COMMENTS ON DOCUMENTS RECEIVED ON AUGUST 31st 2006 FOR THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Etanercept (ENBREL*)

Appraisal of clinical and cost effectiveness of the use of etanercept in the treatment of adults with rheumatoid arthritis

28th September 2006

All communication to be addressed to:-

* Trade mark

1 Summary

The documents received from NICE on August 31st 2006 in relation to the appraisal of adalimumab, etanercept and infliximab for rheumatoid arthritis cover two separate issues. Firstly changes to the BRAM made following the Appraisal Committee meeting and secondly analyses relating to the BSRBR data on switching between TNF targeted therapies.

These documents must be considered however with all the other evidence presented in respect of this Appraisal.

In Wyeth's view the Assessment Report and the Appraisal Consultation Document (ACD) do not fully address all the points set out in the Scope. The Scope states that, if the evidence allows, the appraisal will attempt to identify criteria for selecting patients for whom these treatments would be particularly appropriate, and the stage in the pathway of care when these technologies should be used.

In Wyeth's view this has not been achieved. In particular the Evaluation Report (ER) only considers use in DMARD naïve patients or after 2 DMARDs have failed, without consideration of patients who have failed their first DMARD. Additionally only disease activity has been considered as a criterion for selecting appropriate patients. The appraisal does not appear to have considered factors that identify patients predicted to have persistent, progressive disease with a poor outcome, as described in the recently published, evidenced based, European League Against Rheumatism (EULAR) recommendations for the treatment of early arthritis[1]. This approach has been considered in some detail in our response to the ACD.

From evidence presented in this document Wyeth propose that:

- The BRAM should use zero HAQ progression for patients on ETN + MTX as the base case for assessment of the cost-effectiveness of this intervention
- The BRAM should use the assumption that MTX would not be available after TNF inhibitor monotherapy as the base case for all analyses
- It is reasonable to assume that differences in the effect on HAQ between the various TNF inhibitors observed during initial treatment would also be manifest in a second course of therapy following a lack of response to the first course

Wyeth is of the opinion that the weight of the evidence should lead the Appraisal Committee to recommend that:

◊ Etanercept plus methotrexate is recommended for treatment of patients with severe active RA predicted to have a poor outcome who have had an inadequate response to MTX as first DMARD

◊ Etanercept with or without MTX is recommended for patients with severe active RA who have failed 2 DMARDs

◊ Adalimumab and infliximab should be used in patients with an inadequate response to etanercept except in cases of contraindications or intolerance to etanercept or where an infusion (infliximab) is clinically indicated.

◊ In the event that an alternative was used, etanercept is recommended for patients with severe active RA who have had an inadequate response to their first TNF targeted therapy

2 Comments on documents provided for consultation

As the changes to the BRAM also affect the economic analyses of the sequential data, these will be dealt with first.

2.1 Revisions to the BRAM model following the NICE Appraisal Committee meeting and A note considering the question of TNF inhibitor monotherapy or combination with methotrexate as first line therapy

Wyeth has previously commented on the HAQ values used in the BRAM, both the starting distributions and the progression rates.

The revised rate of HAQ progression of 0.03 per annum that has been assumed for etanercept however contradicts the available evidence. Long term open label extensions to the original placebo controlled studies of ETN have followed patients for up to eight years[2]. (Nine year data will be presented at the American College of Rheumatology meeting in November.) In these patients the mean HAQ value has remained at the level achieved during the controlled studies, that is HAQ progression has been zero. If the BRAM assumptions are correct then the HAQ values would have been expected to have increased by 0.25 over that period. These data are supported by the three year results from TEMPO and its one year extension, where again no progression of HAQ was seen. In the Wyeth model the mean period of treatment with ETN+MTX is 4.8 years, therefore the assumption of zero HAQ progression is justified.

Underlying this lack of progression in HAQ scores is the radiological evidence. Data from the 3 year blinded data show that in patients treated with ETN and MTX over 75% showed no progression in joint damage[3].

