Offset costs were not included in the base case economic analysis. This has been amended in the text of the FAD. See FAD section 4.2.2. The Committee has considered the inclusion of offset costs. See FAD section 4.3.11. The analyses use the NOAR cohort as the distribution of starting HAQ scores at the point of diagnosis. See FAD section 4.2.2. The NOAR cohort is used to define the starting HAQ at the point of diagnosis not at the point of starting treatment with TNF inhibitors. Clinical management increasingly focuses on early diagnosis and early intervention with DMARDs to prevent disability. It would not reflect clinical practice to model a cohort of patients with greater levels of disability at the point of diagnosis.
Abbott	3. It should be recognised that the HAQ improvements observed for patients in the BSRBR and ReACT studies partly reflect historical data for switch patients with long disease duration and a high number of failed prior DMARDs. In this population the HAQ levels are to a large degree driven by irreversible joint damage. Given the evolving trend to treat early in RA to avoid disability, it is likely that future patients failing their 1st TNF inhibitor for efficacy reasons would have a greater propensity to respond to a second TNF inhibitor. Abbott considers that future TNF inhibitor switch patients would therefore be able to achieve higher levels of mean HAQ improvement than were observed in the BSRBR and ReACT studies. Therefore, Abbott considers that the rationale for restricting sequential use of TNF inhibitors based on historical data is unnecessary on cost effectiveness grounds.	The Committee considered both the data from the BSRBR and the ReACT studies. See FAD sections 4.3.4, 4.3.12.

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Abbott	HAQ improvement data from cohorts that have recommended DMARD therapy after inefficacy of a TNF inhibitor are rare. Therefore, data from cohorts that start new DMARD therapy in established rather than early RA are important. It is unclear why the effectiveness of conventional DMARDs from the British Rheumatoid Outcomes Study Group (BROSG) study when used in established RA has not been taken into greater consideration in this appraisal. The initial HAQ improvements of the placebo arm in Genovese as used in the BRAM modelling are not supported by the available evidence on conventional DMARD effectiveness from the BROSG study. Abbott considers that use of a lower HAQ multiplier for conventional DMARDs than applied in the "new" values BRAM analyses using the Genovese data would result in improved cost effectiveness for sequential use of TNF inhibitors versus conventional DMARDs. Abbott is unable to predict what the cost per QALY estimates would be without seeing any sensitivity analyses on this point using the BRAM model. However, it is also important to assess the uncertainty around the effectiveness of conventional DMARDs when the minimum effectiveness required for sequential use TNF inhibitors is analysed.	The Committee has considered the BROSG study. The BROSG study includes 2 treatment arms both of which include a sequence of conventional DMARDs. People start treatment and switch treatment at a point defined by their disease characteristics. Therefore this study cannot be considered a study of an individual DMARD and could not be used in the economic modelling. Without people starting treatment at the same time, and without any comparator arm that does not include DMARDs, the study cannot demonstrate that conventional DMARDs have no effect. The published report 65% and 50% of people in the symptomatic and aggressive treatment arms were defined at the end of the study as treatment successes. The study does show that overtime people on DMARDs get worse (0.12 HAQ units over 3 years), this is incorporated into the cost effectiveness analyses completed for the Institute as underlying HAQ progression of 0.045 units of HAQ a year. See FAD sections 4.1.13, 4.3.8.
Abbott	The committee noted that the incremental cost effectiveness of adalimumab, etanercept and infliximab after the failure of a TNF inhibitor would not be a cost effective use of NHS resources in comparison with the use of rituximab. Abbott considers that the mean retreatment interval for rituximab would be less than 9 months in UK clinical practice when patients would be retreated to maintain adequate DAS28 response. Alternatively, use of a 9 month mean retreatment interval should be associated with commensurately lower QALY gains for rituximab, as patients losing response would suffer a reduction in their quality of life until retreated. Therefore, the cost per QALY for sequential use of TNF inhibitors versus rituximab would be lower than estimated in the latest BRAM modelling and would likely fall within a range considered acceptable for the use of NHS resources.	The Committee has considered the retreatment schedules for rituximab and the loss of benefit between infusions. See FAD section 4.3.19.

Source	Comment	Response
Abbott	Abbott considers that the recommendation that no patients should be allowed to use TNF inhibitors sequentially is unnecessarily restrictive given the cost effective estimates of £31K to £39K per QALY applying mean HAQ improvements of –0.51 from the ReACT study. Abbott considers that the cost per QALY would be lower than these estimates for the reasons outlined above. Abbott is concerned that due consideration has not been given to the cost effectiveness of subgroups of switching patients. In particular, studies that have considered the issue have consistently found a greater propensity to respond among those patients who have lost response to a previous TNF inhibitor. This subgroup is therefore likely to be associated with a lower cost per QALY versus conventional DMARDs and versus rituximab.	The cost effectiveness analyses completed by Pelham Barton at WMHTAC include different analyses for people who were non responders to their first TNF inhibitors and people who had a reduction in response to their first TNF inhibitor, based on the data from the BSRBR. These are indicated in the documents as options B and C. The Committee considered the whether the evidence was sufficient to enable differentiation between primary and secondary non responders. See FAD section 4.2.3, 4.3.5.
Abbott	Emerging data suggest that successful therapy with TNF inhibitors may have an impact on secondary outcomes including work disability, mortality and cardiovascular outcomes in RA, in addition to the core outcomes of disease activity, function and radiographic progression. Although it is accepted that survival benefits of TNF inhibitors have not been proven in randomised controlled trials, the benefits observed in observational studies suggest an important benefit for TNF inhibitors that has not been captured in the current cost effectiveness modelling. Furthermore, inclusion of the societal benefits of maintaining patients in work and reducing reliance on state disability benefits would substantially reduce the cost per QALY for sequential use of TNF inhibitors.	The reference case stipulates that the perspective adopted on costs should be that of the NHS and PSS, and benefits reflect health related quality of life. See section 5.3.3.1. of the Guide to the Methods of Technology Appraisal As both arms of the economic model include treatment with TNF inhibitors for this to be reflected studies would have to demonstrate a differential effect on mortality between the provision of 1 and 2 TNF inhibitors.
Abbott	Abbott is concerned that the provisional recommendations not to allow switching to an alternative TNF inhibitor in case of inefficacy do not appear to have taken account of potential safety issues around sequencing of treatments including rituximab or patient preferences for home treatment with adalimumab or etanercept.	The Committee considered the safety profile of rituximab. See FAD section 4.3.19. Although respect for autonomy and individual choice, are important for the NHS and its users they should not have the consequence of promoting interventions which are not clinically and/or cost effective (Social Value Judgements - Principles for the development of NICE guidance; principle 11).

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Abbott	Given the cost per QALY estimates presented in the ACD and the uncertainty around these results, Abbott considers that the low quality of life of the patient population, patient preferences for home treatment, potential mortality benefits of TNF inhibitors, the societal costs associated with RA and uncertainty around safety with sequences of treatment involving rituximab should also weigh in favour of patients having the option to receive sequential TNF inhibitors in case of inefficacy.	Comments noted, please see responses above.
Abbott	**Do you consider that all of the relevant evidence has been taken into account?** In general, Abbott considers that the majority of published evidence has been identified regarding the effectiveness of TNF inhibitors when used sequentially. However, Abbott considers that a number of relevant aspects of the evidence have not been taken into account. **Data on conventional DMARD effectiveness from BROSG study** It is unclear why the evidence on the effectiveness of conventional DMARDs from the British Rheumatoid Outcomes Study Group (BROSG) study when used in established RA has been consistently overlooked in this appraisal. It is acknowledged that HAQ improvement data from cohorts that have recommenced DMARD therapy after inefficacy of a TNF inhibitor are rare. Therefore, data from cohorts that start new DMARD therapy in established rather than early RA are important. Data from the BROSG Study, a randomised trial of symptomatic versus aggressive use of DMARD therapy, have been published as a HTA monograph in September 2005 and provide estimates of the effectiveness of a sequence of conventional DMARDs used as part of either a symptomatic or aggressive treatment strategy. For all time points and in both treatment arms, regardless of symptomatic or aggressive treatment with a sequence of conventional DMARDs, the HAQ score actually worsened rather than improved (see Figure 1 below). *Figure included but not reproduced*	The Committee has considered the BROSG study. The BROSG study includes 2 treatment arms both of which include a sequence of conventional DMARDs. People start treatment and switch treatment at a point defined by their disease characteristics, they did not all start a new DMARD treatment at the start of the study. Therefore this study cannot be considered to be a study of an individual DMARD and could not be used in the economic modelling. Without people starting treatment at the same time and without any comparator arm that does not include DMARDs, the study cannot demonstrate that conventional DMARDs have no effect. The published report indicates that at the end of the study 50% and 65% of people in the aggressive and symptomatic treatment arms were defined as treatment successes (p33). The study does show that overtime people on DMARDs get worse (0.12 HAQ units over 3 years), this is incorporated into the cost effectiveness analyses completed for the Institute as underlying HAQ progression of 0.045 units of HAQ a year. See FAD sections 4.1.13, 4.3.8.

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Abbott	Abbott considers that the study design of the BROSG is able to answer the question required for the economic modelling, namely what is the effectiveness of conventional DMARDs used sequentially in patients with established RA. It could be argued that the BROSG study does not provide evidence of the effectiveness of individual conventional DMARDs. However, given the use of the Genovese placebo + methotrexate arm HAQ improvement from the abatacept study as a proxy for the effectiveness of all conventional DMARDs, this argument is considered not applicable. Furthermore, the BROSG data highlight that the short term HAQ improvement observed in the Genovese study and used in the economic modelling does not necessarily represent the lower bound of HAQ improvement of conventional DMARDs after failed TNF inhibitor therapy. Figure 2 illustrates the HAQ profile over time for a patient on conventional DMARDs using the Genovese data in the BRAM model. *Figure included but not reproduced*	The Committee considered the BROSG study and the appropriateness of the data from the ATTAIN trial. See FAD sections 4.1.13, 4.3.8, 4.3.15. Figure 2 is for a single patient, the BROSG data reflect a cohort of patients. Therefore the figures are not comparable. When a cohort of patients is run through the economic model people start treatments at different times and experience improvement and worsening of their disease at different times. The only factor that the cohort share is an annual underlying worsening of disease. If the cohort of patients in the economic model were presented graphically, the short term benefits of switching treatments experienced by some people would be cancelled out by the loss of benefits experienced by others, leaving a sloping line showing a gradual worsening of disease, comparable to the BROSG data.
Abbott	These data highlight that a short term HAQ improvement of –0.11 leads to a sustained reduction in the mean HAQ score over 2.5 years. Abbott believes it is therefore misleading to characterise the use of the Genovese placebo data as “no active treatment effect of conventional DMARDs”. The initial HAQ improvements of the placebo arm in Genovese are not supported by the available evidence on conventional DMARD effectiveness from the BROSG study or the US National Databank for rheumatic diseases. Abbott considers that use of a lower HAQ multiplier for conventional DMARDs than applied in the “new” values using the Genovese data would result in improved cost effectiveness for sequential use of TNF inhibitors versus conventional DMARDs. Abbott is unable to predict what the cost per QALY estimates would be without seeing any sensitivity analyses on this point using the BRAM model. However, it is also important to assess the uncertainty around the effectiveness of conventional DMARDs when the minimum effectiveness required for sequential use TNF inhibitors is analysed.	People enrolled in the ATTAIN trial had to be on stable doses of DMARDs prior to randomisation and the start of treatment with either abatacept or placebo. Therefore the 0.11 does not capture the effect of an individual DMARD or an active treatment. All documents seen by the Committee state the values used in the modelling to reflect the efficacy of conventional DMARDs, therefore the Committee were not misled. The values used in the modelling are described in the FAD and the Committee considered the use of the ATTAIN data and the BROSG study. See FAD sections 4.2.3, 4.3.14.

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Abbott	**Modelling of cost offsets and HAQ improvement** In order to have a full understanding of the cost effectiveness estimates from the BRAM, Abbott would like to request an executable version of the model, with a list of the data inputs for key variables in this revised version of the BRAM modelling. It is unclear whether cost offsets are included in the latest analyses using the BRAM model. Section 4.2.2 of the ACD indicates that joint replacement and associated costs were included in sensitivity analyses, however it is unclear where the results of these analyses are presented. For consistency with the modelling conducted for the appraisals of rituximab and abatacept, it is appropriate that cost offsets due to lower non-drug resource utilisation are included in the current revised BRAM modelling. In the BRAM, as in the model submitted by Abbott, cost offsets due to hospitalisation/ surgery are modelled as a function of the HAQ improvement i.e. each HAQ point improvement was associated with a £860 reduction in medical costs. Sensitivity analyses in the Technology Assessment Report indicated that the cost offsets have a negligible impact on the overall model results of the BRAM. However, these analyses were run on the previous base-case model where TNF inhibitors were considered to be broadly similar in effectiveness to conventional DMARDs in terms of the HAQ multipliers used for short-term improvement. Given the greater effectiveness of TNF inhibitors compared to other treatment options in the latest version of BRAM model results, it is important to assess whether the latest results of the BRAM model are sensitive to the absolute value of cost offsets attributable to a one-unit HAQ improvement. Abbott considers inclusion of cost offsets due to lower hospitalisation and surgery costs will further reduce the ICERs for sequential use of TNF inhibitors.	The Institute has responded separately to your request for a fully executable model. See email communication sent 02.07.08. Offset costs were not included in the base case analysis. This has been amended in the text of the FAD. See FAD section 4.2.2. The Committee has considered the impact of inclusion of offset costs. See FAD section 4.3.11.

