National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis (review of TA guidance 130, 186, 224, 234 and part review of TA guidance 225 and 247) [ID537]

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by the **School for Health and Related Research (ScHARR) at the University of Sheffield**. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Acknowledgement and Undertaking Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. If asked, you must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

December 2013

Rheumatoid arthritis - adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab - review [ID537]

Pfizer response to the Sheffield Rheumatoid Arthritis Model

Pfizer welcomes the opportunity to comment on the Sheffield Rheumatoid Arthritis Model from the School of Health and Related Research (ScHARR) for the review of Rheumatoid Arthritis - adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab - review [ID537]. As noted in our response to the Technology Assessment Report (TAR) (25.09.13), there were fundamental aspects of the economic evaluation by the Assessment Group (AG) that Pfizer was unable to review and understand previously without access to the model and due to the insufficient clarity in the methods reported in the TAR. The availability of the model has meant that Pfizer has been able to undertake a more comprehensive appraisal of the economic modelling and enhance our understanding of the approach and methods used by the AG in their economic evaluation.

Following our review of the economic model, Pfizer's main concern is that there are a number of errors in the model that have led to incorrect cost effectiveness estimates being produced and included in the TAR. It is important to note that the complexity and limited transparency of the model makes it difficult to understand the logic behind the visual basic for applications (VBA) code and accordingly difficult to check for errors. In addition, there are a number of discrepancies and differences regarding assumptions and input values reported in the TAR and used in the model released to consultees and the Appraisal Committee. This has made it difficult to identify whether these are reporting errors in the TAR, or errors in the model code.

Pfizer notes that the model could be programmed more efficiently and would therefore allow stakeholders to make more comprehensive quality checks across all populations and scenarios presented in the TAR. Accordingly, due to time limitations, Pfizer has focused on the severe RA population with initial EULAR response and ERAS HAQ progression. This was felt to most closely represent the AG basecase. In addition, it is currently unclear how many patients are needed to be simulated to get consistent results between model runs. It is important to note that there was significant variation between model runs even up to 10,000 patients being simulated for some scenarios. Pfizer suggests the AG clarify the suitable number of simulated patients in order for all stakeholders to be able to reproduce comparable and consistent results.

Nevertheless, Pfizer have identified at least four main errors that are likely to have a significant impact on the AG's main model results:

1. **An error in the model whereby the bDMARD HAQ progression is used for cDMARDs between 6 and 12 months**
   1.1. There is an error in the AG model where the bDMARD HAQ progression analysis from the British Society of Biologic Register (BSRBR) is selected for cDMARDs between 6 and 12 months. This overestimates both the treatment effect of MTX compared to bDMARDs between 6 and 12 months and the ICERs by approximately 20-30% in some model runs for the base case results in severe RA. The error does not appear to affect the linear HAQ progression scenarios.
   1.2. There is a potential further error in the implementation of the BSRBR bDMARD HAQ progression between 6 and 12 months due to variables in the analysis not being specified for cDMARDs.

2. **Time on treatment for cDMARDs has been incorrectly implemented in the model**
   2.1. Different survival (time on treatment) estimates for bDMARDs and cDMARDs have been used in contrast to the TAR. Correcting this error could potentially increase the ICERs by approximately 15% for bDMARDs compared to MTX in AG basecase results in severe RA.

3. **A number of errors concerning how the mortality has been implemented in the model have been identified**
   3.1. Female survival rates have been excluded from the model, survival probabilities have been incorrectly estimated and the age cap in the model has not been implemented correctly. This leads to a decrease in the model ICERs when this error is corrected by approximately 5% for bDMARDs compared to MTX in AG basecase results in severe RA.

4. **An error with the implementation of the pain to HAQ relationship from the Early Rheumatoid Arthritis Study (ERAS) in the model**
   4.1. The TAR reported that the electronic model uses a pain to HAQ relationship from the Early Rheumatoid Arthritis Study (ERAS) in the basecase of the model. Pfizer believes this is a reporting error in the TAR based on the results presented. It appears that the AG actually used the HAQ to pain relationship from the National database of biologics (NDB) in the basecase. Pfizer agrees with the use of the NDB as a more appropriate data source to estimate pain than the ERAS dataset.
   4.2. The ERAS pain to HAQ relationship in the model has not been correctly implemented. This leads to incorrect values being inputted into the model when the ERAS relationship is chosen causing a significant overestimation of pain in the model and reduction in the number of QALYs for both cDMARDs and bDMARDs. ICERs appear to increase by approximately 15% in this scenario for bDMARDs against MTX A inthe ERAS pain to HAQ scenario for severe RA.

Therefore, we believe due to the significant number of errors in the economic model, the cost effectiveness results presented in the TAR and at the NICE Appraisal Committee (AC) Meeting on the 15th October 2013 are incorrect. Given the complexity of the model and the number of lines of code, Pfizer cannot be sure that all errors have been identified. Pfizer has identified errors in every aspect of the model reviewed and therefore believe that both the model and the TAR are not currently fit to inform the NICE AC in making a decision concerning the use of bDMARDs in RA. Overall, we anticipate that the errors identified so far will have a substantial impact on results and may have significantly underestimated the cost effectiveness of bDMARDs compared to MTX or cDMARDs.

In addition to these errors with significant impact on results, we have found a number of additional errors/issues in our review of model and discrepancies between the TAR and the model. Whilst it is felt that these are unlikely to have significant impact on the model results individually, taken together they introduce a large amount of uncertainty into the model results and further increase the lack of transparency in the methods the AG have undertaken in producing the model and the TAR especially given that the detail of some model relationship have not been released to consultees.

Overall, we would like to reiterate our previous concerns and comments regarding the remit and approach taken in the TAR, specifically concerning the modelling of sequential treatments, as outlined in our TAR response (25.09.13) which have been confirmed as a

result of access to the model. We continue to disagree with the conclusions on cost effectiveness being a reasonable interpretation of the evidence due to the choice of data sources being used in the economic model. However, for brevity we have not reiterated our previous concerns and have only developed them where necessary with regards to the errors in the model and/or TAR.

In conclusion, Pfizer deem the economic model unfit for the purpose of informing the appraisal committee's decision making process due to the above errors identified and the potential for further errors to be found. Pfizer recommend:

- **The economic model requires a fully independent technical quality check to ensure that all the errors identified are corrected and there are no further errors in the code**
- **The TAR needs to be updated to reflect the corrected economic model and both the updated TAR and model released for further review and comment to consultees prior to the next appraisal committee meeting**
- **The first Appraisal Committee meeting should be repeated with the revised corrected model and fully updated TAR used as a basis for discussion to avoid any confusion with points raised from the original meeting**

Issue 1 Overview of Pfizer concerns with the model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
We believe due to the significant number of errors in the economic model, the cost effectiveness results presented in the TAR and at the NICE Appraisal Committee (AC) Meeting on the 15th October 2013 are incorrect. Given the complexity of the model and the number of lines of code, Pfizer cannot be sure that all errors have been identified. Pfizer has identified errors in every aspect of the model reviewed and therefore believe that both the model and the TAR are not currently fit to inform the NICE AC in making a decision concerning the use of bDMARDs in RA. Overall, we anticipate that the errors identified so far may have overestimated the ICERs of bDMARDs compared to MTX or cDMARDs. In addition to these errors with significant impact on results, we have found a number of additional errors/issues in our review of model and discrepancies between the TAR and the model. Whilst it is felt that these are unlikely to have significant impact on the model results individually, taken together they introduce a large amount of uncertainty into the model results and further increase the lack of transparency in the methods the AG have undertaken in producing the model and the TAR especially given that the detail of some model relationship have not been released to consultees. Overall, we would like to reiterate our previous concerns and comments regarding the remit and approach taken in the TAR, specifically concerning the modelling of sequential treatments, as outlined in our TAR response (25.09.13) which have been confirmed as a result of access to the model.	**The economic model requires a fully independent technical quality check to ensure that all the errors identified are corrected and there are no further errors in the code** **The TAR needs to be updated to reflect the corrected economic model and both the updated TAR and model released for further review and comment to consultees prior to the next appraisal committee meeting** **The first appraisal committee meeting should be repeated with the revised corrected model and fully updated TAR used as the basis for discussion to avoid any confusion with points raised from the original meeting**	Not applicable

We continue to disagree with the conclusions on cost effectiveness being a reasonable interpretation of the evidence due to the choice of data sources being used in the economic model. However, for brevity we have not reiterated our previous concerns and have only developed them where necessary with regards to the errors in the model and/or TAR.		