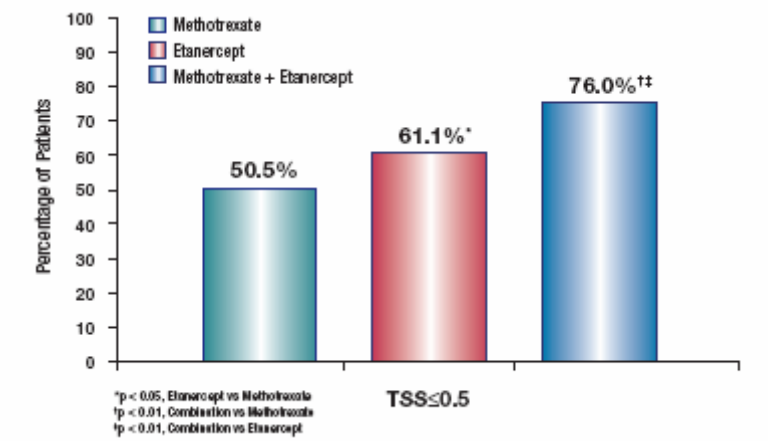
Table 1

Radiographic Endpoints: Change from Baseline at 3 Years (ITT)

	MTX (n=210)	Etanercept (n=211)	MTX+Etanercept (n=217)
TSS	5.95 (2.96, 8.94)	1.61 (0.41, 2.81)*	–0.14 (–1.07, 0.78)†‡
Erosions	3.25 (1.50, 5.01)	0.39 (–0.44, 1.22)*	–0.67 (–1.05, –0.28)†
JSN	2.70 (1.26, 4.13)	1.22 (0.59, 1.84)	0.53 (–0.21, 1.26)†‡

*p<.05, etanercept vs MTX; †p<.05, combination vs MTX; ‡p<.05, combination vs etanercept

Figure 1 Percent of patients with no radiographic progression (<0.5) at 3 years



The relationship between HAQ and TSS has been explored in some detail using data from TEMPO [4]. The analysis showed that not only do patients with a worse radiographic status have demonstrably worse physical function, after adjustment for age, sex, and disease activity, but also those with recent radiographic progression. This finding gains importance in the light of the radiographic progression rates found in TEMPO with the combination treatment.

Importantly, a recent analysis of a longitudinal study of patients with RA using general estimating equations showed that the radiographic disease status as well as the rate of radiographic progression in RA is longitudinally related to physical function, independent of the ESR as a marker of disease activity, and independent of age, sex, RF status, and disease duration[5]. The authors concluded that "If, in a patient, a particular treatment (e.g., a biologic drug) causes an arrest in radiographic progression (a change in progression rate), an immediate improvement in physical function can be expected, even if this drug has no effect on disease activity."

Wyeth would submit therefore that the BRAM should use zero progression on ETN + MTX as the base case for assessment of the cost-effectiveness of this intervention.

The base case progression rates in BRAM and Wyeth models are summarised in Table 2.

Table 2 Comparison of HAQ parameters

Parameter	ETN + MTX			DMARD			
	Wyeth	BRAM			Wyeth	Bram	
Base HAQ	1.74	1.20			1.74	1.20	
Initial change	-0.89	-0.59		MTX	-0.65	-0.54	
				SSZ	-0.29	-0.45	
				Gold	-0.43	-0.39	
				LEF	-0.50	-0.47	
				DMARD	-0.27	-0.39	
		Original	Modified			Original	Modified
Long term per cycle (6 month)	0.00	0.0155	0.015	MTX	0.02	0.0155	0.0225
				Others	0.10	0.0155	0.0225
				Palliation	0.20	0.0155	0.03

The effects of changes made to BRAM in HAQ progression rates on the cost-effectiveness of ETN are summarised in Table 3.

Table 3 Revised BRAM results

	Cost per QALY	
	Original	Revised
Enbrel mono		
1st line	£107k	£49k
3rd line (late RA data)	£88k	£47k
3rd line (early RA data)	£45k	£30k
Last line	£33k	£24k
Enbrel + MTX		
1st line	£631k	£78k
3rd line (late RA data)	£94k	£50k
3rd line (early RA data)	£41k	£28k
Last line	£33k	£24k

As noted in the second document, the results for first line use are paradoxical as clinically ETN + MTX is significantly more effective than ETN monotherapy, but at little

additional cost. Consequently Wyeth only considered combination therapy in its submission.