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Abbott	Similarly, changing the baseline HAQ level had a negligible effect on the original base-case BRAM results. It is unclear whether the latest BRAM results reflect the use of lower starting HAQ scores from the NOAR database, or a more reflective distribution of HAQ scores for the sequential TNF inhibitor population. Given the greater effectiveness of TNF inhibitors compared to other treatment options in the latest version of BRAM model results, it is important to consider whether the results of the BRAM model are sensitive to the starting HAQ level. Abbott considers that use of a HAQ distribution for a population with higher mean HAQ than the NOAR cohort may further reduce the estimated ICERs for sequential use of TNF inhibitors.	The analyses use the NOAR cohort as the distribution of starting HAQ scores at the point of diagnosis. This was stated in the ACD and FAD. See FAD section 4.2.2. The NOAR cohort is used to define the starting HAQ at the point of diagnosis not at the point of starting treatment with TNF inhibitors. Clinical management increasingly focuses on early diagnosis and early intervention with DMARDs to prevent disability. It would not reflect clinical practice to model a cohort of patients with greater levels of disability at the point of diagnosis.

Source	Comment	Response
Abbott	**Uncertainty over retreatment period for rituximab** In the ACD (section 4.3.13) the committee noted that the incremental cost effectiveness of adalimumab, etanercept and infliximab after the failure of a TNF inhibitor would not be a cost effective use of NHS resources in comparison with the use of rituximab. If the cost effective use of NHS resources for sequential use of TNF inhibitors vs. rituximab is to be made, it is critical to ensure that the comparison is appropriate. In TA 130 (for the use of adalimumab, etanercept and infliximab in RA) it is recommended that treatment should only be continued if there is an adequate response at 6 months, such response being defined as a reduction in DAS28 of at least 1.2 from baseline. In TA 126 (for the use of rituximab for the treatment of RA) it is recommended that the treatment should only be continued if there is an adequate response following initiation of therapy (without regard to timeframe). Such adequate response is defined as an improvement in DAS28 of 1.2 or greater. Repeat courses of treatment with rituximab plus methotrexate should be given no more frequently than every 6 months. In order for continued treatment of TNFs, the maintenance of DAS28 reduction of 1.2 is required, such requirement does not appear to be in place for rituximab. The latest BRAM analyses of the cost effectiveness of sequential use of TNF inhibitors versus rituximab are based on a mean cost of £6,848 for rituximab. This cost was taken from NICE TA 126 for rituximab and was based on a mean retreatment period of 9 months (307 days). As noted in TA 126, the cost effectiveness of rituximab is sensitive to the mean retreatment interval applied in the modelling.	The Committee has considered the retreatment schedules for rituximab and the loss of benefit between infusions. See FAD sections 4.3.19.

Source	Comment	Response
Abbott	It should be noted that the timing of retreatment with rituximab was at the investigator's discretion in clinical studies. Abbott considers that the optimal interval for retreatment with rituximab remains to be determined for UK clinical practice. In this respect, it should be noted that according to the NICE criteria for response to rituximab, an adequate response would be defined as a 1.2 point improvement in DAS28 score. At the time of loss of this response the patient should be retreated with rituximab. It can therefore be observed that the mean time to retreatment in the clinical studies of rituximab does not necessarily equate to the mean retreatment interval if a maintenance rule requiring a 1.2 point DAS28 improvement for rituximab therapy in clinical practice were to be applied. It should also be noted that the modelling of rituximab costs should not be independent of treatment effect, that is to say, the modelling of QALY gains achievable with rituximab should take account of lower quality of life improvements when patients have lost response, as defined by maintenance of a 1.2 point DAS28 improvement.	See FAD section 4.3.19.
Abbott	In Keystone et al. the DAS28 of patients prior to re-treatment is assessed. The mean time between treatments for course 1 to course 2 was 33.2 weeks (232 days). This figure of 33.2 weeks is substantially less than the 307 days between re-treatment as cited by the manufacturer in TA 126. The mean DAS28 for the Keystone study population 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. The mean DAS28 just prior to course 3 of re-treatment was 6.01 (with a mean re-treatment interval of 32.2 weeks between courses 2 and 3) resulting in a reduction of –1.00 from baseline. In neither case (between course 1 and course 2 or between course 1 and course 3) does the mean decrease in DAS28 meet the NICE defined level of "adequate response" of >-1.2 from baseline. This is in spite of the fact that the time between re-treatment intervals were in both cases substantially less than the 307 days cited in TA 126. It should also be noted that the manufacturer of rituximab has been asked by the FDA for a post approval commitment of a safety and efficacy trial with respect to the re-treatment of rituximab (NCT00422383). In this trial patients will be dosed at day 0 and day 180. This dosing schedule therefore suggests a 9-month retreatment interval may not be optimal to maintain response with rituximab.	See FAD section 4.3.19.

Source	Comment	Response
Abbott	In summary, Abbott considers that the mean retreatment interval for rituximab would be less than 9 months in UK clinical practice when patients would be retreated to maintain adequate DAS28 response. Alternatively, use of a 9 month mean retreatment interval should be associated with commensurately lower QALY gains for rituximab, as patients losing response would suffer a reduction in their quality of life until retreated. Therefore, the cost per QALY for sequential use of TNF inhibitors versus rituximab would be lower than estimated in the latest BRAM modelling and would likely fall within a range considered acceptable for the use of NHS resources.	See FAD section 4.3.19.
Abbott	**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?** **Minimum effectiveness required for sequential use of TNF inhibitors to be cost effective according to the BRAM model estimates** Consideration should be given to the limited evidence base for RA treatments that is available using HAQ as an outcome measure. Of the 21 studies considered eligible for full review in evaluating the sequential use of TNF inhibitors, 21 reported improvements in DAS, DAS 28, ACR and/ or EULAR criteria compared to only 4 reporting HAQ outcomes. Furthermore, the majority of conventional DMARDs have limited HAQ outcome data available. Given the weaknesses of the evidence base specifically for HAQ improvements, Abbott considers that the ACD recommendations place undue focus on those aspects of the evidence that indicate small HAQ improvements with sequential TNF inhibitor use. It is important that HAQ data are not considered in isolation from the patient population and clinical setting in which the improvements were derived.	The Committee considered the full range of outcomes that had been included in the review by the DSU. See FAD sections 4.1.2, 4.1.4, 4.1.6, 4.3.3 4.3.4. However, the Committee had to consider HAQ specifically as this is what is used to map to EQ-5D in the economic analyses.

Source	Comment	Response
Abbott	The two largest available data sources for HAQ improvement with sequential TNF inhibitor use are the BSRBR and the ReACT study (Bombardieri et al). The BSRBR indicates a mean HAQ improvement of 0.21 when adjusted for confounders. The BSRBR data does not distinguish between types of switch patients. The ReACT study indicates mean HAQ improvements of 0.33 to 0.52 for switches due to inefficacy depending on whether switchers were primary non-responders or those who had experienced a loss of response. This is compared to a mean HAQ improvement of 0.55 for patients receiving their 1st TNF inhibitor. It should be borne in mind that the standard deviation for HAQ improvement is greater than 0.50 for all subgroups, therefore a substantial proportion of switch patients will have a response equal to that achieved on their 1st TNF inhibitor, particularly those patients experiencing loss of response rather than those who were primary non-responders to their 1st TNF inhibitor. The minority of studies that have stratified primary non-responders versus loss of response have consistently found a greater propensity to respond among those who have lost response to a TNF inhibitor. Furthermore, forthcoming data to be presented at the EULAR conference 2008 supports a greater response rate among patients who have lost response to a TNF inhibitor. This subgroup is therefore likely to be associated with a lower cost per QALY versus conventional DMARDs and versus rituximab.	The cost effectiveness analyses completed by Pelham Barton at WMHTAC include different analyses for people who were non responders to their first TNF inhibitor and people who had a reduction in response to their first TNF inhibitor, based on the data from the ReACT study. These are indicated in the documents as options B and C. As part of their deliberations the Committee considered whether the evidence was sufficient to enable differentiation between primary and secondary non responders. See FAD section 4.2.3, 4.3.5.
Abbott	**Effectiveness of a second TNF inhibitor based on US National Databank for Rheumatic Diseases data.** Abbott considers that it is misleading to use the mean HAQ improvement observed in the US National Databank for Rheumatic diseases as justification that the treatment effect of a 2nd TNF inhibitor could be very small. It is unclear why the HAQ improvement in absolute terms is only around 1/3 of that observed for the placebo + methotrexate arm in the Genovese study as used for the modelling of the effectiveness of conventional DMARDs post TNF inhibitor failure. These HAQ changes highlight the dangers of utilising HAQ changes from different studies without detailed consideration of differences in the patient populations. Abbott considers the absolute HAQ improvements in the US dataset are unlikely to be representative of the effectiveness of sequential TNF inhibitor use in the UK.	The Committee considered the NDRD data in light of the other data sources. See FAD section 4.3.4.

Source	Comment	Response
Abbott	**Evolving trend for early aggressive treatment of Rheumatoid Arthritis and implications for HAQ improvements attainable by switching patients** As the committee has recognised, one of the weaknesses of the HAQ measure is that it encompasses aspects of disease activity and functional impairment. In this context it should be recognised that the HAQ improvements observed for patients in the BSRBR and ReACT studies partly reflect historical data for switch patients with long disease duration and a high number of failed prior DMARDs. Given the evolving trend to treat early in RA to avoid disability, it is likely that future patients failing their 1st TNF inhibitor for efficacy reasons would have a greater propensity to respond to a second TNF inhibitor due to having sustained lower levels of irreversible joint destruction. Abbott considers that future TNF inhibitor switch patients would therefore be able to achieve higher levels of mean HAQ improvement than were observed in the BSRBR and ReACT studies. Therefore, Abbott considers that the rationale for restricting sequential use of TNF inhibitors based on historical data is unnecessary on cost effectiveness grounds.	The Committee considered both the data from the BSRBR and the ReACT studies. See FAD section 4.3.12.

Source	Comment	Response
Abbott	**Excessive focus on the BRAM model results compared to the results from the model developed by the BSRBR.** Abbott is concerned that the results of the modelling of sequential use of TNF inhibitors as submitted in the appeal by the BSR, utilising BSRBR data appear to have been dismissed without due consideration. An assertion has been made that the difference in cost per QALY estimates for the BSR modelling compared to the BRAM is largely attributable to the use of different discount rates in the latest version of the BRAM modelling: "The committee noted that the BRAM and BSRBR analyses had used different discount rates, and considered that had the same discount rates been applied to both analyses then the estimates of cost effectiveness would have been similar." Section 4.3.7 ACD, page 24 of 37. However, it should be noted that discount rates of 3.5% in the BSRBR model have not been modelled in the sequential use analyses. To assess the potential impact of the different discount rates, the cost effectiveness results for the 1st use TNF inhibitor can be compared. Applying discount rates of 6% for costs and 1.5% for outcomes the base case ICER reported by Brennan et al. is £23,882 for a 1st TNF inhibitor. Applying discount rates of 3.5% for both costs and outcomes yields an ICER of £32,013 for the 1st TNF inhibitor (a 34% increase). Given the base case ICER for sequential TNF inhibitor use of £24,570 an estimated 34% increase in the ICER would yield a figure of £32,924. This is in the lower range of cost per QALY estimates from the BRAM model and further reinforces the point that the upper range of cost per QALY estimates from the BRAM model up to £164K should be viewed as outliers based on unduly pessimistic assumptions regarding the effectiveness of TNF inhibitors used sequentially.	The BSRBR model has not been submitted to the Institute and has not been independently evaluated. The estimates are not comparable with those in the BRAM analyses because of different discounting. In the BSRBR submission the ICER for first use was £23,000 per QALY rising to £32,000 when a discount rate of 3.5% was used. The ICER of £24,570 per QALY is the comparison in the BSRBR model of 2 TNF inhibitors with no TNF inhibitors. As it is current standard practice to provide 1 TNF inhibitor this is not the correct ICER to consider. The ICER for 2 TNF inhibitors in comparison with 1 TNF inhibitor is £27,000 using discount rates of 3.5% for both cost and benefits. Using the same calculation as Abbott this would increase the ICER to approximately £36,000 which is comparable with the estimates that use ATTAIN and ReACT data in the BRAM. See FAD section 4.3.9. The Committee considered the use of the data for conventional DMARDs from the assessment report. See FAD section 4.3.13.

Source	Comment	Response
Abbott	**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 recommendation that no patients should be allowed to use TNF inhibitors sequentially in case of inefficacy is unnecessarily restrictive given the cost effective estimates of £31K to £39K per QALY applying mean HAQ improvements of –0.51 from the ReACT study. Abbott considers that the cost per QALY would be lower than these estimates for the reasons outlined above in sections 1 and 2. Given the magnitude of these cost effectiveness estimates Abbott believes it is important to also take into account a number of additional reasons why a sequential TNF inhibitor should be allowed as a treatment option in addition to the options of giving the patient rituximab or returning the patient to conventional DMARD therapy.	Comments noted. See responses above.
Abbott	**No consideration of safety issues with using rituximab rather than 2nd TNF inhibitor.** Abbott is concerned that the provisional recommendations not to allow switching to an alternative TNF inhibitor in case of inefficacy do not appear to have taken account of potential safety issues around sequencing of treatments including rituximab. Longer term data and more patient years of experience with rituximab are needed to allow better interpretation and characterisation of the changes seen in immunoglobulin levels and the long term effects of repeated B cell depletion. As yet there have been no full publications of safety data from independent national registries of patients with RA treated with rituximab, although collection of such data are underway. Furthermore, patients not responding to rituximab 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. Some physicians and patients may be concerned about risks of infusion reactions, which although decreased in frequency with increasing courses of rituximab, was significant at first dose in the REFLEX study (23%). Further discussion on these points is available in section 10 of our response to switching further analyses sent to NICE on 27th February 2008.	The Committee considered the adverse effect profile of rituximab. See FAD section 4.3.19.

