Abbott comments on the further analyses of the cost effectiveness of sequential use of TNF inhibitors in Rheumatoid Arthritis

Abbott welcomes the appeal panel's decision that there should be further consideration of the recommendation regarding the sequential use of TNF inhibitors in patients failing their first TNF inhibitor for efficacy reasons. Abbott considers that there is strong evidence to support the clinical effectiveness and cost effectiveness of TNF inhibitors for sequential use. Abbott would like to draw attention to some key aspects of this evidence for the committee's consideration.

1. Limitations of the HAQ

The HAQ score is an important tool in the consideration of cost effectiveness of treatments for Rheumatoid Arthritis (RA). However, one of the important weaknesses of the HAQ is that it measures both disease activity and functional impairment, and can therefore represent different aspects of the disease for patients with early RA compared to late RA. Caution should therefore be taken in applying HAQ improvement data without careful consideration of the characteristics of the population in which the HAQ scores were measured.

Consideration should also be given to the limited evidence base 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. Aletaha 2008 indicates that the HAQ was only been in common use in trials since 1995, which excludes a large proportion of the evidence base for the effectiveness of conventional DMARDs[1].

Both these points should be borne in mind when conclusions are drawn regarding the impact of treatments on HAQ improvements.

2. Use of BSRBR data to inform mean HAQ multipliers in the cost-effectiveness modelling

HAQ improvement data from various sources were used in order to provide a range of cost effectiveness estimates for the sequential use of TNF inhibitors after failure of the first TNF inhibitor for efficacy reasons[2]. One estimate, Option A, was derived using HAQ improvement data from the BSRBR report on sequential use of TNF inhibitors to NICE from patients who have received a 2nd TNF inhibitor, after the first had been inefficacious. A mean HAQ improvement of 0.2146 (after adjustment for confounding factors of treatment effect) at 6 months was cited.

The other estimates, Options B and C, were derived from HAQ improvement data from the ReAct study[3], a 12-week multi-national prospective open-label study of adalimumab in patients with active RA, treated in line with national guidelines. A subgroup of patients in ReAct who had experienced inefficacy of at least one TNF inhibitor therapy experienced mean HAQ improvements of 0.33 – 0.52 depending on the preceding failed therapy and the type of non-response experienced - primary or secondary. For analyses of switching between infliximab and any of the other TNF inhibitor, a HAQ improvement of 0.51 was applied. However, for switches between etanercept and adalimumab, in either direction, Option B was derived from application of mean HAQ improvements from a subgroup of patients that had previously not responded to etanercept therapy (-0.33 +/-0.54) whereas Option C resulted from improvements from those who had experienced loss of previously adequate response to etanercept.

Whilst these data have been derived from appropriate cohorts, *i.e.* those who are administered a second TNF inhibitor after the first has been ineffective, Abbott wishes to highlight that HAQ improvement data from other similarly appropriate cohorts exist. Therefore, whilst the use of HAQ improvement data from individual, specific cohorts to inform cost effectiveness analyses of sequential use of TNF inhibitors is not inappropriate, the committee

should be cautious that the demographics and clinical characteristics of patients in the selected cohorts are representative of the majority or at least a large proportion of the others. Most importantly, the HAQ improvement data utilised from these cohorts should broadly reflect those seen by the majority.

Therefore, Abbott believes that the estimates utilising the HAQ data derived from the BSRBR TNF inhibitor failure cohort to inform the cost effectiveness analysis (Option A), as per page 4 of the Barton 2008 report do not provide an accurate estimate of cost effectiveness for the following reasons:

2.1 Lower mean HAQ improvement in the BSRBR cohort compared to other studies of TNF inhibitor failure cohorts

The lower mean HAQ improvement from the BSRBR cohort in part drives the higher cost effectiveness estimates derived from this analysis, using option A. The estimates should be viewed with caution as the HAQ data are derived from a single data source.

The previous search for evidence regarding sequential use of TNF inhibitors undertaken by the appraisal committee and the WMHTAC (2005) and the updated searches undertaken by the DSU revealed a number of papers and reports on the topic, some of which reported HAQ outcomes from patients who had been prescribed a second TNF inhibitor after the first had been ineffective in a number of settings – clinical practice, open label trials, randomised controlled trial. In general, HAQ improvements in these populations were of greater magnitude than achieved by the BSRBR cohort.

In the ReAct study, described above, a subgroup of patients (n=544) who had experienced inefficacy of at least one TNF inhibitor therapy experienced mean HAQ improvements of 0.33 – 0.52 at week 12 depending on the preceding failed therapy and the type of non-response experienced - primary or secondary.

Haraoui et al[4] reported results from an open-label, single arm, observational study that enrolled 25 patients who discontinued treatment with infliximab, 18 for lack of efficacy. Patients were administered etanercept 25mg twice weekly within 4-10 weeks of their last infusion of infliximab. Of the 22 that completed 12 weeks of treatment, 13 (59%) achieved the minimum clinically important difference in HAQ. (HAQ≥ 0.22), with a mean HAQ improvement of 0.45.

Bennett et al[5] prospectively studied the outcome of 70 RA patients, 26 of who had active disease despite prior treatment with TNF inhibitors. Twenty-one (72%) had experienced primary or secondary inefficacy of previous treatment with TNF inhibitors. After switching therapy to adalimumab 40mg every other week for a mean treatment period of 7.3 months, the group previously exposed to TNF inhibitor therapy experienced a mean HAQ improvement of 0.31 (p=0.01 vs. baseline), very similar to that seen in the TNF inhibitor naive cohort. Furthermore, of the 21 patients that had experienced primary or secondary inefficacy of previous treatment with TNF inhibitors, a mean HAQ improvement of 0.22 and 0.26 was reported, respectively.

Lastly, Favalli et al[6] reported an open-label pilot study undertaken to investigate the safety and efficacy of switching therapy from one TNF inhibitor to another. Eight patients with RA and 7 with juvenile rheumatoid arthritis were administered etanercept after lack of efficacy or adverse events with infliximab. One of the cohort of 15 however was administered infliximab after lack of efficacy of etanercept after 6 months of treatment. A mean HAQ improvement of 0.31 at 6 months was reported for the RA group.

Table 1 demonstrates that the above cohorts had very similar characteristics to the BSRBR cohort whose HAQ improvement was used for the 'Option A' analysis. It is noteworthy that even with similarity in the baseline characteristics that have been demonstrated to independently influence functional and symptomatic responsiveness to treatment [1, 7, 8, 9] *e.g.* duration of disease, number of prior DMARDs and baseline HAQ, the improvements seen in the other cohorts are still greater than that experienced by the BSRBR cohort. This further

highlights the drawbacks of relying only on these data from a single study to inform the cost effectiveness evaluation.

