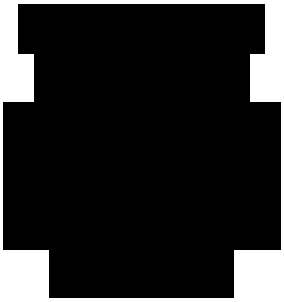
Appendix 1

MODELLING THE COST EFFECTIVENESS OF SEQUENTIAL USE OF TNF-α INHIBITORS IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS: AN UPDATE



DRAFT 3:

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Appendix 1

INTRODUCTION

This report describes an extension to our work on the cost-effectiveness of TNF-α inhibitors in the treatment of rheumatoid arthritis. The original work involved the construction of a decision-analytic model, populated by analysis of data from the British Society for Rheumatology TNFs Registry (BSRBR). The registry was established in October 2001 and now has 5 years follow-up, and over 7000 patients. The model allowed us to estimate the cost-effectiveness of current UK practice, and explore the impact of a number of alternative scenarios.

One of the scenarios explored was the impact of allowing patients withdrawing from their 1st TNF treatment to receive a 2nd TNF (sequential therapy). A problem was encountered in modelling this choice – a lack of data in the registry on patients receiving a 2nd TNF. This made it difficult to model two parameters key to the impact of sequential therapy –

- initial response to a 2nd TNF
- time to withdrawal of 2nd TNF treatment.

Since completion of the original analysis, a much larger set of patients in the BSRBR who have received a 2nd TNF therapy has been accrued. We have analysed this dataset to estimate the two parameters of interest, and updated our economic modelling to reflect the results.

This new analysis is based on 629 patients receiving a 2nd TNF.

This report presents the results of our analysis.

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METHODS

Initial Response to a 2nd TNF

We model the initial response to therapy using DAS response. This categorical variable can take three values – poor (0), moderate (1) or good (2). Short term utility is derived from DAS response. For each therapy (TNF or conventional DMARD), we model the probability of a given DAS response using a proportional odds cumulative Logit model (**Table 1**). This model involves adjusting the predicted probabilities according to values taken by a set of covariates. These covariates are both patient characteristics i.e. age, duration of disease, previous treatments, sex, and issues concerning their current health and treatment i.e. health state utility at baseline, whether they receive a TNF, and whether their response is moderate or good.

In our original analysis we assumed that probabilities of response to a 2nd TNF were equivalent to those for a 1st TNF. Now that data is available from the BSRBR on initial response to a 2nd TNF, we were able to fit the model to this dataset and update the economic model accordingly.

Duration of 2nd TNF Therapy

Time to withdrawal from therapy was estimated by fitting a Weibull survival model to the data. The model is described in table 2. Again, the model adjusts its predictions according to values taken by clinically relevant covariates.

In our original work, we did two analyses. One was the time on treatment with 1st TNF. The other was time on continued TNF therapy irrespective of whether the TNF therapy was 1st, 2nd or even 3rd in a sequence of TNFs. We estimated time on 2nd TNF by subtracting time on 1st TNF time on all TNFs.

The availability of the new dataset on treatment times on 2nd TNF has allowed us to estimate this parameter directly.

We have also undertaken a further sensitivity analysis in which we assume that duration on 2nd TNF therapy is actually no different to that seen on 1st TNF. Although there are differences shown in the BSRBR data, the possible rationale for this sensitivity analysis is that the patients so far receiving a 2nd TNF have been relatively early withdrawals from their 1st TNF and may have a tendency to be short duration patients even after adjusting for EULAR response. There has been no direct analysis of whether there is a correlation between duration on 1st and 2nd TNF that we have seen. This sensitivity analysis matches the assumption made in the NICE/BRAM modelling i.e. that the statistical distribution for 2nd TNF duration on therapy is assumed to be the same as the statistical distribution for 1st TNF duration on therapy.

We have also run a statistical analysis to evaluate how strongly the duration on 2nd therapy is predicted by duration on 1st therapy with the BSRBR data.

