Wyeth

Mr. Mark Taylor
Appeals Committee Chair
National Institute for Health and Clinical Excellence
Midcity Place
71 High Holborn
London WC1V 6NA

4th September 2008

Dear Mr. Taylor,

**Re: Appeal on Final Appraisal Determination – Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after failure of a previous TNF-α inhibitor**

Thank you for your letter dated 21st August 2008, enclosing your initial view of the points of our appeal against the Final Appraisal Determination (FAD) for the above technology appraisal. In response to your letter Wyeth wish to submit this redrafted appeal notice, as well as to further explain the points that you have found unclear.

We acknowledge your acceptance of a number of points of appeal under the sections originally numbered 1.2, 1.3, 2.3, 2.4, 3, 4, and 6, subsequently renumbered in this document as 2.2, 1.1, 2.3, (1.4, 2.4, 2.5), 2.6, 1.5 and 1.7. In your response you outlined that a number of grounds for appeal were invalid or in your view not requested under the appropriate ground for appeal. We have thus attempted to clarify these points (*see text in italics*) and resubmit them under the appropriate ground of appeal.

Wyeth would like to emphasis two key general points with regard to this appeal. Firstly, the level of evidence has been generally criticised throughout the course of the appraisal with regard to the use of TNF-α inhibitors after the first one has failed. This has resulted in the cost-effectiveness analysis evidence being rejected as irrelevant in this technical appraisal. Wyeth firmly believes that the data for the use of TNF-α inhibitors in the NHS and their "real world" effectiveness is superior to many other products that the institute has made positive determinations upon. We remain unclear as to why the appraisal committee has continued to not consider cost-effectiveness analysis especially in light of the specific data analysis requested by the first appeal committee. The Decision Support Unit were requested to complete a series of analyses in order to enable the Appraisal Committee to re-evaluate their decision. Wyeth are concerned that not enough resources were made available to undertake this analysis appropriately and therefore the appraisal committee was unable to come to a reasonable determination based upon the information made available to it.

Secondly Wyeth believes that this guidance is forcing the prescribers to choose rituximab, a pharmaceutical intervention, which has quite specific safety warnings related to long-term use within its marketing authorisation. Thus guidance should state that a rheumatologist should be able to prescribe alternative TNF-α inhibitors if they have specific long-term safety concerns for the individual patient.

Additionally, we do not accept that the Guide to the Methods of Technology Appraisal should not be a mandatory part of the Institute's published procedures. The Guide to the Methods of Technology Appraisal

is one of a set of documents that describes the process and methods that the Institute uses to undertake technology appraisal as listed in the Guide to the Technology Appraisal Process. Section 1.1.2 of the Guide to the Technology Appraisal Process highlights this, by stating that it should be read in conjunction with the Institute's Guide to the Methods of Technology Appraisal.

We hereby confirm that in accordance with the procedure set out in the "Guidance for Appellants", Wyeth wishes to appeal a number of aspects of the appraisal process and the resultant proposed guidance on the grounds of appeal, as set out below.

**Ground 1: The institute has failed to act fairly and in accordance with its published procedures as set out in the institute's Guide to the technology Appraisal Process.**

**1.1. (Formerly 1.3.) Inequitable use of effectiveness data from the BSRBR**

Section 4.3.15 of the FAD indicates that the Appraisal Committee considered that study enrolment could have affected the data for the effectiveness of TNF-α inhibitors taken from the ReACT trial, which would not have been observed in the BSRBR. This led the Appraisal Committee to conclude that it would not be appropriate to combine estimates of clinical effectiveness for TNF-α inhibitors from the ReACT trial with those for conventional DMARDs from the BSRBR. However, we note from Section 4.2.5 of the FAD that the converse was deemed acceptable i.e. using TNF-α inhibitor data from the BSRBR and data for conventional DMARDs as had been used in TA 130 (i.e. from clinical trials of early RA). Whilst it is not transparent as to how the Appraisal Committee thought study enrolment could have affected the data for the effectiveness of TNF-α inhibitors, combining the differing data sets in one scenario but not the other introduces an element of bias in favour of the conventional DMARDS. As efficacy estimates derived from trial data tend to be higher than estimates derived from registry data the most pessimistic estimate of cost effectiveness of the TNF-α inhibitors is presented in Section 4.2.5 of the FAD. However, for the reasons described in section 4.3.15 the more optimistic estimates have not been modeled and discussed in the FAD.