Source	Comment	Response
Abbott	**Insufficient consideration of non-HAQ benefits of TNF inhibitors** Emerging data from recent TNF inhibitor RCTs and registries suggest that successful therapy with TNF inhibitors may have an impact on secondary outcomes including work disability, mortality and cardiovascular outcomes in RA, in addition to the core outcomes of disease activity, function and radiographic progression. Further data on these points is available in Abbott's response to switching further analyses sent to NICE on 27th February 2008. Although it is accepted that survival benefits of TNF inhibitors have not been proven in randomised controlled trials, the benefits observed in observational studies suggest an important benefit for TNF inhibitors that has not been captured in the current cost effectiveness modelling. Furthermore, inclusion of the societal benefits of maintaining patients in work and reducing reliance on state disability benefits would substantially reduce the cost per QALY for sequential use of TNF inhibitors.	The reference case stipulates that the perspective adopted on costs should be that of the NHS and PSS, and benefits should be in health related quality of life. See section 5.3.3.1. of the Guide to the Methods of Technology Appraisal As both arms of the economic model include treatment with TNF inhibitors for this to be reflected studies would have to demonstrate a differential effect on mortality between the provision on 1 and 2 TNF inhibitors.
Abbott	**Rituximab is not suitable for all patients** A course of rituximab is given as two intravenous infusions two weeks apart. This requires admission to a day ward, which must be equipped with full resuscitation equipment. Further, the concomitant administration of intravenous prednisolone with rituximab and oral prednisolone throughout the two-week period is mandated. Some patients may have significant difficulty to undertake this treatment regimen several times per year, including the journey to the hospital and back. Such patients may benefit from the option of therapy administered in the home, for instance with adalimumab and etanercept therapy. Further, many patients may prefer a subcutaneous route of administration afforded by adalimumab or etanercept as opposed to an intravenous route. In addition, rituximab is less effective in Rheumatoid factor seronegative (RF-) RA patients which account for >20% of the RA population, whereas TNF inhibitors have shown comparable efficacy in both RF+ and RF- patients. Given the above, the patient and his/her physician should be given the option to select the most appropriate therapy with careful benefit-risk assessment of the options driving the choice of sequential therapy in this situation.	The Committee considered the use of a second TNF inhibitor in the group of people who were seronegative, as well as those who were contraindicated to either rituximab or methotrexate. See FAD section 4.3.19, 4.3.20.

Source	Comment	Response
Abbott	**Are there any equality related issues that may need special consideration?** No issues that Abbott is aware of.	Comment noted, no action required.
Schering Plough	Schering-Plough welcomes the opportunity to comment on the Appraisal Consultation Document for the appraisal of the sequential use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. We concur with the Appraisal Committee's view that TNF-α inhibitors are clinically effective when used sequentially. Indeed there is good evidence from the British Society for Rheumatology Biologics Registry (BSRBR) that a similar proportion of patients achieve a good response to their first and second TNF-α inhibitors. However, Schering-Plough has a number of serious concerns regarding the Appraisal Committee's interpretation of evidence as set out in the ACD as well as the overall manner in which evidence has been incorporated within this appraisal.	Comments noted, see responses below
Schering Plough	Our response is set out in the main body of this letter, under the headings requested by the Institute for consultee feedback. In summary, Schering-Plough would like to make the following broad comments on the ACD: The recommendations of the Committee are based on an inappropriately restrictive analysis and interpretation of the evidence. In Schering-Plough's view, this has resulted from the failure of the Institute to approach this separate appraisal of the sequential use of anti-TNFs in accordance with its published procedures. This departure from the usual process was not justified to consultees and is, in Schering-Plough's view, highly unsatisfactory.	The appeal panel requested that the Institute carry out a series of sensitivity analyses based on those that had previously been completed. This is not therefore a separate appraisal. The guidance for first use of TNF inhibitors was published so as not to delay guidance to the NHS on the use of adalimumab or the recommendation for sequential use in people experiencing an adverse event. In addition publication allows the guidance to be incorporated into the ongoing clinical guideline.
Schering Plough	The recommendations set out in the ACD reflect the Committee's view that TNFα inhibitors are unlikely to be a cost-effective use of NHS resources for patients who have previously failed treatment with a TNFα inhibitor and DMARDs. Schering-Plough believes that this view is, in large part, based on an evaluation of the clinical effectiveness of DMARDs that overestimates the effectiveness of DMARDs and so is likely to underestimate the incremental effectiveness associated with TNF-α inhibitors.	The Committee considered the clinical effectiveness of conventional DMARDs. See FAD sections 4.3.6, 4.3.7, 4.3.14, 4.3.15.
Schering Plough	The Committee argues that estimates of cost-effectiveness for infliximab taking account of vial optimisation (no vial wastage) are not appropriate for the purposes of its decisions. Since the Appraisal Committee was instructed to consider an appropriate range of doses for infliximab and to take account of vial wastage following the Appeal against the FAD for TA130, it is surely perverse to ignore ICERs that take account of vial optimisation.	The appeal panel requested that analyses be carried out and considered. See appeal decision paragraphs 137 and 142. The Committee has considered the analyses that were carried out at the request of the appeal panel. See FAD sections 4.3.17, 4.3.18.

Source	Comment	Response
Schering Plough	**Do you consider that all of the relevant evidence has been taken into account?** **A separate appraisal for the sequential use of TNF inhibitors** Further to our comments in response to the additional analyses that were circulated to consultees earlier this year, Schering-Plough would like to reiterate its continuing concerns regarding procedural aspects of this appraisal. In the Institute's written request for consultee comments on the additional analyses we are asked to note that these reports are only one component of the evidence that the Appraisal Committee will use to inform their recommendations to the Institute. Other components are reported to include the assessment report, the comments received during this consultation, submissions received from consultees and the views and experience of clinical specialists and patient experts.	The appeal panel requested that the Institute carry out a series of sensitivity analyses based on analyses that had previously been completed. Therefore the assessment report and the previous additional work for sequential use remain relevant to the appraisal. Comments received on the new additional work following consultation have also been presented to the Committee and clinical specialists and patient experts attended the Committee meeting.
Schering Plough	Importantly however, consultees have not been given an opportunity to submit evidence in relation to the specific issue under consideration in this separate appraisal – i.e. sequential use. Given the separation of the original appraisal into two parts – first use and sequential use, and given the broadening of the scope of this appraisal to include consideration of rituximab as a comparator, it is surprising that additional evidence (aside from consultee comments) is only being submitted by the Assessment Group and the Decision Support Unit. This restrictive approach to the separate appraisal of sequential use is contrary to the Institute's procedures and this has put Schering-Plough and other consultees at a major disadvantage. The ACD indicates that this appraisal of the sequential use of TNF-α inhibitors is an individual appraisal [conducted pursuant to Directions from the Secretary of State]. Under such circumstances, the Institute's own procedures allow stakeholders the opportunity to make submissions.	Consideration of sequential use was included as a specific consideration in the final scope of this appraisal and is covered in the remit as it was referred from the Department of Health. When the appraisal started consultees had the opportunity to submit evidence on sequential use, and Abbott, Wyeth and ARMA chose to do so. Their evidence is reflected in the FAD document. See FAD sections 4.2.1.
Schering Plough	It is also apparent that other ongoing appraisals, albeit within the Single Technology Appraisal process, allow further evidence submission by consultees subsequent to the splitting of an appraisal – e.g. infliximab for ulcerative colitis. It is not clear why the Institute decided to limit the provision of further evidence within the appraisal of TNF-α inhibitors for sequential treatment of rheumatoid arthritis. Indeed there was, to our knowledge, no consultation outside the Institute on this matter. However, Schering-Plough believes that the separate appraisal of sequential use should have allowed for formal consultee evidence submissions.	In the single technology appraisal process the manufacturer is the main source of the evidence used by the Committee. Therefore in the STA where a manufacturer submits insufficient evidence to support decision making the Institute has to request that the manufacturer supplies this evidence. For the multiple technology appraisal process there is an independent source of evidence and therefore the requirement for the manufacturer to provide evidence is not the same.

Source	Comment	Response
Schering Plough	Vial wastage In section 4.3.11 of the ACD, the Committee notes that it was: "mindful that the analyses of the cost effectiveness of infliximab assumed no sharing of vial contents between people and that if it was possible to minimise vial wastage then the cost effectiveness would be improved. The Committee considered that it could not be assumed that there would be no vial wastage and that the original estimates of cost effectiveness that assumed that infliximab vials were not shared were appropriate." The Committee had been specifically asked to consider a wider range of doses for infliximab by the Institute, following the Appeal against the original FAD for the Appraisal of TNF inhibitors for rheumatoid arthritis. The Institutes request that this matter be investigated properly confirms its relevance and importance to the Committee's deliberations. When taking account of vial wastage, using an average patient weight of 70kgs and an average dose of 210mgs per infusion, the Assessment Group estimates the ICER for infliximab to be in the range 22-33k/QALY.	The appeal panel requested that analyses be carried out and considered. See appeal decision paragraphs 137 and 142. The Committee has considered the analyses that were carried out at the request of the appeal panel. See FAD section 4.3.17, 4.3.18.

Source	Comment	Response
Schering Plough	Schering-Plough argues that it must be perverse for the Institute to address the issue consistent with the directions of the Appeal Panel, and subsequently to rule the results inappropriate. In the guidance for TA130, the Institute recognises that a number of issues are important in the choice of TNF inhibitor for rheumatoid arthritis. Section 1.7 the Institute recommends that: "Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules." This guidance recognises the importance of required dose and implies that this should be a central consideration in the decision to prescribe. It is also clear that there are a number of parameters that will vary considerably across patients and that this in turn will affect estimates of cost-effectiveness. In the current ACD for the sequential use of TNF-α inhibitors, the Committee argues that it cannot assume infliximab vials will be used efficiently and on this basis it does not accept the revised ICERs as appropriate. Schering-Plough agrees that the optimally efficient use of vials cannot be assumed uniformly across the NHS, but argues that since vial wastage is such a crucial consideration affecting estimates of cost-effectiveness, ICERs for infliximab assuming no vial wastage must inform the Committee's recommendations. Therefore it is not possible to conclude that all relevant evidence has been taken into account.	The appeal panel decision (paragraph 142) states that "the Panel wishes to state clearly that it is not for it to direct the Committee as to the content of its guidance after reconsideration. It is open to the Committee to reaffirm its earlier guidance, or to change it, as it thinks fit". The Institute has completed analyses in accordance with the appeal panel requests and the appraisal Committee has considered the issue of vial wastage. See FAD sections 4.3.17
Schering Plough	**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?** Schering-Plough does not believe that the summaries of clinical and cost-effectiveness are reasonable interpretations on the evidence. We believe that the Committee's interpretation of the evidence is unsound in two main regards.	Please see responses below

Source	Comment	Response
Schering Plough	**Estimation of treatment effects for the economic evaluation of sequential use of TNF inhibitors** For the evaluation of TNF-α inhibitors against both conventional DMARDs and rituximab, ICERs ranging from £31,000–919,000/QALY are presented in the ACD (section 4.2.5). These are based on a number of sources for estimates of the effectiveness of anti-TNFs and DMARDs. *Table included but not reproduced*	Comments noted, please see responses below
Schering Plough	Schering-Plough believes that the ReACT trial provides the most relevant estimates for the effects of TNF-α inhibitors. The ReACT trial included a washout period in which patients did not receive TNFα inhibitor treatment for 2 months before enrolment., This trial design allows for an accurate estimate of the incremental treatment effect of TNF-α inhibitors over DMARDs since there is no carry-over of the effect of the preceding TNFα inhibitor. This is in contrast to the BSRBR study where measurement of the incremental effect treatment effect of a second TNFα inhibitor compared to a DMARD is problematic as described in some detail in the report by Mark Lunt ("Effect of a second course of anti-TNF therapy on HAQ following lack of response to the first course").	The ReACT study is specifically a study investigating the effect of adalimumab when used sequentially, rather than the effect of TNF inhibitors more generally. The Committee considered the use of both the ReACT study and the BSRBR data. See FAD section 4.3.12.
Schering Plough	We also believe that it is most important to model the effectiveness of DMARDs, as a comparator to sequential TNF-α treatment, using data from a late RA patient population. Scenarios 3 and 4 use evidence from the ATTAIN trial and this appears to be more appropriate than scenarios 1 and 2 which rely on early RA evidence as reported in TA130 (Chen et al. 2006). Using early RA data for DMARDs in the sequential TNF-α setting is likely to overestimate their effectiveness. . Overall we believe that, of the four scenarios presented in the ACD, Scenario 4 is the most relevant to the clinical population for sequential TNF-α treatment..	The Committee considered both the use of the data for conventional DMARDs from the original assessment report and that from the ATTAIN trial. See FAD sections 4.3.13, 4.3.14.

Source	Comment	Response
Schering Plough	The cost-effectiveness of a second TNF-α inhibitor compared to conventional DMARDs in scenario 4 is estimated in the range 31-39k/QALY. The ICER for infliximab falls to 22k/QALY if vial wastage is minimised. Under scenario 4, the cost-effectiveness of a second TNF-α inhibitor compared to rituximab is estimated to be in the range 32-55k/QALY. Within scenario 4, the range of ICERs reported is based on a range of HAQ reduction observed in the ReACT study from 0.33 to 0.51; The lowest estimate for HAQ reduction (0.33) is derived from a small sample of 63 patients HAQ reduction estimates in the remaining treatment groups (accounting for 595 patients) in the REACT study were 0.51, 0.52, 0.46, 0.55, 0.54. The overall mean estimate for HAQ reduction (n=899) was 0.48. Of the range of ICERs suggested by the Institute, the expected ICER will be towards the lower end of the reported range (£31k/QALY) and certainly not as high as the estimates, as shown in the table above, that are reported elsewhere in the ACD.	The Committee considered a scenario that used both data from the ReACT trial for TNF inhibitors and from the ATTAIN trial for conventional DMARDs. See FAD sections 4.3.12, 4.3.13, 4.3.14, 4.3.19, 4.3.20.
Schering Plough	**Treatment effect for DMARD after TNF** Whilst we argue that scenario 4 appears to be the most clinically relevant, it appears to underestimate the incremental treatment effect of a second TNF-α inhibitor as the effects of DMARDs, in patients who have already failed multiple DMARDs, are overestimated. Response to DMARDs in the economic model presented to the Committee has been assumed to be the same as the response seen in the methotrexate plus placebo arm of the ATTAIN trial. Importantly however, many patients are likely to receive DMARDs such as MTX alongside their anti-TNFs (e.g. 69% in ReACT study). The estimated effect of 2nd line anti-TNF treatment from the ReACT trial is already net of the effect of any background DMARDs such as MTX given alongside an anti-TNF, as patients received baseline DMARDS during the baseline period.	People in the ATTAIN study were on stable doses of DMARDs prior to randomisation to either placebo or abatacept. Therefore the effect of a conventional DMARD would not be captured in this study. See FAD sections 4.3.14, 4.3.15. In the ReACT study adalimumab was also added to an ongoing DMARD regimen, this will capture the effect of adalimumab and any synergistic effect of combining adalimumab with methotrexate, but, as Schering Plough state no effect of methotrexate.

