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

All results presented are for the population 2 (severe MTX-experienced)

Issue 1

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model is not user-friendly and has been coded in a convoluted way which makes it difficult to assess the accuracy of the modelling. It is therefore difficult to determine whether an appropriate process has been followed. Key issues were: • Many of the model inputs are not referenced. • The VBA code is not explained; as a result it is time consuming to work out what the code is supposed to be doing before checking it is doing this! • The model is not as efficient as it could be. If the manufacturer wants to run 5,000 patients, it takes approximately 50 minutes to run (and the user is unable to use other Office applications while this is running). If you want to make a change to the model and check this change, it takes a long time.	Reference the model inputs. Provide explanation for the VBA code so it is transparent, through the use of comments Provide a tornado diagram to demonstrate clearly to which variables the model is most sensitive. Amend the model to make it more efficient by: • the use of ".copy" and ".PasteSpecial" uses the clip board when recording results however when just recording results using ".value" is quicker and less computer intensive • Reduce the unnecessary use of variables, for example: instead of using the line "bio_prog_mod_i = Range("bio_prog_mod_i").Value and using the variable bio_prog_mod_i in calculations, simply using Range("bio_prog_mod_i").Value in the calculations would save defining each variable.	Although these changes would not themselves have directly changed the results, they may have facilitated additional insight and potentially the detection of further issues. Improving the transparency of the model would have increased the ability of manufacturers to understand and quality check the model. The inefficiencies within the model have implications on how much time is required to interrogate the model thoroughly.

Issue 2

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
'CON_DMARD' is stated on the 'Model instructions' sheet to be MTX, but the survival time is different to that of MTX. In the 'Survival' sheet, the survival time on CON_DMARD is the same as for SSZ. The survival time on MTX is the same as for SSZ only if Cell S15 on 'Front page' is not 0 – but this is 0 in the base case and does not appear to change. The survival time on MTX is therefore much longer than on CON_DMARD	Set cell G95 on 'Survival' sheet to be =G99 (or sample from the same distribution using a different random number, if more appropriate).	The costs for SEQ10 will decrease, and the QALYs increase, because CON_DMARD is cheaper and more effective than PC, and patients will spend longer on CON_DMARD. The same will happen for biologics followed by sequence 10. In the incremental results, the ICERs increase to a median of £37,000 / QALY.

Issue 3

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The HAQ changes (dependent upon response) appear to be halved in the toshRA code, but it is not entirely clear why. The code reads "haq = PreResponseHAQ + tx_haqr / 2"	If this is not correct, and the HAQ change should not be halved, the code should read: "haq = PreResponseHAQ + tx_haqr"	The QALYs increase for all sequences, but this increase is greater for the biologics. The incremental QALYs versus SEQ10 therefore increase, so the ICERs decrease to a median of £43,000/QALY.

Issue 4

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
I and S for HAQ progression are not defined for DMARDs when HAQ progression for biologics is set to 0. The HAQ response code defines i and S only if the treatment class is BIO. I (which is empty) and S (which equals zero) are then used in calculating HAQ progression on the DMARDs. The HAQ score and hence QALYs on the DMARDs therefore vary depending on whether HAQ progression on biologics is set to zero or not.	The code “ If tx_resp = "GOOD" Then i = bio_prog_good_i + (bio_prog_good_i_age * dm_age) + (bio_prog_good_i_pgen * dm_sex) + (bio_prog_good_i_dd * dm_dd) + (bio_prog_good_i_das * dm_das) + (bio_prog_good_i_dmards * dm_dmards) S = bio_prog_good_s + (bio_prog_good_s_age * dm_age) + (bio_prog_good_s_pgen * dm_sex) + (bio_prog_good_s_dd * dm_dd) + (bio_prog_good_s_das * dm_das) + (bio_prog_good_s_dmards * dm_dmards) Else i = bio_prog_mod_i + (bio_prog_mod_i_age * dm_age) + (bio_prog_mod_i_pgen * dm_sex) + (bio_prog_mod_i_dd * dm_dd) + (bio_prog_mod_i_das * dm_das) + (bio_prog_mod_i_dmards * dm_dmards) S = bio_prog_mod_s + (bio_prog_mod_s_age * dm_age) + (bio_prog_mod_s_pgen * dm_sex) + (bio_prog_mod_s_dd * dm_dd) + (bio_prog_mod_s_das * dm_das) + (bio_prog_mod_s_dmards * dm_dmards) End If” Should come before the code: “If tx_class = "BIO" Then	The QALYs increase for the DMARD sequences, but this increase is minimal. Overall the ICERs increase slightly to a median of around £58,000 / QALY.

	If bio_prog_switch = 0 Then” And thus be outside of the If statement, and not dependent upon bio_prog_switch, and be defined for all DMARDs.	

Issue 5

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Lifetables are looking up the age of death for a male patient, regardless of the sex of the patient. In the ‘Lifetables’ sheet, the formula in cell I25 (and those below) is IF(basesex = 0, VLOOKUP(H25,$A$9:$E$109,3), VLOOKUP(H25,$A$9:$E$109,3))	In the ‘Lifetables’ sheet, the formula in cell I25 should be IF(basesex = 0, VLOOKUP(H25,$A$9:$E$109,5), VLOOKUP(H25,$A$9:$E$109,3))	Impact on result will be minimal.

Issue 6

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The AE costs are categorised as ‘HAQ costs’ in the results. If HAQ costs are set to	Add a new category / variable in the VBA for AE costs, or	No difference to overall results.

zero, there still appear to be HAQ costs in the results breakdown.	clarify that the HAQ costs are HAQ and AE costs	

Issue 7

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Inconsistent results when using the same sequence on all the calculation sheets.	In the HAQADJUST macro the code uses a random number which samples each time the code is ran. A solution would be to sample a random number for each patient, similar to the method that is used for the other random numbers. Whilst it is acknowledged that ideally a random number would not be fixed for each time a patient entered the HAQADJUST macro, the only other feasible solution would be to remove the HAQADJUST macro and add in the calculations to the code.	Minimal or no impact on results.

Issue 8

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The random number used within the survival page for HCQ is not set to random in cell F96, set to a fixed value (0.984)	Set equal to random (= rand())	None, as not used in base case