Issue 2 An error in the AG model whereby the bDMARD HAQ progression is used for cDMARDs between 6 and 12 months

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The TAR (section 6.3.14, p.370-372) states that the HAQ trajectory [progression] following initial 6 month response for cDMARDs used in the electronic model base case is taken from a modified analysis of Norton et al using the ERAS dataset[1]. However, in contrast to the TAR, the electronic model appears to be using the analysis for bDMARDs HAQ progression which has been estimated from the BSRBR between 6-12 months. Only after 12 months the Norton et al/ERAS analysis is then used for cDMARDs in the model. Pfizer believes this represents an error in the code of the model given that the AG provided no justification or evidence to support such an assumption. Pfizer notes that this error only impacts the results where the Norton et al/ERAS relationship has been used and not the linear HAQ progression scenarios. Pfizer argues that available data from the BSRBR between baseline and 12 months does not support the assumption that clinical response over this time period will be same for bDMARDs and cDMARDs[2]. We would suggest the evidence supports that on average patients on cDMARDs will start to progress after the first 6 months of treatment and progression should be	Pfizer requests the model be corrected so that cDMARD HAQ progression in the model starts at 6 months as reported in the TAR. If the BSRBR HAQ progression has been intentionally included by the AG for cDMARDs, then, Pfizer asks the AG to justify the assumption within the TAR. Pfizer notes that this represents a key model uncertainty and significantly alters model results and should be explored further for all populations. **Please see appendix A for details of the error**	Pfizer has rerun the model using just the Norton et al progression for cDMARDs from 6 months instead of 12 months. Pfizer has found variation in this scenario and ICERs have been found to be significantly overestimate bDMARDs compared to MTX in some model runs. **A screen shot of the model basecase run by Pfizer is in Appendix B**. **Please see appendix C for model results after correcting this error**. It is believed that this represents the fact that cDMARDs will experience a delay of 6 months before starting HAQ progression. But, depending on how patients are allocated to HAQ

modelled from 6 months for cDMARDs.		progression the results may vary substantially. Pfizer believes that only the ERAS HAQ progression scenarios will be affected by this error, as the linear HAQ progression scenarios appear to be unaffected.

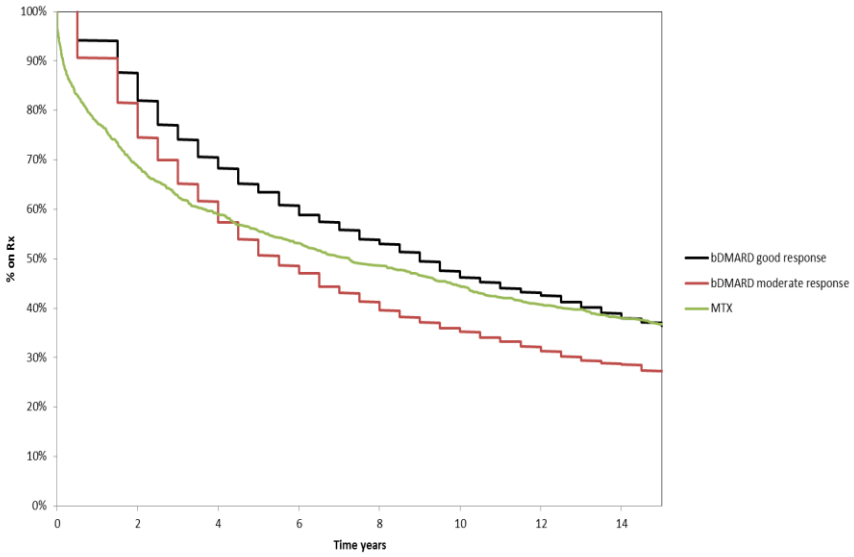
Issue 3 An error identified in the implementation of the BSRBR HAQ progression for cDMARDs between 6 and 12 months due to variables in the analysis not being specified

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
If the BSRBR HAQ progression data is used for cDMARDs between 6-12 months in the model, then, Pfizer notes a further possible error in the model. Some variables in the VBA code used to estimate the BSRBR HAQ progression have not been correctly specified. Variables *i* and *s* are used to specify patient characteristics to improve prediction of HAQ progression for patients on bDMARDs. However, when a cDMARD is selected in the model these variables are not re-calculated and can sometimes be empty (resulting in 0s being used) or may be recycled from the previous (bDMARD) treatment in the sequence.	Pfizer disagree with the use of the BSRBR analysis for cDMARDs. However, If HAQ progression for cDMARDs from 6-12 months from the BSRBR analysis has been intentionally included and can be justified by the AG, then, the error, which fails to specify key patient characteristics should be corrected. **Please see appendix D for details of the error**	Pfizer has not explored the impact of this error given Issue 1 above. Pfizer believes that change in HAQ could be being underestimated in the model for cDMARDs given that 0s are being used for variables in the analysis. This is not clear however. Nevertheless, it is thought that this error would affect the results in all strategies, but have a proportionally greater effect in the MTX strategy, because in bDMARD strategies not all patients ever receive cDMARDs (some will die first) and this will be

		subject to increased discounting at this stage in the model.

Issue 4 Time on treatment for cDMARDs has been incorrectly implemented in the model in contrast to the TAR

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
There is a large discrepancy in how the cDMARDs survival duration is reported in the TAR and how it is implemented in the model. The TAR (section 6.3.15, p.373) reports that 'based on the assumption that cDMARDs are not likely to be more toxic than biologics used in combination with a cDMARD, it was assumed that survival duration for each EULAR response category for bDMARDs would be applicable for cDMARDs.' Pfizer's review of the model, in contrast to the TAR, has found that cDMARD survival is sampled from a Weibull distribution taken from Chen and colleagues[3] (previous AG for NICE TA130). This is believed to represent an error in the model. Chen et al used overall survival from the literature for cDMARDs and therefore survival curves for cDMARDs are not based on EULAR response, as reported in the TAR. The survival curves for bDMARDs and MTX used in the model are illustrated in Figure 1 below. Pfizer notes that overall MTX survival is longer after 4 years in figure 1 than time on treatment for moderate EULAR responders in the model with bDMARDs.	As outlined previously in our TAR response, Pfizer suggests that the cDMARD cohort from the BSRBR should be used to estimated time on treatment based EULAR response for MTX and cDMARDs as this is a more applicable source than using bDMARD time on treatment. (Pfizer TAR response, section 5.1, p.14-15). Nevertheless, the model should be corrected so that method of estimating time on treatment is consistent for both cDMARDs and bDMARDs and to ensure consistency with the TAR. Pfizer requests that the Chen et al[3] estimation for MTX and cDMARDs is not applicable to be used in the model due to the historic nature of the source. Pfizer's analysis from the	There is significant variation around the expected impact of this error in the model as it is associated with a number of other assumptions and errors in the model. Simply, correcting for this error results in the ICERs of bDMARDs compared to MTX increasing by approximately 15% in a Severe RA population. **Please see Appendix F for results correcting this error in a Severe RA population.** Pfizer has also run a scenario where overall time on treatment for Sufalsalazine has been used for MTX from Chen et al and notes the ICERs for bDMARDs compared to MTX decrease by approximately 10%. Highlighting the sensitivity of this

Figure 1: Model estimated time on treatment *<u>for patients who respond to therapy</u>*  Furthermore, Pfizer notes that the mean time on treatment for MTX is likely to be significantly longer than good EULAR responders after 14 years of treatment, with a mean time to withdrawal of 30.4 years (Figure 2). Pfizer believes that this is likely to be an overestimation of time on treatment for MTX and is unlikely to reflect current time on treatment for MTX seen in current clinical practice. This is because a large proportion of these historic patients will have remained on MTX indefinitely in the absence of further	BSRBR for cDMARDs would be a more applicable data source to be used in a scenario If necessary. **Please see appendix E for details of the error**	input on model results. Given the variation in ICERs depending on which drug survival estimate is taken, Pfizer would like to note our previous concerns with the AG approach that have not been taken into account when correcting for this error. Namely the AG has not currently taken into account the reduction in time on treatment for subsequent therapies like rituximab and tocilizumab (or observed differences between treatments) in the treatment pathway (Pfizer TAR response, Section 1.2, p.5-6).

treatments (like bDMARDs) to try.

Figure 2: Survival parameters used in the AG model and mean time on treatment taken from Chen et al 2006

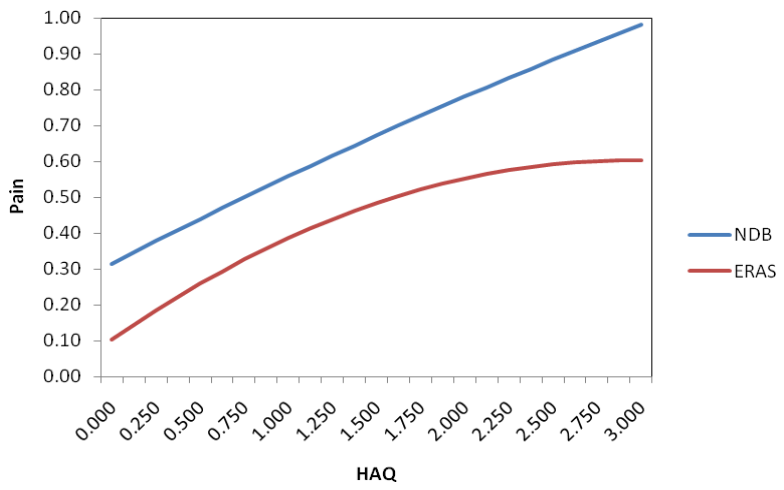
DMARDS	shape (a)	scale (b)	mean (years)
AST_DMARD			
CON_DMARD	0.46	4.66	11.0
HCQ	0.49	3.52	7.3
INT_CON_DMARD	0.49	3.52	7.3
LEF	1	5.98	6.0
MTX	0.51	15.73	30.4
SSZ	0.46	4.66	11.0
SD	0.46	4.66	11.0
TICORA	0.49	3.52	7.3

From our own analysis of the BSRBR (Pfizer MTA submission, Section 4.3.4.5 p.151-156), which contains patients that received cDMARDs after the introduction of bDMARDs, we note that the time to withdrawal between ETN and MTX is very similar. Furthermore, Pfizer also argues that there is no reason for the time to withdraw to be any longer for MTX than other cDMARDs.

