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

Pro-forma Response

Executable Model

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262) [ID695]

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by **School of Health & Related Research University, University of Sheffield (ScHARR)**. 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).

July, 2014

Issue 1 The modelled assumption on dose escalation does not employ an escalation rate that is reflective of the population modelled and the adalimumab licence.

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The rate of dose escalation (27.4%) used in the model would not reflect the use of adalimumab according to the licence, which states that some patients who experience a decrease in their response may benefit from a dose increase.[1] As the ULTRA2 trial employed a non-responder imputation (NRI) method to classify responders and non-responders, anyone who dose escalated would be considered a non-responder. As result, using dose escalation at the rate applied in the model overestimates the cost of adalimumab.	The proportion of patients receiving every week (i.e. escalated) adalimumab maintenance should be zero (parameter 137)	The model has not been re-run to determine the PSA ICER. The deterministic ICER vs. conventional therapy decreases by £12,890 and it is expected that the PSA ICER will show a similar decrease. The base case ICER vs. surgery has not changed – adalimumab is still dominated by surgery.

Issue 2 The model does not account for the efficacy of adalimumab dose escalation.

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model discontinues patients who were classified as non-responders in the clinical trial, which is not in line with the clinical trial protocol where patients who were non-responders could continue treatment. The indirect assumption in the model that	Ideally, the mode should be changed to incorporate the additional benefit that dose escalation with adalimumab offers those who do not respond by re-conducting the network meta-analysis (NMA) This will require that patient numbers used in the NMA be	The model has not been re-run with alternative patient numbers as this requires updating the NMA. Making this amendment is expected to lower the ICER for adalimumab as fewer patients

patients who dose escalate would stop their adalimumab treatment does not take into account that patients could have achieved better efficacy.	amended following re-analysis of the patient level data: those patients who were counted as non-responders due to dose-escalation should now be classed according to their response following dose-escalation i.e. patients who responded but was not in remission in the current model is considered a non-responder in the trial even if they subsequently go into remission, and is counted as a non-responder in the NMA. If the data is re-analysed to incorporate the effect of dose-escalation, then these patients would not be counted as non-responders, but as being in remission.	will be classified as non-responders. The cost will not be different in the model as the cost of dose escalation has already been incorporated in the existing model structure.

Issue 3 The treatment sequence strategy assumed in the model does not reflect UK clinical practice

Description of problem	**Description of proposed amendment**	**Result of amended model or expected impact on the result (if applicable)**
The model assumes that all patients in the anti-TNF arm who discontinue therapy at week 8 due to non-response will receive conventional treatment and will only be able transition to surgery after receiving at least one cycle of conventional treatment. As discussed in the AbbVie response to the Assessment Report, it seems counterintuitive to require that all patients who failed anti-TNFs start with treatment they are intolerant to or treatment that has shown to be less effective than another treatment option,	AbbVie proposes that at least some, if not all patients be allowed to proceed directly to surgery following failure on anti-TNFs. This would require a change to the “Transition Matrices” tab in the model, revising the transition probability matrices to have all or some patients directly transition to surgery once they lost remission or response on adalimumab. For instance, in the example below, all patients transition to surgery as per the changes highlighted in yellow. (Please use the page zoom option to increase the text in the object below).	In the probabilistic base case, the costs associated with adalimumab treatment decrease from £89,289 in original model to £52,096. The QALYs increase from 10.83 to 15.43. The new probabilistic ICER for adalimumab vs. surgery using the assumption that all patients proceed to surgery following anti-TNF failure is £14,316/QALY gained. The probabilistic base case vs. conventional therapy also changes: the cost of conventional therapy decrease to £42,787 from £71,657 and the QALYs increased to 14.74 from 10.44. The new probabilistic ICER for adalimumab vs.