In addition the BRAM, unlike the Wyeth model, is exquisitely sensitive to changes in the rate of HAQ progression. This is demonstrated clearly in the note on first line therapy.

The Table 4 below shows the ICERs for combination therapy for each TNF targeted therapy with base case progression (0.03 pa) and zero progression.

Table 4 Effect of HAQ progression on BRAM results for 1st line treatment

Comparison	ICER (£/QALY)	
	Base	Zero progression
ADL+MTX	£165,000	£38,100
ETN+MTX	£79,200	£27,700
IFX+MTX	£552,000	£44,900

In contrast the Wyeth model does not show such sensitivity to assumptions on progression. In the initial Wyeth submission the base case ICER for 1st line therapy (zero long-term HAQ progression) the ICER was £16,379, which should be compared with the sensitivity analysis using the value of 0.05 per cycle (0.1 pa) of £16,749.

The removal of MTX from the sequence following TNF targeted therapy as first line therapy does indeed explain the paradox of monotherapy being more cost-effective than combination therapy. In practice however the use of these treatments as 1st line therapy is extremely unlikely given the results that can be obtained with MTX. If it were deemed appropriate on clinical grounds in cases of particularly aggressive disease then combination with MTX would be used in any case.

2.2 General observations on the BRAM

Whilst the use of the NOAR HAQ distribution to represent a general population with RA is appropriate, only a subset would be considered as candidates for TNF targeted therapy, particularly as first line therapy. Obviously disease progression in a proportion would, over time, make more patients eligible. The Assessment Group made no attempt to explore the identification of a sub-group of patients for which these treatments would be cost-effective, as required by the scope.

In the response to the ACD, Wyeth characterised patients with active, progressive disease with a poor prognosis, for whom etanercept plus MTX would be a cost-effective option, in patients who had an inadequate response to MTX as first DMARD.

Even when changes in progression rates were incorporated into BRAM the results are still very different from the company models.

It is important that efforts are made to understand why the models show such different responses to changes in long term HAQ progression on the TNF targeted therapies.

Several possibilities have been identified but others may exist that are not apparent with the information available to Wyeth.

2.2.1 HAQ distributions

The methods to estimate HAQ changes used beta distribution rather than the normal distributions in the Wyeth model. Because beta distributions bind values by a lower limit of zero, it would appear that this is not an appropriate distribution for parameters whose mean value is zero (i.e. that of the long-term HAQ change for ETN+MTX in the Wyeth model). Instead, it is recommended that a normal distribution is used, with an appropriate standard deviation. This would allow both positive and negative changes in HAQ, and would enable to long-term mean change to be zero. As such, a given proportion of patients would experience sufficient worsening of HAQ to require treatment switching, whilst the mean change would remain at zero. This difference between the Wyeth and BRAM models may account for the variation in results.

2.2.2 The effect of HAQ increments on utility

The BRAM utilises the categorical scoring of HAQ whereas the Wyeth model assumes this is a continuous variable. These differences will have consequences for the derivation of utilities. For example as HAQ increases by increments of 0.125 it is 4 years in BRAM before a patient treated with a TNF targeted therapy has an increase in HAQ. It is unclear what occurs if the patient stops within a few days of starting treatment or just prior to 4 years. This approach also leads to stepwise changes in utilities of 0.04 for a HAQ change of 0.125 using the regression used in the BRAM. The impact of this needs to be further evaluated.

2.2.3 HAQ changes at treatment change

In the BRAM, when a treatment period ceases for whatever reason the HAQ increases by the amount of the initial improvement in HAQ. Therefore if HAQ progression has occurred then HAQ increases to above the baseline value (see Figure 2). This seems an unreasonable assumption. Evidence in this respect is limited, but in an early ETN study it was reported that on stopping treatment clinical parameters had not returned to baseline 2 months later[6] (Figure 3). In the Wyeth model it was assumed that on stopping HAQ scores returned to the starting value.