Issue 5 Pfizer believes there is an reporting error in theTAR and the HAQ to pain relationship estimated from NDB dataset has been used in the model basecase

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The TAR states that the electronic model uses data from ERAS to estimate the pain score from HAQ to improve the prediction of the utility function in the model (Section 6.3.18, p.378). Pfizer believes that the TAR is incorrect and that the NDB relationship has been used in the basecase based on the model results presented in the TAR (Table 194, p.387) given that the ERAS pain score is presented as a scenario analysis. Pfizer notes that there NDB HAQ to pain relationship does not appear to closely match the data presented in TAR (Figure 98, p 378, where the relationships looks similar). Pfizer has reproduced the relationships from the NDB and ERAS datasets on the same axis in Figure 3 below.	Pfizer suggest that the AG clarify whether the NDB relationship was used in the model basecase and the TAR is amended to reflect this if true. Pfizer believes that the NDB relationship is more applicable than the ERAS dataset for reasons previously outlined in our original TAR response. Pfizer also suggests that the graphs representing the pain to HAQ relationships from ERAS and specifically the NDB be checked, as it is felt they do not reflect the model data.	Not applicable

Figure 3: Pain to HAQ relationships in the model estimated from the NDB and ERAS datasets



Pfizer would like to reiterate that the differences in the estimated relationships are likely to reflect the differences in the populations of the two registries. Patients in ERAS have early RA and therefore are unlikely to have experienced significant progression of their disease and accordingly registerlower pain scores. This is in contrast to the patients in the NDB who have more severe disease with greater progression. Pfizer suggests this is further evidence that suggests that ERAS datasets generalisability to a moderate and severe population is very low and should not be used in the AG model (as outlined previously in the Pfizer TAR response specifically p.19-20). Pfizer agrees that the NDB relationship is more applicable than the ERAS dataset, however, the TAR needs to be updated to reflect this.

Issue 6 An error with the implementation of the HAQ to pain relationship from the Early Rheumatoid Arthritis Study (ERAS) in the model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Pfizer believes that there is an error in the electronic model which means HAQ to pain relationship estimated from the ERAS dataset is incorrectly implemented in the model when selected. The code to facilitate this is performed within the *qaly* sub procedure and the switch variable *pain_switch* is not defined within the model. Therefore the 2nd option (NDB analysis noted to be a temporary option) is always selected. It is believed that selecting the first option (ERAS quadratic regression, as reported by the TAR), will therefore lead to incorrect estimates in a number of scenario analyses. This occurs because the 2 algorithms differ in coefficients, but also in scale • the NDB values are on the scale 0-1 • whilst the ERAS estimates are on the scale 0-100 It appears the Hernandez at al utility[4] mapping algorithm requires values in the 0-1 range, and as such if the ERAS estimates are selected, the model *should* divide these estimates by 100. Currently the utility relationship expects pain on a scale of between 0 and 1, but instead the model currently uses pain scores that will always be more than 1.	Pfizer requests that scenarios which involve the ERAS HAQ to pain relationship be corrected. We reiterate our point that that ERAS pain to HAQ relationship scenario has limited generalisability to Moderate and Severe RA populations as outlined in our original TAR response (Section 4.1. p.10-11) **Please see Appendix G for details of the error.**	If there ERAS scenario is selected then utility values will be underestimated. This effect is difficult to observe in use, because the Hernandez at al[4] algorithm will never produce an EQ-5D estimate outside of the range -0.594 – 1.000. **Appendix H presents basecase results in a Severe RA population after correction of this error.** Correcting the error leads to noticeable changes in total QALYs and ICERs appear to be increase by approximately 15%. The results of AG report Table 202 provides a scenario explicitly stating that the ERAS HAQ to pain estimate was used; and these results seem to be broadly congruent with those estimated here.

Issue 7 HAQ to Pain relationship in the AG model has a significant affect on model results and few details of the relationship have been released to consultees to review

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Pfizer continues to reiterate its previous concerns highlighted in our original response to the TAR (p.21) concerning the use of pain scores in the utility estimates. The AG has simulated the expected pain score based on the HAQ score in TAR (section 6.3.18 page 378). The AG reports that the estimation of EQ-5D utility scores is substantially more accurate when based on HAQ and pain than on HAQ alone. Pfizer feels that this is somewhat contradictory. The AG is improving predictability of the relationship between HAQ and utility but is still using HAQ to improve this relationship and not independent pain values. After reviewing the model, Pfizer notes the large impact that the pain coefficients have on utility and hence model results. Pfizer notes that no details of how this relationship between pain and HAQ from the ERAS and NDB has been estimated. Given the impact that this relationship has on model results, Pfizer suggest that details of the regression analysis should be shared with consultees and NICE to enable the relationship to be critiqued.	Given that the pain estimates in the model have a large impact on the model results; full details of the regression should be released to consultees and NICE. Currently basic information has not even been reported and Pfizer believes this to be a major element of uncertainty in the AG model	Not applicable

Issue 8 A number of errors in how mortality has been implemented in the model have been identified

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The probability of survival is based on from 2009-11 lifetables, however it appears that an error has been introduced whereby the model only uses mortality rates for males. This has the effect of underestimating the Person's life expectancy and therefore the total number of QALYs estimated within the model (because women live longer than men). The model also assumes that hazard ratios are equivalent to relative risks; a more appropriate methodology would be to convert the probabilities to rates, apply the hazard ratio, and then convert back to probabilities. The model therefore currently simulates probabilities of mortality greater than 1 at older ages, which should not be possible. We note that the published lifetables themselves confusingly refer to these values (q_x) as both a rate and probability, but we believe that they truly represent probabilities[5] The table range used in these vlookups do not include 'age=101' and therefore the reported age cap of 101 years reported by the TAR is not correctly implemented (TAR, Section 6.3.5. p.353).	A number of errors identified with regards to mortality in the model should be corrected. **Errors are outlined in Appendix I.**	The cumulative consequences of these corrections on ICERs are approximately 5% however they do overestimate the ICERs for bDMARDs compared to MTX and cDMARDs **Results are presented in Appendix J**

Issue 9 A discrepancy has been indentified between the TAR and the model in the values used for HAQ change conditional on EULAR response

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model or expected impact on the result (if applicable)</th></tr>
<tr>
<td>
There appears to be a discrepancy in the values used for HAQ change conditional on EULAR response within the model and those reported in the in the TAR report (Section 6.3.13, p.364). The AG specify that they assume that the HAQ change conditional on EULAR response is the same for cDMARDs as bDMARDs and that the data is reproduced in Figure 4 below.

Figure 4: HAQ change by EULAR response as reported in the AG report (Table 188)

<table>
<tr><td></td><td colspan="6">HAQ</td></tr>
<tr><td colspan="7">EULAR response baseline>6month visits</td></tr>
<tr><td></td><td>mean</td><td>se</td><td>z</td><td>p</td><td>lcl</td><td>ucl</td></tr>
<tr><td>None</td><td>-0.050</td><td>0.025</td><td>-2.03</td><td>0.043</td><td>-0.098</td><td>-0.002</td></tr>
<tr><td>Moderate</td><td>-0.509</td><td>0.035</td><td>-14.67</td><td>0.000</td><td>-0.577</td><td>-0.441</td></tr>
<tr><td>Good</td><td>-0.650</td><td>0.043</td><td>-15.10</td><td>0.000</td><td>-0.735</td><td>-0.566</td></tr>
</table>

Se = standard error

lcl = lower 95% confidence interval; ucl = lower 95% confidence interval

The data used in the model is reproduced in Figure 5 below. There is a large difference in the response rates reported and used in the model. Specifically, the model assumes no benefit for non-responders and the HAQ change for moderate response has been reduced notably (-03.17vs -0.509, model vs report, respectively.
</td>
<td>
Pfizer is unsure of where the data in the model is has been taken from as this has not been reported in the TAR. Pfizer asks the AG to clarify where the data in the model has been taken from and to update the model or TAR with the correct data.
</td>
<td>
Pfizer has not run this analysis and has assumed the data in the model is the correct data.
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</tr>
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Figure 5: HAQ change by EULAR response used in model

Parameter Set	Parameter	Parameter Name	LIVE	Deterministic	Probabilistic
1. HAQ Change	HAQ change (no EULAR response)	eular_none	0.000	0.000	0.000
	HAQ change moderate EULAR response)	eular_mod	-0.317	-0.317	-0.364
	HAQ change (good EULAR response)	eular_good	-0.672	-0.672	-0.821

Issue 10 Assumption regarding what should be used as last treatment for each sequence has signifciant impact on model results