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RESULTS

Initial Response to a 2nd TNF

Table 3 gives the resulting coefficients from the proportional odds cumulative Logit model predicting DAS response. It gives results from the original analysis and results generated from fitting the model to the new data on patients receiving a 2nd TNF.

These coefficients can be used to estimate probable DAS response to 1st and 2nd TNF treatment, adjusting for the characteristics of a particular patient. However, they are difficult to interpret intuitively. Table 4 describes a hypothetical patient whose characteristics are 'typical' of the BSRBR (the values chosen for the parameters are close to their means in the database).

Figure 1 gives the probabilities of alternative responses to treatment for this typical patient. The probability of good response is equally likely on the 2nd TNF treatment as on the 1st TNF (20% versus 20%). However, the probability of moderate response being achieved is much lower (36% on 2nd TNF versus 64% on 1st TNF). Correspondingly, the probability of a poor response increases substantially (44% on 2nd TNF versus 16% on 1st TNF). As we shall see this has consequences also for duration on therapy.

Duration of 2nd TNF Therapy

Table 5 gives the results of fitting the Weibull survival model to patients receiving their 1st and 2nd TNF.

Figure 2 shows the resulting survival curves for the typical patient of table 4, calculated for each possible DAS response. The graphs can be interpreted as 'survival on therapy' curves for a hypothetical cohort of patients who are similar to our 'typical' patient. The results show that withdrawal from treatment occurs much more rapidly for patients who are on their 2nd TNF treatment. Also, DAS response has less of an effect on survival time for these patients.

Appendix 1` shows the results of the statistical analysis to evaluate how strongly the duration on 2nd therapy is predicted by duration on 1st therapy with the BSRBR data. The coefficients for each categorised duration on 1st therapy show a tendency that longer duration on 1st therapy has some effect on longer duration on 2nd therapy (i.e. the coefficients for patients in the group 12-24 and 24+ months are positive). However, none of them are significant (see p values) and the strength of the association is small, and much less significant than for example the patient's age, disease duration or number of previous DMARDs.

Cost-Effectiveness

Table 6 gives the results of updating the economic model with analysis of the new dataset on patients receiving a 2nd TNF. The original basecase analysis showed that the incremental cost per QALY of using a single TNF as compared against using only conventional DMARDs was £23,882.

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This new analysis comparing 2 TNFs in a sequence with conventional therapy only gives an incremental cost per QALY of £24,570. We have also undertaken a probabilistic sensitivity analysis on this. Figure 3 shows that the probabilistic sensitivity analysis suggests gives an 85% chance that the true cost-effectiveness is less than £30,000.

We might also examine the incremental change in policy of moving from single use of TNFs only to a policy of 2 TNFs in sequence. The resulting incremental cost per QALY is estimated at around £27,063.
The sensitivity analysis assuming duration on 2nd TNF therapy has the same distribution as that for 1st TNF is shown in Table 7 and Figure 4. The results show that the mean costs of patients receiving the intervention are increased because of the extra time on therapy, but that the mean QALY received also increases. These increases balance each other and the cost-effectiveness ratios remain at the same order of magnitude (£23,618 for 2 TNFs v conventional DMARDs, £23,444 and for the incremental analysis of 2 TNFs versus TNF single use). The probabilistic sensitivity analysis suggests an 86% chance of cost-effectiveness at a £30k threshold.

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DISCUSSION

Relationship between This Analysis and that Undertaken by NICE using BSRBR data and the Birmingham Rheumatoid Arthritis Model

This analysis is independent of that undertaken by NICE using BSRBR data and the Birmingham Rheumatoid Arthritis Model. It differs in the following ways.

1. This analysis accounts for evidence on EULAR (DAS) response on a 2nd TNF. The probability of EULAR response is modelled with a covariate adjusted logit model using only patients receiving a 2nd TNF. Patients have different costs and benefits accruing depending on whether they are poor, moderate or good EULAR responders.