Source	Comment	Response
Schering Plough	To illustrate this issue further with respect to the ACD: in the Institute's analysis, the response to a DMARD that might be given instead of or after a 2nd line anti-TNF is taken as the response seen in the MTX+Placebo arm of the ATTAIN trial. If the placebo effect seen in the ATTAIN trial was due to MTX, the use of MTX is already accounted for in the estimate from ReACT analysis. It is not clear that this response can be attributed to other, unnamed DMARDs that might be used instead of TNF-α inhibitors. If the response is due a placebo effect, it is not clear that this effect could be attributed to other DMARDs. Overall, Schering-Plough argues that reliance on the treatment effect observed in the placebo arm of the ATTAIN trial to represent the effect of DMARDs in patients who have previously failed DMARDs is inappropriate and is likely to underestimate the incremental effect of TNF-α inhibitors.	In the ATTAIN trial patients had to be on a stable dose of MTX or other DMARDs to ensure that the effect captured was not of DMARDs but of abatacept versus placebo. See FAD sections 4.3.14, 4.3.15. The Committee considered the appropriateness of the ATTAIN data as a measure of the treatment effect of a conventional DMARDs. See FAD section 4.3.14.
Schering Plough	**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?** Further to the comments set out above, Schering-Plough does not consider the provisional recommendations of the Appraisal Committee to be sound.	See responses to comments above
Schering Plough	**Are there any equality related issues that may need special consideration?** Schering-Plough is not aware of any particular equity related issues that require special consideration.	Comments noted
Wyeth	Whilst it would appear that the relevant evidence has been taken into account Wyeth has a number of concerns regarding the interpretation of the clinical and cost effective evidence and therefore do not consider that the provisional recommendations of the Appraisal Committee are sound or constitute a suitable basis for the preparation of guidance to the NHS.	Please see responses below.

Source	Comment	Response
Wyeth	**Executive Summary** Our concerns are set out below and explanation of each point is set out in the section following the Executive Summary. • There is no evidence that patients who do not respond to their first TNF-α inhibitor experience any further HAQ improvements on conventional DMARDs. • Balance of evidence in relation to HAQ values for a second TNF-α inhibitor has fundamentally changed and it is now not appropriate to consider BSRBR data as the primary source. • There have been serious breaches of NICE processes with regards to including rituximab as a comparator which has led to inappropriate analysis, and changing the discount rates which has introduced bias in the analysis which may have misled the appraisal committee. • Wyeth has update its economic model to incorporate consideration of these key points which clearly demonstrates that etanercept is not only cost-effective as a first-line TNF-α inhibitor, but also when used as sequentially after the failure of a first TNF-α inhibitor vs. non-biologic DMARDs and rituximab. This is substantiated by an analysis by the University of Sheffield on behalf of the BSR. • Wyeth believes that the current ACD is perverse in its consideration of the evidence, and that the institute has not followed its own procedures. This has led to an inappropriate preliminary recommendation for rheumatoid arthritis patients in England and Wales.	Please see responses below.
Wyeth	**There is no evidence that patients who do not respond to their first TNF-α inhibitor experience any further HAQ improvements on conventional DMARDs.** Studies identified by the DSU on the effectiveness of non-biologic DMARDs after TNF-α inhibitor failure investigated the use of novel treatments, in people in whom TNF-α inhibitor treatment had failed in comparison with placebo when added to an ongoing DMARD. The ACD correctly states that the placebo arm of these studies are not measuring the effect of an individual DMARD, but may provide an indication of the effect of conventional DMARDs when used in TNF-α inhibitor failures (mean Health Assessment Questionnaire (HAQ) improvement of 0.11). This improvement in HAQ can not be attributed to a switch to DMARDs as the patients in the study continued to receive DMARDs plus an added placebo. The improvement seen must be attributed to placebo effect and protocol driven care instead. Therefore this is inappropriate evidence to utilise this effectiveness values within the cost-effectiveness modelling.	The Committee recognised that the data from the abatacept clinical trial reflected the effect of placebo and study enrolment. However, no studies were identified that investigated the effect of an individual DMARD. Comparable data were used in the appraisals of rituximab and abatacept. See FAD section 4.3.14

Source	Comment	Response
Wyeth	This has led to an overestimation of the HAQ improvements of conventional DMARD therapy in patients whom have experienced a lack of efficacy with a TNF-α inhibitor, driving higher cost-effectiveness ratios. In the updated review of the effectiveness of conventional DMARDs after TNF-α inhibitor failure the DSU was not able to identify any evidence that directly considers the effectiveness of non-biologic DMARDs in the population of interest. Evidence from the BSRBR suggests that the response from a DMARD post TNF-α inhibitor maybe only slightly different in terms of EULAR response. However, new evidence from the BSRBR is available demonstrating no further improvement based on HAQ.	The Committee considered the use of the ATTAIN data. See FAD section 4.3.14. The evidence from the BSRBR demonstrates no change in average HAQ. This is not necessarily no effect as RA is a progressive disease. The data in the Hyrich paper also demonstrate variation in response with 22% of people having a HAQ improvement of 0.22 or more. See FAD section 4.1.14, 4.3.7.
Wyeth	**Appropriate evidence for no HAQ improvement on conventional DMARDs** Hyrich, et al. used data from the BSRBR to assess whether switching improves longer term outcomes, by comparing changes in HAQ scores one year following lack of response to a first TNF-α inhibitor. This study concluded that patients with long-standing disease who do not respond to their first TNF-α inhibitor, discontinue this drug and receive no further biologic treatment in the subsequent 12 months do not experience any further mean improvement in HAQ score over this period. Patients who continue on their first TNF-α inhibitor despite suboptimal improvement in disease activity gain further improvements in HAQ, however the best improvement was seen in patients whom switched to a second TNF-α inhibitor. Table included but not reproduced	The Committee considered the data from the BSRBR. See FAD section 4.3.7. In addition, as Wyeth notes in their comments about its use to measure the effectiveness of TNF inhibitors, there are issues with the generalisability of the data set and an issue of timing because the point at which people change treatment does not coincide with follow up assessment. These factors affect both the interpretation of the TNF inhibitor and the conventional DMARD data.
Wyeth	Whilst the ACD implies a reasonable response based on EULAR response, this recent publication by Hyrich and colleagues from the BSRBR demonstrates no HAQ improvement. In the absence of any evidence on return to a conventional DMARD the BRAM should be rerun with a zero HAQ multiplier as the base case. Any short-term improvement must be so small that it will be less than 0.045 which is the accepted measure for HAQ deterioration for DMARD therapy.	The evidence from the BSRBR demonstrates no change in average HAQ. This is not necessarily no effect of treatment because RA is a progressive disease. The data also demonstrate variation in response with 22% of people having a HAQ improvement of 0.22 or more. See FAD section 4.1.14, 4.3.7.

Source	Comment	Response
Wyeth	**Balance of evidence in relation to HAQ values for a second TNF-α inhibitor has fundamentally changed and it is now not appropriate to consider BSRBR data as the primary source.** The mean HAQ improvements reported by salient studies support the use of higher effectiveness values for a second TNF-α inhibitor. In the present technology appraisal, evidence for the clinical effectiveness of the use of a second TNF-α inhibitor was taken from a systematic review completed by the DSU. The lower HAQ improvement from the BSRBR data drives the higher cost-effectiveness values. The literature search by the DSU found a number of articles showing that the HAQ improvements in these patients were greater than in the data from the BSRBR.	The Committee considered both the use of the BSRBR values and the values reported in the adalimumab ReACT study. See FAD section 4.3.7, 4.3.12, 4.3.15.
Wyeth	The majority of studies identified from the literature considered eligible for inclusion in the full analyses reported DAS and EULAR scores. Only a minority reported HAQ scores. The largest data sources for HAQ scores with sequential TNF-α inhibitors were the ReACT trial and the BSRBR. Due to population included in the register and the timing of collection of the efficacy measures the BSRBR should not be used to inform the effect size of a second TNF-α inhibitor. The ReACT study in contrast identifies HAQ values collected at the appropriate time points. However, it may underestimate the true treatment effect for etanercept following adalimumab or infliximab, given the reasons mentioned elsewhere in this document. The HAQ changes observed in the different data sources are provided in table 2. *Table included but not reproduced*	The Committee considered both the use of the BSRBR values and the values reported in the adalimumab ReACT study. See FAD section 4.3.7, 4.3.12, 4.3.15.
Wyeth	The mean HAQ improvements reported by these studies support the use of a higher effectiveness value for the TNF-α inhibitors which will result in lower cost-effectiveness results. These findings together with no HAQ improvements on non-biologic DMARDs influences the cost-effectiveness results of the two TNF-α inhibitor strategy compared to a single TNF-α inhibitor and then DMARD, or rituximab as shown in the outputs from the Wyeth model in table 3. These results indicate, that the use of sequential TNF-α therapy is a cost-effective use of NHS resources, and should therefore be recommended. *Table included but not reproduced*	The studies have been considered by the Committee. The effectiveness data from these studies are comparable to those in the ReACT study. See FAD sections 4.1.2, 4.1.4, 4.1.6.

Source	Comment	Response
Wyeth	**Secondary loss of efficacy demonstrates higher efficacy for 2nd TNF.** In the ReACT study, Bombardieri, et al. evaluated the effectiveness and safety of adalimumab in patients with RA who previously discontinued TNF-α antagonists for any reason in clinical practice. They reported an over all mean HAQ improvements of 0.33 – 0.55 at week 12 for patients whom required switch. These patients included those with intolerance to, no response, or lost response to a TNF-α inhibitor over time. The average weighted mean HAQ response was the lowest in patients whom showed no response to TNF-α inhibitor (0.44), and highest in patients with a loss of response (0.51). There is no reference within the ACD to the fact that the range of ICERs for sequential TNF-α inhibitor therapy in patients with secondary loss of efficacy is less than for those with primary efficacy failure. By incorporating these HAQ change estimates into our model, it was demonstrated that a second TNF-α inhibitor would be considered cost-effective, when compared against either a conventional DMARD or rituximab. Specifically, it was shown that, when a HAQ change of 0.4 was used for the second TNF-α inhibitor, cost-effectiveness ratios of £13,841 (versus DMARD) and £6,966 (versus rituximab) were observed. When discount rates of 3.5% were used, the ICERs were £23,538 and £10,526 respectively (Table 3). Again, this estimation of HAQ change indicates that the use of a second TNF-α inhibitor would be considered to be a cost-effective use of NHS resources.	The Committee considered the clinical effectiveness data available comparing response rates in people with primary and secondary failure. See FAD section 4.3.5. New data are only accepted by prior agreement with the Centre Director. See the guide to the technology appraisal process section 4.5.2.10. See email communication sent 11.06.08. The Committee has considered the assumptions that underpin these analyses. See FAD sections 4.3.12, 4.3.14, 4.3.15, 4.3.19, 4.3.20.

Source	Comment	Response
Wyeth	**Current cost effectiveness analyses in the ACD of the sequential use of TNF-α inhibitors have failed to estimate the full cost-effectiveness of two sequential TNF-α inhibitors compared with one TNF-α inhibitor and a standard DMARD** The Birmingham Rheumatoid Arthritis Model (BRAM), like the Wyeth RA model, was designed to estimate the costs and benefits (in terms of QALYs) derived from a sequence of treatments of RA and to compare the costs and benefits of different treatment sequences. However the analysis of the sequential use of TNF-α inhibitors conducted to date only counts costs and benefits from the point of initiation of a second TNF-α inhibitor thus failing to capture the full cost effectiveness of a sequence of two TNF-α inhibitors. Given that the benefit derived from a second TNF-α inhibitor would be expected to be dependent on its relative effectiveness compared with the first TNF-α inhibitor (see below) this serves to underestimate the total cost effectiveness of a more effective TNF-α inhibitor followed by a less effective TNF-α inhibitor compare with the converse (i.e. a less effective TNF-α inhibitor followed by a more effective treatment). This bias would be avoided if the BRAM was rerun for each combination of first and second TNF-α inhibitor and corresponding comparator sequence of TNF-α inhibitor followed by return to standard DMARD, counting costs and benefits from the point of initiation of the first TNF-α inhibitor.	This appraisal considers the decision as to whether to initiate a second TNF inhibitor once the first has failed, suggesting that the approach taken by the assessment group model is appropriate. The committee did not consider that there was sufficient evidence to distinguish between the TNF inhibitors in terms of their clinical effectiveness for either first or second use (see below).
Wyeth	**Some HAQ improvement values utilised in the further cost effectiveness analysis of sequential TNF-α inhibitors, have been extrapolated from the ReAct study inappropriately** From its systematic review the West Midlands Health Technology Assessment Group identified a rank order for the effectiveness and cost effectiveness of the initial use of the available TNF-α inhibitors (etanercept > adalimumab > infliximab). It is reasonable to assume that differences in the effect on HAQ between the various TNF-α inhibitors observed during initial treatment would also be manifest in a second course of therapy following lack or lost of response to the first.	For the first use of TNF inhibitors the Committee concluded that in the absence of any head to head comparisons the data were insufficient to distinguish between the 3 TNF inhibitors of clinical or cost effectiveness grounds. See TA130 section 4.3.3. The Committee have also considered whether there is sufficient evidence to distinguish between the TNF inhibitors for their second use, and between different sequences of TNF inhibitors. See FAD section 4.3.5.