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Pfizer notes that there are two treatments that can be used as the last treatment in the model ('assorted DMARDs' and 'palliative care'). Depending on which one is selected as the last treatment in the MTX, or the bDMARD sequence will have a significant impact on results due to their HAQ progression assumptions. 'Assorted DMARDs' is assumed by the AG to reflect post-biologic/rescue/palliative use DMARD use with HAQ progression based on the ERAS/Norton et al analysis. This has been used in the AG base case (TAR, Section 6.3.14). Palliative care uses a linear HAQ progression 0.06 per year based on previous AG assumptions in TA195.[6] This has been used in a sensitivity analysis by the AG (TAR, Section 6.3.14). Pfizer suggest that this is an assumption that introduces considerable uncertainty into the model, as	We suggest that the TAR should justify the use of 'Assorted DMARDs' using the ERAS dataset to estimate HAQ progression for the last treatment in the model. Pfizer believes that it is unrealistic for the last treatment in the model to have the same HAQ progression as the first. Given this has considerable impact on model results the AG should make this clear within the TAR that	The model results differ significantly if assorted DMARDs or palliative care are used as the last treatment in the sequence. **Results of the model from using the two treatments as the last therapy in the sequence are in Appendix K.** Pfizer notes that the difference in the base case results means that the using 'palliative care' as the last treatment instead of 'assorted DMARDs' decrease ICERs for

it assumes that if 'assorted DMARDs' is selected then the HAQ progression until the end of the model will be the same as the first cDMARD i.e MTX. Pfizer suggests that this is a big assumption and the available clinical evidence as suggested in our TAR response suggest a reduction in treatment effect for subsequent lines of therapy. Again Pfizer suggests that subsequent lines of therapy should be modelled realistically or this could have a significant impact on model results. (Pfizer TAR response, Section 1, p 4-7).	this represents a key uncertainty in the model. The impact of this assumption was not realised from reading the TAR and only became apparent when examining the model.	bDMARD compared to MTX by approximately 40% in the Severe RA population.

Issue 11 Adverse Events in the model are not consistent with how they are reported in TAR

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Pfizer believes that there are discrepancies with the TAR report and the economic model provided to consultees in terms of how adverse events (AEs) have been handled in the model. Subsequent bDMARDs (rituximab and tocilizumab as recommended in TA195 and TA247) do not have the cost of AEs applied or QALY decrement applied to them. It is felt that applying these costs and QALY decrements to first line of therapy, but not applying them to subsequent lines of therapy may reduce the cost of failing the first line of treatment. The AG model diagram in the TAR (Figure 86, p.352) states that patients are subject to discontinuation due to AEs. Pfizer notes that AEs do not explicitly lead to discontinuation. It may be argued that they implicitly contained with all-cause discontinuation curves. However, this is not explicitly stated in the TAR.	Pfizer requests that the minor errors in the TAR are corrected to represent how the economic model handles AEs	Pfizer believes the errors identified with the model will have minimal effect on results. Therefore, they have not been amended in the model and new results run.

Issue 12 Reporting of how the HAQ progression based on the Norton/ERAS analysis implies higher precision in the relationship due to the use of more predictive variables than is reported in the TAR

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Pfizer note the probability of class membership to determine the HAQ progression for cDMARDs using the ERAS dataset uses the several variables, which are not correctly detailed within the TAR (Section, 6.3.14, p.370-371). In addition, several variables have been reported but not included in the model, and others have been incorrectly detailed. Varables affected are: • Age at disease onset is reported in the TAR, but age *at the start of the current therapy* is used in the model • Deprivation level is missing in the model • Disease duration is hard-coded to 2 years in the model • Rheumatoid factor positive is missing in the model • ACR criteria is missing in the model • The report says baseline DAS is used, but DAS at the start of the current therapy is used in the model • Failed 2 DMARDs is missing in the model • DAS response is missing in the model We argue that the TAR is misleading and suggests that the regression used to predict cDMARD class membership is more sophisticated than it actually is in the model. Pfizer questions how well the model allocates patients to the different classes given that a number of the predictive variables are missing or mis-specified. Furthermore, no validation is reported in TAR. Given that the AG has access to the patient level data this would be an easy	No details of how well this regression analysis performs in allocating patients to HAQ trajectories are presented by the AG in the TAR. Pfizer questions how well the model allocates patients to the different classes given that a number of the predictive variables are missing or mis-specified. Furthermore, no validation is reported in TAR. It is believe that the AG has access to patient level data from ERAS and Pfizer suggests that this could be checked to ensure how well the modified regression predicts class membership compared to the original model presented by Norton et al[1].	Not applicable

check to ensure how well the modified regression predicts class membership compared to the original model presented by Norton et al[1].		

Issue 13 The mapping relationship of ACR to EULAR is still is not available for consultees to critique as this has been calculated outside of the model and values 'hard coded' into the model.

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model does not contain the details of the ACR to EULAR mapping. It is believed that this relationship is estimated within the network meta-analysis (NMA). The details of this relationship are also redacted in the TAR (Table 187, p.360). Pfizer reiterates its concerns expressed in our TAR response concerning the VARA database used to estimate this relationship (Pfizer TAR response, Section 4.3 p.11-13). Accordingly Pfizer requests that the detail of this estimate is released to consultees to appraise. Pfizer would argue that the strength of this relationship is a fundamental concern which determines whether an ACR or EULAR based model is most appropriate to inform the decision question. Furthermore, Pfizer notes that due to this relationship being estimated outside of the model it means the uncertainty in this relationship is not characterised within the probabilistic sensitivity analysis (PSA).	Pfizer continues to request that the detail and also how the ACR to EULAR relationship has be estimated is released to consultees to allow an appraisal of the relationship to be undertaken. The relationship should be included in the model to characterise the uncertainty in the relationship within the probabilistic sensitivity analysis.	Not applicable

Issue 14 Pfizer believes that AG model has not simulated enough patients to ensure that the incremental analyses aremeaningful. The model results have considerable variation in them at the reported number of patients especially in a Moderate RA Population

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The incremental cost and QALY differences between bDMARD strategies	The AG should identify how	Not applicable

are very small. This could very easily lead to presentation of dominated/extendedly dominated results which, in another model run, will be reversed. Basing results for the moderate population on 1,000 patients seems worrying, as from Pfizer's review of the model at least 10,000 patients are needed to stabilise results sufficiently. We note that the authors of the Birmingham Rheumatoid Arthritis Model (BRAM) used in TA130 employed a strategy for ensuring a high degree of precision while minimising computational burden: *"The model was first run with 10,000 patients. If any major comparison gave insufficiently precise results, then the number of patients was increased to 20,000, then to 40,000, then to 100,000, then to 200,000, and so on as necessary until all major comparisons gave sufficiently precise results."* Chen et al[3] Pfizer believes this represents best practice. It is also observed that the standard deviation reported by the model results page is not an estimate of precision, including a quasi-standard error estimate would be useful in determining the precision of the model results.	many patients are needed to be run to stabilise model results to ensure the model is consistent between different runs of the model. The incremental cost effectiveness results, especially in a moderate RA population, are currently meaningless at the limited number of patients simulated. Pfizer suggests that there is significant variation in the result up to 10,000 patient's runs and possibly above and running the model for 1,000 patient runs in moderate is not sufficient to estimate sufficiently robust results. Pfizer requests the moderate RA population results in the TAR should be updated.	

Issue 15 Unrealistic assumption regarding patients on bDMARDs will recieve a hospital outpatient visit every month on combination bDMARDs + MTX and bDMARD monotherapy

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Pfizer notes that the total monthly cost of etanercept was estimated as £924.49. This was annualised by multiplying by 12. This leads to a total annual cost of £11,094 including methotrexate, administration, and monitoring. A relatively large proportion of this cost is driven by the monthly cost of monitoring, estimated at £134 based on a FBC (£3), hospital outpatient appointment (£128), and BCP (£3). Pfizer disagrees with the AG that etanercept + MTX and etanercept monotherapy patient will have an outpatient appointment every month. Pfizer suggests that this is a significant overestimate of the monitoring costs of etanercept and other subcutaneous bDMARDs. Pfizer suggest that original monitoring assumption used in TA130 is more applicable. It was assumed that monitoring would occur every 3 months after the first 12 weeks of treatment. [3] Pfizer suggest that this is not a plausible assumption, especially for etanercept monotherapy where there is not MTX concomitant treatment.	Pfizer suggest that the previous monitoring assumption should be used from Chen and colleagues and TA130 should be used, which suggest monitoring every 3 months after the first 12 weeks of treatment.[3]	This assumption is felt to overestimate the subcutaneous bDMARDs compared to MTX.

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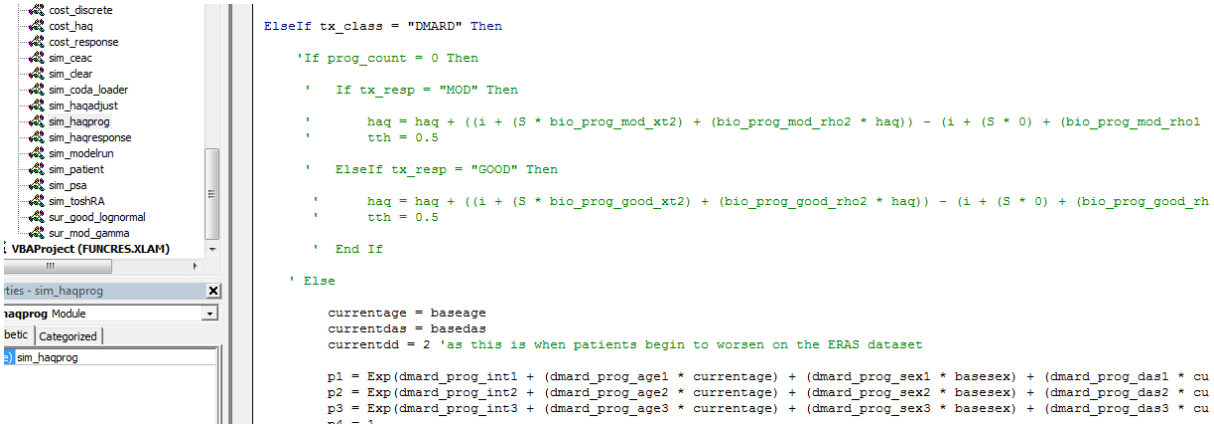
6. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, Connock M, Jobanputra P, Moore D, Fry-Smith A, Chen YF. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technol Assess. 2011 Mar;15(14):1-278. doi: 10.3310/hta15140.