Table 1. Baseline Demographics For TNF Inhibitor Sequential Use Cohorts That Switched For Inefficacy Reasons

	ReAct (Bombardieri et al)	BSRBR (Hyrich et al)	Haraoui et al	Bennett et al
Number of patients	544	503	25 (19 for inefficacy)	70
Age* +/-SD years (range)	54 +/- 12	54 +/-12	50 (22-74)	54 (19-77)
Disease duration* +/-SD years (range)	12 +/-8	13 +/-9	10.8 (2-36)	
DAS28* +/-SD	6.4 +/-1	6.8 +/-1		6.3
HAQ score* +/-SD	1.91 +/-0.63	2.2 +/- 0.5	1.53	
Number of prior DMARDs* +/-SD (range)	5.1 +/-1.9	4	4.8 (2-11)	3.4 (2-7)
Receiving concomitant DMARDs (%)	68	73	96	74
Receiving concomitant MTX (%)		58	88	
Mean HAQ improvement	**0.33 – 0.52**	**0.2146**	**0.45**	**0.26 (secondary non-responders) / 0.22 (primary non-responders)**

* mean

2.2 Reduced use of concomitant DMARD therapies in the BSRBR cohort

In the BSRBR cohort that switched TNF inhibitor therapy secondary to inefficacy of the first treatment, only 58% of patients received a TNF inhibitor in combination with methotrexate[10]. It has been clearly established that the concomitant use of traditional DMARDs, in particular methotrexate (MTX), with TNF inhibitors, improves disease activity and functional outcomes compared to treatment with TNF inhibitor alone[10,11].

Given this evidence, assuming the patient is not intolerant of methotrexate, to maximise effectiveness of therapy, patients receiving sequential TNF inhibitor therapy should receive concomitant methotrexate therapy in line with the marketing authorisations for all three drugs. The large proportion of these patients who may not be receiving optimal therapy will therefore reduce the overall HAQ response seen from this cohort. Use of these data, without adjustment for the lower than optimal use of a TNF inhibitor+ MTX combination, may help to explain the lower effectiveness for sequential use of TNF inhibitors observed in the BSRBR compared to other observational data.

3. Differential effectiveness of switching depending on prior TNF inhibitor used

Use of HAQ improvement data from the ReAct study) in the cost effectiveness analyses of sequential use of TNF inhibitors, (options B and C), should occur only after due consideration of the limitations of the data and after making appropriate adjustment for relevant treatment effect modifiers.

In the cost effectiveness analyses of sequential use of TNF inhibitors, in considering HAQ improvements when switching between adalimumab and etanercept therapy in either direction, for inefficacy of the first TNF inhibitor therapy, it is incorrect to accept that the diminished HAQ response of 0.33 is a typical and accurate reflection of the HAQ improvements that occur for this scenario. Abbott proposes that the HAQ responses seen

when switching from etanercept to adalimumab and vice versa are equivalent to those seen after switching between any other combination of licensed TNF inhibitors. The diminished HAQ response seen in this subgroup from ReAct may be attributable to the following:

Patients who had previous exposure to etanercept therapy at study entry had marginally worse functional and disease activity indices and greater disease duration than patients previously exposed to infliximab therapy.

Table 2. ReAct Study- Baseline Demographics And Responses By Prior TNF Inhibitor

	Prior Etanercept only	**Prior infliximab only**
Number of patients	188	591
Age*	80	80
Disease duration*	13	12
DAS28* +/-SD	6.5 +/-1.2	6.2 +/-1.1
HAQ score* +/-SD	1.85 +/-0.66	1.83 +/- 0.67
Patient's global assessment of pain +/-SD	73 +/-19	68 +/-21
Not receiving concomitant DMARDs (%)	50	25
HAQ improvement*	**0.43 +/-0.61**	**0.51 +/-0.60**
ACR 20/ 50 / 70	**57 / 34 /13**	**64 / 34 / 13**
DAS28 CHANGE* +/-SD	**-2.0 +/1.4**	**-2.0 +/1.4**

*mean

Table 2 compares baseline parameters of these two groups and demonstrates the slightly higher disease activity state and increased limitation in physical function experienced by the prior etanercept cohort compared to the prior infliximab cohort, which may have contributed to the lower HAQ improvement score observed in the prior etanercept cohort.

Similarly, the proportion of patients in the prior etanercept cohort that were not receiving concomitant DMARDs at study entry was twice as high as that in the prior infliximab group, 50% vs. 25% (Table 2). The proven superior functional and clinical outcomes experienced by patients on TNF inhibitor + DMARD combination therapies compared to TNF inhibitor monotherapy is well established.

Further, whilst the overall HAQ and ACR20 responses for the prior etanercept cohort were somewhat lower than those of the prior infliximab group, it should be noted that ACR 50 and 70 and DAS-28 improvements for this cohort were of the same order of magnitude. Therefore, Abbott considers that the HAQ responses seen when switching from etanercept to adalimumab, and vice versa, are equivalent to those seen after switching between any other combination of licensed TNF inhibitors.

4. Further evidence of the effectiveness of conventional DMARDs in those failing prior conventional DMARDs

In evaluating the cost effectiveness of using a second TNF inhibitor vs. use of late DMARDs, HAQ improvement data from the placebo arm of the Genovese study[12], a RCT of abatacept in TNF inhibitor inadequate responders, (-0.11 $\pm$ 0.46) has been adopted as the average improvement seen when DMARDs are used after failed TNF inhibitor therapy. This is compared in option A to HAQ improvements from the BSRBR cohort (with all its limitations as described above), which are essentially data from an observational study.

Abbott wishes to highlight that general differences between data derived from observational studies and RCTs have been previously described[13]. Selecting placebo data from only one study (Genovese et al) and accepting that this is the lower bound of HAQ improvements of DMARDs after failed TNF inhibitor therapy represents a weakness of this analysis. Further,

the DSU in its initial report to the institute on sequential use of TNF inhibitors (DSU report to NICE, August 2006) highlighted the bias in combining data from two different datasets. In this case, use of placebo data from a randomised trial has led to the overestimate of HAQ improvements expected from patients who recommence DMARDs after experiencing lack of efficacy with a TNF inhibitor therapy and introduces further bias toward conventional DMARDs. Therefore, caution must be used when interpreting information involving comparison of data from these two settings.

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 after failure of multiple DMARDs may serve as a useful proxy. Evidence from the BeSt and BROSG ("British Rheumatoid Outcome Study Group") studies highlight that HAQ improvement for conventional DMARDs in such cohorts are at best minimal.