Section 3.1.1 of the Guide to the Methods of Technology Appraisal states that consideration of a comprehensive and high quality evidence base is fundamental to the appraisal process and that to ensure that the guidance issued by the Institute is appropriate and robust, it is essential that the evidence and the analysis and their interpretation are of the highest standard and are transparent to scrutiny. Furthermore, Section 3.1.3 of the same Guide states that similarly the analysis and modeling should be methodologically sound and, in particular, minimise any bias. Wyeth considers that, in defining the datasets to be included in the analysis of cost effectiveness the Institute did not follow these requirements of the appraisal process.

In utilizing TNF-α inhibitor but not conventional DMARD effectiveness data from the BSRBR, the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods of Technology Appraisal.

**1.2. (Formerly 2.1.) Failure to incorporate all relevant factors in the estimate of the cost-effectiveness of sequential TNF-α inhibitor treatment**

*In your initial view you were not minded to allow this point of appeal on the grounds that you did not agree with the premise that an examination of the minimum effectiveness of a second TNF-α inhibitor for it to be marginally cost-effective was not appropriate. However, as indicated below, this examination was expressly requested by the Appeal Panel in its previous ruling. Wyeth content that the failure of the Institute to confirm to the Appeal Panel's recommendations is a valid point of appeal and therefore requests that this appeal point be allowed to proceed.*

The original Appeal Panel's decision from April 2007 was that the guidance must be reconsidered by the Appraisal Committee. The Appeal Panel suggested that the Appraisal Committee reassess the evidence for the cost-effectiveness of a second TNF-α inhibitor with a more complete examination of the minimum effectiveness that would be required of a second TNF-α inhibitor for it be marginally cost-effective (see in particular paragraph 140 of the Appeal decision). This analysis has not been conducted in a transparent way that allows maximum understanding by consultees and stakeholders, as required by the Guide to the Technology Appraisal Process (Section 1.1.1). Therefore the Appraisal Committee was, based on the information provided to them, not able to reach a robust and informed decision. Wyeth conducted such an analysis, which, as described below in more detail, was not accepted by the Institute for consideration by the Appraisal Committee. As a consequence the Appraisal Committee did not have this information available in to inform their decision making.

To achieve such an examination of the minimum effectiveness, the impact of a number of factors on the estimation of cost effectiveness, namely:

1. the effectiveness of conventional DMARDS,
2. the inclusion of offset costs, and
3. the use of appropriate discount rates

would need to have been explicitly identified and included in the calculation of cost effectiveness.

As the magnitude of each of these factors has not been established and their cumulative impact on the cost effectiveness of a second TNF-α inhibitor has not been established it has not been possible for the Appraisal Committee to comply with the request of the Appeal Panel. As a consequence the Institute has failed to act fairly and in accordance with its published procedure as set out in the Institute's Guide to the Technology Appraisal Process.

**1.3. (Formerly 2.2.)Failure to incorporate offset costs**

*In you initial view you did not consider the failure to incorporate offset costs into the analysis of cost effectiveness to be procedurally unfair. However as the Institute was directly responsible for instructing the ASU on the analyses to be undertaken, the failure to prevent the introduction of bias would appear to be a procedural issue. Wyeth therefore request that this point of appeal be considered.*

Section 4.2.2 of the FAD states that joint replacements and associated costs were not included in the analysis of the sequential use of TNF-α inhibitors, although they were included in the sensitivity analysis of the first use of TNF-α inhibitors (TA130). Such offset costs were also included in the economic evaluation of rituximab (TA126). As the incorporation of offset costs invariably reduces the ICER of the technology being appraised, failure to incorporate such costs in the analysis of the cost effectiveness of the sequential use of TNF-α inhibitors introduces bias disadvantaging the sequential use of TNF-α inhibitors relative to the initial use of TNF-α inhibitors and rituximab.