<table>
<tr>
<td>such as surgery. Also, allowing less than 1% of patients to proceed to surgery whilst on conventional treatment (which has shown to be less effective than surgery), appears counterintuitive and does not seem ethical or reflective of clinical practice.</td>
<td>
Adalimumab - induction (0-8 weeks)
<table>
<tr><th></th><th></th><th colspan="3">On biological treatment</th><th colspan="3">On standard care</th><th></th></tr>
<tr><th></th><th></th><th>No response</th><th>response</th><th>remission</th><th>No response</th><th>response</th><th>remission</th><th>Post-surgery</th></tr>
<tr><td>On biological treatment</td><td>No response</td><td>-</td><td>0.32</td><td>0.19</td><td>0.00</td><td>-</td><td>-</td><td>0.49</td></tr>
<tr><td></td><td>response</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>remission</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>On standard care</td><td>No response</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>response</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>remission</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>Post-surgery</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
Adalimumab - maintenance (8 to 32 weeks)
<table>
<tr><th></th><th></th><th colspan="3">On biological treatment</th><th colspan="3">On standard care</th><th></th></tr>
<tr><th></th><th></th><th>No response</th><th>response</th><th>remission</th><th>No response</th><th>response</th><th>remission</th><th>Post-surgery</th></tr>
<tr><td>On biological treatment</td><td>No response</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1.00</td></tr>
<tr><td></td><td>response</td><td>-</td><td>0.26</td><td>0.23</td><td>-</td><td>-</td><td>-</td><td>0.51</td></tr>
<tr><td></td><td>remission</td><td>-</td><td>0.17</td><td>0.41</td><td>-</td><td>-</td><td>-</td><td>0.43</td></tr>
<tr><td>On standard care</td><td>No response</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>response</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>remission</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>Post-surgery</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1.00</td></tr>
</table>
Adalimumab - maintenance (32 to 52 weeks and subsequent)
<table>
<tr><th></th><th></th><th colspan="3">On biological treatment</th><th colspan="3">On standard care</th><th></th></tr>
<tr><th></th><th></th><th>No response</th><th>response</th><th>remission</th><th>No response</th><th>response</th><th>remission</th><th>Post-surgery</th></tr>
<tr><td>On biological treatment</td><td>No response</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1.00</td></tr>
<tr><td></td><td>response</td><td>-</td><td>0.33</td><td>0.22</td><td>-</td><td>-</td><td>-</td><td>0.45</td></tr>
<tr><td></td><td>remission</td><td>-</td><td>0.08</td><td>0.83</td><td>-</td><td>-</td><td>-</td><td>0.08</td></tr>
<tr><td>On standard care</td><td>No response</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>response</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>remission</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td></td><td>Post-surgery</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1.00</td></tr>
</table>
</td>
<td>conventional therapy using the assumption that all patients proceed to surgery following anti-TNF failure is £13,467/QALY.</td>
</tr>
</table>

Issue 4 The model uses probabilities of going to surgery that may not be reflective of the patient population under evaluation.

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model uses Solberg et al. as source of surgery rates. As outlined in the AbbVie response, Solberg et al. likely	As the literature on surgery rates vary considerably, it is problematic to recommend a definitive amendment to the	In the example where the surgery rate is doubled, the cost of the anti-TNF and conventional therapy cohorts will decrease as

underestimates the probability of surgery given the differences in patient populations between Solberg et al. and the evaluation population.	model. To illustrate the principle, the existing surgery rate (and the corresponding confidence intervals) was doubled in the model so that parameter 120 has an alpha of 46.96 and a Beta of 4278.73	more patients will proceed to surgery (which in the model has a lower overall cost). At the same time, the QALYs in these arms will increase as more patients experience the benefit of surgery. The base case ICER vs. conventional therapy results in a slightly higher ICER for the anti-TNFs (but infliximab and golimumab is still dominated, with the adalimumab ICER now £55,511/QALY). This is because the conventional treatment cohort will have a higher rate of patients proceeding to surgery, which in the model has a better outcome than the other treatment options. The outcome on the probabilistic ICER vs. surgery does not change (all treatments are still dominated by surgery).

Issue 5 The model does not fully account for the cost and disutilities of surgery-related complications

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model assumes that patients may experience both transient and chronic complications related to surgery, and that transient complications can only arise during the same cycle as surgery, but not in subsequent cycles. The model does not employ a disutility for	As the literature on utilities associated with surgical complications provide a range of utility values and are based on different health instruments, it is problematic to recommend a definitive amendment to the model. As such, only recommendations on the type of utilities to be incorporated are made by AbbVie: • Disutility for surgery	The model has not been re-run with amended utilities and costs as the most appropriate values are uncertain. It is expected that the QALYs for all the treatment cohorts will decrease, but that the surgical cohort will decrease the most. Anti-TNFs will have the smallest change in QALY as it is more effective than conventional

transient complications.
 	
Only chronic pouchitis is considered as a chronic surgery-related complication and uses a rate has been established among non-Western patients in a Japanese healthcare setting.
 	
No disutility is associated with surgery, a major procedure that requires hospitalisation, in the model.
	• Disutility for transient complication
	• Disutility for multiple transient complications
	• Disutility for delayed transient complications
	• Disutilities for the other chronic complications
	  ○ Pouch failure
	  ○ Sexual dysfunction
	  ○ Reduced fertility
	• Disutility for surgery
	
	The costs for treating the relevant complications outlined above should also be incorporated in the model.
		therapy at keeping patients in remission or in response, and thus fewer patients will proceed to surgery. This will result in a lower ICER for anti-TNF therapies compared to surgery and conventional therapy.
		