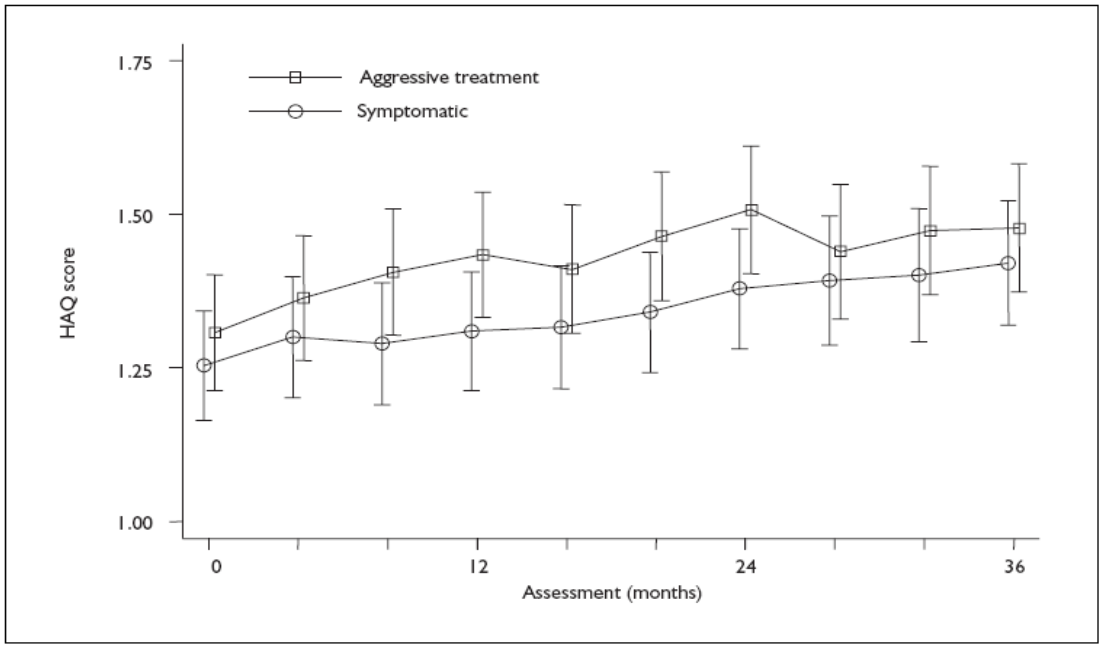
Data from the BROSG Study, a randomised trial of symptomatic versus aggressive use of DMARD therapy, have been published as a HTA monograph in September 2005 and provide estimates of the effectiveness of a sequence of conventional DMARDs used as part of either a symptomatic or aggressive treatment strategy[14]. 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 Table 3 and Figure 1 below).

Table 3. HAQ change over time in an RCT of symptomatic control of RA using conventional DMARDs or aggressive control of RA using conventional DMARDs

		Assessment (months)									
		0	4	8	12	16	20	24	28	32	36
Symptomatic	Mean	1.25	1.30	1.29	1.31	1.32	1.34	1.38	1.39	1.4	1.42
	SD	0.68	0.74	0.74	0.72	0.73	0.71	0.71	0.73	0.75	0.72
	N	233	225	220	217	212	210	206	195	190	201
	Response (%)	–	97	94	93	91	90	88	84	82	86
Aggressive treatment	Mean	1.31	1.36	1.41	1.43	1.41	1.46	1.51	1.44	1.47	1.48
	SD	0.72	0.77	0.77	0.77	0.76	0.76	0.75	0.77	1	1
	N	233	228	225	224	210	209	207	196	192	203
	Response (%)	–	98	97	96	90	90	89	84	82	87
Total	Mean	1.28	1.33	1.35	1.37	1.36	1.4	1.44	1.42	1.44	1.45
	SD	0.70	0.75	0.76	0.74	0.74	0.74	0.73	0.75	0.73	0.73
	N	466	453	445	441	422	419	413	391	382	404
	Response (%)	–	97	95	95	91	90	89	84	82	87

Taken from Symmons et al. 2005, Table 15, p36.

Figure 1. HAQ change over time in an RCT of symptomatic control of RA using conventional DMARDs or aggressive control of RA using conventional DMARDs



Taken from Symmons et al. 2005, Figure 3, p39.

In the BeSt study, after six months of therapy, 44% (99/225) of all patients in Groups 1 and 2 did not respond (DAS> 2.4) to MTX 25 mg weekly. From these patients, in Group 1, most patients also failed on SSA (80%, 39/49) and then leflunomide (83%, 30/36)[15].

In Group 2, a treatment strategy of step-up therapy, 73% (36/49) of patients failed when SSA was added, 66% (23/35) failed after further addition of DMARD, HCQ and 50% (10/20) failed when prednisone was added to this triple therapy.

Although these data do not specifically consider the effectiveness of conventional DMARDs in patients who have failed a TNF inhibitor, they do provide compelling evidence of the limited effectiveness of additional conventional DMARDs for patients who have failed methotrexate. These data, particularly from the BROSG, indicate that a HAQ improvement of 0.11 is unlikely with the use of conventional DMARDs in this population and therefore the 0.11 estimate from Genovese et al. may overestimate the effectiveness of conventional DMARDs in UK clinical practice.

5. Impact of disease duration and failing prior treatment on probability of treatment response

Abbott welcomes greater consideration of the impact of disease duration and failure of prior treatment on the estimated effectiveness of conventional DMARDs.

5.1 Data on prior conventional DMARD failure in the Genovese et al study of abatacept

Although patients in the Genovese et al. study for abatacept have failed prior TNF inhibitor therapy, data on prior conventional DMARD failures have been marked commercial in confidence in the manufacturer's submission to NICE. It is therefore unknown to Abbott whether there are important differences in the number of prior DMARD failures in the Genovese *et al.* study compared to patient populations from other studies.

5.2 Impact of prior treatment failure in the REFLEX study of rituximab

The Appraisal Committee noted in the FAD when discussing sequential use, that there was a smaller effect size observed with the use of a 2nd TNF inhibitor following inefficacy with a first. Yet, the data provided by Roche from the REFLEX study for the appraisal of rituximab also provide evidence that failing a prior treatment in RA has an impact in reducing the response rate of all treatments[16].

Table 4: Impact of failing prior treatments in reducing response rate in RA patients

				% Reduction in effectiveness	
		Rituximab + MTX (n=179)	**Placebo + MTX (n=121)**	**Rituximab + MTX (n=179)**	**Placebo + MTX (n=121)**
1 prior TNF inhibitor	ACR 20	58%	21%		
	ACR 50	30%	7%		
	ACR 70	14%	1%		
		(n=119)	(n=80)		
≥ 2 prior TNF inhibitors	ACR 20	42%	14%	**-28%**	**-33%**
	ACR 50	22%	3%	**-27%**	**-57%**
	ACR 70	10%	3%	**-29%**	**+200%***

*Note the reverse trend observed for ACR 70 in the placebo+ MTX arm may be attributable to the small number of placebo+ MTX ACR 70 responders.