Figure 2 Representation of HAQ response from BRAM

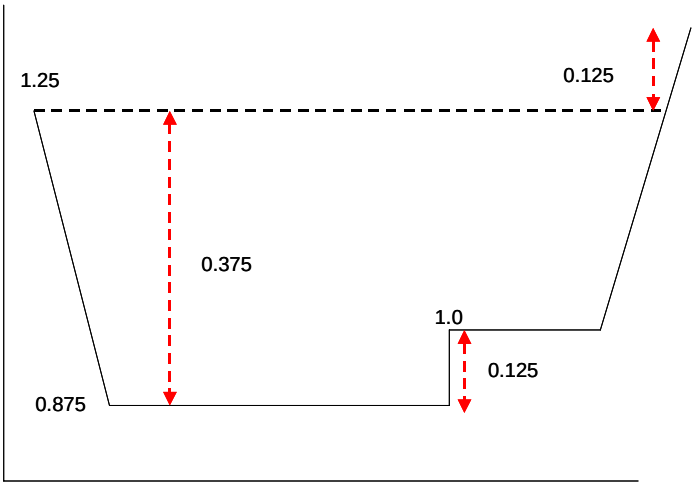
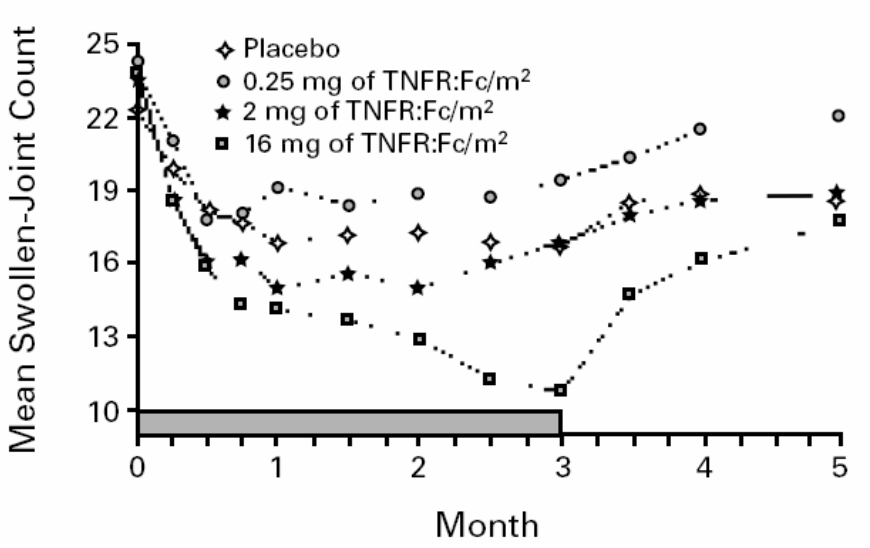