Source	Comment	Response
Wyeth	This interpretation is supported by the albeit limited evidence identified in the update report by the Decision Support Unit (DSU) on the sequential use of TNF-α inhibitors dated January 2008. In particular the large open label trial of the effectiveness of adalimumab in patients with a history of TNF-α inhibitor therapy (ReAct) clearly identifies that response to adalimumab is greater in patients failing infliximab than in patients failing on etanercept treatment. Whilst utilising HAQ improvements for sequential use of adalimumab after failure of either etanercept or infliximab from this study would seem entirely appropriate to assume the converse i.e. the same effect for etanercept and infliximab after failure of adalimumab is without foundation, would lead to an underestimation of the relative effectiveness of etanercept and should be used with caution.	The estimates from the ReACT adalimumab study are comparable to or higher than the estimates from the etanercept studies included in the Wyeth table 2. Therefore the interpretation that the effectiveness of etanercept has been underestimated in the current analyses is not supported by the evidence available.
Wyeth	**There have been serious breaches of NICE processes with regards to including rituximab as a comparator which has led to inappropriate analysis, and changing the discount rates which has introduced bias in the analysis which may have misled the appraisal committee.** Inclusion of rituximab as a comparator Rituximab was not considered as part of the original scope of this appraisal. Therefore it should not be included for consideration. Rituximab has not assessed within the BRAM to the same extent as the existing TNF agents. This could have biased the analysis and led to an inappropriate decision by the appraisal committee.	Rituximab was included in this appraisal with agreement of the Department of Health because of the publication of NICE guidance on rituximab. The scope of this appraisal does not preclude the inclusion of rituximab, as the scope states both treatment strategies without TNF inhibitors and other TNF inhibitors as appropriate comparators. The data for rituximab were based on the assumptions accepted by the Committee in the appraisal of rituximab. The data are taken from the registration trial. Rituximab is a comparator in this appraisal and therefore may not be assessed in the same way as the technologies for which recommendations would be made.

Source	Comment	Response
Wyeth	Strong medical reasons to prefer sequential TNF-α inhibitor use over the use of rituximab. The manufacturers of licensed TNF-α inhibitor drugs are required to follow up and collect safety data on patients in their RA clinical trial programmes. Safety data from these databases have supported the long-term use of this drug class for the treatment of moderately to severely active RA, with the adalimumab and etanercept safety databases contributing 16,973 and 6,448 (early RA + longstanding RA) patient years of clinical trial and clinical practice experience, respectively. The European licence for rituximab in RA states that rituximab should be given in combination with methotrexate. It does not provide any option for the treatment of patients who are intolerant of MTX with rituximab monotherapy. This leaves these patients, according to current NICE RA guidance, with no options but to return to treatment with ineffective traditional DMARDs and corticosteroids, many of which they would have already failed.	The Committee considered the adverse effect profile of rituximab. See FAD section 4.3.19. The Committee considered the use of TNF inhibitors in people who were contraindicated to rituximab or to methotrexate. See FAD section 4.3.20.
Wyeth	The administration of rituximab requires admission to a day ward, which must be equipped with full resuscitation equipment. Adalimumab and etanercept in contrast can be administered at home, which is more convenient for the patient. Published data from the rituximab clinical trial safety database are currently limited, and non-responders to rituximab 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. Therefore, not recommending a sequential use of TNF-α therapy will further severely limit the already limited treatment options for patients with RA.	Costs of administration are considered in the model. The Committee considered the adverse effect profile of rituximab. See FAD section 4.3.19.

Source	Comment	Response
Wyeth	A nine month dosing interval for rituximab, compared with 7 months seen in clinical practice, results in overestimation of its cost-effectiveness vs. second TNF-α inhibitor. The current cost-effectiveness analyses of TNF-α therapy vs. rituximab are based on a cost of rituximab taken from TA126, which was based on a mean retreatment period of 9 months. Roche have also published an analysis of the open label extension study which included additional repeated treatment courses in order to establish the optimum frequency of repeated treatment with rituximab. This analysis identified a consistent period for 30 weeks between first and second retreatment courses (30.9 and 30.1 weeks respectively). An estimate of time between multiple repeat treatment courses is more representative for inclusion in a long-term treatment model than an estimate based on time to first retreatment only. A period of 30 weeks (210 days) is the most appropriate estimate of the interval between repeat rituximab treatment courses. This value should be included in the economic model of the long-term cost-effectiveness of rituximab in patients who have failed at least one TNF-α therapy. Inclusion of this increased dosing frequency in the Wyeth economic model results in the following estimates of cost-effectiveness (Table 4). *Table included but not reproduced*	The Committee considered the use of a more frequent dosing schedule for rituximab. See FAD section 4.3.19.

Source	Comment	Response
Wyeth	**It is inappropriate to change the discount rate from that used in TA130.** The consideration of TNF-α inhibitors for sequential use was part of the original scope of the technology appraisal for etanercept, adalimumab and infliximab in RA. In order to avoid delay in issuing guidance on the use of these technologies after traditional DMARDs, the use of these technologies for sequential use was deferred. Therefore, this ACD merely extends the guidance in TA130 and does not represent a new appraisal. This status is backed up by the Institute not issuing a new scope, nor inviting consultees to submit updated evidence for the consecutive use of TNF-α inhibitors. Therefore, it is surprising that the Institute has changed its decision-making criteria for this extension to TA130. Using the discount rate originally used in TA130 would have resulted in considerably lower incremental cost-effectiveness ranges for all the TNF-α inhibitors, thereby making it more likely that the TNF-α inhibitors would have been recommended for sequential use. Further, an additional comparator, rituximab, was added to this extension of TA130 and consultees were not invited to submit evidence with regards to this agent versus our own. Consequently, the analysis should be re-run using the original discount rates. In addition, we enclose in our response (Table 4) data comparing etanercept with rituximab which we believe will materially affect the provisional recommendations in the ACD.	The Committee considered the use of the different discount rates noting that the 3.5% discount rates have been in operation for several years and have been used in other appraisals for the same condition. However, the Committee concluded that the use of different discount rates would not alter their consideration of the clinical effectiveness evidence. See FAD section 4.3.16.

Source	Comment	Response
Wyeth	**Effect of the tone of the Overview on the Appraisal Committees decision making** Wyeth are concerned that the balance of the Overview prepared for the Appraisal Committee may inadvertently lead the Committee to not recommend the sequential use of TNF-α inhibitors. For example the net effect of changing the discount rate was not explained within the report. With all else being equal this serves to raise the incremental cost effectiveness ratios of analysis performed to inform this ACD compared with values used to inform TA130. The Overview repeatedly refers to the use of an initial HAQ improvement of 0.11 for DMARDs derived from the abatacept study as 'assuming no treatment effect while on conventional DMARDs'. This is misleading; utilisation of a zero for HAQ improvement would assume no treatment effect. This scenario actually assumes a treatment effect of up to a third of that seen on sequential TNF-α inhibitors despite the lack of evidence to attribute such benefit. Wyeth also believe that it should be make clear to the appraisal committee that the results presented from the BRAM do not include costs of hospital admissions or joint replacement surgery which would serve to further lower the incremental cost effectiveness ratios for TNF-α inhibitors compared to standard DMARD therapy.	The overview is one of a number of documents seen by the Committee and summarises the analyses completed. The additional analyses were not completed using both sets of discount rates. Therefore the effect of changing them could not be included in the overview. The overview provides a summary of the clinical effectiveness data from which the model inputs were derived, therefore the value used in the model is clearly shown not to be zero (see table 4 presenting the results of the abatacept clinical trial, and the text on page 17 describing the source of this value). The overview does not state "assuming no treatment effect" rather it states "assuming no active treatment effect" the data from the ATTAIN study cannot be considered to reflect the efficacy of DMARDs as it is taken from the placebo arm of a clinical trial. Therefore the effect seen in the ATTAIN trial cannot be attributed to an active treatment. The FAD clearly states the input that was used in the model and which formed the Committee consideration. See FAD section 4.2.3, 4.3.14. The Committee considered the inclusion of offset costs in the economic model. See FAD section 4.3.11.

Source	Comment	Response
Wyeth	**Wyeth have update its economic model to incorporate consideration of these key points which clearly demonstrates that etanercept is not only cost-effective as a first-line TNF-α inhibitor, but also when used as sequentially after the failure of a first TNF-α inhibitor.** Results from the updated economic model demonstrate cost-effectiveness of sequential TNF- α inhibitor use compared with conventional DMARDs and rituximab. A deterministic Markov model was developed to predict the lifetime costs and health outcomes associated with treatment for patients with RA in the United Kingdom. Two treatment sequences are considered side by side. It is important to consider the impact of treating patients with different treatment sequence combinations so a number of alternative scenarios were studied. For each treatment the initial (i.e. first six months), medium-term (first three years) and long-term (after three years) effects on the Health Assessment Questionnaire (HAQ) score are predicted. HAQ scores at each time period determine each patient's utility (QALYs), resource use and mortality.	New data are only accepted by prior agreement with the Centre Director. See the guide to the technology appraisal process section 4.5.2.10. A separate response has been sent regarding submission on new data. See email communication sent 11.06.08.

Source	Comment	Response
Wyeth	Effectiveness data (HAQ progression, serious adverse events and mortality) were derived from a combination of the results from the published literature cited in this appraisal. The TNF-α inhibitor data was pooled to establish the effectiveness of an average TNF-α inhibitor for use as a first TNF-α inhibitor therapy and then the effectiveness of a second TNF-α inhibitor was varied across a range of values to incorporate the range of values reported in the literature. Costs were also pooled in this way to create a generic cost of a standard TNF-α inhibitor. Unit cost data were drawn from established national (UK) databases, and were multiplied by resource use to predict the total cost. Resource use was estimated through published data and expert clinical opinion. Costs and outcomes were both discounted at 3.5% in the base case and then discounted at 6% costs and 1.5% outcomes in an alternative scenario. The cost-effectiveness results of the two TNF-α inhibitor strategy compared to a single TNF-α inhibitor and then DMARD strategy are shown in the table below. The table also shows the cost effectiveness of switching between each TNF-α inhibitor. The comparison with rituximab has been shown previously (Table 4). Please note that, because HAQ outcomes are measured using increments of 0.125 units, the model's outcomes are not sensitive to very small changes in HAQ inputs. As such, results are presented for ranges of HAQ changes. *Table included but not reproduced*	New data are only accepted by prior agreement with the Centre Director. See the guide to the technology appraisal process section 4.5.2.10. A separate response has been sent regarding submission on new data. See email communication sent 11.06.08.
Wyeth	**Additional model using different methods demonstrates the cost-effectiveness of the use of a second TNF-α inhibitor.** Economic modelling carried out using the BSRBR data of sequential TNF-α inhibitors indicates that use of a second TNF-α inhibitor is equally cost-effective as the use of a first one. This analysis is based on 629 patients receiving a second TNF-α inhibitor from the BSRBR data.	The Committee considered the modelling carried out using the BSRBR data. See FAD section 4.3.9.

Source	Comment	Response
Wyeth	The response to a second TNF-α inhibitor was modelled using Disease Activity Score (DAS) response, which is a different approach to that applied by NICE/BRAM and the manufacturers which assumes that mean HAQ improvement is the key driver. Further this model takes into account the shorter duration of therapy with a second TNF-α inhibitor vs. the time on therapy with a first TNF-α inhibitor. The NICE analysis assumes the duration of therapy on a second TNF-α inhibitor to be equivalent to that on a first agent, which raises the costs for these therapies and therefore leads to higher cost-effectiveness results.	The cost effectiveness analysis submitted by ARMA is based on a model that uses DAS as a means of categorising patients before calculating the mean HAQ improvement for people according to their response criteria. The mean HAQ improvement is then mapped to EQ-5D. It does not therefore avoid weaknesses of HAQ. The model from Wyeth also uses mean HAQ improvement, and produces low ICERs. Therefore the use of mean HAQ per see does not appear to be driving the difference in the ICERs. See FAD section 4.3.9. The BSRBR analyses were completed using both an assumption that people remain on their second TNF inhibitors for as long as their first, and using the rates actually observed in the BSRBR. The estimates of cost effectiveness are higher if the rates observed in the BSRBR are used, rather than the assumption that duration of therapy is the same for first and second TNF inhibitor. This is because the longer that someone is on a TNF inhibitor the greater the benefits that are accrued from differential underlying disease progression.

Source	Comment	Response
Wyeth	The BSR analysis comparing 2 TNF-α inhibiotrs in a sequence with conventional therapy results in an incremental cost per QALY of £24,570. Probabilistic sensitivity analysis gives an 85% chance that the true cost-effectiveness is less than £30,000. This is a substantially lower cost/QALY as from the BRAM model on which the committee based its decision.	The BSRBR data comparing a scenario with a single TNF inhibitor with a scenario where two TNF inhibitors are used in a sequence produces and ICER of £27,063 per QALY. The ICER of £24,570 relates to a comparison of no TNF inhibitors versus 2 TNF inhibitors which does not reflect current standard care. PSA was not completed for the comparison of 1 TNF inhibitor versus 2 TNF inhibitors See FAD section 4.3.9. £27,063 is not substantially lower than the lower estimates in the BRAM if you take into consideration the different discount rates used. Sensitivity analyses for first use of a TNF inhibitor in the ARMA submission demonstrated that using discount rates of 3.5% instead of 1.5% and 6.0% increase the ICERS from approximately 23,000 to 32,000 per QALY. The ICERs for sequential use would change in a similar magnitude. See FAD section 4.3.9.