In the FAD it is stated that the sequential use Guidance should be read in conjunction with TA130. Inclusion of offset costs in TA130 but not in this Guidance is misleading as the estimates of cost-effectiveness are based upon different assumptions and are therefore not comparable

Section 3.1.1 of the Guide to Methods of Technology Appraisal states that consideration of a comprehensive and high-quality evidence base is fundamental to the appraisal process. Section 3.3.1 of this Guide states that for costs, evidence requirements include quantifying the effect of the technologies on resource use in terms of physical units and valuing those effects in monetary terms using appropriate prices and unit costs. Section 5.2.1.1 of this Guide states that in order to inform the Appraisal Committee's decision-making, all relevant evidence needs to be assembled systematically and synthesized in a transparent and reproducible manner.

Therefore, by not including these cost offsets in the current appraisal of sequential TNF-α inhibitor use the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institutes Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods of Technology Appraisal.

**1.4. (Formerly 2.4.) Change in discount rate constitutes a failure to act fairly and a breach of published procedures**

The current FAD and TA130 are considered to be part of the same appraisal. As a consequence all the conditions and criteria used in the preparation of TA130 must apply to the preparation of guidance on the sequential use of TNF-α inhibitors. However, the cost-effectiveness analyses carried out to compare the sequential use of TNF-α inhibitors with non-biologic DMARDs and rituximab used a discount rate of 3.5% for costs and benefits, instead of the discount rates of 1.5% and 6% which were used during the preparation of TA130.

In Section 4.3.16 of the FAD the Appraisal Committee notes that the use of different discount rates in the new sequential analyses would reduce the estimates of incremental cost-effectiveness.

In the FAD it is stated that the sequential use Guidance should be read in conjunction with TA130. Use of different discount rates in TA130 and in this Guidance is misleading as the estimates of cost-effectiveness are based upon different assumptions and are therefore not comparable.

In splitting the appraisal into 2 pieces of guidance, and changing the underlying decision criteria for TNF-α inhibitors (e.g. by applying a changed discount rate) the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods of Technology Appraisal.

**1.5. (Formerly 4.) Inclusion of rituximab as new comparator without consultation**

The Scope for this appraisal refers to comparator technologies as "current standard comparators", which are management strategies with of without anti TNF-α inhibitors, and other anti TNF-α inhibitors. Wyeth considers that "current" to mean as of the immediate present or the most recent or up-to-date and therefore, those competitive technologies that were accepted as standard at the time of the scoping.

As rituximab received its license during the course of this appraisal, the Institute should have, following section 1.1.1 of the Guide to the Technology Appraisal Process, sought the views of consultees on the inclusion of rituximab and, in the event of inclusion, requested updated submissions.

By including rituximab as a comparator in this appraisal without consultation with consultees, and not requesting additional submissions from consultees the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process.

**1.6. (Formerly 5.) Failure to establish cost effectiveness vs. rituximab in accordance with UK clinical practice**

*In your initial view you were unclear as to whether this point constitutes a ground for appeal on its own right. In essence Wyeth considers that the failure to incorporate assumptions on the use of rituximab based on current UK clinical practice resulted in a flawed analysis of the relative cost-effectiveness of a second TNF-α inhibitor compared to rituximab. We would therefore request that this point of appeal be considered.*

Section 4.3.19 of the FAD states that the Appraisal Committee noted that if there were increased costs of rituximab treatment, and a deterioration in response to rituximab between infusions, then this reduces the estimate of incremental cost-effectiveness relative to a second TNF-α inhibitor. However, the FAD does not include the respective cost-effectiveness results for this scenario. Section 1.1.1 of the Guide to

the Technology Appraisal Process states that all appraisals are conducted following a uniform, open and transparent process.