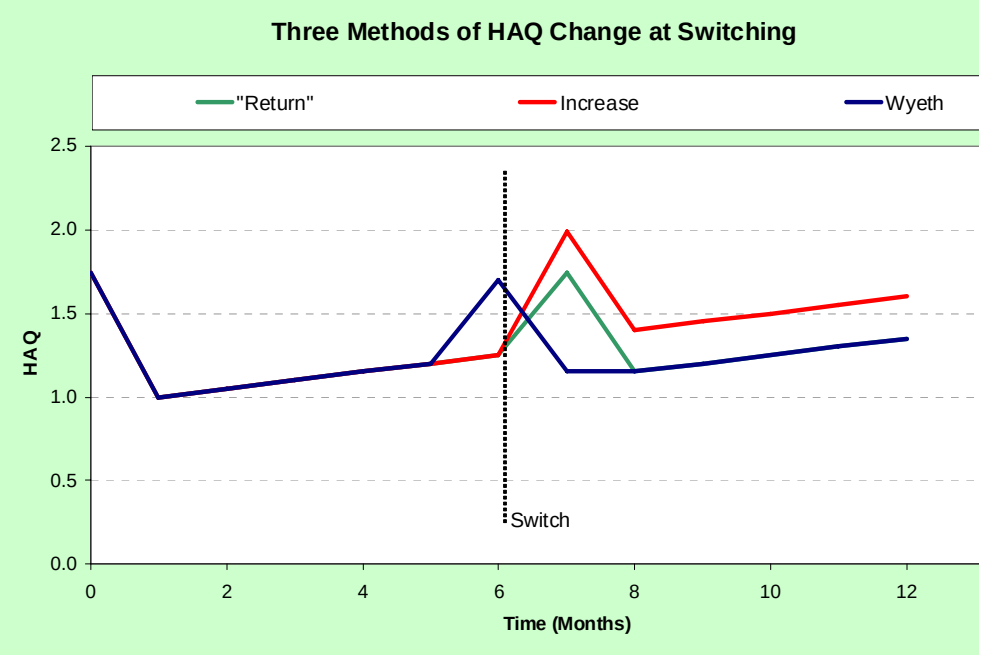
Figure 3 Effect of stopping ETN on swollen joint count[6]



16 mg/m is approximately equivalent to 25 mg

The alternative methods of dealing with HAQ at the point of switching are shown in Figure 4

Figure 4 Methods of modelling HAQ at point of treatment switch



These 3 different approaches have now been evaluated in the Wyeth model. The starting HAQ was set at 1.74 with ETN+MTX third line. The results (discounted ICER) were:

Return	£11,639
Increase	£15,155
York	£13,192

It can be concluded that in this model the method used for HAQ inputs around stopping treatment do not have a substantial effect on the results

The inputs used in BRAM (see Table 3) have now been used in the Wyeth model to try and evaluate the overall impact these have on the results. The results are summarised in Table 5 and 6.

Table 5 Discounted results for ETN+MTX 2nd line v DMARDs using BRAM values

	Discounted Results		
	Comparator	**Treatment**	**Incremental**
Cost	£23,462	£75,951	£52,489
QALYs	11.785	12.450	0.665
ICER			£78,925

Table 6 Discounted results for ETN+MTX 3rd line v DMARDs using BRAM values

	Discounted Results		
	Comparator	**Treatment**	**Incremental**
Cost	£23,456	£48,947	£25,491
QALYs	11.625	11.971	0.346
ICER			£73,572

The model was then re-run but with the HAQ progression rate set at zero rather than 0.03 pa.

Table 7 Discounted results for ETN+MTX 3rd line v DMARDs using BRAM values but with long term progression as zero

	Discounted Results		
	Comparator	**Treatment**	**Incremental**
Cost	£23,519	£48,639	£25,120
QALYs	11.642	12.310	0.668
ICER			£37,600

The ICER results using the BRAM inputs in the Wyeth model are similar to those obtained using BRAM, confirming that is the interaction between the input assumptions that produces the significant differences, rather than the model structures themselves. We have been unable to assess the effect of a beta rather than a normal distribution and a categorical rather than a continuous scoring of HAQ in the Wyeth model. The

sensitivity to long-term HAQ progression may be as a result of the smaller differences in initial HAQ response between TNF inhibitor and DMARD treatments used in the BRAM compared with the Wyeth model.

Taking all the economic evidence together then Wyeth is of the opinion that the Appraisal Committee should recommend the use of ETN in patients with severe active disease predicted to have a poor outcome (see ACD response for details) despite treatment with MTX as their 1st DMARD and in patients who have failed treatment with 2 DMARDs and who meet the eligibility criteria set out in the BSR guideline[7].

In light of the results from BRAM, which consistently show ETN to have better cost-effectiveness than the monoclonal antibodies, the Committee should consider whether ETN should be the preferred treatment option. This could be incorporated into Guidance similarly to the recent recommendations on psoriasis and psoriatic arthritis.

2.3 Effect of a second course of anti-TNF therapy on HAQ following lack of response to the first course.

Sequential use of TNF-α inhibitors for the treatment of Rheumatoid Arthritis. Report by the NICE Decision Support Unit.