Source	Comment	Response
Wyeth	In comparison to analyses based on the BSRBR data, using this DAS driven model, the model which led to the current ACD probably reduces the size of effect of the second TNF due to its focus on the mean HAQ reduction, produces a greater effect for conventional DMARDs, as well as increasing the cost of the TNF-α inhibitor side of the equation through the assumption of equivalent duration of treatment. This combination drives higher cost-effectiveness results for consecutive TNF-α inhibitor use. Additionally, the patients enrolled in the BSRBR have longer disease duration. The mean disease duration was 12 years at which time the reversibility of HAQ is limited. The patients enrolled in the BSRBR have been the more severe established cases, but now these have been treated patients with shorter disease duration and thus a greater potential for HAQ improvement will be receiving treatment. Consequently the BSRBR data represent a worse case scenario. By using a DAS driven model Brennan et al have avoided this weakness of HAQ driven models for late stage disease. A further strength of this analysis is that the control cohort of patients not receiving TNF-α inhibitors is used to estimate the efficacy of conventional DMARDs. These patients may have a higher response as patients whom received a previous TNF-α inhibitors. This analysis supports the cost-effectives of the sequential use of TNF-α inhibitors.	The cost effectiveness analysis submitted by ARMA is based on a model that uses DAS as a means of categorising patients before calculating the mean HAQ improvement for people according to their response criteria. The mean HAQ improvement is then mapped to EQ-5D. It does not therefore avoid weaknesses of HAQ. The model from Wyeth also use mean HAQ improvement, and produces low estimates of cost effectiveness. Therefore the use of mean HAQ reduction per see does not appear to be driving the difference in the ICERs. See FAD section 4.3.9. The Committee considered the data from the BSRBR and the economic analyses submitted by ARMA. See FAD section 4.3.9.

Source	Comment	Response
Wyeth	**Conclusion** In conclusion Wyeth maintains that the analyses which led to this current ACD were insufficient. The institute must use the same discount rate as used in TA130. Further, the institute should to take into account the higher effectiveness of a second TNF-α inhibitor as reported from recent clinical trials, and apply a zero HAQ improvement for non-biologic DMARDs. In addition the institute may choose to perform subgroup analyses in patients whom experience intolerance to TNF-α inhibitor, no response, or lost response over time, which will lead to a range of cost-effectiveness result which will be more in favour for the sequential use of TNF-α inhibitors. Taken together these requirements will lead to lower cost-effectiveness results for the consecutive use of TNF-α inhibitors and the decision that such use would represent cost effective use of NHS resources.	The Committee considered the use of different discount rates. See FAD section 4.3.16. The Committee considered the clinical effectiveness of TNF inhibitors and conventional DMARDs. See FAD sections 4.3.3, 4.3.4, 4.3.6, 4.3.7, 4.3.8, 4.3.12, 4.3.14. NICE recommends a sequential TNF inhibitor for people who experience intolerance to their first TNF inhibitor in the first 6 months. The analyses option B and option C take into account primary and secondary non responders. See FAD section 4.2.3, 4.3.5.

Source	Comment	Response
ARMA	**i). Do you consider that all of the relevant evidence has been taken into account?** We feel that the committee has failed to take all of the evidence into account on three counts: Returning to conventional disease modifying drugs following the failure of the first anti-TNF therapy. Page 5 of the report from Abbott shows data from the British Rheumatoid Arthritis Outcome Study Group. Patients randomised to either an aggressive treatment or symptomatic treatment arm (both arms employing conventional disease modifying drugs) showed progressive deterioration of HAQ over a three year follow up. These patients had a mean disease duration of 12.5 years, had failed on a mean of 1.4 previous DMARDs, and had a gradual HAQ deterioration of 0.15 over the three year follow-up. This is important data on the response to conventional DMARDs in UK clinical practice, albeit in patients not exposed to anti-TNF at the time of follow-up.	The Committee has considered the BROSG study. The BROSG study includes 2 treatment arms both of which include a sequence of conventional DMARDs. People start treatment and switch treatment at a point defined by their disease characteristics. Therefore this study cannot be considered a study of an individual DMARD and could no be used in the economic modelling. Without people starting treatment at the same time and without any comparator arm that does not include DMARDs, the study cannot demonstrate that conventional DMARDs have no effect, the published report indicates that in the aggressive and symptomatic treatment arms 50% and 64% of people were defined at the end of the study as treatment successes, respectively. The study does show that overtime people on DMARDs get worse, this is incorporated into the cost effectiveness analyses as underlying HAQ progression of 0.045 units of HAQ a year. See FAD sections 4.1.13, 4.3.8.
ARMA	An important report from the BeSt study was discussed by the clinical specialists in the Appraisal Committee meeting, in which patients failing on methotrexate (up to 25mg) were highly unlikely to respond to any other disease modifying drug, either if replaced in sequential DMARD monotherapy, or if added to methotrexate in a combination therapy. All patients going onto anti-TNF must have had a trial of methotrexate according to NICE guidelines, and therefore returning to conventional DMARDs following the failure of a first anti-TNF is highly unlikely to be an effective strategy. The ACD fails to adequately reflect this.	The BeST study investigates the efficacy of different treatment sequences. As with the BROSG study people switch treatments based on their disease characteristics. The point at which people switched treatments was when they stopped having low disease activity (DAS44 equal to or greater than 2.4). The 2 year results show that a proportion of patients were maintained on DMARDs with low disease activity after the failure of their first DMARD. See FAD section 4.1.12, 4.3.8.

Source	Comment	Response
ARMA	The fact that the BSRBR data is on patients where only 58% received concomitant methotrexate was discussed at committee, but is not mentioned in the ACD. This is important because a large amount of data has emerged supporting the increased efficacy of combinations of anti-TNF with methotrexate. Consequently current UK practice would be always to combine the two unless methotrexate is not tolerated. No account has been taken of this in the analyses.	The Committee recognised that data from the BSRBR may not reflect current clinical practice. See FAD section 4.3.12.
ARMA	There was considerable discussion at the Appraisal Committee about concerns over rituximab being the only available biological therapy following the failure of the first anti-TNF. In particular our concerns surrounded the efficacy of these drugs in seronegative disease. The DANCER trial showed no efficacy in seronegative disease compared with placebo. In REFLEX, the efficacy of rituximab in seronegative disease was reduced in comparison with seropositive disease. The European League Against Rheumatism guidelines on the use of Rituximab suggest that it should not be used in seronegative disease. Current trials of rituximab and the humanised form of the drug ocrelizumab are only being conducted in patients with seropositive RA. In the BSRBR 28% of patients were seronegative for rheumatoid factor. This suggests that a substantial proportion of patients who go onto rituximab following the failure of a first anti-TNF are unlikely to gain a satisfactory response. By contrast, rheumatoid factor status does not predict the response to a second anti-TNF. The ACD makes no mention of the considerable discussion that took place around this point, which is not acceptable.	The Committee considered the use of a second TNF inhibitor in the group of people with seronegative RA. See FAD section 4.3.20.

Source	Comment	Response
ARMA	**ii). 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?** We feel that the committee has failed to take all of the evidence into account on three counts: 1. We strongly disagree with the concluding sentence in 4.3.9 on page 25 of the ACD, and feel for all the reasons stated above, and the evidence we presented at the Appraisal Committee, that the effect of conventional DMARDs would be substantially less than that achieved in the placebo arm of the abatacept trial. We mentioned at committee that there is a considerable placebo effect of participating in a trail, receiving regular care and attention and placebo injections. This would artificially elevate the benefits of the placebo arm in the abatacept trial. We feel that the overall evidence would support substantially less benefit from patients returning to conventional DMARDs following the failure of anti-TNF, and the ACD does not interpret the evidence appropriately.	The Committee considered the clinical effectiveness of conventional DMARDs when used in this patient population. See FAD sections 4.3.6, 4.3.7, 4.3.8, 4.3.14, 4.3.15.
ARMA	2. The comments in 4.1.10 do not reflect the highly contentious nature of analysis performed by the Decision Support Unit in the paper entitled “The effectiveness of non-biological DMARDs after anti-TNF α inhibitor failure.” In summary, this analysis was performed on patients that have not previously failed a biological therapy, looks at EULAR response criteria and not change in HAQ, and makes assumptions about the impacts of increasing age, and disease duration that go well beyond the robustness of the data. We feel that it is inappropriate for the ACD to state that this study shows only slight decrease in EULAR response, when it is our strong feeling (expressed at the Appraisal committee) that this conclusion requires too many steps of faith.	The regression analysis used to perform this analysis is similar to that performed in the BSRBR economic analyses. The FAD clearly states that this is the EULAR response data is for a group of people who had not failed a TNF inhibitor. See FAD section 4.1.10.

Source	Comment	Response
ARMA	3. We have no recollection of the conclusions of the discussions on discounting that are mentioned in 4.3.7 on pages 23 and 24 of the ACD. We know of no evidence to suggest that different discount rates would alter the cost-effectiveness of the BSRBR analysis which used DAS28 as opposed to HAQ. We continue to feel strongly that the over-reliance on the BRAM to the exclusion of other models is inappropriate. We re-iterate that HAQ scores mainly reflect joint damage in established RA and the impact on disease activity of biologics is more relevant in this group of patients than impact on function.	The ARMA submission includes sensitivity analyses for first use of a TNF inhibitor using both sets of discount rates 1.5% and 6% and 3.5% and 3.5%. These show that using discount rates of 3.5% the analyses of first use increase the ICERS from approximately 23,000 to 32,000 per QALY. In the sequential analyses the ICER of 27,000 would rise in a comparable way to the analyses of first use. The cost effectiveness analysis submitted by ARMA was also based on utility derived from EQ-5D which was mapped from HAQ. The model used DAS as a means of categorising patients before calculating the HAQ improvement for people according to their response criteria. See FAD sections 4.3.9, 4.3.16.
ARMA	**iii). 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?** For all the reasons stated above we do not feel that these provisional recommendations are sound, and therefore do not constitute a suitable basis for the preparation of guidance to the NHS.	Please see responses above
ARMA	**iv). Are there equality issues that may need special consideration?** We believe there are two equality issues that need consideration: Patients elsewhere in the world, including near neighbours such as the republic of Ireland and France, have far greater access to a first and a second anti-TNF at a time when the EC is trying to harmonise aspects of healthcare across different member states. Patients who are very disabled with high disease activity are discriminated against by the BRAM for the reasons we have highlighted above.	The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. Please see response above

Source	Comment	Response
Arthritis Care	We welcome the opportunity to respond to NICE's preliminary recommendations on the sequential use of TNF-α inhibitors in the treatment of rheumatoid arthritis. Rheumatoid arthritis is a debilitating long-term condition, which can have a profound impact on the lives of those who have the condition. Successful treatment with TNF-α inhibitors has been positively life-changing for many people with rheumatoid arthritis. We are disappointed that following the successful appeal in 2007 and re-consideration of the topic, NICE has not recommended the sequential use of these therapies.	For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 2). Please see responses to comments below.

Source	Comment	Response
Arthritis Care	This recommendation comes immediately after the NICE decision not to recommend abatacept for rheumatoid arthritis. Arthritis Care is concerned that people with rheumatoid arthritis in England and Wales are step by step having their choices limited and will be missing out on therapies which could have a profound positive effect on their quality and length of life. In concert with clinical evidence suggesting the efficacy of sequential use, (as detailed in the Arthritis and Musculoskeletal Alliance submission supported by Arthritis Care) people currently using TNF-α inhibitors feel very strongly that they must be given the opportunity to switch from one therapy to another if the first fails to work for them. One user in her thirties is frightened that one day her current therapy may cease to work. She says: "I recently had an operation which required me to take 9 weeks off from my anti-TNF therapy. As a result I experienced a severe flare up. As well as experiencing constant pain I had no concentration and my energy levels were low. My work was badly affected. This made me realise what life could be like if I were denied an effective treatment. I have a very aggressive type of rheumatoid arthritis and getting the right drugs is very important or I find it hard to have a "normal" life. I want to work, I want to pay my way, don't want to be stuck at home or taking up hospital beds. This decision is very short-sighted. Since taking anti-TNF therapies, there has been no further deterioration in my condition for the first time ever. Without the correct medication I would end up costing more in benefits and NHS resources for the rest of my life. Once you know that life can be better, it's a scary prospect that it could have been you who was denied this treatment, had the option of that life taken away. The more people know about this decision, the angrier they will be. How can people be in better health and then denied it? Don't deny people the right to live their life when the means are right in front of them."	For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 2). The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendations.
Arthritis Care	Furthermore, this decision is in conflict with the precedent set in other EU nations, where sequential use is already available. When making a decision that goes against the grain of policy in Europe there must be extremely compelling evidence which we believe is not apparent in this case. To disallow switching to alternative TNF-α inhibitors when it is allowed elsewhere is unjust and will lead to England and Wales being the "poor man" of Europe, indeed of the UK itself.	The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions.

Source	Comment	Response
Arthritis Care	A person with arthritis in Northern Ireland or Scotland may still have access to further TNF-α inhibitors, creating stark inequalities across the UK. The following quote is from a man who has had access to three TNF-α inhibitors over the past 5 years, in Northern Ireland; "I have had rheumatoid arthritis for 27 years, I was diagnosed aged 12. I had been through many different kinds of medication- anti-inflammatories, gold injections and methotrexate. After receiving my first anti-TNF therapy in 2001, my life completely changed. I didn't need anti-inflammatory medication any more, I was active and able to live my life to the full. Unfortunately, in spring 2006 I unexpectedly developed an allergic reaction to the therapy and it gradually stopped working. I experienced a heavy and frightening relapse. Unable to get out of bed, I relied on my son to care for me where before I had been independent. I ended up being hospitalised for several weeks, given morphine for the pain. I switched to a different anti-TNF therapy. This pulled me out of the worst of it. It managed the condition, but I still felt fatigued and required anti-inflammatories. After several months it was decided that this was not working as well as it could, and I switched to a third anti-TNF. This brought me back completely, I got my old energy back. In fact, I feel stronger now than I was on my first therapy. I never understood what it must be like to be diagnosed with arthritis late in life, to lose the mobility you once had. Now I know. When my anti-TNF therapy failed, I was agitated, depressed, house-bound and reliant on other people. I have a new appreciation for life now. You cannot and should not put a price on someone's quality of life. These drugs mean the difference between a full life and one of dependence, pain and depression for me. The decision not to allow switching to alternative anti-TNF therapies is frightening".	The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 2).