Table 4 illustrates that line of treatment has an important impact on the response to therapy in both the rituximab and placebo treatment arms. As the reduction in effectiveness is equal for both treatment arms, this would suggest that the cost effectiveness of the treatment would not be affected by whether the patient had failed one or more prior TNF inhibitors. The NICE recommendation for rituximab for RA does not give differential recommendations for rituximab based on the number of prior TNF inhibitors failed, despite the observation that the response

rate is lower in patients failing two or more prior TNF inhibitors. Abbott considers this is inconsistent with the logic of the current FAD recommendation for sequential use of TNF inhibitors.

5.3 Relationship between disease duration and number of prior treatment failures in trials of conventional DMARDs

Aletaha *et al* (2008) demonstrated that the HAQ responsiveness/ effect size at 6 months decreased considerably with increasing duration of disease activity in RA biologic trials. The same degree of decrease was not evident for the DMARD trials, where the effect size was less evident across all evaluated disease durations and where few trials have collected data on the HAQ score. At 12 months however the decrease in HAQ responsiveness for DMARDs is greater than at 6 months and may be proportional to the decreases seen over time for biologics, with a near halving of responsiveness. Further, if only methotrexate or leflunomide were tested, the effect sizes decreased significantly with disease duration (data in paper). This may also be because more trials have considered the effectiveness of methotrexate and leflunomide than other conventional DMARDs.

The overall effect of duration on HAQ was marginally statistically significant (p=0.06) at 6 months and (p=0.07) at 12 months. The DSU has also highlighted a key weakness of this study in that the number of previous DMARDs failed is not considered. This factor is likely correlated with disease duration. Anderson *et al* evaluated functional and disease activity outcome data from 1435 patients in 14 diverse, randomised, controlled trials of second-line drugs or devices in RA. The authors used logistic regression to analyse the factors affecting the likelihood of patient response, with initial tests performed on each of the candidate factors separately. The univariate analyses identified four important treatment effect modifiers including longer disease duration and prior DMARD use which were associated with a reduced likelihood of treatment response. In multivariate analyses the odds of response to treatment were 0.62 for prior DMARD use and the disease duration effect on odds of response was 0.74 when expressed per 15-year increase in disease duration (0.98 per extra year of disease duration). Interestingly, these factors maintained an independent effect in the multivariate analysis despite the possibility of strong correlations between them. The authors concluded that RA patients with longer disease duration do not respond as well to treatment compared with patients with early disease, and prior DMARD use and disease functional class, also have effects on the likelihood of patient response to treatment. This has important implications for interpretation of response data from clinical trials and observational studies in RA patients.

6. BSR Model results for sequential TNF inhibitor use

Further economic modelling using the BSRBR data of sequential TNF inhibitor use is now available to be considered in detail by the appraisal committee[17]. These data indicate that use of a second TNF inhibitor is equally cost effective as use of a first TNF inhibitor. This conclusion stems from the categorical modelling of response in this analysis and discontinuation in line with poor response. Patients on a second TNF inhibitor not fulfilling the DAS-28 response criteria would stop therapy. In contrast the BRAM model does not explicitly link continuation of therapy and response. Therefore, assuming that there is an appropriate stopping rule for non-responders, it is considered that use of a second TNF inhibitor would be similarly cost effective as the first TNF inhibitor. The use of DAS-28 response in the BSRBR model may avoid some of the problems associated with use of the HAQ score in severe patients.

One of the strengths of the BSRBR analysis is that the control cohort of patients not receiving TNF inhibitors is used to estimate the efficacy of conventional DMARDs. However, it should be noted that these patients might have a higher response than patients who have failed a first TNF inhibitor because the control cohort has less refractory disease than patients receiving TNF inhibitors in the BSRBR (fewer prior conventional DMARDs failed). Nevertheless, despite this potential bias against the TNF inhibitors, the BSRBR modelling results indicate that sequential use of TNF inhibitors is cost effective.

7. Modelling of cost offsets and HAQ improvement

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 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.

In order to assess the impact of including HAQ offset costs it is first necessary to adjust the HAQ multipliers to reduce the effectiveness of conventional DMARDs when used as later lines of therapy as per the latest BRAM analyses using options B and C. After this adjustment has been made it will then be possible to see whether the results of the BRAM model are sensitive to the absolute value of cost offsets attributable to a one-unit HAQ improvement.

Similarly, changing the baseline HAQ level had a negligible effect on the original base-case BRAM results. This may be because this sensitivity analysis also applies the HAQ multipliers from the base-case analysis, which are similar for TNF inhibitors and conventional DMARDs. After adjustment has been made for the HAQ multipliers for conventional DMARDs when used as later lines of therapy using options B and C, it will be possible to see whether the results of the BRAM model are sensitive to the baseline level of HAQ severity, as was the case for the model submitted by Abbott.

8. Use of 3.5% discount rates in the modelling

The present analyses use the current NICE reference case recommendations for discounting future costs and outcomes at 3.5%. It should be borne in mind that the cost per QALY estimates from these analyses would likely be higher than those previously estimated using the earlier reference case figures of 6% and 1.5% for costs and outcomes respectively. In order to compare the present analyses with those conducted previously for this appraisal, it may be helpful for the committee to see to what extent use of the different discount rates changes the cost per QALY estimates.

9. Schedule of infliximab dosing

For the first year of infliximab therapy a patient should receive 8 intravenous infusions and will alternate between receiving 6 and 7 infusions for subsequent years, assuming no shortening of the dose interval. This does not appear to be reflected in the dosing for infliximab used in the modelling, where it is assumed that patients will receive 7 infusions during the first year and 6 treatments in subsequent years. Abbott considers a more accurate costing would apply 8 treatments in the first year and 6.5 for subsequent years of infliximab therapy. This underestimate of the number of treatments required by patients on infliximab would appear to bias the cost effectiveness analyses between infliximab and other TNF inhibitors for the updated base case analyses and for the sensitivity analyses for alternative dosing assumptions for infliximab.