Section 3.1.1 of the Guide to the Methods of Technology Appraisal identifies that the consideration of a comprehensive and high quality evidence base is fundamental to the appraisal process and that to ensure that the guidance issued by the Institute is appropriate and robust, it is essential that the evidence and the analysis and their interpretation are of the highest standard and are transparent to scrutiny.

Wyeth considers that in UK clinical practice the treatment interval for rituximab is more likely to be 7 months, rather than 9 months. This is also supported by data from clinical studies with rituximab, in order to maintain an adequate response with rituximab. Therefore, the cost per QALY of TNF-α inhibitors compared to rituximab would be lower and, we believe, within the range that the Institute has previously considered to be an acceptable use of NHS resources, in line with sections 6.2.6.10 and 6.2.6.11 of the Guide to the Methods of Technology Appraisal.

Consideration has not been given by the Appraisal Committee to UK clinical practice for re-treatment with rituximab. This requires loss of efficacy which leads to worsening of HAQ and reduction in utility. This has not been included in the modeling. Wyeth considers this a fundamentally flawed analysis of the evidence in breach of both section 1.1.1 of the Guide to the Technology Appraisal Process and section 3.1.1 of the Guide to the Methods of Technology Appraisal.

Therefore, by failing to incorporate either a reduction in response to rituximab or increased costs associated with a higher frequency of infusions in estimating the incremental cost-effectiveness of a second TNF-α inhibitor compared to rituximab the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institutes Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods of Technology Appraisal.

**1.7. (Formerly 6.) Failure to accept additional data**

NICE has chosen to add rituximab as a comparator into this appraisal even though this comparator, as discussed earlier in this document, is outside of the Scope for this appraisal. By not initiating a new appraisal in order to include this new comparator, commentators and comparators have not been given the opportunity to submit any further data relevant to this wider appraisal. Therefore, the Institute has not complied with section 1.1.1 of the Guide to the Technology Appraisal Process, which requires maximum input from consultees and stakeholders.

The original submission for this appraisal took place in 2005. Since then a considerable amount of new evidence on the sequential use of TNF-α inhibitors has become available. Therefore, Wyeth updated its literature review and cost-effectiveness analysis for the use of a second TNF-α inhibitor after the failure of a first one taking into account aspects which have not been covered by the analysis during this appraisal either using the BRAM or by the DSU.

Section 4.5.2.10 of the Guide to the Technology Appraisal Process states that, at the ACD stage, new data will be accepted only if they are likely to materially affect the provisional recommendations in the ACD, and only by prior agreement with the Appraisal Programme Director. Therefore, Wyeth asked for agreement to submit our further evidence on the cost-effectiveness of the sequential use of TNF-α inhibitors, which includes a comparison with rituximab. Given that this further data on cost-effectiveness includes a direct comparison with rituximab as well as allowing for a comparison of the impact of different key parameters, such as the use of different discount rates, and effectiveness ranges for the different treatment options, Wyeth considers this information likely to materially affect the provisional recommendations in the ACD and therefore to be critical to the Appraisal Committees decision-making,

particularly as these analyses were not included in the additional work performed by the DSU utilising the assessment groups model.

However, our request to submit this information was declined on the grounds that the Committee had already considered the points we made.

It is Wyeth's view that these data are likely to materially affect the provisional recommendations in the ACD. This updated evidence demonstrates the impact of the changed discount rate on the cost-effectiveness results, demonstrating ICERs between £12,242 and £20,102/QALY in comparison with conventional DMARDs and £5,342 and £24,753/QALY in comparison with rituximab.

Therefore, by rejecting Wyeth's updated evidence on the cost-effectiveness of the sequential use of TNF-α inhibitors the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process.

