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

Issue 1 Transparency

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
There is a general lack of transparency in the model. The report provides limited information on the detailed design of the model, such as how time to events are drawn and how different sequences of events are accounted for in the model. Similarly, the VBA codes contain very few notes describing the model, making it difficult to review in detail. Parameterisation also lacks transparency. For instance, treatment survival has only been discussed briefly in the report and there is no formula provided.	Detailed information on the modelling approach, VBA codes, and parameterisation should be provided.	Not applicable.

Issue 2 Random Number draws

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
By using worksheet rand() functions rather than pre-defining the seed and populating the random numbers, the model's results are not consistent across runs (convergence happens eventually but still not exact) and this is a source of unnecessary stochastic variability across	Random numbers should be generated in VBA so that the model can be re-run to provide consistent results.	Not applicable.

replications and runs.		

Issue 3 CODA sheets

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
One step of the CODA macro is to copy the results from the different CODA sheets into the Effectiveness worksheet. CODA 5, CODA 6, CODA 7, and CODA 9 reference the wrong columns and copy in blank results.	Correction to the sheets required.	Not applicable.

Issue 4 Constant mortality

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
For each patient followed, a unique time to death is drawn and this time to death applies regardless of which treatments are given. In the AG report, it states that 'little data have been published on the relationship between change in HAQ and change in expected mortality, which is the key relationship that is required if there is to be proof that a [*sic*] increase in HAQ score is associated with a [*sic*] increase in mortality'. Following the AG's logic, it can be inferred	Further justification needs to be provided for the logic behind the assumption of a constant mortality, as well as the description of the model implementation.	Not applicable.

that only one HAQ score during patient life time is relevant to mortality; that is the HAQ at treatment initiation, given that change in HAQ does not affect mortality. Nevertheless, different initial HAQ scores have been used for population 1 (COMET trial, mean 1.7) and population 2/3 (BSRBR, mean 2.0), contradicting this assumption. If the model logic were to be followed, mortality should have been associated with the HAQ at initiation before each treatment line.		

Issue 5 Discounting

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model has employed several types of discounting: • For discrete treatments (i.e. those that require intravenous administration): discounted at the end of the administration period • For continuous treatments (i.e. those that require subcutaneous or oral administration): continuous compounding has been used, which means that the cost occurs at each moment during a period • For response cost (including cost	The discounting approach may require harmonisation.	It is not easy to check the exact impact on the results due to the design of the model (an individual patient simulation) and how random numbers are generated. Nevertheless, assuming a total of £1,000 occurs at 6 months, continuous over 6 months, or occurs at 3 months, the discounted cost at baseline is £982.95, £991.45, or £991.44, respectively. It is unclear what the cumulative effect of these inconsistencies will be.

of medications, response, and pre-treatment over the first 6 month period from initiation of a treatment line), the cost is discounted at the mid-point of the treatment period (i.e. 3 months) The justification for discounting is not provided. Nevertheless, when looking at golimumab (subcutaneous) and tocilizumab (intravenous), they are administered at sufficiently similar intervals (one month or four weeks). Following the logic in the model, the cost of golimumab is assumed to occur continuously over the time period, and the cost of tocilizumab will only occur at administration, leading to discrepancies in discounting factors. As for the response cost, it is unclear why it is discounted at 3 months. The cost of medication in the response cost does not occur aggregately at 3 months.		

Issue 6 VBA: `sim_toshRA` module

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Line 353/360: for the response assessment of certolizumab, it states that 'code to exclude the first 12 weeks of CTX treatment' but in the formula, it is 13.99/52. It is unclear why 13.99 is used.	Clarification needs to be provided. If it is incorrect, rectification is needed.	It is not easy to check the exact impact on the results due to the design of the model (an individual patient simulation) and how random numbers are generated. For discounting, the discount factor is 0.9829