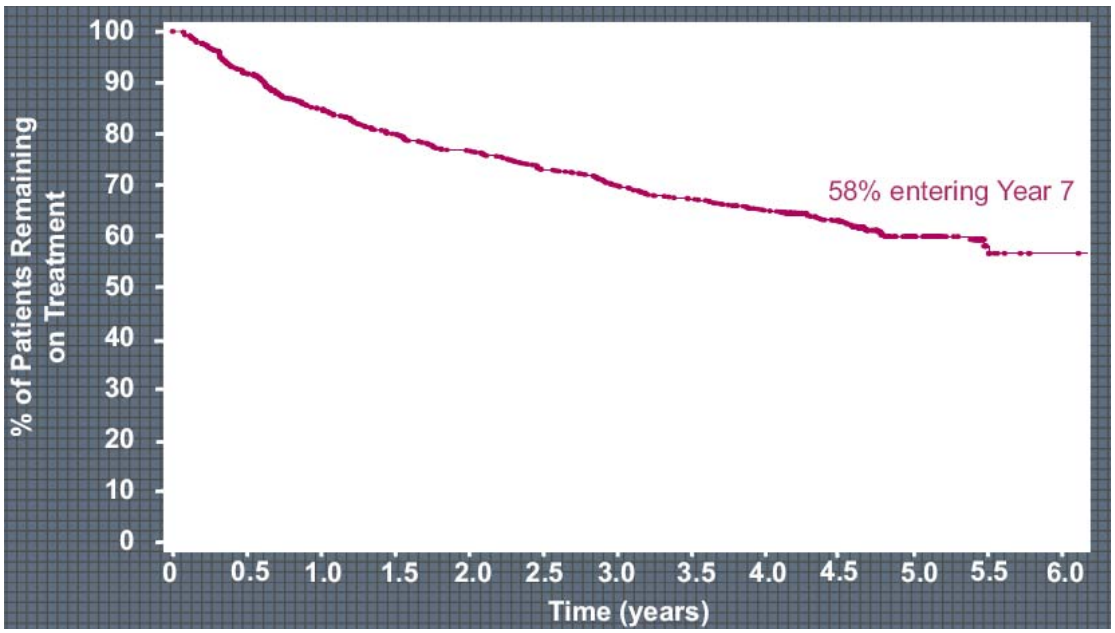
10. Use of a second TNF inhibitor versus use of rituximab

This section discusses evidence supporting the use of a second anti-TNF agent as the most preferable treatment option following inefficacy with a first TNF inhibitor, versus use of the anti-CD20 monoclonal antibody, rituximab.

10.1 Long-term efficacy of TNF inhibitors – signs and symptoms / function / quality of life

Analysis of data from open label extension studies of American phase II and III trials of adalimumab, in which RA patients received up to 7 years of therapy with adalimumab + MTX, (DE019x and DE020; n=1469), showed that 34.7% of patients achieved DAS28 remission (DAS28<2.6)[18]. In addition, the overall mean HAQ improvement was 0.5 for the whole cohort at last observation up to year 7 (p<0.001 vs. baseline) and Kaplan-Meier survival analysis of the data estimated that 58% of enrolled patients would continue treatment into Year 7 (Figure 2). These analyses also showed long-term maintenance of disease activity and quality of life improvements. Furthermore, in another analysis of long-term efficacy data from a smaller cohort of patients (n=644), Weinblatt *et al.* found that patients with long standing RA, treated with etanercept for up to 9 years, experienced a mean HAQ improvement of 0.6 from baseline and achieved ACR20/50/70 scores of 74/41/22, respectively[19].

Figure 2: Kaplan-Meier analysis showing the percentage of patients continuing on adalimumab treatment from first dose



10.2 Long term efficacy of TNF inhibitors - inhibition of radiographic progression

The ability of TNF inhibitors to inhibit radiographic progression in patients with early and established RA has been proven in RCTs for periods of up to 2 years for all three TNF inhibitors, with statistically significant differences between placebo + DMARD arms and TNF inhibitor + DMARD arms seen as early as 24 weeks[11, 20, 21, 22]. Indeed in DE019, a study of adalimumab + MTX vs. MTX+ placebo in established RA, radiographic improvement was seen in the mean radiographic score (modified total sharp score, mTSS) of patients in the adalimumab arm at year 1 (ΔmTSS -0.62; p<0.001 vs. MTX + placebo). Furthermore, long term follow up of these patients demonstrated that inhibition of radiographic progression was maintained in the majority after 5 years of adalimumab therapy with 58% experiencing no change in their total sharp score (ΔmTSS +0.83)[23].

10.3 Improvements in secondary outcomes with TNF inhibitors – Work disability / cardiovascular end points / mortality

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.

A 56-week study of adalimumab + MTX combination therapy vs. MTX alone in 140 MTX naive patients with early aggressive RA and self reported work disability (PROWD) demonstrated

that adalimumab + MTX combination therapy can significantly reduce the number of days lost from work compared to MTX monotherapy (8.6% vs. 18.4%; p=0.038)[24]. Whilst the study missed its primary endpoint of 'all-cause job loss and/or imminent job loss (measured as a worsening work instability scale score plus failure to achieve an ACR20 from week 16-56) (p=0.092), analysis of this outcome for the entire period of the study (Weeks 0-56) demonstrated a highly statistically significant difference between the combination therapy and MTX monotherapy arms. A companion study to the PREMIER study (adalimumab + MTX vs. both therapies as monotherapy in MTX naïve early RA patients; DE032) evaluating work related outcomes, supported the findings from PROWD and demonstrated that patients on combination therapy missed significantly fewer days of work (11.1 vs. 24; p<0.001) and experienced greater improvements in work performance compared to patients on MTX alone after 2 years of therapy[25].

Ischaemic heart disease is the major cause of mortality and a significant cause of morbidity for RA patients. In 2007, Dixon et al[26] undertook an analysis of comparative rates of cardiovascular outcomes in 8,760 EULAR responders and non-responders to treatment in the TNF inhibitor cohort of the BSRBR. The rates for myocardial infarction (MI) were found to be 3.5 events per 1,000 person-years in responders and 9.4 events per 1,000 person-years in non-responders. The adjusted incidence rate ratio for responders compared with non-responders was 0.36 (95% CI 0.19–0.69). Wolfe et al[27] examined a longitudinal data bank for MI in 25,343 patients with rheumatic diseases 79.5% of who had RA. 56.2% of the RA patients were administered TNF inhibitors. Conditional logistic regression analysis of data from these patients demonstrated that TNF inhibitor therapy was associated with a reduced risk of MI RR 0.7 (CI 95% 0.5-0.9).

Analysis of the Spanish TNF inhibitor observational registry, BIOBADASER, suggests that RA patients treated with TNF inhibitors have a reduced rate of mortality due to a significant decrease in non-infectious causes of mortality compared to patients from a non-TNF inhibitor exposed cohort of RA patients in Spain (EMECAR)[28]. The analysis showed that in 5,341 patients enrolled over a 6-year period, there were 61 deaths in BIOBADASER (Standardised Mortality Ratio (SMR), reference National Vital Statistics (INE 2002) database, 0.81, 95% CI 0.6-1.0) and 75 in EMECAR (1.49, 95% CI 1.17-1.87). Direct comparison of all cause SMR of the two groups resulted in a ratio of 0.42 (CI 95% 0.3-0.5) in favour of the TNF inhibitor treated cohort.