Appendices

Appendix A: Error in HAQ progression for selecting the BSRBR progression

Error location: VBA module – haqprog, lines–253 to 267
Error consequence: BSRBR progression should not be included for cDMARDs:
Details: BSBR HAQ progression is being used for cDMARDs
Fix: Remove line 253-267 and the 'if' control statements on line 321

Figure 6: Section of haqprog sub procedure with error in the model selecting BSRBR HAQ progression between 6-12 months for cDMARDs



Appendix B: Model set-up for base case results run by Pfizer

SHEFFIELD RHEUMATOID ARTHRITIS MODEL

The University Of Sheffield.

MODEL VERSION: NICE MTA 2013

Load CODA | SIMULATION | CLEAR

Number of Patients	10000	Discount Costs	3.5%
Number of PSA runs	1	Discount QALYs	3.5%
Deterministic or Probabilistic?	Deterministic		
Infliximab Readministration (months)	1.85		
Rituximab Readministration (months)	9		
Mortality Hazard Ratio	1.33		
% of self-injectors needing district nurse	10%		
DMARD HAQ Progression (AST_DMARD)	0.06		
CODA start point (1 is default)	1		
Adverse event - bDMARD utility impact	0.0001		
Adverse event - bDMARD cost impact	£ 13.30		

Model Version	Debug mode
Utility model	Hernandez Mixture
Pain	NDB Quadratic Regression (Temporary)
Infusion Cost	£154 - Tocilizumab FAD
HAQ Adjust	Simulate
HAQ/EULAR Response	Fixed Values
Biologics Progression	Progression Model
CODA	EULAR main
Reference Sequence	SEQ1
Population	BSRBR Population
bDMARD monotherapy	Concomitant MTX

POPULATION CONTROLS

Minimum age	18	
HAQ Range	0	3
DAS Range	5.1	10
Previous DMARDs	2 previous monotherapy DMARDs	

	SEQ1	SEQ2	SEQ3	SEQ4	SEQ5	SEQ6	SEQ7	SEQ8	SEQ9	SEQ10
Treatment 1	MTX	ABT_MTX	ABTS_MTX	ADA_MTX	CTZ_MTX	ETN_MTX	GOL_MTX	IFX_MTX	TCZ_MTX	CON_DMA
Treatment 2	AST_DMAR	RTX_MTX	RTX_MTX	RTX_MTX	RTX_MTX	RTX_MTX	RTX_MTX	RTX_MTX	RTX_MTX	PC
Treatment 3	AST_DMAR	TCZ_MTX	TCZ_MTX	TCZ_MTX	TCZ_MTX	TCZ_MTX	TCZ_MTX	TCZ_MTX	MTX	PC
Treatment 4	AST_DMAR	MTX	MTX	MTX	MTX	MTX	MTX	MTX	AST_DMAR	AST_DMAR
Treatment 5	AST_DMAR	AST_DMAR	AST_DMAR	AST_DMAR	AST_DMAR	AST_DMAR	AST_DMAR	AST_DMAR	PC	AST_DMAR
Treatment 6	INT_CON_	MTX	AST_DMAR	MTX	INT_CON_	CON_DMA	PC	PC	INT_CON_	INT_CON_
Treatment 7	PC	AST_DMAR	PC	AST_DMAR	PC	PC	PC	PC	PC	PC

Appendix C: Error in HAQ progression for selecting the BSRBR progression and revised model results

Figure 7: Pfizer Base-case model run

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gainec	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death	MTX - AST	CON DMARD
SEQ1	3.268	2.476	£ 36,950	£ 28,283	11.813	£ 23,000	£ 17,729	£ 13,950	£ 10,554	11.81		
SEQ2	4.912	3.660	137302.492	107063.336	11.810	127672.871	99667.378	9629.623	7395.958	11.810	£ 66,577	£ 39,327
SEQ3	4.639	3.461	109172.457	86394.551	11.810	98872.119	78508.134	10300.339	7886.418	11.810	£ 59,006	£ 31,568
SEQ4	4.948	3.686	119768.779	93037.980	11.810	110229.510	85707.056	9539.270	7330.924	11.810	£ 53,511	£ 31,319
SEQ5	4.642	3.462	105555.516	82768.039	11.810	95184.899	74831.784	10370.618	7936.254	11.810	£ 55,265	£ 29,362
SEQ6	5.044	3.766	123897.029	96199.253	11.810	114554.222	89047.560	9342.808	7151.693	11.810	£ 52,674	£ 31,665
SEQ7	4.947	3.688	120143.872	93369.711	11.810	110615.504	86054.022	9528.369	7315.689	11.810	£ 53,717	£ 31,469
SEQ8	5.085	3.784	114027.626	88490.947	11.810	104782.062	81367.986	9245.564	7122.961	11.810	£ 46,054	£ 27,486
SEQ9	4.737	3.565	119227.085	94311.356	11.810	109130.186	86653.558	10096.900	7657.797	11.810	£ 60,638	£ 34,197
SEQ10	2.143	1.803	£ 45,913	£ 34,057	11.813	£ 27,916	£ 21,166	£ 17,997	£ 12,891	11.81		
st dev	0.913	0.625	£ 31,999	£ 25,403	0.001	£ 34,412	£ 27,062	£ 2,671	£ 1,797	0.00		

Figure 8: Results following removal of BSRBR-based code for HAQ cDMARD HAQ progression: Run 1

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gainec	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death	MTX - AST	CON DMARD
SEQ1	2.600	2.042	£ 38,125	£ 28,984	11.747	£ 22,873	£ 17,647	£ 15,252	£ 11,337	11.75		
SEQ2	4.744	3.552	£ 136,251	£ 106,338	11.747	£ 126,404	£ 98,808	£ 9,847	£ 7,529	11.75	£ 51,206	£ 40,780
SEQ3	4.514	3.392	£ 108,548	£ 85,876	11.747	£ 98,154	£ 77,956	£ 10,394	£ 7,920	11.75	£ 42,138	£ 32,167
SEQ4	4.831	3.614	£ 119,257	£ 92,594	11.747	£ 109,664	£ 85,244	£ 9,594	£ 7,350	11.75	£ 40,459	£ 31,935
SEQ5	4.473	3.362	£ 104,949	£ 82,264	11.747	£ 94,438	£ 74,267	£ 10,511	£ 7,996	11.75	£ 40,367	£ 30,502
SEQ6	4.954	3.711	£ 122,982	£ 95,484	11.747	£ 113,662	£ 88,358	£ 9,320	£ 7,126	11.75	£ 39,836	£ 31,825
SEQ7	5.021	3.753	£ 120,035	£ 93,181	11.747	£ 110,865	£ 86,148	£ 9,171	£ 7,033	11.75	£ 37,511	£ 29,984
SEQ8	4.722	3.536	£ 113,878	£ 88,278	11.747	£ 103,994	£ 80,724	£ 9,885	£ 7,554	11.75	£ 39,679	£ 30,896
SEQ9	4.590	3.486	£ 118,087	£ 93,527	11.747	£ 107,866	£ 85,840	£ 10,221	£ 7,687	11.75	£ 44,683	£ 34,867
SEQ10	2.107	1.776	£ 45,668	£ 33,907	11.747	£ 27,738	£ 21,052	£ 17,930	£ 12,855	11.75		
st dev	0.972	0.670	£ 31,520	£ 25,068	0.000	£ 34,156	£ 26,867	£ 2,785	£ 1,882	0.00		

Figure 9: Results following removal of BSRBR-based code for HAQ cDMARD HAQ progression: Run 2