These reports attempt to use data from the BSRBR to determine the response to switching between TNF targeted therapies and to use these data as inputs into the BRAM to evaluate the cost-effectiveness of this strategy.

The DSU state that the primary question should be:

> *What is the cost effectiveness of a second TNF-α inhibitor compared to traditional DMARD treatment in patients with late RA that are withdrawn from a first TNF-α inhibitor due to inadequate response?*

The approach taken uses sequences after the 1st anti-TNF has failed. As a consequence complex statistical techniques have had to be used to obtain the required data from the BSRBR observational study. This was necessary as the HAQ value at the point of switch often was not recorded, as the protocol only required 6 monthly measurements.

An alternative approach would have been to ask the question:

> *What is the cost effectiveness of strategies involving a second TNF-α inhibitor compared to traditional DMARD treatment in patients with late RA that are withdrawn from a first TNF-α inhibitor due to inadequate response?*

In this case the sequences would diverge after DMARD failure. The question is whether a sequence involving switching is more cost effective than a DMARD sequence rather than a sequence involving one inhibitor. This approach avoids the complex statistics needed to derive the inputs used in the BRAM analyses, as the HAQ over the period from initiation is required, not at the point of switch.

This approach was used in the Wyeth submission (see section 3.1)

The BSR statistical report identified 3 main groups:

1. Patients who failed according to BSR criteria but continued treatment
2. Patients who failed and stopped taking anti-TNFs

3. Patients who failed one anti-TNF and switched to another
    a. A subgroup was identified with >6 months on the 2nd drug

The unadjusted HAQ change data was:

Group 1	-0.07
Group 2	-0.01
Group 3	-0.12
Group 3a	-0.15

These changes are substantially less than seen in the clinical trials or reported for the overall response in the BSRBR. Adjustments were also made to account for changes in disease activity after failure.

	Confounders	Activity change
Group 1	-0.1332	-0.1363
Group 2	NR	NR
Group 3	-0.1652	-0.2069
Group 3a	-0.2146	-0.2594

It has been noted that no adjustments have been made to the results for group 2. It would be expected that data from this group would be used for the comparator sequence.

The unadjusted results show that switching is more effective than stopping, but improvement was less that that observed with the 1st biologic in the BSRBR, of 0.4.

The DSU report analyses the requirements for modelling sequential use and the methodology used by the BSR to provide estimates from the BSRBR.

The report highlights some key issues:

- ◊ Caution must be exercised in combining evidence from different data sources which relate to different patient groups. That is clinical trial data used in BRAM and BSRBR.
- ◊ The BRAM does not model withdrawal before 24 weeks whereas NICE Guidance recommends stopping in the case of inefficacy after 12 weeks.
- ◊ The BSRBR data are for all patients taking a second TNF inhibitor, including non-responders.
- ◊ Drug survival estimates are from non-UK sources with results for etanercept being different from the other 2 drugs.
- ◊ Treatment multipliers are very different between the TNF-α inhibitors in the BRAM whereas in the BSRBR they are similar.
- ◊ The data from the BSRBR is for all 3 drugs.

Wyeth agrees with these comments but in addition is concerned that the statistical techniques used provide different estimates of HAQ changes, which introduces even greater uncertainty to a model that already appears to be sensitive to changes in assumptions.

The DSU report also has an appendix summarising studies reporting sequential use, as did the Wyeth response to the ACD. These have been compared and it was found that both contained references not included in the other. In addition the DSU summary had an error regarding the study by Ang et al[8] where the number of patients treated with ETN and IFX were reversed. A revised summary table is attached to this report.

3 New results for 2nd TNF inhibitor August 2006

The inputs for BRAM were identified by consultation between NICE, the DSRU, BSR and the Birmingham modeller, Pelham Barton.

The updated model assumptions were used.