2. This analysis accounts for evidence concerning duration of therapy on a 2nd TNF. The evidence shows that duration of therapy on a 2nd TNF is considerably shorter than on a first, with substantially reduced cost of a course of therapy. It also accounts (as did our original analysis) for differential duration of therapy according to good, moderate or poor response.

3. In contrast, the NICE / BRAM analysis is based primarily on the mean HAQ improvement of patients receiving a 2nd TNF. The cohort of 2nd TNF recipients is then treated as a group. On the benefits side, it is effectively assumed that the utility accruing is in direct proportion to the mean HAQ improvement. The utility accruing is therefore assumed to be lower than in the case of a 1st TNF because the mean HAQ improvement on a 2nd TNF is considered approximately 70% of that seen on a 1st TNF. The result of this assumption is effectively that all patients are assumed to have a diminished effect, whereas the evidence from BSRBR on response shows that there is a similar proportion of good responders between 1st and 2nd TNF recipients.

4. Also in contrast, the NICE/BRAM analysis assumes that the duration of therapy on a 2nd TNF is equivalent to that on 1st TNF. The NDSU report indicates that duration on therapy analyses were considered by the NICE/BRAM team. They note that duration on therapy recorded on the BSRBR could be an under-estimate because the database does not yet have very long follow-up and the patients who have received 2nd TNF so far could be a biased subgroup of patients who have short durations both on 1st and 2nd TNF. It is true that there will be uncertainty around this. Nevertheless to assume that duration on 2nd TNF will be identical to that on 1st TNF and use evidence based elsewhere rather than using the available evidence on the BSRBR patients is a weakness of that analysis.

5. A further big difference is that the NICE/BRAM analysis of the effect of conventional DMARD is based on clinical trial evidence for leflunomide in a relatively early RA cohort. This may well not represent recipients of TNFs in the UK currently. Our analysis uses the control arm of the BSRBR for this data including covariate adjustment.

The effect of these differences is to change both the numerator and the denominator in the cost-effectiveness ratio. In comparison to analysis based on the BSRBR data using our model, the NICE/BRAM analysis probably reduces the size effect of the TNF due to the focus on mean HAQ reduction, definitely produces a greater effect for the conventional DMARD arm, and certainly increases the cost of the TNF side of the equation through the assumption of equivalent duration. The combination of using different assumptions and evidence than our BSRBR data for this analysis results in higher (worse) estimates of cost-effectiveness for the use of a 2nd TNF. In our model, the assumption that the distribution for duration on 2nd TNF is the same as that on 1st TNF makes little difference to the cost-effectiveness ratios and so it appears that it is the diminished effectiveness assumption and the lack of modelling response categories rather than the duration of therapy assumption in the NICE/BRAM analysis that drives changes in the results.

Some of these problems, particularly around response are well known to the committee, which is why statements in the original ACD and indeed FAD required adjusted analyses.

CONCLUSIONS

1. This analysis has used evidence on probability of response to a 2nd TNF and duration on therapy for a 2nd TNF to extend the previous independent analysis of the BSRBR data to investigate cost-effectiveness of TNF therapies in RA

2. The results suggest that 2nd TNF is similarly cost-effective to 1st TNF.

3. The NICE/BRAM analysis which assumes that mean HAQ improvement is the key driver rather than EULAR response, that duration of therapy is the same on 2nd TNF as on 1st TNF, that DMARD effectiveness is based on clinical trial evidence from relatively early RA patients gives higher i.e. worse cost-effectiveness ratios.

4. Our analysis of UK data on 2nd TNF response rates and duration of therapy together with earlier analysis of DMARD effectiveness, utility and cost all taken from the BSRBR indicates that 2nd TNF therapy is as cost-effective as 1st TNF therapy.