**1.8. (Formerly 8.) Refusal to use DMARD efficacy from BSRBR in combination with ReAct data for TNF-α inhibitors**

*In your initial view you regarded this point not to be valid, as you argue that the Guide to the methods of Technology Appraisal is not a mandatory part of the Institute's procedures. Section 1.1.2 of the Guide to the Technology Appraisal Process highlights that the Guide to the Methods of Technology Appraisal is one of a set of documents that describes the process and methods that the Institute uses to undertake technology appraisals. Furthermore, we consider that this point contravenes the Guide to the Technology Appraisal Process. We therefore would ask for this appeal point to be accepted.*

Section 1.1.1 of the Guide to the Technology Appraisal Process states that appraisals should be conducted in a uniform, open and transparent way. In this appraisal, the cost-effectiveness analysis uses efficacy data, in terms of HAQ improvement, for sequential TNF-α inhibitor from the BSRBR registry, and efficacy data for conventional DMARDs from rheumatoid arthritis clinical trial data (placebo arms). These latter efficacy estimates show greater HAQ improvements, and lack face validity in light of the evidence available. This also means that the two interventions can not be adequately compared.

The use of these inputs in the appraisal has resulted in bias. As a consequence the modeling cannot be considered methodologically sound and the analysis and interpretation of the evidence cannot be considered to be of the highest standard, and open and transparent.

If, however, the Institute accept these data, it should have also examined the converse scenario, using TNF-α inhibitor effectiveness data from clinical trials such as ReACT in combination with the DMARD effectiveness data from the BSRBR.

Additionally, section 3.1.1 of the Guide to the Methods for Technology Appraisal states that consideration of a comprehensive and high quality evidence base is fundamental to the appraisal process, and that to ensure that the guidance issued by the institute is appropriate and robust, it is essential that the evidence and the analysis and their interpretation are of the highest standard and are transparent to scrutiny. Wyeth considers that the Appraisal Committee did not follow this requirement of the appraisal process for the reasons above.

Section 4.3.7 of the FAD states that the Appraisal Committee noted that the data from the BSRBR showed variation in response and that a proportion of people had a response to conventional DMARDs after the failure of a first TNF-α inhibitor. The clinical specialists agreed that there would be variation in response and accepted that an assumption that nobody would have a response was unlikely. This means that the Appraisal Committee made its decision based on expert opinion. However, in section 3.2.1.2 of the Guide to

the Methods of Technology Appraisal expert opinion is described as the lowest evidence grade (level 4). Therefore, the appraisal should have used the higher grade of data from the BSRBR (level 2) to inform the effectiveness of conventional DMARDs after TNF-α inhibitor treatment, especially as this is the only direct, real-life evidence on the effectiveness of conventional DMARDs post TNF-α inhibitors.

In this appraisal, the cost-effectiveness analysis uses efficacy data, in terms of HAQ improvement, for sequential TNF-α inhibitor from the BSRBR registry. However, rather than source the estimates of HAQ improvements for the comparator conventional DMARD sequence from the same registry database, values from rheumatoid arthritis clinical trial data (placebo arms) were used instead. These efficacy estimates show greater HAQ improvements, and lack face validity in light of the evidence available. This also means that the two cannot be compared.

Therefore, by including results from the above mentioned flawed analysis in the FAD the Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process, which incorporates the Guide to the Methods for Technology Appraisal.

**Ground 2: The institute has prepared a FAD which is perverse in the light of the evidence submitted.**

**2.1. (Formerly 1.1.) Failure to utilize DMARD effectiveness data from the BSRBR**

*In your initial view, you mentioned that you regard this point as invalid, as the Appraisal Committee can only take into account the data before it at the time of the appraisal. As section 4.1.14 of the FAD refers to this data, it was clearly available at the time of the appraisal. We therefore would ask that this point is considered.*

In the conclusion of the Decision of the Appeal Panel regarding the previous appeal of this appraisal in April 2007, the Appeal Panel suggested that the Appraisal Committee should reassess the evidence for the cost-effectiveness of a second TNF-α inhibitor with an extended sensitivity analysis that considers a wider possible range of effectiveness for conventional DMARDs when used after a TNF-α inhibitor.

The subsequent review of the effectiveness of non biologic DMARDs after TNF-α inhibitor failure conducted by the DSU, whilst failing to identify any evidence that directly considers the effectiveness of non biologic DMARDs in the population of interest, did identify relevant evidence from two sources; namely the abatacept and rituximab studies and the British Society for Rheumatology Biologics Registry (BSRBR).