Source	Comment	Response
Arthritis Care	A TNF-α inhibitors user from Scotland adds; “I had an allergic reaction to infliximab and was put on etanercept. I was shocked by how bad my condition got when I could no longer take infliximab. I spoke to my rheumatologist and he told me that without the option of using etancercept he doesn’t know what we could have done. Thankfully it worked. Preventing someone from accessing alternative anti-TNF therapies is ruining their quality of life. I don’t necessarily mean in terms of jobs, employment, I mean down to the little day to day things you just can’t do. NICE must listen to patients”. Although we acknowledge that there will remain the possibility of sequential use in cases of adverse reaction, these examples clearly illustrate the need for this to be an option for all people with severe RA.	For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations” (Social Value Judgements - Principles for the development of NICE guidance; principle 2).
Arthritis Care	Rheumatoid arthritis is a debilitating condition which if not managed effectively can lead to a high burden on NHS resources in lifelong care. It would appear that the prior recommendation and relative cost-effectiveness of rituximab has distorted the market, making cost-effectiveness greatly outweigh clinical effectiveness in all subsequent considerations of TNF-α inhibitors. This short-sighted view fails to take into account that long term costs in ongoing care, including surgery, and palliative care which accompany ineffectively managed rheumatoid arthritis, in many cases will outweigh the short-term cost of switching to alternative TNF-α inhibitors. Through this decision, the appraisal committee is asking people with rheumatoid arthritis to accept a future of pain, disability and eventually palliative care, rather than effective treatment. The positive changes to quality of life afforded by TNF-α inhibitors are profound and should not be easily dismissed. Decisions of such impact as this must be made only with compelling evidence which examines more than the cost-effectiveness of the treatment. We consider that the balance of cost-effectiveness to quality of life needs more careful consideration, and urge NICE to reconsider its decision.	Cost effectiveness takes into account the benefits and costs of a treatment. The benefits of a treatment are derived from the clinical effectiveness evidence. The Committee considered the clinical effectiveness of TNF inhibitors and of comparator treatments. See FAD sections 4.3.3, 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.8.

Source	Comment	Response
British Society of Rheumatology	I am writing on behalf of The British Society for Rheumatology (BSR) to endorse the joint response submitted by the Arthritis and Musculoskeletal Alliance (ARMA), Arthritis Care, The British Society for Rheumatology, the National Rheumatoid Arthritis Society and the Royal College of Nursing Rheumatology Forum. We have worked very closely with ARMA on this response and fully support all the points raised within the submission.	Comments noted. See responses to ARMA, Arthritis Care, NRAS and RCN.
NRAS	NRAS Response to Appraisal Consultation Document Sequential use of Adalimumab, etanercept and Infliximab for the treatment of RA I would like to thank NICE for the opportunity comment on the above ACD. I would first of all like to state that NRAS supports and endorses the joint submission by ARMA and I do not propose to repeat all the points made in that submission here, however I do wish to comment on the questions asked in the ACD from the patient perspective.	Comments noted, please see responses below.
NRAS	**Do you consider that all of the relevant evidence has been taken into account?** There is clearly a lack of evidence available of people returning to DMARD therapy following use of an Anti-TNF because this would be a retrograde step, given current clinical practise. With this ACD, we are not addressing the clinical and cost effectiveness of a new therapy, the Appraisal Committee are recommending not to switch to a second TNF on grounds of inefficacy, in spite of the fact that this has been successful clinical practise in the UK for a number of years. As a patient, I have to have faith in and trust the best advice of my Rheumatology Consultant and the team, and when they recommended that I switch from the first TNF to a second and a year and half later, to a third TNF, I did so on the grounds that this was the best medical advice and in the knowledge that I had a 70% chance of responding (pretty good odds to someone with a destructive, disabling and painful disease like RA, and odds which I chose to accept). The option of going back onto DMARDs on which I had already failed and to have to start taking steroids again, which I have managed to do without for the last four years entirely due to Anti-TNF, was simply not even discussed as it is not a course of action which any rheumatologist would have considered a viable option by comparison with going onto a second or third TNF – it would make no sense at all. This point was made time and time again by the Clinical Experts at the Review.	For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 2).

Source	Comment	Response
NRAS	I believe that there has been a fundamental failure on the part of the Committee to appreciate just how complex and individual a disease RA is. There are a number of clinical subsets of this disease and we don't know why one person responds to a particular biologic and the next one doesn't. This is why it is so vital to have many treatment options in the patient pathway, a view held by the entire rheumatology community, not just the patients. If you are diagnosed with RA at age 25 and are unlucky enough to have severe, progressive disease, you have many years to live, in spite of the fact that your life expectancy may be reduced, and you will need many options available to you over the years. It is therefore with great disappointment and dismay that we see our options diminishing rapidly.	The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendations.
NRAS	I am concerned that the committee display a lack of interest in patient quality of life evidence. As a patient expert for many years now, I can confirm that with the exception of the Chair of the various Appraisal Committees I have attended (who does give the patient experts the opportunity to speak), only on one occasion have I or any other patient expert with me ever been asked a question by any other member of the Committee. The majority of the time is spent on health economics, cost effectiveness, the model and clinical data from trials.	The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendations.
NRAS	Rituximab therapy is not suitable for all patients. In particular the evidence that it works in sero-negative patients (those that are negative for anti-CCP and rheumatoid factor) is lacking. For example, in the DANCER study the placebo was as effective as rituximab (for ACR20 responses). Therefore, under current NICE guidelines for patients who are sero-negative and failed TNF blockade it is only possible to offer ineffective therapy with potential side-effects. The availability at least of a second TNF for a restricted group of patients would therefore be more logical, more effective (including cost-effective) and safer.	The Committee considered the use of a second TNF inhibitor in the group of people who were seronegative. See FAD section 4.3.20.
NRAS	**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?** We agree with the statement in the ARMA response that the over-reliance on the BRAM model to the exclusions of other models is inappropriate. We continue to point out that reduction in HAQ score is not a sensitive enough measure of outcome in this group of patients, most of whom have had the disease for many years and failed on 3 or 4 DMARDs and sustained substantial joint damage.	The Committee considered the use of the BRAM in this appraisal. See FAD section 4.3.9. The HAQ score is not used to derive the utility that is used in the economic models. HAQ is used to predict EQ-5D scores and utility is derived from EQ-5D. Therefore a small change in HAQ does not necessarily lead to a small change in utility. See FAD section 4.3.9.

Source	Comment	Response
NRAS	We understand that under the present NICE remit, the wider societal costs cannot be taken into account in the economic modelling, however, we are fully aware of the recommendations by the Health Select Committee in this regard in January this year and feel strongly that this is something which NICE itself should be actively addressing and encouraging government to change the remit. When Dame Carol Black addressed the British Society for Rheumatology annual conference in Liverpool recently, she identified that sickness absence and health related worklessness amounted to over £100 Billion per year, i.e. more than the budget of the NHS. Costs of medication represent a comparatively small proportion of direct costs. Indirect costs caused by work disability can be substantially higher than direct costs, particularly in working-age patients. This must now be addressed with some urgency by NICE.	The reference case stipulates that the perspective adopted on cost should be that of the NHS and PSS; see section 5.3.3.1. of the Guide to the Methods of Technology Appraisal
NRAS	**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?** In short, NO, for all the above reasons and those covered by our fellow stakeholders.	Comments noted, please see responses above.
NRAS	**Are there any equality related issues that may need special consideration?** The patients who are sero-negative and Anti-CCP negative are disadvantaged by comparison to those patients who are sero-positive.	The Committee considered the use of a second TNF inhibitor in the group of people who were seronegative. See FAD section 4.3.20.

Source	Comment	Response
NRAS	The patients in the UK are disadvantaged by comparison to other people with RA in Europe and I detail below a comment in this regard by Prof. Paul Emery in his capacity as President-Elect of Eular which we support: "Dear Sir One of the remits of EULAR is to ensure there is reasonable access to effective therapies for all patients with arthritic conditions in Europe. The U.K. now has the lowest use of biologics of the Western countries, and also the most restricted and illogical use. Anti-TNF use is restricted until late in disease and if TNF fails have only access to B-cell depleting therapies as switching is not permitted. This means that biologics will be used at a time when they are less effective and that inappropriate patients will be treated, particularly with B-cell depleting therapy. In terms of its provision of care for these sick patients it would be appropriate to have an overview of UK policy rather than piecemeal approval. Yours faithfully Professor Paul Emery President-Elect – EULAR"	The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions.
NRAS	It seems ironic that on the 12th May, two british researchers, Emeritus Professor Sir Ravinder Maini and Professor Marc Feldmann, who pioneered Anti-TNF therapies at the Kennedy Institute, have been awarded the prestigious 2008 Dr. Paul Janssen Award for Biomedical Research by an international committee including Nobel Laureates and other world-renowned scientists. One has to wonder what their view of recent NICE decisions would be and what effect these decisions may have on the future of research and development in the UK. Attached to our submission is a list of comments which have been emailed to NRAS in the last week or two from some of our members and I would be grateful if you could ensure that the Committee do read these comments. They surely describe very eloquently what a negative decision would mean to the half million or so people in the UK living with RA. *Comments received and tabled, not reproduced*	For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 2).

Source	Comment	Response
RCN	**RCN Response to the ACD on the Sequential Use of Anti-TNFs** We thank NICE for giving us the opportunity to comment on this document and will respond under the following general headings: **i). Do you consider that all of the relevant evidence has been taken into account?** We feel that the Committee has failed to take all of the evidence into account for the following reasons: Since the introduction of biologic therapies the patients who have had access to these drugs earliest, in routine practice, are those with longer disease duration and worse disease. They have already had numerous, if not all, the DMARD's prior to commencing anti-TNF. We agree there is a sparsity of evidence, due to the fact that we have not had the experience using these drugs and having to go back to conventional therapy. To expect these patients to return to traditional DMARD's following failure of one anti-TNF agent, having already failed this group makes no sense, especially when there is a potential for success with another untried agent.	For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 2).
RCN	Whilst the Appraisal Committee considered Rituximab, as the alternative treatment where patients had failed on one anti-TNF therapy, we have concerns that the DANCER trail showed no efficacy in seronegative disease compared with placebo. In addition the REFLEX study showed reduced efficacy in seronegative disease in comparison to seropositive disease. For this group of patients there is a reluctance to use Rituximab, indeed the EULAR guidelines for Rituximab advise the avoidance in seronegative disease. In addition to this we have concerns that there is no data on the use of Rituximab long term in RA and the cumulative effect of B cell depletion on the immune system in these patients.	The Committee considered the use of a second TNF inhibitor in the group of people with seronegative RA. See FAD section 4.3.20. The Committee considered the adverse effect profile of rituximab. See FAD section 4.3.19.
RCN	We are not familiar with the US National Databank for Rheumatic Diseases and would question whether the data collected (given the completely different healthcare system and the propensity to private practice) is accurate or transferable to the UK system. We would also query the use of including unpublished data in the ACD as we were under the impression that the Committee preferred to use published data as evidence?	A description of the US National Database for Rheumatic Diseases was provided in the evaluation report. The Committee will make use of both published and unpublished evidence in making decisions.

Source	Comment	Response
RCN	**ii). 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?** We have commented in previous appraisals on our concerns of the BRAM and its continued use in appraisals. We continue to contest that fall in HAQ is not a sensitive enough measure of outcome in this group of patients. We would also wish to comment that for patients on anti-TNF therapies, having had to fail at least 2 DMARDs before being allowed therapy, there is almost certainly considerable joint damage which will not lead to a significant reduction in HAQ as a result of anti-TNF and continues to falsely affect the economic models. We also believe that it is unreasonable to assess health economics and not attempt to look at wider health and social care costs. Whilst it may be argued that these are not available, is emerging evidence as seen in the article by Weiss et al worth considering? As representatives of rheumatology nurses who deal with these patients on a day to day basis, it is us who will be discussing options for treatment with them and strongly feel that to accept the ACD as it stands, without looking at some sort of wider health and social care cost is condemning a group of patients with the worst disease to nothing less than palliative care.	The Committee considered the use of the BRAM in this appraisal. See FAD section 4.3.9. The HAQ score is not used to derive the utility that is used in the economic models. HAQ is used to predict EQ-5D scores and utility is derived from EQ-5D. Therefore a small change in HAQ does not necessarily lead to a small change in utility. See FAD section 4.3.9. The reference case stipulates that the perspective adopted on costs should be that of the NHS and PSS. See section 5.3.3.1. of the Guide to the Methods of Technology Appraisal
RCN	**iii). 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?** There may be an additional factor that has not been considered in this judgement. Patient's perceptions and anxieties about being taken off treatment may result in extreme vigilance in relation to possible adverse event and thus focus on this issue. This has the potential to distort evidence in relation to the long term safety and efficacy data on these therapies. For all the reasons stated above we consider that these provisional recommendations are not sound, and do not constitute a suitable basis for the preparation of guidance to the NHS. We request that this issue is explored further for the benefit of our patients.	The Committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness

Source	Comment	Response
Department of health	Thank you for the opportunity to comment on the Appraisal Consultation Document and Evaluation Report for the above appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comments noted, no actions required.
NHS Quality Improvement Scotland	**Whether you consider that all the relevant evidence has been taken into account.** Yes, There are several other European registries – I do not believe that interrogating these will provide any additional information.	Comments noted, no actions required.
NHS Quality Improvement Scotland	**Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.** Clinical effectiveness – the information has been very effectively summarised and I agree with the interpretations. Cost effectiveness – This is not an area of my expertise but the arguments put forward have in view been undertaken with appropriate diligence.	Comments noted, no actions required.
NHS Quality Improvement Scotland	**Whether 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.** Yes – I agree with all the provisional recommendations and constitute a very useful guidance for clinicians.	Comments noted, no actions required.
Somerset PCT	Somerset pct response to this consultation And the set questions in your letter of 21 April are 1) Yes 2) Yes 3) Yes 4) No No additional comments	Comments noted, no actions required.
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment on the above appraisal. We are content with the technical detail of the evidence supporting the appraisal and have no further comments to make at this stage.	Comments noted, no actions required.