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gained	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death		MTX - AST	CON DMARD
SEQ1	3.191	2.417	£ 36,926	£ 28,178	11.835	£ 23,036	£ 17,718	£ 13,891	£ 10,460	11.84			
SEQ2	4.875	3.631	£ 135,423	£ 105,628	11.835	£ 125,768	£ 98,239	£ 9,655	£ 7,390	11.84		£ 63,831	£ 38,502
SEQ3	4.631	3.451	£ 108,446	£ 85,703	11.835	£ 98,165	£ 77,858	£ 10,281	£ 7,845	11.84		£ 55,666	£ 30,757
SEQ4	5.083	3.777	£ 118,994	£ 92,364	11.835	£ 109,721	£ 85,255	£ 9,273	£ 7,110	11.84		£ 47,188	£ 29,065
SEQ5	4.604	3.429	£ 104,862	£ 82,084	11.835	£ 94,488	£ 74,178	£ 10,374	£ 7,906	11.84		£ 53,272	£ 28,971
SEQ6	5.003	3.726	£ 123,491	£ 95,723	11.835	£ 114,030	£ 88,486	£ 9,462	£ 7,237	11.84		£ 51,602	£ 31,547
SEQ7	4.960	3.698	£ 119,950	£ 93,018	11.835	£ 110,481	£ 85,791	£ 9,469	£ 7,227	11.84		£ 50,641	£ 30,610
SEQ8	4.808	3.578	£ 113,875	£ 88,199	11.835	£ 103,996	£ 80,640	£ 9,879	£ 7,558	11.84		£ 51,696	£ 29,965
SEQ9	4.728	3.550	£ 119,148	£ 93,893	11.835	£ 109,034	£ 86,239	£ 10,115	£ 7,654	11.84		£ 58,016	£ 33,646
SEQ10	2.099	1.773	£ 46,113	£ 34,096	11.835	£ 27,953	£ 21,146	£ 18,160	£ 12,950	11.84			
st dev	0.922	0.630	£ 31,666	£ 25,132	0.000	£ 34,083	£ 26,783	£ 2,684	£ 1,793	0.00			

Appendix D: Potential error in HAQ progression correctly defining patient characteristic variables ‘I’ and ‘s’

Error location: VBA module – haqprog, lines–253 to 267
Error consequence: variables ‘i’ and ‘S’ are not defined for cDMARD patients. These are empty when passed to code to estimate the change in HAQ and evaluated to 0.
Details: For cDMARD patients, VBA variables ‘i’ and ‘S’ are not defined when used in the BSRBR analysis (**Error! Reference source not found.**).
Fix: If BSRBR progression should be included here for cDMARDs: Define ‘i’ and ‘S’ as per the code for bDMARDs in 197-191

Figure 10: Section of haqprog sub procedure which may contain error

```
ElseIf tx_class = "DMARD" Then

    If prog_count = 0 Then

       If tx_resp = "MOD" Then

           haq = haq + ((i + (S * bio_prog_mod_xt2) + (bio_prog_mod_rho2 * haq)) - (i + (S * 0) + (bio_prog_mod_rho1 * phaq)))
           tth = 0.5

       ElseIf tx_resp = "GOOD" Then

          haq = haq + ((i + (S * bio_prog_good_xt2) + (bio_prog_good_rho2 * haq)) - (i + (S * 0) + (bio_prog_good_rho1 * phaq)))
          tth = 0.5

       End If
    |
   Else

        currentage = baseage
        currentdas = basedas
        currentdd = 2 'as this is when patients begin to worsen on the ERAS dataset

        p1 = Exp(dmard_prog_int1 + (dmard_prog_age1 * currentage) + (dmard_prog_sex1 * basesex) + (dmard_prog_das1 * currentdas) + (dmard_prog_dd1 * currentdd))
        p2 = Exp(dmard_prog_int2 + (dmard_prog_age2 * currentage) + (dmard_prog_sex2 * basesex) + (dmard_prog_das2 * currentdas) + (dmard_prog_dd2 * currentdd))
        p3 = Exp(dmard_prog_int3 + (dmard_prog_age3 * currentage) + (dmard_prog_sex3 * basesex) + (dmard_prog_das3 * currentdas) + (dmard_prog_dd3 * currentdd))
        p4 = 1
```

This is the BSRBR analysis. Note it is only called on the first loop and only for EULAR Good/moderate responders; but **i and S are not defined for cDMARDs**

Both i and S evaluate to 0 for the MTX strategy. For bDMARD strategies, i and S used in previous (bDMARD) loops are used, because these are not destroyed at the end of each call to the procedure

This it the beginning of the Norton et al/ ERAS analysis used subsequently

Appendix E: Error in the time to withdrawal (drug survival) using Chen et al instead of being a function of EULAR response for cDMARDs

Error location: VBA module – simulation_toshRA, lines – 512 to 514
Error consequence: Assessment Group report states time to withdrawal is based on ELAUR response. Instead, estimates from Chen et al 2006 are used
Details: Time to withdrawal is based on Chen et al. instead of being a function of EULAR response.
Fix: Remove code limiting the use of EULAR-based time to withdrawal to biologics.

Figure 11: Error in the time to withdrawal for cDMARDs in the simulation_toshRA module

```
'===========TX PROGRESSION TO WITHDRAWAL===========

        'There is a response and so use a loop to estimate progression (costs and HAQ changes) while on treatment

        'set time to event parameters

        'This code was being run even when there was non response
        'matt has added this code
        If tx_resp <> "NONE" Then
            'If tx_class = "BIO" Then
                If tx_resp = "GOOD" Then
                    Call survival_ln(ttw, currentdmards, haq, t, r_tx)
                Else
                    Call survival_gamma(ttw, currentdmards, haq, t, r_tx)
                End If
                ttw = ttw - withdraw_time
           ' Else
           '     ttw = tx_time - withdraw_time
           ' End If

            If ttw < 0 Then
                 ttw = 0
            End If
```

Appendix F: Model base case results and error in time to withdrawal (drug survival) corrected

Figure 12 Pfizer Base-case model run

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gainec	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death	MTX - AST	CON DMARD
SEQ1	3.268	2.476	£ 36,950	£ 28,283	11.813	£ 23,000	£ 17,729	£ 13,950	£ 10,554	11.81		
SEQ2	4.912	3.660	137302.492	107063.336	11.810	127672.871	99667.378	9629.623	7395.958	11.810	£ 66,577	£ 39,327
SEQ3	4.639	3.461	109172.457	86394.551	11.810	98872.119	78508.134	10300.339	7886.418	11.810	£ 59,006	£ 31,568
SEQ4	4.948	3.686	119768.779	93037.980	11.810	110229.510	85707.056	9539.270	7330.924	11.810	£ 53,511	£ 31,319
SEQ5	4.642	3.462	105555.516	82768.039	11.810	95184.899	74831.784	10370.618	7936.254	11.810	£ 55,265	£ 29,362
SEQ6	5.044	3.766	123897.029	96199.253	11.810	114554.222	89047.560	9342.808	7151.693	11.810	£ 52,674	£ 31,665
SEQ7	4.947	3.688	120143.872	93369.711	11.810	110615.504	86054.022	9528.369	7315.689	11.810	£ 53,717	£ 31,469
SEQ8	5.085	3.784	114027.626	88490.947	11.810	104782.062	81367.986	9245.564	7122.961	11.810	£ 46,054	£ 27,486
SEQ9	4.737	3.565	119227.085	94311.356	11.810	109130.186	86653.558	10096.900	7657.797	11.810	£ 60,638	£ 34,197
SEQ10	2.143	1.803	£ 45,913	£ 34,057	11.813	£ 27,916	£ 21,166	£ 17,997	£ 12,891	11.81		
st dev	0.913	0.625	£ 31,999	£ 25,403	0.001	£ 34,412	£ 27,062	£ 2,671	£ 1,797	0.00		

Figure 11: Error corrected in the time to withdrawal (drug survival)

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gainec	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death	MTX - AST	CON DMARD
SEQ1	3.250	2.469	£ 36,812	£ 28,199	11.780	£ 22,950	£ 17,707	£ 13,862	£ 10,492	11.78		
SEQ2	4.661	3.471	£ 133,753	£ 104,470	11.780	£ 124,619	£ 97,432	£ 9,133	£ 7,039	11.78	£ 76,145	£ 47,123
SEQ3	4.471	3.333	£ 107,722	£ 85,313	11.780	£ 98,001	£ 77,841	£ 9,721	£ 7,472	11.78	£ 66,107	£ 37,938
SEQ4	4.701	3.502	£ 118,492	£ 92,190	11.780	£ 109,497	£ 85,251	£ 8,995	£ 6,938	11.78	£ 61,954	£ 38,241
SEQ5	4.468	3.330	£ 104,074	£ 81,683	11.780	£ 94,345	£ 74,203	£ 9,729	£ 7,480	11.78	£ 62,135	£ 35,388
SEQ6	4.825	3.598	£ 122,331	£ 95,094	11.780	£ 113,783	£ 88,511	£ 8,548	£ 6,582	11.78	£ 59,240	£ 37,766
SEQ7	4.743	3.532	£ 119,316	£ 92,750	11.780	£ 110,429	£ 85,894	£ 8,887	£ 6,856	11.78	£ 60,702	£ 37,856
SEQ8	4.652	3.463	£ 113,137	£ 87,732	11.780	£ 103,955	£ 80,648	£ 9,182	£ 7,084	11.78	£ 59,909	£ 36,279
SEQ9	4.549	3.421	£ 116,529	£ 92,414	11.780	£ 107,057	£ 85,221	£ 9,473	£ 7,193	11.78	£ 67,453	£ 40,501
SEQ10	2.348	1.954	£ 44,419	£ 32,987	11.780	£ 27,235	£ 20,667	£ 17,184	£ 12,320	11.78		
st dev	0.769	0.517	£ 31,511	£ 25,042	0.000	£ 33,987	£ 26,749	£ 2,655	£ 1,796	0.00		

Appendix G: Error in the HAQ to pain relationship estimated for the ERAS relationship