		It is expected that the cost of the post-surgical health state, and thus the overall cost, will increase for all the treatment cohorts. The cost in the surgical cohort is expected to increase the most compared to the other treatment options as patients on the anti-TNFs and conventional therapy who remain in remission or response, will not proceed to surgery. This will result in a lower ICER compared to surgery.
		
		Compared to conventional therapy, the costs in the anti-TNF arms are expected to increase the least as it is more effective in keeping patients in remission or on response. The ICER is also expected to improve against conventional therapy.

Issue 6 The cost of the surgical procedure is underestimated in the model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model only incorporates the cost of one surgical procedure for patients who proceed to surgical intervention	AbbVie suggests the cost of surgery be amended to account for the fact that more than one surgical procedure may be necessary. Tsai et al. calculated the assuming ileostomy to be equivalent to	The model has not been re-run to determine the PSA ICER. However, if the cost of elective surgery is taken as an average of the cost of ileostomy and IPAA

<table>
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<td>two complex procedures and IPAA to be equivalent to two complex and one major procedure.

Using the 2012/13 NHS reference costs, the following codes would be applicable:

Ileostomy:
<table>
<tr><td>FZ74F</td><td>Complex Large Intestine Procedures, 19 years and over with CC Score 0-2</td><td>104</td><td>Colorectal Surgery</td><td>£ 6,830</td></tr>
<tr><td>FZ74F</td><td>Complex Large Intestine Procedures, 19 years and over with CC Score 0-2</td><td>104</td><td>Colorectal Surgery</td><td>£ 6,830</td></tr>
<tr><td colspan="4">TOTAL</td><td>£13,659*</td></tr>
</table>
IPAA:
<table>
<tr><td>FZ74F</td><td>Complex Large Intestine Procedures, 19 years and over with CC Score 0-2</td><td>104</td><td>Colorectal Surgery</td><td>£ 6,830</td></tr>
<tr><td>FZ74F</td><td>Complex Large Intestine Procedures, 19 years and over with CC Score 0-2</td><td>104</td><td>Colorectal Surgery</td><td>£ 6,830</td></tr>
<tr><td>FZ77 E</td><td>Major Large Intestine Procedures, 19 years and over with CC Score 0</td><td>104</td><td>Colorectal Surgery</td><td>£3,675</td></tr>
<tr><td colspan="4">TOTAL</td><td>£17,334*</td></tr>
</table>
*Total cost differ from individual level cost due to rounding

A weighted average of IPAA and ileostomy based on UK clinical practice should then be applied to determine the cost of surgery and parameter 210 updated accordingly</td>
<td>(£15,496.55) the conclusion for the deterministic ICERs for all treatment options vs. surgery is not changed – all treatments are still dominated vs. surgery. It should be noted though that the incremental costs are now smaller, ranging from £23,692 to £43,437 vs. £29,695 to £49,474.

The incremental cost between anti-TNFs and conventional therapy is also lower: ranging from £13,589 to 19,745 vs. £13,617 to £19,780. As result the deterministic ICER for all anti-TNFs improve slightly vs. conventional therapy.</td>
</tr>
</table>

Issue 7 Hospitalisation risk in the model may not reflect the relative risk (RR) observed in clinical trials of adalimumab

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
As stated in the AbbVie submission, adalimumab reduced the risk by 30% for all cause hospitalisation compared to placebo and by 50% for all UC-related-	AbbVie believes it is not appropriate to use the results from the MSD NMA and recommends that the RR from the Feagan publication is used, specifically, if the RR is for UC-related hospitalisations, then parameter 189 should be 0.50	The model has not been re-run to determine the PSA ICER. The deterministic ICER vs. conventional

hospitalisation compared to placebo. In the model a relative risk (RR) of 0.70 was used when comparing hospitalisations between adalimumab and placebo, based on the MSD NMA. It is acknowledged in the report that there is lack of clarity on the MSD NMA model, specifically, the methods whereby the results therein were obtained. It is also not clear to AbbVie if this figure relates to all-cause or UC-related hospitalisations.		therapy decreases by £963 and it is expected that the PSA ICER will show a similar decrease. It is expected that surgery will still dominate all other treatment options.