5. This suggests that perhaps the NICE decision concerning 1st TNF and 2nd TNF should be the same i.e. approval for 1st and 2nd under conditions of adequate response etc. or rejection of both 1st and 2nd TNF if the committee does not believe the BSRBR evidence is representative of UK practice. The committee has already decided that a 1st TNF is recommended provided adequate monitoring of ongoing successful response is in place. Our analysis of the evidence indicates that a similar conclusion for a 2nd TNF could be made.

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Table 1 Statistical modelling of proportional odds cumulative Logit model for predicting type of response

Let π_1 π_2 and π_3 be the probability of a DAS response 0 (poor), 1 (moderate) or 2 (good)

$$L_1 = \log\left(\frac{\pi_1}{1-\pi_1}\right)$$

$$L_2 = \log\left(\frac{\pi_1+\pi_2}{1-(\pi_1+\pi_2)}\right)$$

We fit the model

$$L_j = \alpha_j - \gamma^T x$$

To predict the probability of a DAS response we use the equations

$$P(\text{DAS}=0) = \frac{1}{1+\exp\left(-\left(\alpha_1 - \gamma^T x\right)\right)}$$

$$P(\text{DAS}=2) = 1 - \frac{1}{1+\exp\left(-\left(\alpha_2 - \gamma^T x\right)\right)}$$

$$P(\text{DAS}=1) = 1 - P(\text{DAS}=0) - P(\text{DAS}=2)$$

where the γ are the coefficients for the covariates.

Table 2 Statistical Modelling of Weibull survival analysis

The baseline hazard function is

$$h_0(t) = \frac{\alpha}{\beta^\alpha} t^{\alpha-1}$$

Where α is the shape and β the scale parameter and t is the time in months. A proportional hazards model is fitted for adjusting the survival for covariates.

$$h(t) = h_0(t)\exp\left(\gamma^T x\right)$$

The survival curve is

$$s(t) = \exp\left(-\int_0^t h(u)du\right)$$

$$= \exp\left(-\exp\left(\gamma^T x\right)\left(\frac{t}{\beta}\right)^\alpha\right)$$

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Table 3: Results from DAS response proportional odds logit model

	Response to first anti-TNF (original analysis)		Response to second anti-TNF (additional analysis)	
	SF6D	EQ5D	SF6D	EQ5D
Health state utility	2.2691	1.0275	0.4309	-0.6110
Age (years)	-0.0209	-0.0182	-0.0026	-0.0026
Disease duration (years)	0.0097	0.0098	-0.0238	-0.0225
Previous number of DMARDs	-0.0676	-0.0624	0.0210	0.0114
Gender (0=Male, 1=Female)	-0.3162	-0.2932	-0.1979	-0.1999
Whether on TNF inhibitor (1=Yes)	0.5608	0.6318	0.7909	0.9051
None | Moderate or Good intercept	-1.1451	-1.6849	0.3232	-0.0891
None or Moderate | Good intercept	1.3917	0.8650	3.1763	2.7368

Table 4: Characteristics of a typical patient from the BSRBR

Health state utility (SF6D/EQ5D)	0.48 / 0.27
Age (years)	58
Disease duration (years)	19
Previous number of DMARDs	6
Gender (0=Male, 1=Female)	0.5
Concomittant DMARD given with TNF inhibitor	0.72

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Figure 1: Predicted response to treatment for a typical patient