The HAQ improvement for the switch population was taken from the BSR report and was 0.2146 (SD 0.4216) in a population with a starting HAQ of 2.05 (SD 0.6). The basecase results give ICERs between £59k and £63k. This reduces to £35k to £39k if it is assumed that post-biologic DMARDs are 50% less effective than if used before a biologic.

It is unclear however from the report what input values were used for the comparator sequence. From the reported results it would appear that original parameters derived from studies were used and that as sensitivity analyses these were adjusted by 50% above and below the basecase. Data however is available from the BSRBR group 2, which shows a minimal change in HAQ on stopping the TNF targeted treatment.

The poor efficacy of DMARDs in late disease is well documented from a meta-analysis of clinical trials[9]. A recent publication has confirmed this effect in relation to HAQ[10] and a UK study has shown limited effects of DMARD treatment in late disease[11]. This reflects the irreversible nature of joint damage that accumulates over time, and further supports the early use of the most effective agents to prevent such damage. Even in early disease after failure of the initial DMARD the response to subsequent treatments is often inadequate as demonstrated by the randomised BeST[12, 13] study.

These observations would support the case for the efficacy of DMARDs post TNF to be substantially reduced and should be the base case in the evaluation of sequential use.

An alternative analysis was used to adjust for the different population in the BSRBR to that in the trials. The observation that the HAQ change in switchers from the BSRBR was approximately 70% of that seen with the first biologic was used to adjust the trial data. The α parameter of the HAQ multiplier was reduced to 70% of the original value whilst keeping $\alpha + \beta$ fixed.

In this analysis it was assumed that there was no HAQ progression on TNF inhibitors.

If the adjusted clinical trial data is used than ICERs are £31k - £49k in the basecase and £23k - £35k with DMARDs 50% less effective. As described above the latter scenario reflects the available evidence.

Although most studies of switching have not looked at possible predictors of response to the 2nd agent, Buch et al [14] showed in primary IFX failures, that in patients who did not respond at the beginning of treatment, different patterns of response could be identified. Patients who showed no reduction in CRP at week 2 or 12 and who were switched to ETN had a good response with 68% achieving an ACR 20 response and 51% an ACR 50 response. These are similar to primary responses to ETN reported in clinical trials.

These data suggest that in selected patients, identified by initial change in CRP, response to ETN after another TNF inhibitor may be similar to 1st line use.

3.1 Wyeth model results for sequential use

The results using various sequential use pathways, which assumed similar primary and secondary responses, were evaluated in the Wyeth submission in comparison with the DMARD sequence. The results are summarised in Table 5 (the scenario number refers to the original submission).

Table 7 Cost effectiveness of sequential use

Scenario	Sequence	ICER (£/QALY)
4	ETN+MTX → IFX+MTX	£15,495
5	ETN+MTX → ADL+MTX	£22,749
6	IFX+MTX → ETN+MTX	£15,950
7	ADL+MTX → ETN+MTX	£24,455
8	MTX → ETN+MTX → IFX+MTX	£16,697
9	MTX → ETN+MTX → ADL+MTX	£17,409
10	MTX → IFX+MTX → ETN+MTX	£15,211
11	MTX → ADL+MTX → ETN+MTX	£19,158

These results show that a strategy involving sequential use of TNF targeted therapies is a cost-effective option when compared to a DMARD sequence.

These have now been re-run using the 30% reduction in effect on HAQ reported in the BSRBR statistical analysis and applied in the BRAM speculative analysis. The results are summarised below.

Table 8 Cost effectiveness of comparisons of sequential use of TNF inhibitors

Sequence	ICER (£/QALY)
MTX → IFX+MTX → ETN+MTX MTX → IFX+MTX → ADL+MTX	£19,249
MTX → ADL+MTX → ETN+MTX MTX → ADL+MTX → IFX+MTX	£15,781

The results show that ETN+MTX is cost effective when used after ADL+MTX or IFX+MTX when compared to the alternative TNF targeted therapy, even when the HAQ improvements are reduced by 70%.