10.4 Well characterised long-term safety profile of TNF inhibitors

As part of a commitment to the drug licensing regulatory authorities in the EU and the US, the manufacturers of licensed TNF 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[29,19]. The adalimumab safety database covers a wide spectrum of RA patients including those with very early progressive disease (PREMIER), those with long-standing severe disease with a history of multiple DMARD failures and severe disability (DE011), and those who have previously failed TNF inhibitor therapy (ReAct).

Schiff *et al.* performed a review of the adalimumab RA clinical trials database in 2006 and presented incidence rate data for TNF inhibitor adverse events of interest[30]. The authors compared the rates of TNF inhibitor adverse events of interest as of April 2005 to those as of last major database review in August 2002. There had been no significant increases in the rates of the adverse events reviewed. Indeed there were decreases in the incidence rate of some events in Europe, notably lymphoma (see Table 5 below).

Table 5: Rates of Selected Adverse Effects from the Adalimumab RA Clinical Trials Safety Database

Table 2 Rates of selected adverse events

	All RA trials as of 31 August 2002* (E/100 PYs)	All RA trials as of 15 April 2005† (E/100 PYs)
Tuberculosis	0.27	0.27
Histoplasmosis	0.06	0.03
Demyelinating diseases	0.08	0.08
Lymphoma	0.21	0.12
SLE/lupus-like syndrome	0.08	0.10
Congestive heart failure	0.29	0.28

*n=2468, 4870 PYs; †n=10 050, 12 506 PYs.
E/100 PYs, events per 100 patient-years.

From Schiff et al, Table 2, p891.

The overall rate of serious infections as of April 2005 was 5.1 per 100 patient years. This was comparable to that reported on 31 August 2002 (4.9/100 PYs), and that from the BSRBR analysis of serious infection rates (5.3/100Pys: 4.89–5.78 95%CI)[31], and reassuringly also for those in published reports of RA populations naive to TNF inhibitor therapy[32, 33].

Furthermore, TNF inhibitor manufacturers support many independent academic groups and national registries worldwide that collect and publish long-term safety data on many thousands of TNF inhibitor treated patients in 'real world' settings[31, 28, 34]. Safety information from these databases have allowed physicians and regulators to adequately characterise the risks associated with TNF inhibitor therapy and to advise and apply adequate precautions to achieve the optimum benefit-risk balance for each patient starting therapy. These precautions have helped to minimise the number of serious adverse events that may be associated with these drugs [28, 29].

- **Rituximab**

Rituximab was first licensed in the EU for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other DMARDs including one or more TNF inhibitor therapies in July 2006. Currently this is the only RA treatment licence for rituximab in the EU. Rituximab is not licensed for treatment of RA patients who have failed DMARDs without failure of TNF inhibitor therapies; nor is it licensed for inhibition of radiographic progression, improvement of physical function, use in MTX naïve patients with severe active progressive disease or for use as monotherapy for those that are intolerant of MTX, unlike adalimumab and etanercept.

10.5 Unknown long-term safety profile of rituximab therapy - limited clinical data on the safety of re-treatment in RA.

Published data from the rituximab clinical trial safety database are currently limited. The most recent published data on long-term safety follow up is available for 1,053 RA patients exposed to rituximab, representing 2438 PYs of exposure and data on up to 7 treatment courses[35]. In those that receive up to 4 courses, the rate of serious infection is in line with that published for the background population (5.41/ 100 PYs (2.03-14.41 95% CI). After 4 courses however, a slight upward trend is observed in the rate of infections, particularly in patients with at least one IgG subtype below the lower limit of normal. Notably, the authors report the proportion of patients with IgM and IgG levels below the lower limit of normal increased with further treatment courses although no opportunistic infections, viral reactivations or TB were reported[36]. 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.

Thus the long-term safety profile of rituximab is still largely unknown due to the limitations of sufficient RA patient numbers who fulfill the current licensing criteria for treatment with rituximab and length of time on treatment.

10.6 Limited data for re-treatment regimen for rituximab responders

Currently, the Rituximab SPC advises against offering patients re-treatment courses of rituximab at intervals of less than 24 weeks after the prior course[37]. This guidance is echoed in the NICE STA guidance for rituximab for the treatment of RA[38] and is reflected in the recommendations from the working group on the Rituximab consensus statement[39].

Longer term follow up of RA patients treated with rituximab indicate that the time interval between courses is variable, with the majority of patients receiving further therapy 6-12 months after the previous course. There exists some uncertainty then as to when to re-treat patients with active disease. The working group on the Rituximab consensus statement suggests re-treatment if the DAS28 score worsens by >0.6. However, if this occurs before the 6-month limit for re-treatment, patients may be left with few treatment options including increased use of corticosteroids before the next infusion.

10.7 Unknown effect of B cell depletion on future treatment options

In the REFLEX study[40], significantly more rituximab-treated patients achieved good or moderate EULAR responses compared with placebo treated patients (65% versus 22%; $P < 0.0001$). Therefore 35% of patients had at best a poor response. Given that in REFLEX treatment with rituximab was associated with a rapid and complete depletion of CD19 positive peripheral B cells, (with some recovery of cell counts beginning between weeks 16 and 20) with a non-existent median CD19+ve B cell count at week 24, poor responders to rituximab will, thus, have severely limited treatment options as the safety of further biologic therapy in patients with low or no circulating peripheral B cells is largely unknown.

Preliminary data from patients who withdrew from rituximab therapy during rituximab clinical trials and then started treatment with either traditional DMARDs and/or TNF inhibitor therapies have been reported (n=153)[41] and show a near doubling of the serious infection rate in those that switched to TNF inhibitors. However, the overlapping 95% confidence intervals do not permit inference of a significant difference between rates before and after TNF inhibitor therapy in this analysis.