Error location: VBA module – calc_qaly, lines–90
Error consequence: variable 'pain_switch' is not defined, so pain is never divided by 100, which is erroneous for the ERAS HAQ to pain relationship scenario
Details: Although a named range 'pain_swich' exists in the spreadsheet, this is never actually defined in the code, so is 'Empty' when evaluated in line 90 (Figure).
Fix: Change 'pain_switch' to 'range("pain_switch").value'

Figure 14: code from qaly sub procedure, showing variable pain_switch is not defined

```
'Hernandez Utility Parameters (62.82 is the mean age of the sample in the Hernandez study)
If pain_switch = 1 Then
  pain_switch = Empty _c + (haq * pain_coef) + (pain_coef2 * haq ^ 2)) / 100
Else
    pain = pain_c + (haq * pain_coef) + (pain_coef2 * haq ^ 2)
End If

currentage = ((baseage + t) - 62.82) / 10
```

Appendix H: Results from the ERAS HAQ to pain algorithm and results with error corrected

Figure 15: Results from running with ERAS HAQ to pain algorithm (as described in the AG report but for which there is a possible error)

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gainec	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death	MTX - AST	CON DMARD
SEQ1	1.073	0.819	£ 37,218	£ 28,442	11.866	£ 23,099	£ 17,774	£ 14,119	£ 10,668	11.87		
SEQ2	2.193	1.611	136317.030	106231.443	11.866	126641.979	98804.991	9675.052	7426.452	11.866	£ 98,237	£ 67,545
SEQ3	2.018	1.485	109362.643	86366.755	11.866	98992.170	78420.460	10370.474	7946.295	11.866	£ 87,064	£ 55,481
SEQ4	2.215	1.626	119984.418	93101.016	11.866	110376.438	85722.900	9607.981	7378.116	11.866	£ 80,131	£ 54,442
SEQ5	2.023	1.488	105602.016	82640.128	11.866	95286.305	74732.275	10315.712	7907.852	11.866	£ 81,010	£ 51,305
SEQ6	2.343	1.722	123874.686	96006.518	11.866	114474.478	88807.978	9400.208	7198.540	11.866	£ 74,825	£ 52,465
SEQ7	2.213	1.626	119942.361	93073.844	11.866	110293.970	85677.700	9648.392	7396.144	11.866	£ 80,083	£ 54,409
SEQ8	2.387	1.743	114903.526	88751.361	11.866	105718.183	81671.659	9185.344	7079.703	11.866	£ 65,262	£ 45,477
SEQ9	2.091	1.564	117655.058	93222.898	11.866	107395.861	85462.153	10259.198	7760.745	11.866	£ 86,926	£ 57,859
SEQ10	0.628	0.546	£ 46,362	£ 34,317	11.866	£ 28,016	£ 21,202	£ 18,345	£ 13,115	11.87		
st dev	0.555	0.384	£ 31,718	£ 25,160	0.000	£ 34,211	£ 26,871	£ 2,764	£ 1,855	0.00		

Figure 16: Results from running with ERAS HAQ to pain algorithm (with error in use of pain_switch corrected)

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gainec	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death	MTX - AST	CON DMARD
SEQ1	5.489	4.169	£ 36,179	£ 27,779	11.658	£ 22,709	£ 17,563	£ 13,470	£ 10,216	11.66		
SEQ2	6.473	4.880	133035.165	104241.689	11.658	123743.184	97086.765	9291.983	7154.923	11.658	£ 107,550	£ 60,984
SEQ3	6.324	4.769	107992.606	85664.898	11.658	98088.915	78063.371	9903.693	7601.527	11.658	£ 96,395	£ 49,690
SEQ4	6.503	4.902	117336.060	91544.377	11.658	108150.477	84474.584	9185.584	7069.793	11.658	£ 87,009	£ 49,100
SEQ5	6.325	4.769	104235.555	81960.836	11.658	94274.804	74308.447	9960.752	7652.389	11.658	£ 90,220	£ 46,156
SEQ6	6.562	4.948	121994.711	95008.958	11.658	113024.696	88102.749	8970.016	6906.209	11.658	£ 86,261	£ 50,062
SEQ7	6.501	4.902	118307.004	92221.626	11.658	109053.999	85107.714	9253.005	7113.912	11.658	£ 87,942	£ 49,677
SEQ8	6.594	4.964	112770.336	87699.462	11.658	103899.609	80841.263	8870.728	6858.199	11.658	£ 75,369	£ 43,551
SEQ9	6.361	4.818	115358.098	91720.215	11.658	105543.638	84266.798	9814.461	7453.417	11.658	£ 98,532	£ 53,017
SEQ10	4.740	3.721	£ 45,071	£ 33,563	11.658	£ 27,504	£ 20,932	£ 17,567	£ 12,632	11.66		
st dev	0.569	0.388	£ 31,252	£ 24,908	0.000	£ 33,630	£ 26,551	£ 2,635	£ 1,782	0.00		

Appendix I: Errors in the mortality used in the model

Error location: Sheet – Mortality, Column I
Error consequence: Female survival is not used in the model
Details: 'Vlookups' in column I both use column index 3, meaning female life-table data will never be selected (**Error! Reference source not found.**).
Fix: Second vlookup should index column 5

Figure 17: Estimation of mortality error; note that the vlookups use the same column index number, meaning that the female probabilities are never used

SUM =IF(basesex = 0, VLOOKUP(H25,$A$9:$E$109,3),VLOOKUP(H25,$A$9:$E$109,3))

	A	B	C	D	E	F	G	H	I	J	K	L
1	Interim Life Tables, England & Wales							0				
2								38				
3	Period expectation of life											
4	Based on data for the years 2009-2011											
5												
6		Males		Female								
7	Age		LIVE		LIVE							
8	x	q_x	q_x	q_x	q_x							
12	3	0.000123	0.000492	0.000134	0.000536		0.5	.5-.875	1.5	1.5	2.5	
13	4	0.000102	0.000408	0.000113	0.000452		1	1-1.375	1.8	1.8	2.9	
14	5	0.000115	0.000460	0.000090	0.000360		1	1.5-1.875	2.7	2.7	4.5	
15	6	0.000092	0.000368	0.000083	0.000332		2	2-2.375	4.0	4.0	7.0	
16	7	0.000074	0.000296	0.000069	0.000276		2.5	2.5-3	5.5	5.5	11.5	
17	8	0.000105	0.000420	0.000076	0.000304			RAND (PSA)	0.864	0.864		
18	9	0.000101	0.000404	0.000081	0.000324							
19	10	0.000088	0.000352	0.000063	0.000252							
20	11	0.000092	0.000368	0.000085	0.000340							
21	12	0.000107	0.000428	0.000094	0.000376				hr	4		
22	13	0.000109	0.000436	0.000088	0.000352				Age at Dea	75		37
23	14	0.000136	0.000544	0.000124	0.000496							
24	15	0.000199	0.000796	0.000131	0.000524					RN		
25	16	0.000240	0.000960	0.000156	0.000624			38	=IF(basese	0.470723	999	
26	17	0.000378	0.001512	0.000188	0.000752			39	0.00568	0.577855	999	
27	18	0.000477	0.001908	0.000205	0.000820			40	0.006248	0.648272	999	
28	19	0.000476	0.001904	0.000212	0.000848			41	0.006612	0.660058	999	
29	20	0.000531	0.002124	0.000209	0.000836			42	0.007172	0.862719	999	
30	21	0.000592	0.002368	0.000216	0.000864			43	0.007416	0.781199	999	
31	22	0.000563	0.002252	0.000205	0.000820			44	0.00854	0.407785	999	
32	23	0.000577	0.002308	0.000249	0.000996			45	0.009052	0.265057	999	
33	24	0.000564	0.002256	0.000239	0.000956			46	0.009468	0.861611	999	
34	25	0.000609	0.002436	0.000272	0.001088			47	0.009684	0.517916	999	
35	26	0.000626	0.002504	0.000276	0.001104			48	0.010836	0.728408	999	
36	27	0.000623	0.002492	0.000322	0.001288			49	0.011744	0.957839	999	
37	28	0.000700	0.002800	0.000334	0.001336			50	0.012632	0.937553	999	
38	29	0.000723	0.002892	0.000317	0.001268			51	0.014308	0.633843	999	
39	30	0.000792	0.003168	0.000378	0.001512			52	0.015956	0.451669	999	

Error location: Sheet – Mortality, Column I

Error consequence: 'Cap' at age 101 is not included in the vlookups for probabilities
Details: The range used by the vlookups in column I do not include age 101, therefore the probability of death at this age (which is 100%) is never used (**Error! Reference source not found.**).
Fix: Extend table range by one row (to include row 110) in both vlookups in column I

Error location: Sheet – Mortality, Column C and E
Error consequence: Annual probability of mortality exceeds 1
Details: Hazard ratios are treated like relative risks, and therefore probabilities exceeding 1 are generated at older ages (**Error! Reference source not found.**)
Fix: Convert annual probabilities to rates, apply hazard ratio, then convert back to probability. We used the actuarial formula to achieve this: assuming a time of 1-year, $rate = -(\ln(1-p))$, and $p = 1 - e^{-rate}$. We also change column k