4 Conclusions

When all the evidence and comments are considered Wyeth believe the following conclusions can be drawn:

Although Wyeth has expressed concerns about certain aspects of the BRAM (see below for additional discussion) this economic model consistently finds that ETN (with or without MTX) is the most cost-effective TNF targeted therapy. If the precedent of recently issued Guidance on psoriasis and psoriatic arthritis is followed then ETN should be the preferred treatment option.

When BRAM is run with zero HAQ progression (which is supported by the available evidence) on ETN or ETN+MTX then the ICERs fall below £30,000 for all positions in the sequence that were evaluated. It would be reasonable, therefore, to recommend that ETN+MTX be made available when MTX alone has proved ineffective as first line therapy. The evidence for this was discussed in detail in Wyeth's response to the ACD.

The clinical evidence for the effectiveness of switching when patients fail to respond to the first TNF targeted therapy is clear, with responses being similar or slightly less than the first agent. The BSRBR data, even with sophisticated statistical techniques, provides data that has a considerable degree of uncertainty. When the reduced effectiveness seen in that analysis is applied to the BRAM clinical trial data then switching to ETN from other biologics (in the case when ETN was not first choice) is cost effective. This is supported by similar results from the Wyeth model. Consequently this option should be included in Guidance.

References

1. Combe, B. et al. Eular recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Annals of the Rheumatic Diseases Online 1st, 10.1136/ard.2005.044354 (2006).
2. Klareskog, L. et al. Safety and efficacy of over 8 years of continuous etanercept therapy in patients with rheumatoid arthritis in North America and Europe. EULAR Annual Meeting FRI0132 (2006).
3. van der Heijde, D., Klareskog, L., Wajdula, J., Pedersen, R. & Fatenejad, S. Sustained halting of joint damage with combination etanercept and methotrexate: 3-year results from the TEMPO trial. EULAR Annual Meeting SAT0194 (2006).
4. van der Heijde, D., Landewe, R., van Vollenhoven, R., Fatenejad, S. & Klareskog, L. Radiographic Progression Determine Physical Function in Patients With Rheumatoid Arthritis: A Longitudinal Analysis of the TEMPO Trial. EULAR Annual Meeting (2006).
5. Odegard, S. et al. Association of early radiographic damage with impaired Physical Function in Rheumatoid Arthritis. A Ten-Year, Longitudinal Observational Study in 238 Patients. Arthritis & Rheumatism 54, 68 - 75 (2006).
6. Moreland, L. W. et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. New England Journal of Medicine. 337, 141-147 (1997).
7. Ledingham, J., Deighton, C. & on behalf of the British Society for Rheumatology Standards, G. a. A. W. G. Update on the British Society for Rheumatology guidelines for prescribing TNF{alpha} blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology 44, 157-163 (2005).
8. Ang, H. T. & Helfgott, S. Do the clinical responses and complications following etanercept or infliximab therapy predict similar outcomes with the other tumor necrosis factor-alpha antagonists in patients with rheumatoid arthritis? Journal of Rheumatology.30(11):2315-8 (2003).
9. Anderson, J. J., Wells, G., Verhoeven, A. C. & Felson, D. T. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis & Rheumatism.43(1):22-9 (2000).
10. Aletaha, D. & Ward, M. M. Duration of rheumatoid arthritis influences the degree of functional improvement in clinical trials. Annals of the Rheumatic Diseases 65, 227-233 (2006).
11. Symmons, D. et al. Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs--results of the British Rheumatoid Outcome Study Group randomized controlled clinical trial.[see comment]. Rheumatology 45, 558-65 (2006).
12. Goekoop-Ruiterman, Y. P. et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis & Rheumatism.52(11):3381-90 (2005).
13. van der Kooij, S. M. et al. What Treatment Strategy Should be Chosen after Initial Failure on Methotrexate 25 mg in Early Rheumatoid Arthritis? Data from the BeSt Study. American College of Rheumatology Annual Meeting Abstract 1865 (2005).
14. Buch, M. H. et al. C-reactive protein as a predictor of infliximab treatment outcome in patients with rheumatoid arthritis: Defining subtypes of nonresponse

and subsequent response to etanercept. Arthritis & Rheumatism.52(1):42-8 (2005).