Issue 8 The doses used for oral 5-aminosalicylates costs do not reflect UK clinical practice for moderate to severe UC patients in the UK

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model uses the lowest doses for induction and maintenance for the 5-ASA tablets.	AbbVie suggest that the cost of 5-ASAs is based on the weighted average cost of all drugs within a class. For the induction phase the cost of the 4.8g/day dose would be used. Similarly, for the maintenance of remission in patients with moderate to severe UC, the higher maintenance dose should be used, i.e. 2.4g/day.	The model has not be re-run however, the expected results is a small increase in the ICER vs. conventional therapy as all patients will move on to the conventional therapy before proceeding to surgery. The result vs. surgery is not expected to change (all treatments will be dominated by surgery).

Issue 9 The methods used to determine cost used for 5-ASAs in the model is not reflective

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The cost in the model is based on the lowest cost preparation (Ipocol®)	Parameter 196 should be amended to reflect an average cost of all the mesalazine tablet preparations listed in the Premodel tab	The model has not be re-run however, the expected results is a small increase in the ICER vs. conventional therapy as all patients will move on to the conventional therapy before proceeding to surgery. The result vs. surgery is not expected to change (all treatments will be dominated by surgery).

Issue 10 The cost of stoma care is not incorporated in 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 incorporate the cost of stoma care.	The cost of stoma bags and accessories should be added as an additional cost in the premodel tab	The model has not be re-run, however, as the cost of surgery will increase it is expected that the total cost will increase for all the treatment cohorts. The cost in the surgical cohort is expected to increase the most compared to the other treatment options as patients on the anti-TNFs and conventional therapy who remain in remission or response, will not proceed to surgery. This will result in a lower ICER compared to surgery. Compared to conventional therapy, the total cost in the anti-TNF arms are expected to increase the least as anti-TNF therapies are more effective in keeping patients in remission or on response. The ICER is therefore also expected to improve against

		conventional therapy.

Issue 11 The model does not incorporate the cost of dying, and in particular, the cost of dying following surgery

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
No costs have been allocated to the death state in the model.	The cost of terminal care, in particular for patients who die due to surgery, should be added as an additional cost in the premodel tab.	The model has not be re-run, however, as the cost in the post-surgery health state is expected to increase, the total cost will increase for all the treatment cohorts. The total cost in the surgical cohort is expected to increase the most compared to the other treatment options as fewer patients on the anti-TNFs and conventional therapy will proceed to surgery and will thus incur lower surgery related mortality costs. This will result in a lower ICER compared to surgery. Compared to conventional therapy, the total costs in the anti-TNF arms are expected to increase the least as it is more effective in keeping patients in remission or on response. The ICER is therefore also expected to improve against conventional therapy.

Issue 12 Source for the life expectancy tables does not correspond to the life expectancy figures used in the Assessment Group model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The mortality rate (qx) data in the model as it appears on the Premodel tab does not correspond to the source of the life expectancy table quoted in the Assessment Report. The source is give as *Office for National Statistics. Interim life tables, England and Wales, 2009-11. 2011; available from http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2009-2011/stb-2009-2011.html* Using the link from the source provided in the Assessment Report takes the reader to a webpage with a PDF. Within the PDF is a link to the Interim life tables for England and Wales (http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2009-2011/index.html). This link opens a new webpage where, amongst others, the Reference Tables can be found (http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-274529). This re-directs to the 21 March 2013, National Life Tables, 2009-2011. The table entitled "England and Wales, interim Life Tables, 1980-82 to 2009-11" (http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2009-2011/rft-england-and-wales.xls) does not contain the same mortality (qx) figures	The most up to date mortality rate (qx) data from the March 2013 interim life tables should be used: (http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2009-2011/rft-england-and-wales.xls) Alternatively, the reference for the original source may require correcting.	The model has not been re-run to determine the PSA ICER. Depending on the treatment option, the deterministic ICER either decrease or increases marginally (-£28 to +£5)

as shown in the model (Pre-model tab)		

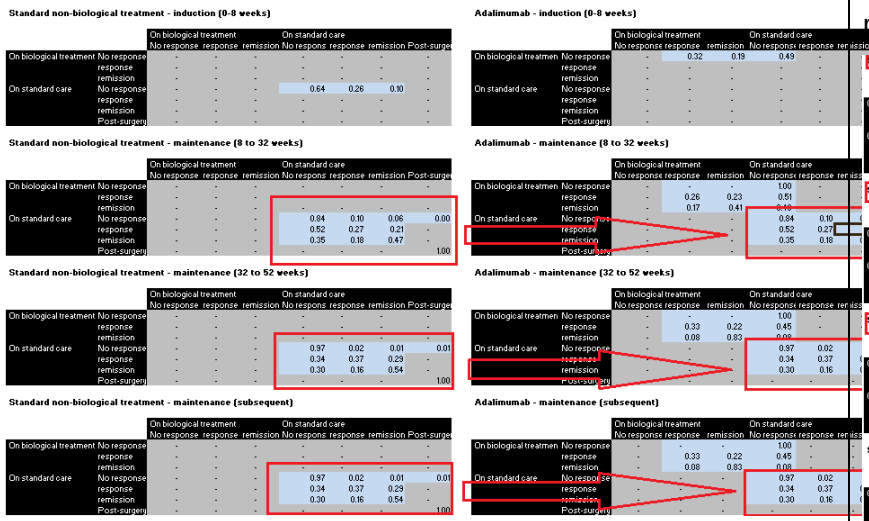
Issue 13 The source for colectomy rate in the model does not correspond to the numbers used or the Assessment Report