Whilst, following consultation with the Institute, effectiveness data from the abatacept trial were included in the further cost-effectiveness analysis of sequential TNF-α inhibitors for rheumatoid arthritis patients performed by Pelham Barton, critically the effectiveness data from the BSRBR was not included. Given the paucity of available data and the significant impact of a decision not to recommend sequential use of TNF-α inhibitors on patients with RA who have failed one TNF-α inhibitor, Wyeth contend that in order to provide robust guidance to the NHS a cost effectiveness analysis utilizing the BSRBR data should have been performed.

Given that the above-mentioned review by the DSU acknowledged that 'the availability of registry data from the same source as estimates of the effectiveness of second TNF-α inhibitors does offer advantages in terms of consistency', Wyeth considers the failure to include effectiveness data from the BSRBR as a major omission.

Evidence from the BSRBR indicates a lower effectiveness of medical management in the absence of a TNF-α inhibitor than placebo treatment in the abatacept study which would be expected to translate into a lower incremental cost effectiveness ratio (ICER) for a second TNF-α inhibitor. As the existing analysis

cites the ICER for a second TNF-α inhibitor in the event of secondary failure to a first as being between £31 - £34,000 it would be anticipated that the ICER based on the BSRBR data would be less than £30,000 and therefore within the range that the Appraisal Committee has previously considered to be an effective use of NHS resources.

In not recommending sequential TNF-α inhibitor treatment, based on an analysis which does not take the above-mentioned data into account, the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

**2.2. (Formerly 1.2.) Inappropriate exclusion of the DMARD effectiveness data from the BSRBR**

Section 4.3.7 of the FAD highlights that the Appraisal Committee uses the presence of a proportion of people in the BSRBR with a response to conventional DMARDs after the failure of a TNF-α inhibitor to conclude that an assumption of no positive effect was not supported by the evidence. Such an assumption would be valid in this sub-population of responders, but given that the mean HAQ change across the entire group was zero, the FAD fails to indicate or acknowledge that a proportion of the patients must also have suffered deterioration in response to conventional DMARDs.

Given that the BRAM is designed to model a response with a variable distribution, to not include an assumption of net zero HAQ improvement on conventional DMARDs, on the grounds of a sub-population of responders, has led to the Institute preparing guidance which is perverse in the light of the evidence submitted.

**2.3. (Formerly 2.3.) Failure to incorporate offset costs on the ICER for sequential use of TNF-α inhibitors**

*In your initial view you considered this point only valid under ground 1. However, as inclusion of cost offsets would reduce the ICERs of the technologies being appraised, and the existing analysis cites the ICER for a second TNF-α inhibitor in the event of secondary failure to a first as being between £31 - £34,000 it would be anticipated that the ICER which incorporates offset costs would be less than £30,000 and within the range that the Appraisal Committee has previously considered to be an effective use of NHS resources. Whilst a cost-effectiveness analysis incorporating cost offsets have not been performed it is reasonable to conclude that the Institute had prepared a FAD that is perverse in the light of the evidence submitted, and therefore we would ask this point to be considered under ground 2 also.*

Section 4.3.11 of the FAD states that the Appraisal Committee noted that sensitivity analyses including offset costs had been explored in the first-use analyses of TNF-α inhibitors and that these had not demonstrated a significant impact on the incremental cost-effectiveness ratios. The Appraisal Committee concluded that consideration of offset costs was important, but that this had been explored by the Assessment Group in their original analyses and had been shown not to be a key driver of cost effectiveness.

The fact that the offset costs were not considered having a significant impact on the ICERS for the first use analyses of TNF-α inhibitors does not justify the failure to include them in the analysis of the sequential use of TNF-α inhibitors. As mentioned in Section 1.2 of this document, any cost offsets would need to be included in the cost effectiveness model, in order to establish the minimum effectiveness that would be required of a second TNF-α inhibitor for it to be marginally cost-effective. The magnitude of the impact of offsets costs on the ICER is dependent on the difference of HAQ response between TNF-α inhibitor and comparator. The difference in HAQ response and therefore the impact of offset costs may be greater in the case of the sequential use of TNF-α inhibitors compared with their initial use. As the existing analysis cites the ICER for a second TNF-α inhibitor in the event of secondary failure to a first as being between £31 - £34,000 it would be anticipated that the ICER which incorporates offset costs would

be less than £30,000 and within the range that the Appraisal Committee has previously considered to be an effective use of NHS resources.