Table 6: Serious infection rates in patients who received additional RA therapies following rituximab treatment

Table Serious infection rates in pts who received additional RA therapies following RTX

	All Pts receiving any DMARD or biologic		Pts receiving DMARD/non-TNF inhibitor biologic		Pts receiving TNF inhibitor	
	Before	**After**	**Before**	**After**	**Before**	**After**
Total Exposure, pt-yr	143.22	147.55	50.13	42.02	100.83	97.79
Serious Infections, n	6	12	1	2	6	9
Serious infections/100 pt-yr	4.19	8.13	1.99	4.76	5.95	9.20
95% CI	1.88, 9.33	4.62, 14.32	0.28, 14.16	1.19, 19.03	2.67, 13.25	4.79, 17.69

DMARD: Disease-Modifying Antirheumatic Drug

10.8 Option for sequential TNF inhibitor therapy for MTX intolerant patients

The EMEA licence for rituximab in RA stipulates 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 NICE RA guidelines, with no options but to return to treatment with ineffective traditional DMARDs and corticosteroids, many of which they would have already failed. In a 2 year RCT of

Leflunomide vs. MTX in 999 patients with active RA, 15% of patients receiving MTX withdrew from the study due to adverse events at the end of the first year, with a further 6% withdrawing for similar reasons by the end of year 2[42]. These data serve as a useful guide to the not insignificant proportion of patients who may be intolerant of MTX and consequently ineligible for rituximab therapy. Both adalimumab and etanercept are licensed for use as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate, thus providing patients with recalcitrant disease in this situation with an option for further effective therapy should the first TNF inhibitor be proved ineffective.

10.9 Provision for patients who wish to receive treatment at home

A course of rituximab is given as 2 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 2-week period is mandated.

Some physicians and patients may wish to largely avoid risks of infusion reactions, which although decreased in frequency with increasing courses of rituximab, was significant at first dose in the REFLEX study (23%).

Some patients may have significant difficulty or may simply be unable to undertake this twice-yearly treatment regime, including the journey to the hospital and back. Such patients may benefit from therapy administered in the home, for instance with adalimumab and etanercept therapy.

Whilst the short-term efficacy and safety in RA patients who have failed at least one TNF inhibitor therapy has been proven, there exist many unknowns regarding the safety and efficacy of repeated courses of rituximab therapy in the long-term. This can only be addressed by analyses of larger numbers of patients with sufficiently long exposure to rituximab. Further, there are many issues surrounding the optimum re-treatment regime for rituximab and mode of administration of rituximab for physicians and healthcare payors respectively. The safety and efficacy of long-term repeat administration of TNF inhibitors in a broad range of RA patients, including those for whom prior TNF inhibitor therapy was ineffective, is well characterised and supported by data from considerable numbers of patients enrolled in independent observational treatment registries worldwide.

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.

Conclusions

In conclusion, Abbott considers that options B and C “New Values” in the Barton 2008 report provide more accurate estimates of the cost effectiveness of the sequential use of TNF inhibitors versus conventional DMARDs (£31-£39K per QALY) than previous analyses using the BRAM. Abbott considers that these results support a positive recommendation for sequential use of TNF inhibitors. Furthermore, economic modelling using the model submitted by the BSR supports the cost effectiveness of sequential use of TNF inhibitors. These data indicate that use of a second TNF inhibitor is equally cost effective as use of a first TNF inhibitor. This conclusion stems from the categorical modelling of response in this analysis and discontinuation in line with poor response. Patients on a second TNF inhibitor not fulfilling the DAS-28 response criteria would stop therapy. Therefore, assuming that there is an appropriate stopping rule for non-responders, it is considered that use of a second TNF inhibitor would be similarly cost effective as the first TNF inhibitor.

Abbott also considers that there are a number of reasons why sequential use of TNF inhibitors may be preferred to use of rituximab. Given the uncertainty over the long-term safety and efficacy of rituximab, Abbott considers that the sequential use of TNF inhibitors represents an important treatment option in patients who have failed their first TNF inhibitor.

References

[1] Aletaha D, Strand V, Smolen JS, Ward MM. Treatment-related improvement in physical function varies with duration of rheumatoid arthritis: a pooled analysis of clinical trial results. *Ann Rheum Dis.* 2008 Feb;**67**(2):238-43.

[2] Barton P. Further cost-effectiveness analyses of sequential TNF inhibitors for rheumatoid arthritis patients. West Midlands Health Technology Assessment Collaboration (WMHTAC).

[3] Bombardieri S, Ruiz AA, Fardellone P, Geusens P, McKenna F, Unnebrink K, Oezer U, Kary S, Kupper H, Burmester GR; Research in Active Rheumatoid Arthritis (ReAct) Study Group. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology* (Oxford). 2007 Jul;**46**(7):1191-9.

[4] Haraoui B, Keystone E, Carter Thorne J, Pope J, Chen I, Asare C, Leff J. Clinical Outcomes of Patients with rheumatoid arthritis after switching from infliximab to etanercept. *Journal of Rheumatology* 2004 Dec;**31**(12):2356-2359.

[5] Bennett A, Peterson P, Zain A, Grumley J, Panayi G, Kirkham B. Adalimumab in clinical practice. Outome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure. *Rheumatology* 2005;**44**:1026-1031.

[6] Favalli E. Anti-tumour necrosis factor alpha switching in rheumatoid arthritis and juvenile chronic arthritis. Letters to the Editor *Arthritis & Rheumatism* 2004 Apr;**51**(2):299-304.

[7] Aletaha D, Ward M. duration of rheumatoid arthritis influences the degree of functional improvement in clinical trials. *Annals of Rheumatic Disease* 2006;**65**:227-233.

[8] Hyrich K, Watson K, Silman A, Symmons D and BSR Biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Scoiety for Rheumatology Biologics Register. *Rheumatology* 2006;**45**:1558-1565.

[9] Anderson J, Wells G, Verhoeven A, Felson D. Factors predicting response to treatment in rheumatoid arthritis. *Arthritis & Rheumatism* 2000;**43**(1):22-29.

[10] Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ; British Society for Rheumatology Biologics Register. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum. 2007 Jan;56(1):13-20.

[11] Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006 Jan;54(1):26-37.

[12] Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, Birbara C, Box J, Natarajan K, Nuamah I, Li T, Aranda R, Hagerty DT, Dougados M. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005 Sep 15;353(11):1114-23.

[13] Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, De Gendt CM, Ronday KH, Jansen TL, van Oijen PC, Brus HL, Adang EM, van Riel PL. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007 Nov;66(11):1473-8.

[14] Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL. The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and

cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis. Health Technol Assess. 2005 Sep;9(34):iii-iv, ix-x, 1-78.

[15] Van Der Kooij S, De Vries-Bouwstra J, Goekoop-Ruiterman Y, Van Zeben D, Kerstens P, Peeters A et al. What treatment strategy should be chosen after initial failure on methotrexate 25mg in early rheumatoid arthritis? Data from the BeSt study. *American College of Rheumatology Annual Scientific Meeting*, San Diego, CA, USA. 12-17 November 2005. Session 19A. Presentation No. 1865.

[16] Manufacturer submission for the appraisal of rituximab for the treatment of refractory rheumatoid arthritis. 21 November 2006.

[17] Modelling the cost effectiveness of sequential use of TNF-α inhibitors in the management of rheumatoid arthritis: an update. Appendix 1 to ARMA notice of appeal. 6 December 2006.