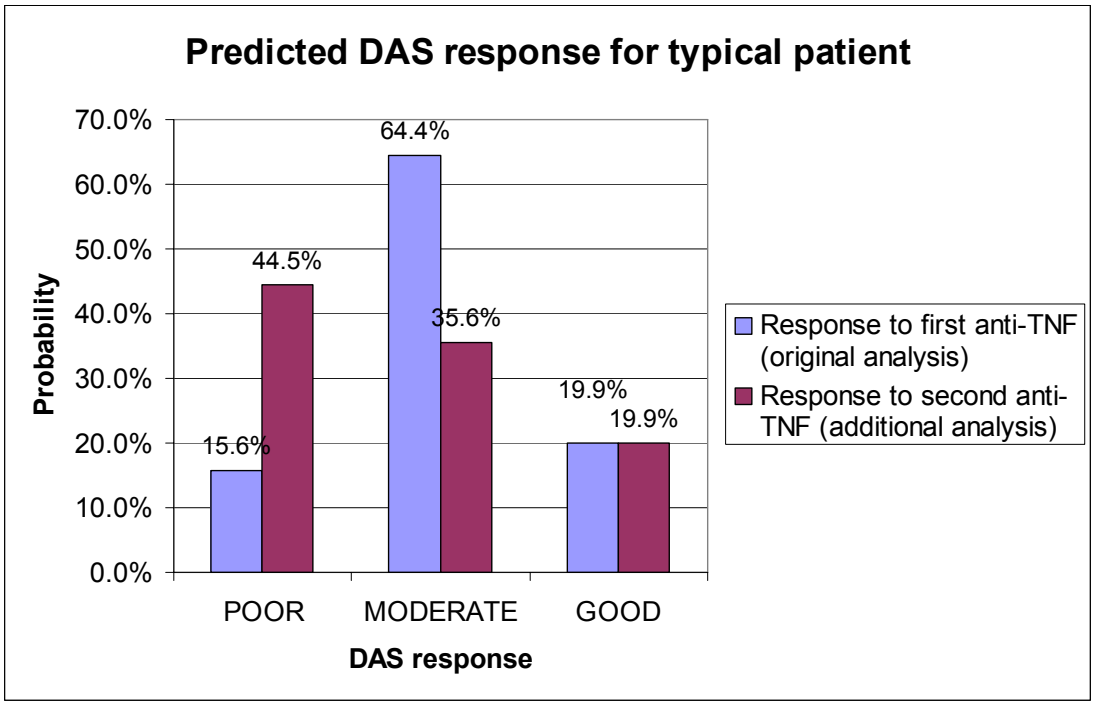

Table 5: Weibull survival analysis to predict time on 1st and 2nd TNF antagonist treatments.

Description	First TNF inhibitor (original analysis)		Second TNF inhibitor (additional analysis)	
	SF6D	EQ5D	SF6D	EQ5D
Age (years)	-0.003	-0.003	0.009	0.008
Disease duration (years)	0.001	0.002	0	-0.001
Previous number of DMARDs	0.066	0.066	0.056	0.049
Gender (1=Male?)	-0.75	-0.454	-0.106	-0.045
On concomitant DMARD	0.042	0.078	-0.316	-0.309
Utility	-0.750036	-0.454446	-0.91	-0.571
Moderate DAS response	-1.264	-1.232	-0.495	-0.516
Good DAS response	-1.882	-1.777	-0.298	-0.238
log(scale)	3.764	3.772	3.52900	3.516
log(shape)	0.588	0.582	-0.19000	-0.183

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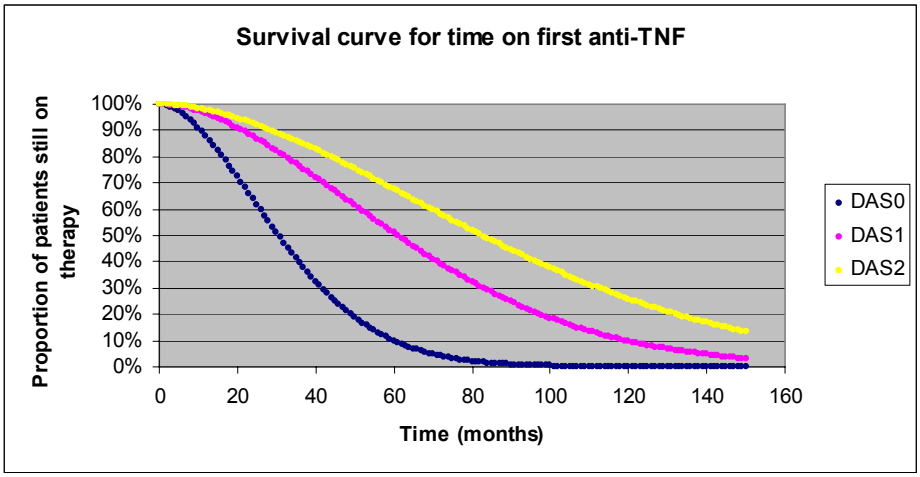
Figure 2:

a) Survival curves for time to withdrawal of first TNF therapy



b) Survival curves for time to withdrawal of first TNF therapy

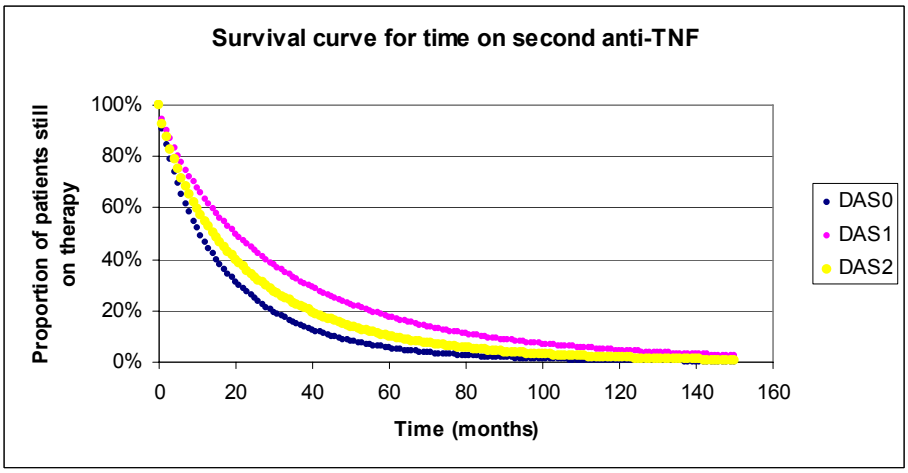


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Table 6: Cost-effectiveness of single use and sequential use of anti-TNF compounds

Intervention	Comparator	Cost		QALY		Incremental cost	Incremental QALYs	ICER (£ / QALY)
		Intervention	Comparator	Intervention	Comparator			
Single-use TNF inhibitor	DMARDs alone	£57,919	£20,706	5.15	3.59	£37,214	1.56	£23,882
Sequential TNF inhibitor	DMARDs alone	£69,562	£20,706	5.58	3.59	£48,856	1.99	£24,570
Sequential TNF inhibitor	Single-use TNF inhibitor	£69,562	£57,919	5.58	5.15	£11,643	0.43	£27,063

Figure 3: Cost-effectiveness acceptability curve for sequential use of anti-TNF vs. DMARDs only.