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The source of the colectomy rate quoted on the Premodel tab (Gustavsson et al, AJG, 2007) does not correspond to the source in the Assessment Report (Solberg et al, Scan J Gastroenterol, 2009). The values used in the model do not correspond to Gustavsson et al., but to Solberg et al.	As the values used in the model are from Solberg et al. the source quoted in the model require correcting.	No impact on the ICER.

Issue 14 The transition matrices for the anti-TNF treatments incorporates transition probabilities for patients who proceed to conventional treatment that do not relate to the appropriate corresponding time points

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The transition matrices for all the anti-TNFs apply transition	AbbVie is unable to propose an exact amendment as the results from	The model

probabilities for the patients who transition to conventional treatment that correspond the same phase in the conventional treatment arm (please use the page zoom to obtain a larger image):



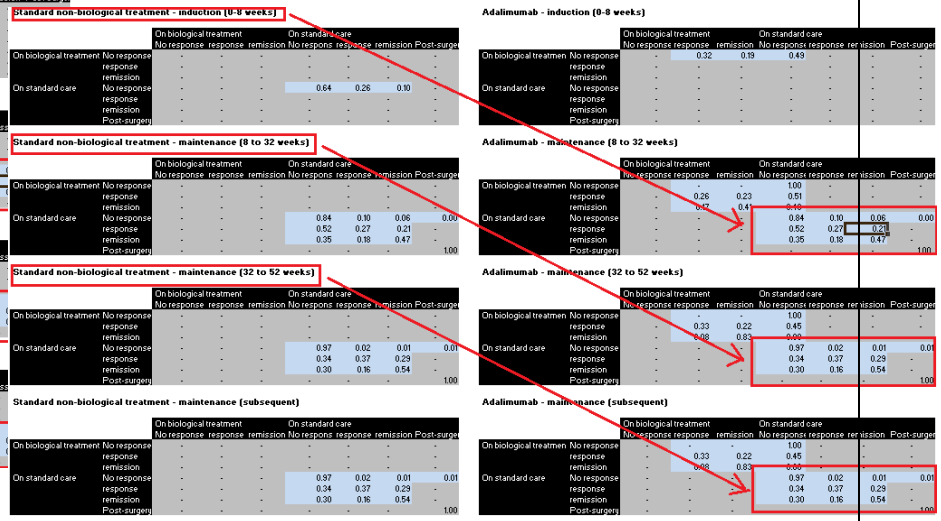
The assumption is therefore e.g that patients who start on conventional therapy following anti-TNF treatment failure during induction will do so with the transition probabilities for conventional treatment as per maintenance 8-32 weeks, i.e. not the induction phase transition probabilities for conventional therapy. The maintenance phase transition probabilities for conventional treatment is applied to the <u>same</u> maintenance phase as anti-TNFs <u>instead of the preceding phase.</u>

As can be seen from the tables above, different transition probabilities exist for all treatments at the different time points (induction 0-8 weeks, maintenance 8-32 weeks, maintenance 32-52 weeks, subsequent maintenance), based on the results from the NMA.

It should be borne in mind that patients in maintenance phase 32-52

the NMA would require re-analysis for the conventional therapy arm to match the duration for each phase.

The principle of the amendment is illustrated below (please use the page zoom to obtain a larger image):



has not been re-run and the impact is therefore unclear.

in the anti-TNF cohorts who are taking conventional treatment are in fact one phase behind i.e. in the maintenance phase 8-32 of conventional therapy. To assume that patients who failed anti-TNFs in e.g. maintenance 32-52 and start on conventional treatment will do so with the same probabilities as in maintenance 32-52 in the conventional treatment cohort, does not reflect the data as it disregards the induction phase for conventional treatment.		

[1] AbbVie. Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/medicine/21201 [Accessed: 31 July 2014]