In not recommending sequential TNF-α inhibitor treatment, based on a cost effectiveness analysis which does not incorporate offset costs, the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

**2.4. (Formerly 2.4) Change in discount rate during appraisal) Undue weight given to clinical effectiveness**

In Section 4.3.16 of the FAD the Appraisal Committee notes that the use of different discount rates in the new sequential analyses would reduce the estimates of incremental cost-effectiveness. However, the Appraisal Committee still concluded that it did not alter their conclusions regarding the lack of robustness in the current evidence base for the clinical effectiveness of second use TNF-α inhibitors upon which the estimates of cost-effectiveness were based.

In reaching its decisions, the Appraisal Committee, according to sections 4.4.1.4, 4.5.1.8 of the Guide to the Technology Appraisal Process and sections 1.3.2.1, 3.3.1, 5.1, 5.3.1.1, 5.3.4, of the Guide to the Methods of Technology Appraisal, needs to consider both clinical effectiveness and cost-effectiveness evidence. Additionally, an assessment of cost-effectiveness is required by the final scope and protocol of this technology appraisal. Furthermore, the Appeal Panel for the first appraisal (TA130) suggested that the Appraisal Committee reassess the evidence for the cost-effectiveness of a ,second TNF-α inhibitor.

However, even though evidence on both clinical and cost-effectiveness was available to the Appraisal Committee in this technology appraisal, the Institute has given undue weight to the aspects of clinical effectiveness to reach its conclusion presented in section 4.3.16 of the FAD.

Therefore, by giving undue weight on the clinical effectiveness during the appraisal, and consequently not recommending sequential use of TNF-α inhibitors despite demonstrating an ICER within the range typically considered acceptable, the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

**2.5. (Formerly 2.4.) Use of inconsistent discount rates**

The current FAD and TA130 are considered to be part of the same appraisal. As a consequence all the conditions and criteria used in the preparation of TA130 must apply to the preparation of guidance on the sequential use of TNF-α inhibitors. However, the cost-effectiveness analyses carried out to compare the sequential use of anti TNF-α inhibitors with non-biologic DMARDs and rituximab used a discount rate of 3.5% for costs and benefits, instead of the discount rates of 1.5% and 6% which were used during the preparation of TA130.

In Section 4.3.16 of the FAD the Appraisal Committee notes that the use of different discount rates in the new sequential analyses would reduce the estimates of incremental cost-effectiveness.

Therefore, in not recommending sequential use of TNF-α inhibitors despite demonstrating an ICER within the range typically considered acceptable, the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

**2.6. (Formerly 3.) Failure to distinguish subgroups**

The Final Scope of this technology appraisal states that if the evidence allows, the appraisal will attempt to identify criteria for selecting patients for whom these treatments are particularly appropriate.

Section 4.3.20 of the FAD notes that the Appraisal Committee was not persuaded that the current clinical evidence available supported a decision that TNF-α inhibitors when used after the failure of a previous one for the treatment of people who were intolerant of or had contraindications to rituximab or methotrexate, or because of the presence of seronegative disease, would be an appropriate use of NHS resources. In doing so, the Appraisal Committee has failed to identify criteria for selecting patients for whom these treatments are particularly appropriate. Instead it is applying a blanket decision to all patients.

In section 4.3.5 of the FAD the Appraisal Committee concluded that there was insufficient evidence to distinguish between the clinical effectiveness of the second TNF-α inhibitor when used in people whose condition did not show any response to their first TNF-α inhibitor (that is, primary failure) and people who, after an initial response to their first TNF-α inhibitor, had experienced a reduction in response (that is, secondary failure).