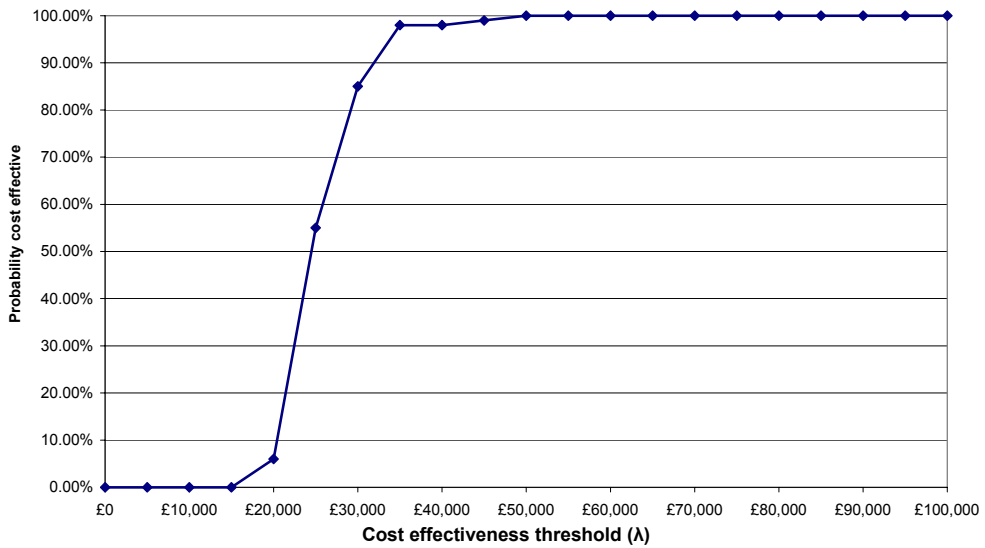

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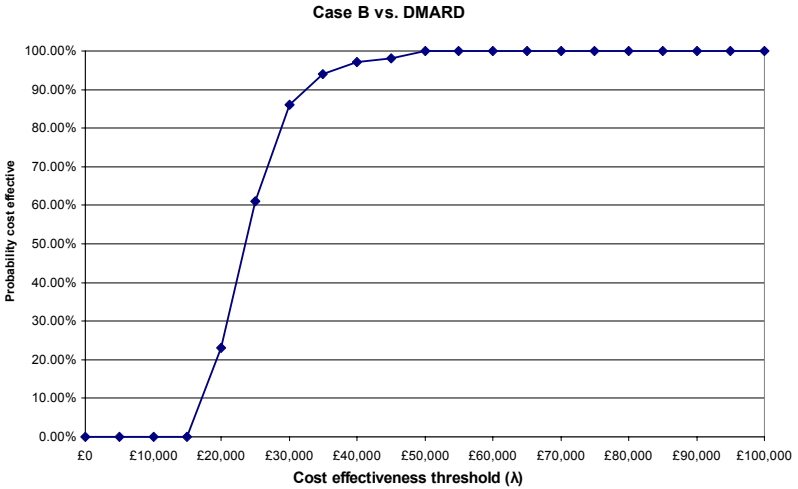
Table 7: Sensitivity Analysis Assuming Duration on Therapy is the same as on 1st TNF

Intervention	Comparator	Cost		QALY		Incremental cost	Incremental QALYs	ICER (£ / QALY)
		Intervention	Comparator	Intervention	Comparator			
Sequential TNF inhibitor (case B)	DMARDs alone	£77,822	£20,742	6.00	3.58	£57,080	2.42	£23,618
Sequential TNF inhibitor (case B)	Single-use TNF inhibitor	£77,822	£57,919	6.00	5.15	£19,903	0.85	£23,444

Figure 4: Cost-effectiveness acceptability curve for sequential use of anti-TNF vs. DMARDs only Sensitivity Analysis Assuming Duration on Therapy is the same as on 1st TNF



Appendix 1: Results of Duration of 2nd Therapy Model including Duration on 1st therapy as a factor

Call:
weibreg(formula = Surv(time3, status3) ~ age + disdur + num_dmard +
    eq + pgen + as.factor(dur_first))

Covariate	Mean	Coef	Exp(Coef)	L-R p	Wald p
age	55.623	-0.011	0.990		0.102
disdur	14.536	-0.018	0.982		0.071
num_dmard	5.267	0.081	1.085		0.055
eq	0.251	0.346	1.414		0.272
pgen	0.780	-0.260	0.771		0.151
as.factor(dur_first)					
0	0.106	0	1	(reference)	
3	0.296	-0.341	0.711		0.283
6	0.277	0.003	1.003		0.993
12	0.240	0.363	1.438		0.219
24	0.080	0.096	1.101		0.798
log(scale)		5.089	162.203		0.000
log(shape)		-0.108	0.897		0.096

Events	159
Total time at risk	19834
Max. log. likelihood	-911.32
LR test statistic	25.4
Degrees of freedom	11
Overall p-value	0.00795041