[18] Weinblatt ME, Keystone EC, Furst DE, Kavanaugh A, Perez J, Segurado O. Change over time in the safety, efficacy and remission profiles of patients with rheumatoid arthritis receiving adalimumab for up to 7 years. *71st American College of Rheumatology Annual Scientific Meeting*, Boston, MA, USA, 6-11 November 2007.

[19] Weinblatt ME, Genovese MC, Moreland LW, Bathon JM, Kremer JM, Fleischmann RM, Schiff MH *et al.* Efficacy and safety of over 9 years of etanercept therapy in North American patients with early and long-standing rheumatoid arthritis. *70th American College of Rheumatology Annual Scientific Meeting*, Washington, DC, USA, 10-15 November 2006.

[20] Van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, Tornero-Molina J *et al.* Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis. *Arthritis & Rheumatism* 2006 Apr;**54**(4):1063-1074.

[21] Keystone E, Kavanaugh A, Sharp J, Tannenbaum H, Hua Y, Teoh L, Fischkoff S, Chartash E. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumour necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomised, placebo-controlled, 52-week trial. *Arthritis & Rheumatism* 2004;**50**(5):14001-411.

[22] Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, St.Clair EW *et al.* Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis & Rheumatism* 2004 Apr;**50**(4):1051-1065.

[23] Keystone EC, kavanaugh AF, Sharp JT, Patra K, Perez JL. Inhibition of radiographic progression in patients with long-standing rheumatoid arthritis treated with adalimumab plus methotrexate for 5 years. *European League Against Rheumatism Annual European Congress of Rheumatology*, 13-16 June 2007, Barcelona, Spain.

[24] Bejarano V, Quinn MA, Conaghan P, Reece R, Keenan A, Walker D, Gough A, Green M, McGonagle D *et al.* Improved work stability and reduced job loss with adalimumab plus methotrexate in early rheumatoid arthritis: results of the Prevention Of Works Disability (PROWD) study. *European League Against Rheumatism Annual European Congress of Rheumatology*, 13-16 June 2007, Barcelona, Spain.

[25] Van Vollenhoven RF, Ferraccioli G, Breedveld F, Ray S, Cifaldi M. Effect of adalimumab combination therapy on work performance: results from a companion study to PREMIER. *European League Against Rheumatism Annual European Congress of Rheumatology*, 13-16 June 2007, Barcelona, Spain.

[26] Dixon WG, Watson KD, Lunt M, Hyrich KL. Reduciton in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumour necrosis factor-alpha therapy. *Arthritis & Rheumatism* 2007;**56**(9):2905-2912.

[27] Wolfe F, Michaud K. The effect of rheumatic disease treatment on the risk of myocardial infarction: increased risk from rofecoxib, valdecoxib and celecoxib; deceased risk from anti-TNF therapy. *71st American College of Rheumatology Annual Scientific Meeting*, Boston, MA, USA, 6-11 November 2007.

[28] Gomez-Reino JJ, Carmona L, Perez Pampin E, Descalzo M. mortality rate is reduced in rheumatoid arthritis patients treated with TNF antagonists. Data from BIOBADASER. *Ann Rheum Dis* 2006;**65**(Suppl II):318.

[29] Burmester GR, Mease PJ, Dijkmans BAC, Gordon KB, Lovell DJ, Panaccione R, Perez JL, Pangan A. Adalimumab safety profile in global clinical trials and reduction in standardised mortality ratios (SMR) across multiple indications. *71st American College of Rheumatology Annual Scientific Meeting*, Boston, MA, USA, 6-11 November 2007.

[30] Schiff M H, Burmester G R, Kent J D, Pangan A L, Kupper H, Fitzpatrick S B, Donovan C. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US post-marketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;**65**:889-894.

[31] Dixon WG, Watson K, Lunt M, Hyrich K. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-TNF therapy. *Arthritis & Rheumatism* 2006;**54**(8):2368-2376.

[32] Doran M, Crowson C, Pond G, O'Fallon M, Gabriel S. Frequency of infection in patients with rheumatoid arthritis compared with controls. A population based study. *Arthritis & Rheumatism* 2002;**46**(9):2287-2293.

[33] Baecklund E, Askling J, Rosenquist R, Ekbom A, Klareskog L. Rheumaroid arthritis and malignant lymphomas. *Current Opinion in Rheumatology* 2004;**16**:254-261.

[34] Askling J. RA-patients exposed to TNF-antagonists are not at increased risk of malignant lymphoma compared to other RA-patients. Results from the Swedish Biologics Register 1999-2006. *European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology*, 13-16 June 2007, Barcelona, Spain.

[35] Van Vollenhoven R, Emery P, Bingham III C, Keystone E, Greenwald M, Moreland L, Sweetster M, Rowe K *et al.* Extended follow-up of the long-term safety of rituximab in rheumatoid arthritis. *71st American College of Rheumatology Annual Scientific Meeting*, Boston, MA, USA, 6-11 November 2007.

[36] Genovese M, Enery P, ruderman E, Keystone E, Furst D, Van Vollenhoven R, Sweetster M *etal.* Immunoglobin levels and infection rates in patients with RA treated with repeated courses of rituximab. *71st American College of Rheumatology Annual Scientific Meeting*, Boston, MA, USA, 6-11 November 2007.

[37] Rituximab (Mabthera) Summary of Product Characteristics. Electronic Medicines Compendium (eMC); last updated on the eMC on 31 January 2008.

[38] Technology Appraisal Guidance TA126 Rituximab for the treatment of refractory rheumatoid arthritis. National institute for Health and Clinical Excellence. http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11821 Last accessed 26 February 2008.

[39] Smolen JS, Keystone EC, Emery P, Breedveld FC, Betteridge N, Burmester GR *et al.* Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;**66**:143-150.

[40] Cohen S, Emery P, Greenwald M, Dougados M, Furie R, Genovese M, Keystone E *et al.* Rituximab therapy for rheumatoid arthritis refractory to anti-tumour necrosis factor therapy. Results of a multicentre, randomised, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at 24 weeks. *Arthritis & Rheumatism* 2006;**54**(9):2793-2806.

[41] Genovese MC, Breedveld FC, Emery P, Moreland L, Keystone E, Matteson E, Baptiste Y. Safety of TNF inhibitors and non-biologic DMARDs in rheumatoid arthritis patients previously treated with rituximab. *71st American College of Rheumatology Annual Scientific Meeting*, Boston, MA, USA, 6-11 November 2007.

[42] Emery P, Breedveld F, Lemmel E, Kaltwasser J, Dawes P, Gomor B, Van den Bosch F *et al.* A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000;**39**:655-665.