Line 374/376: for the cost of subcutaneous abatacept + methotrexate, a loading dose at initiation is considered. However this cost is discounted at response (`tx_r_t`, i.e. 6 months). Should not the discounting be applied at treatment initiation?	The cost should be discounted at treatment initiation.	at 6 months (periodic), 0.9914 at 3 months (periodic), and 1.0000 at baseline. The cost of the initiation or the loading dose is therefore underestimated. With regard to the misspelling of `CON_DMARD`, the model has been rerun for 10,000 patients, using population 1 with the exact inputs as received from NICE. The results vs. `SEQ10` (`CON_DMARD` → `INT_CON_DMARD` → `2CON_DMARD` → `PC` → `AST_DMARD` → `INT_CON_DMARD` → `PC`) have changed slightly. It is unclear whether these settings are AG's base case.
Line 385/388: similarly, for the cost of intravenous abatacept + methotrexate, a loading dose at week 2 is considered. However it is discounted at `tx_r_t+2/52`.	The same as above.	
Line 413: for time to HAQ progression, `CON_DMARD` is misspelled as `CON-DMARD`.	This needs to be rectified.	
Line 503: response cost (cost of medications, response, and pre-treatment over the first 6 months) is only applied to continuous treatments. It seems that this should be applied to discrete treatments as well, so that the cost of response and pre-treatment over the first 6 months can be accounted for.	Justification is needed. If it is incorrect, rectification is needed.	
Line 673/676/678: costs and disutilities associated with adverse events are not discounted (the same costs and disutilities have been used).	It is understood that this might be due to the fact that the cost (£13.30) and the utility weight (0.0001) are relatively small. Nevertheless, it has to be clearly noted and considered as a limitation.	
In multiple places, the code of the function overrides user defined values. This is not transparent. If death occurs during the response period some treatments administrations are overridden resulting in differing dosing changes to different	Justification is needed. If it is incorrect, rectification is needed.	

treatments. Baseline HAQ draws: Since HAQ is a discrete distribution, draws from HAQ should be done in a discrete not continuous manner.		

Issue 7 VBA: `sim_haqprog` module

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Line 199: for moderate responders, it is noted in the VBA codes that '[n]othing happens to HAQ at first cycle (`prog_count = 0`) because this is called when it's the response time' but the code indicates that HAQ is adjusted. Variable `phaq` (presumably previous HAQ score): `phaq` does not take a value at the beginning of the module. In a test run, it seems that in the first cycle of the first patient it has a value of 0, and in the first cycle of subsequent patients it maintains the value in the last cycle of the previous patient.	Justification is needed. If it is incorrect, rectification is needed. Justification is needed. If it is incorrect, rectification is needed.	It is not easy to check the exact impact on the results due to the design of the model (an individual patient simulation) and how random numbers are generated.

Issue 8 VBA: `calc_qaly` module

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In the model, `basesex = 1` refers to a woman and `basesex = 0` refers to a man. There are many instances in this module where the dummy variable `basesex - 1` is used, i.e. the value can be either 0 or -1. No publication available to provide the hardcoded values and recursion within the Hernandez mixture and normal algorithms. This impedes the ability to review.	Justification is needed. If it is incorrect, rectification is needed.	It is not easy to check the exact impact on the results due to the design of the model (an individual patient simulation) and how random numbers are generated.

Issue 9 Excel: `Costs` sheet

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Although not directly used, cells `B3`, `B4`, `B27` and `B28` should be `DISCRETE` instead of `CONTINUOUS` (abatacept or tocilizumab +/- methotrexate).	It needs to be rectified for consistency.	It is not easy to check the exact impact on the results due to the design of the model (an individual patient simulation) and how random numbers are generated.
Different number of weeks per year has been used (e.g. 52.1775 in cell `K5` and 52.25 in cell `G21`, whereas 52 has been used in the VBA codes).	It needs to be rectified for consistency.	
Although not used, it is unclear why the response period cost for infliximab (cell `G18`) is based on five times the monthly	Justification is needed. If it is incorrect, rectification is needed.	

cost, when the response period is 6 months. For TICORA (methotrexate, prednisolone and sulfasalazine), a cost of £98.06 has been applied in addition to the administration costs and other costs (cells `G29` and `I29`). It is noted that this cost is the '[a]verage costs […] per month for HCQ used'. Is this correct? There is no mention of this cost in the report.	Justification is needed. If it is incorrect, rectification is needed.	

Issue 10 Excel: `Progression` sheet

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
It is unclear why good response and moderate response have the same variance-covariance matrix for Cholesky decomposition. It is stated in the report that they are regressed separately. In the variance-covariance matrix, cell `J3` should correspond to the variance of intercept. However, this value (0.0025) is different from the value in cell `F31` (0.2593), which is described as `VAR I`. The same is true for the variance of slope (cells `K4` and `F33`) and the covariance between the intercept and the slope (cells `J4` and `F32`).	Clarification is needed. Clarification is needed.	Not applicable.

Issue 11 Excel: `Lifetables` sheet

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In cells `I25:I108`, the `VLOOKUP` formula is incorrectly implemented. The model uses the mortality of males, regardless of the sex of the sampled patient.	Rectification is needed.	It is not easy to check the exact impact on the results due to the design of the model (an individual patient simulation) and how random numbers are generated.
In addition, the `table_array` field of the `VLOOKUP` formula should be until age 101, as the table suggests.	Rectification is needed.	When assuming a patient enters the model at 50 years old, with an initial HAQ score between 2 and 2.375 (hazard ratio 4.0), the life expectancy is underestimated for females by approximately 3.4 years (by sampling 1,000 patients). As female patients account for approximately three quarters of the target population, this may have some impact on the results.