Figure 18: Probabilities of death exceeding 1

	Males		Female	
Age		**LIVE**		**LIVE**
x	q_x	q_x	q_x	q_x
86	0.112992	0.451968	0.085749	0.342996
87	0.127193	0.508772	0.095838	0.383352
88	0.140875	0.563500	0.107790	0.431160
89	0.160713	0.642852	0.121602	0.486408
90	0.166367	0.665468	0.135352	0.541408
91	0.178196	0.712784	0.146525	0.586100
92	0.188878	0.755512	0.160748	0.642992
93	0.214681	0.858724	0.180517	0.722068
94	0.237662	0.950648	0.202789	0.811156
95	0.256292	1.025168	0.223947	0.895788
96	0.275704	1.102816	0.240167	0.960668
97	0.294811	1.179244	0.259706	1.038824
98	0.315562	1.262248	0.278215	1.112860
99	0.327281	1.309124	0.296932	1.187728
100	0.344584	1.378336	0.318222	1.272888
101	1	4	1	4

Appendix J: Base case results and results with mortality error corrected

Figure 19: Pfizer Base-case model run

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gainec	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death	MTX - AST	CON DMARD
SEQ1	3.268	2.476	£ 36,950	£ 28,283	11.813	£ 23,000	£ 17,729	£ 13,950	£ 10,554	11.81		
SEQ2	4.912	3.660	137302.492	107063.336	11.810	127672.871	99667.378	9629.623	7395.958	11.810	£ 66,577	£ 39,327
SEQ3	4.639	3.461	109172.457	86394.551	11.810	98872.119	78508.134	10300.339	7886.418	11.810	£ 59,006	£ 31,568
SEQ4	4.948	3.686	119768.779	93037.980	11.810	110229.510	85707.056	9539.270	7330.924	11.810	£ 53,511	£ 31,319
SEQ5	4.642	3.462	105555.516	82768.039	11.810	95184.899	74831.784	10370.618	7936.254	11.810	£ 55,265	£ 29,362
SEQ6	5.044	3.766	123897.029	96199.253	11.810	114554.222	89047.560	9342.808	7151.693	11.810	£ 52,674	£ 31,665
SEQ7	4.947	3.688	120143.872	93369.711	11.810	110615.504	86054.022	9528.369	7315.689	11.810	£ 53,717	£ 31,469
SEQ8	5.085	3.784	114027.626	88490.947	11.810	104782.062	81367.986	9245.564	7122.961	11.810	£ 46,054	£ 27,486
SEQ9	4.737	3.565	119227.085	94311.356	11.810	109130.186	86653.558	10096.900	7657.797	11.810	£ 60,638	£ 34,197
SEQ10	2.143	1.803	£ 45,913	£ 34,057	11.813	£ 27,916	£ 21,166	£ 17,997	£ 12,891	11.81		
st dev	0.913	0.625	£ 31,999	£ 25,403	0.001	£ 34,412	£ 27,062	£ 2,671	£ 1,797	0.00		

Figure 20: Base-case model run with mortality error corrected

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gainec	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death	MTX - AST	CON DMARD
SEQ1	3.809	2.784	£ 44,391	£ 32,767	14.128	£ 27,238	£ 20,259	£ 17,152	£ 12,508	14.13		
SEQ2	5.791	4.165	£ 159,518	£ 120,462	14.128	£ 147,606	£ 111,666	£ 11,912	£ 8,795	14.13	£ 63,484	£ 35,774
SEQ3	5.492	3.959	£ 126,780	£ 97,339	14.128	£ 114,088	£ 88,004	£ 12,692	£ 9,335	14.13	£ 54,919	£ 28,057
SEQ4	5.848	4.207	£ 141,321	£ 106,326	14.128	£ 129,622	£ 97,681	£ 11,698	£ 8,645	14.13	£ 51,673	£ 28,945
SEQ5	5.455	3.933	£ 123,156	£ 93,740	14.128	£ 110,387	£ 84,345	£ 12,768	£ 9,394	14.13	£ 53,059	£ 26,643
SEQ6	6.154	4.432	£ 144,864	£ 108,990	14.128	£ 133,779	£ 100,807	£ 11,085	£ 8,183	14.13	£ 46,240	£ 27,417
SEQ7	5.819	4.190	£ 140,960	£ 106,090	14.128	£ 129,139	£ 97,364	£ 11,821	£ 8,726	14.13	£ 52,128	£ 29,057
SEQ8	5.887	4.236	£ 133,312	£ 100,010	14.128	£ 121,679	£ 91,424	£ 11,633	£ 8,586	14.13	£ 46,283	£ 25,858
SEQ9	5.558	4.043	£ 135,283	£ 104,047	14.128	£ 122,677	£ 94,866	£ 12,606	£ 9,181	14.13	£ 56,587	£ 30,104
SEQ10	2.279	1.916	£ 56,134	£ 40,006	14.128	£ 33,320	£ 24,372	£ 22,813	£ 15,633	14.13		
st dev	1.152	0.757	£ 36,514	£ 28,187	0.000	£ 39,600	£ 30,226	£ 3,462	£ 2,227	0.00		

Appendix K: Results using Palliative care as the last therapy in the in each treatment sequence instead of 'assorted DMARDs'

Figure 21 Pfizer Base-case model run using 'assorted DMARDs' as the last treatment in each sequence

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gainec	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death	MTX - AST	CON DMARD
SEQ1	3.268	2.476	£ 36,950	£ 28,283	11.813	£ 23,000	£ 17,729	£ 13,950	£ 10,554	11.81		
SEQ2	4.912	3.660	137302.492	107063.336	11.810	127672.871	99667.378	9629.623	7395.958	11.810	£ 66,577	£ 39,327
SEQ3	4.639	3.461	109172.457	86394.551	11.810	98872.119	78508.134	10300.339	7886.418	11.810	£ 59,006	£ 31,568
SEQ4	4.948	3.686	119768.779	93037.980	11.810	110229.510	85707.056	9539.270	7330.924	11.810	£ 53,511	£ 31,319
SEQ5	4.642	3.462	105555.516	82768.039	11.810	95184.899	74831.784	10370.618	7936.254	11.810	£ 55,265	£ 29,362
SEQ6	5.044	3.766	123897.029	96199.253	11.810	114554.222	89047.560	9342.808	7151.693	11.810	£ 52,674	£ 31,665
SEQ7	4.947	3.688	120143.872	93369.711	11.810	110615.504	86054.022	9528.369	7315.689	11.810	£ 53,717	£ 31,469
SEQ8	5.085	3.784	114027.626	88490.947	11.810	104782.062	81367.986	9245.564	7122.961	11.810	£ 46,054	£ 27,486
SEQ9	4.737	3.565	119227.085	94311.356	11.810	109130.186	86653.558	10096.900	7657.797	11.810	£ 60,638	£ 34,197
SEQ10	2.143	1.803	£ 45,913	£ 34,057	11.813	£ 27,916	£ 21,166	£ 17,997	£ 12,891	11.81		
st dev	0.913	0.625	£ 31,999	£ 25,403	0.001	£ 34,412	£ 27,062	£ 2,671	£ 1,797	0.00		

Figure 22: Model run with 'palliative care' as the last treatment in the sequence

DETERMINISTIC	QALYs	Discounted QALYs	Cost	Discounted Cost	Life Years Gainec	Treatment Costs	Discounted Treatment Costs	HAQ related Costs	Discounted HAQ related Costs	Age at Death	MTX - AST	CON DMARD
SEQ1	2.695	2.184	£ 53,452	£ 38,175	14.021	£ 32,409	£ 23,704	£ 21,044	£ 14,471	14.02		
SEQ2	5.886	4.268	£ 158,595	£ 119,753	14.021	£ 147,102	£ 111,371	£ 11,494	£ 8,382	14.02	£ 39,135	£ 37,152
SEQ3	5.483	4.003	£ 126,975	£ 97,038	14.021	£ 114,379	£ 87,952	£ 12,595	£ 9,086	14.02	£ 32,363	£ 30,465
SEQ4	5.655	4.106	£ 140,032	£ 105,230	14.021	£ 127,955	£ 96,436	£ 12,077	£ 8,794	14.02	£ 34,883	£ 32,955
SEQ5	5.280	3.862	£ 123,787	£ 93,734	14.021	£ 110,631	£ 84,266	£ 13,155	£ 9,468	14.02	£ 33,116	£ 31,024
SEQ6	5.853	4.248	£ 144,931	£ 108,819	14.021	£ 133,351	£ 100,380	£ 11,580	£ 8,439	14.02	£ 34,231	£ 32,460
SEQ7	5.736	4.162	£ 141,038	£ 105,951	14.021	£ 129,195	£ 97,324	£ 11,843	£ 8,627	14.02	£ 34,258	£ 32,412
SEQ8	5.632	4.087	£ 134,234	£ 100,487	14.021	£ 122,098	£ 91,646	£ 12,135	£ 8,841	14.02	£ 32,751	£ 30,912
SEQ9	5.491	4.052	£ 137,364	£ 105,126	14.021	£ 124,660	£ 96,081	£ 12,704	£ 9,045	14.02	£ 35,844	£ 33,813
SEQ10	2.508	2.082	£ 54,106	£ 38,532	14.021	£ 32,408	£ 23,704	£ 21,697	£ 14,828	14.02		
st dev	1.223	0.794	£ 35,031	£ 27,288	0.000	£ 38,688	£ 29,610	£ 3,704	£ 2,347	0.00		