Source	Comment	Response
Roche Products	**1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT** Roche believe that the majority of relevant evidence has been taken into account in this appraisal. Roche feel that further evidence could have been considered regarding: **Long term HAQ progression while on rituximab treatment** Roche believe that assuming zero HAQ progression for TNF inhibitors and 0.03 for rituximab may be unfair. Evidence suggests that rituximab is associated with an on treatment zero HAQ progression in the post TNF inhibitor patient population, whereas the evidence supporting zero HAQ progression for TNF inhibitors is likely to be from a first-line TNF inhibitor patient population. Given the additional effectiveness of rituximab compared to TNF inhibitors in the patient population of interest for this appraisal (Finckh et al (2007)) it seems unreasonable to assume a worse HAQ progression rate for rituximab than for the TNF inhibitors. The Finckh paper (discussed by the Decision Support Unit report) illustrated a greater DAS28 score decrease with rituximab therapy (-1.61) compared with TNF inhibitor therapy (0.98), p=0.01, when comparing patients who had already been treated with one or more TNF inhibitors, showing the additional benefit of rituximab compared to a second or third TNF inhibitor for these patients.	The Committee was aware that the analyses had applied differential HAQ progression rates for TNF inhibitors and rituximab. See section 4.3.19.
Roche Products	Analysis of the REFLEX study which evaluates HAQ changes up to and including week 80 confirms it may be reasonable to propose a zero HAQ progression over time in patients treated with rituximab (previously submitted to NICE in response to the ACD for the STA of rituximab for the treatment of rheumatoid arthritis, 23/04/07). Over the time-horizon of the REFLEX study, Figure 1 below illustrates a flat to negative slope to the HAQ progression curve. The number of patients analysed at each timepoint (N), mean HAQ scores and means plus and minus one standard error for each time point are presented. Also, an estimate for the change in HAQ over 6 months has been calculated by fitting a regression model to patient HAQ scores over time using HAQ score raw data and time relative to the first treatment with rituximab + MTX as independent variables. This led to an estimate that in the long term HAQ scores are actually expected to fall while on treatment with rituximab + MTX.	The Committee was aware that the analyses had applied differential HAQ progression rates for TNF inhibitors and rituximab. See FAD section 4.3.19.
Roche Products	Given this evidence Roche believes that if a zero HAQ progression rate is assumed for TNF inhibitors in a sequencing scenario a similar assumption should be made for rituximab. Figure and tables included but not reproduced	The Committee was aware that the analyses had applied differential HAQ progression rates for TNF inhibitors and rituximab. See FAD section 4.3.19.

Source	Comment	Response
Roche Products	**Long term safety profile of rituximab** Roche note that this topic was mentioned by one of the manufacturer's in their response to the further analysis undertaken. The publication by Keystone et al (Arth Rheum 2007; 56:3896-3908) showing safety after 2 courses and the abstract by van Vollenhoven et al (ARD 2007; 66 (suppl II): 88 demonstrating safety after 4 courses of rituximab should reassure the Committee of the long term safety profile of rituximab. Safety analyses were performed on 1053 RA pts exposed to RTX as of September 15, 2006 in the clinical trial program. Data on patients receiving up to 4 treatment courses have been reported (Keystone et al Arth Rheum 2007; 56:3896-3908, van Vollenhoven et al (ARD 2007; 66 [suppl II]: 88) : Acute infusion reactions decrease with repeat courses: acute infusion reactions (first infusion, each course) decreased from 26% during Course 1 to 10-15% during Courses 2 to 4. Also, fewer acute infusion-related events occurred during or within 24 hours of the second infusion for all courses than the first infusion After 4 courses, a slight upward trend was observed in the rate of infections; however, the rate of serious infections remained stable with repeated treatment. No opportunistic infections, viral reactivations or tuberculosis were seen. 25% of patients had low IgM and 6% of patients had low IgG at some point post rituximab, however, there was no increase in rate of serious infection in these patients; the rates of serious infections were all consistent with those expected with biologic RA therapy. Conclusions: This further update on the long-term follow-up (2438 pt-yrs) of RA pts receiving rituximab showed a safety profile consistent with that reported previously.	The Committee considered the adverse effect profile of rituximab. See FAD section 4.3.19.

Source	Comment	Response
Roche Products	**Evidence on radiographic progression** Roche wish to highlight that rituximab is the only biologic to have demonstrated inhibition of progressive joint destruction in a TNF inhibitor-inadequate responder population. The REFLEX trial provided strong evidence that rituximab inhibits radiographic progression in RA as measured by the total Genant-modified Sharp score, joint space narrowing and erosion scores (Keystone et al, 2008 ARD online: doi:10.1136/ard.2007.085787). Furthermore, additional analyses have shown that patients who do not exhibit a clinical response to rituximab are still able to experience the benefit of reduced radiographic progression relative to placebo-treated patients (Keystone et al. Arthritis Rheum 2006;54 (Abstract 1307)).	Comment noted, this level of detail is not provided in the FAD for comparator treatments. No changes made to the FAD.
Roche Products	**Cost effectiveness after treatment with more than one TNF inhibitor** Roche note that in their response, one of the manufacturer's questioned the logic of NICE's previous recommendation for rituximab which did not differ depending on the number of prior TNF inhibitors a patient had been treated with, given that response rates for all treatments fall when they are given at a later stage. It is unclear how the Appraisal Committee took this comment into account and Roche would like to point out that the evidence included in the rituximab technology appraisal illustrated the cost effectiveness of rituximab both after one prior TNF inhibitor and after 2 or more TNF inhibitors (Manufacturers Submission, Rituximab for the treatment of rheumatoid arthritis, November 2006)	Comment noted, no changes made to the FAD.
Roche Products	**2 Whether 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** Roche considers the range of the clinical and cost effectiveness analysis undertaken by the Decision Support Unit and WMHTAC to be appropriate based on the evidence considered however as noted above Roche does not endorse all of the assumptions made in the economic modeling.	Comments noted, please see responses above.

Source	Comment	Response
Roche Products	**3 Whether 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** Based on the broad range of scenario analysis undertaken in order to tackle the uncertainty surrounding this appraisal, Roche believe that the provisional recommendations of the Appraisal Committee are sound.	Comments noted, no actions required.
GDG	Thank you for asking for comments on the Appraisal Consultation Document (ACD) on sequential use of Anti-TNF Therapy. On behalf of the Guideline Development Group (GDG) that is currently developing the NICE Clinical Guideline for Rheumatoid Arthritis in Adults, I should like to make the following points: 1. The GDG totally supports and endorses the comments made in the response sent to you by the Arthritis and Musculoskeletal Alliance (AMRA) an organisation that includes the British Society for Rheumatology (BSR) and the National Rheumatoid Arthritis Society (NRAS).	Comments noted, please see responses to ARMA, BSR and NRAS comments.
GDG	2. The GDG is particularly concerned about rituximab now being the only allowable biological therapy for seronegative patients following the failure of a first anti TNFα inhibitor. We believe that the evidence of comparative lack of efficacy of rituximab in this particular group of patients, alluded to in the BSR response, could be interpreted as specifically disadvantaging this important group of patients. At the very least, we would urge that the use of a second TNFα inhibitor should be allowed in this group of patients.	The Committee considered the use of a second TNF inhibitor in the group of people with seronegative RA. See FAD section 4.3.20.

Source	Comment	Response
GDG	3. Although our draft guideline is still under preparation, it is very likely that we shall be recommending that a composite score of disease activity (such as DAS28) should be measured over time in all patients with RA and that it should be used as an indicator of when to increase treatment to suppress active disease and also when to cautiously decrease medication when disease activity is low. Our Guideline will of course be totally supporting the current NICE Technology Appraisal on anti-TNF therapy, which also uses the DAS28 as a criterion for initiating these drugs and for monitoring response. We therefore strongly feel that it is illogical to base cost effectiveness recommendations in this ACD on HAQ scores (which reflect joint damage) rather than a measure which is a much better reflection of disease activity and the therapeutic need to suppress active inflammation. As a GDG, we all take very seriously our responsibility to prepare evidence-base recommendations. We feel that the conclusions reached in this ACD do not constitute a suitable basis for the preparation of guidance to the NHS.	Technology appraisal 130 of the first use of TNF inhibitors for the treatment of rheumatoid arthritis used the same model which was based on HAQ scores mapped to EQ-5D. The Committee recognised that HAQ scores were not the most appropriate method for defining continuation of treatment. Therefore the guidance included DAS28 for initiating and monitoring response. The use of the BRAM does not preclude the use of DAS28.
Web comment Pharmaceutical Industry	2.6: Abatacept, a selective T-cell co-stimulation modulator, is another treatment licensed for use in combination with methotrexate for the treatment of moderate to severe active RA in adult patients who have had an insufficient response or intolerance to other DMARDs, including at least one TNF-Ã¡ inhibitor. Rituximab is licensed for patients with severe RA only.	Comments noted, the abatacept marketing authorisation and NICE guidance about abatacept had been added to the FAD. See section 2.6.

Source	Comment	Response
Web comment Pharmaceutical Industry (cont)	4.2.3: Data from placebo arm from the REFLEX trial should also have been used. This study was identified in the DSU systematic review it is unclear why data from the two studies (ATTAIN and REFLEX) was not pooled to estimate efficacy of conventional DMARDs in patients who failed treatment with TNF-alpha inhibitors. 4.2.5: ?slightly greater? is not an appropriate qualification, given the borderline cost-effectiveness in this scenario. If threshold analysis had been performed, the actual value of the increase in effectiveness required to reach acceptable cost-effectiveness should be reported. 4.2.6 It is unclear why different HAQ progression rates were applied for treatments used in the same patient population. At minimum, a clear justification for this assumption should be provided. However, given lack of head-to-head efficacy data or evidence on HAQ progression rates, the same value should be used for both second anti-TNF agent and rituximab.	Neither the ATTAIN nor REFLEX trials specifically reflect the effectiveness of conventional DMARDs as they are both taken from the arms of clinical trials where placebo was added to an ongoing DMARD regimen. Given this limitation of the data pooling it would not have increased its validity for this analysis. The threshold analysis provided the effectiveness of TNF inhibitors at thresholds of £20,000 and £30,000 per QALY. It reports this as a HAQ multiplier, but HAQ multipliers are difficult to interpret unless they are benchmarked against HAQ change scores. The Committee was aware that the analyses had applied differential HAQ progression rates for TNF inhibitors and rituximab. See section 4.3.19.
Web comment Pharmaceutical Industry (cont)	The preliminary recommendation contained in this ACD further limits access to care for RA patients who have insufficient response to a first anti-TNF agent. This is particularly concerning in light of the recent NICE guidance not recommending abatacept for the same patient population, also on cost-effectiveness grounds as NICE seem to acknowledge the significant humanistic, medical and economical burden of RA, particularly in treatment-refractory patients.	For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 2).
Web comment Patient	I understand that this has been under review for almost two years, while NICE are considering this, many AS patients including find the condition getting worse, untill NICE make a decision local PCTs including my own (Staffordshire) will not recommend the use of this drug.	Recommendations in this appraisal relate only to the use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after the failure of a first TNF inhibitor. A separate NICE appraisal TA143 gives guidance on the use of TNF inhibitors for the treatment of ankylosing spondylitis.

Source	Comment	Response
Web comment Patient (cont)	Due to the longevity use of NSAIDs the majority of patients suffer from intesinal problems, also some AS patients suffer the onset on Crohns, as in my case, when this occurs there is then a conflict of what drugs to use, Anti TNT help to control both conditions. The use of NSAIDs (Meloxicam)is not recommended by the Crohns specialist, however DMARDs control this condition, (Azathiorine) but has very little effect on the AS condition. In my case as I have stopped talking Meloxicam, my condition has rapidly deteriorated over the last two years. I am currently still working, but in the next 2/3 years I will certainly not be able to work.	Recommendations in this appraisal relate only to the use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after the failure of a first TNF inhibitor. A separate NICE appraisal TA143 gives guidance on the use of these drugs for the treatment of ankylosing spondylitis.
Patient letter	I have been treated with anti-TNFs for the past 3 years. In addition I am treated with methotrexate 25mg sub cut weekly and 10mg prednisolone daily. I have recently turned 50 and am extremely grateful for the NHS treatment which I have received, without which I would certainly have had to give up work and be dependant on State handouts. I am able to lead a reasonable quality of life although in almost constant pain and with restricted mobility. I am very distressed to see that NICE has made a preliminary ruling that will prevent people like me with severe rheumatoid arthritis from trying a second 'anti-TNF' treatment if the first does not work. In my case I have used two others which initially worked well but within six months I was reacting negatively to each of them. I am now treated with Humira but, based on your preliminary ruling, I will be condemned to a life of very severe pain, joint replacement surgery at huge cost and a certain dependence on State benefits. There are many others who are in the same position as me and I appeal to you to allow patients who genuinely require these new treatments to have access to them. Regrettably arthritis will probably not kill me but it has the potential to take away my ability to remain economically independent and have a reasonable quality of life. Whilst I understand health budgets are under strain please consider the cost of people like me being dependant on the state and requiring expensive treatment of complications of this debilitating disease.	The guidance section 1.2 states that people with rheumatoid arthritis currently receiving adalimumab, etanercept or infliximab after the failure of a TNF inhibitor should have the option to continue therapy until they and their clinicians consider it appropriate to stop. (FAD section 1.2). In addition, Technology Appraisal 130 recommends that people experiencing an adverse event to adalimumab, etanercept or infliximab should have the option of trying a different TNF inhibitor. For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 2).