However, although the evidence is limited, what evidence there are, e. g. the ReACT trial, shows consistently higher effectiveness in patients with secondary failures compared to those with primary failure. Therefore the Institute should have included this evidence in its decision making.

Furthermore, with respect to the BSRBR DMARD data the committee decided to overrule the evidence of no effect because, according to clinical opinion, some patients might respond to a DMARD post TNF-α therapy and yet with respect to subset data or indeed the overall switch data they would not accept clinical opinion and the overall trend in the data.

Wyeth considers that by omitting this evidence in its decision making the Institute was unreasonable and perverse; therefore the Institute has prepared a FAD which is perverse in the light of the evidence submitted.

**2.7. (Formerly 7.) Splitting of the appraisal**

*Wyeth accepts that the publication of guidance for the use of a first TNF-α inhibitor had the desired outcome that patients could enjoy the benefits of a positive recommendation for first use at once, without having to wait for an appraisal of subsequent use to be completed. Therefore we do not wish to proceed with this point of appeal.*

**2.8. (Formerly 8.) Refusal to use DMARD efficacy from BSRBR in combination with ReAct data for TNF-α inhibitors**

*In your initial view you regarded this not to be a valid point of appeal. However Wyeth contends that, only comparing DMARDs based on clinical trial data and TNF-α inhibitors based on registry data, and not the converse comparison, introduces bias into the analysis, resulting in a perverse recommendation. We therefore would ask for this appeal point to be accepted.*

The cost-effectiveness analysis used for this appraisal uses efficacy data, in terms of HAQ improvement, for sequential TNF-α inhibitor from the BSRBR registry. However, rather than source the estimates of HAQ improvements for the comparator conventional DMARD sequence from the same registry database, values from rheumatoid arthritis clinical trial data (placebo arms) were used instead. These efficacy estimates show greater HAQ improvements, and lack face validity in light of the evidence available. This also means that the two cannot be compared. If, however, the Institute accept these data, it should have also examined the converse scenario, using TNF-α inhibitor effectiveness data from clinical trials, such as the ReACT in combination with the DMARD effectiveness data from the BSRBR.

The selective use of the inputs in the appraisal has resulted in bias. As a consequence the modeling cannot be considered methodologically sound and the analysis and interpretation of the evidence cannot be considered to be of the highest standard.

The Appraisal Committee also appears to have given undue reliance on BRAM with less weigh being given to the independent BSRBR model.

Therefore, by including results from the above mentioned flawed analysis in the FAD the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

**2.9. (Formerly 9.) Some HAQ improvement values utilised in the further cost effectiveness analysis of sequential TNF-α inhibitors have been extrapolated from the ReAct study inappropriately**

*In your initial view you regarded this not to be a valid point of appeal. However Wyeth contends that, the extrapolation of data for the effectiveness of etanercept from the ReACT study, which was utilised in the economic analysis, is perverse in light of the clinical effectiveness data submitted. We therefore would ask for this appeal point to be accepted.*

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. Wyeth considers that 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 TNF-α inhibitors therapy following lack or loss of response to the first.

This interpretation is supported by the evidence identified in the update report by the 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 therefore the cost-effectiveness of the TNF-α inhibitors. The use of these inputs into the appraisal has resulted in bias.

By accepting these flawed results and making recommendations based on them the Institute has prepared a FAD that is perverse in the light of the evidence submitted.

**Conclusion**

**Had the Institute taken into account the data referred to in this document and included it in its analysis and decision-making, Wyeth believes the result of the economic modeling would have been very different, with lower ICERs. It is highly likely that the result of the economic evaluation carried out using the BRAM would have been below the threshold to be considered an acceptable use of NHS resources which is likely to have led to a positive recommendation for the sequential use of TNF-α inhibitors, consistent with recommendations for other indications of TNF-α inhibitors made in previous appraisals by the Institute. As the combined impact of the points raised above has not been considered, the Committee have failed in its duty. Consequently, Wyeth wishes to make an appeal based on the above mentioned points. Wyeth reserves its rights generally in relation to the points it raises above.**

Yours sincerely

p.p.