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

Pro-forma Response

ERG report

Everolimus for preventing organ rejection in liver transplantation

You are asked to check the ERG report from Peninsula Technology Assessment Group (PenTAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **5th December 2014** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Clinical Inaccuracies

Issue 1 Median survival numbers quoted from Barber 2007

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg14 - 'To note (sic) is that Barber 2007 also reports the median survival for specific underlying liver disease. Patients with alcoholic, HCV and cancer liver disease….' The quote taken from Barber is not quite correct.	The sentence should be amended to 'Patients with alcoholic, HCV and cancer **primary** liver disease…'	To accurately reflect the reference quoted.	Pg 14 Change made 'Patients with alcoholic, HCV and cancer **primary** liver disease…'

Issue 2 Consideration of BTS NASH Guidelines

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg15 - The ERG report discusses the Novartis submission with reference to the BTS NASH guidelines with the following sentence (italics by ERG) 'therefore it is not clear to the ERG why the company considered that *no single guideline was identified for the immunosuppression of adult patients with allogeneic liver transplantation*' This does not accurately reflect the submission which states 'but no single guideline was identified for all' The recommendations on immunosuppression in these guidelines are largely focussed on NASH patients - for example, below is a specific quote from the document which highlights this fact: 'Alongside immunosuppression with CNI and an anti-metabolite, consideration should be given to either a steroid free regime or early steroid withdrawal (within three months) in patients with NASH'. Steroid-free regimes or early steroid withdrawal would not be necessary in all liver transplant patients - an assumption validated by the ERG	The manufacturer states that the BTS guidance was specific for NASH patients and not all liver transplant patients. The manufacturer acknowledges that the BTS NASH guidelines would be of interest but disagrees with the ERG statement that they are 'extremely relevant'. We suggest that this passage is amended to highlight that the NASH guidelines are specific to this patient sub-group so may not be relevant to all liver transplant patients.	The ERG report does not adequately convey that the immunosuppression recommendations outlined in the BTS NASH guidelines apply specifically to patients whose liver transplant was due to non-alcoholic steato-hepatitis which therefore could potentially be misleading due to the statement that the ERG '…deemed this [the NASH guidance] extremely relevant to the decision problem'	Pg 14-15 Change made Agreed. The discussion around additional guidelines has been removed.

clinical advisor elsewhere in the report where steroids were accepted to be withdrawn 6 months post-transplant in most patients (pg.16 of the ERG report)			

Issue 3 UK Clinical Practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg15 - The ERG report makes the following comment with reference to the manufacturer submission: 'There is not much consideration given to the main immunosuppressive therapies used in the UK apart from mentioning there is variance in practice and that most regimens contain tacrolimus in combination with other drugs' The ERG's clinical advisor agrees with the statement that there is huge variance in clinical practice with regards to post-transplantation immunosuppressive treatment regiments in the UK (pg. 15 in the ERG report). However, the manufacturer submission has adequately considered current practice in the UK by adopting the final scope from NICE which states the comparators to be: Standard immunosuppressive therapy with a calcineurin inhibitor (such as ciclosporin or tacrolimus) and a corticosteroid, in combination with: azathioprine or mycophenolic acid	We suggest this statement is amended to state: 'The submission concurs with the clinical opinion given to the ERG that there is significant variation with regard to clinical practice with respect to post-liver transplant immunosuppressive therapy in the UK'	To clearly reflect that the submission acknowledges that there is variation in UK practice and that the final scope from NICE is taken into consideration.	No issue of factual accuracy identified. We are happy with the original wording as the ERG only mention examples of other immunosuppressive therapies used in the NHS such as Sirolimus.

The current comment in the ERG report could be misinterpreted and could imply that the manufacturer did not consider current UK treatment practice in the development of the submission.			

Issue 4 BTS NASH Guidelines mentioning other UK therapies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg15 - The ERG report contains the following sentence: 'However for example, the NASH guidance mention tacrolimus monotherapy and sirolimus as relevant therapies' As stated previously in Issue 2, the NASH guidance is most relevant to non-alcoholic steato-hepatitis patients undergoing liver transplantation. The information in the statement above taken from page 33 of the NASH guidance also refers to everolimus as an mTOR inhibitor that may be used- it is not clear why the ERG report chose to omit this whilst mentioning sirolimus. Furthermore, at the time of writing of the NASH guidance, everolimus did not have a UK license for use in liver transplantation and sirolimus SPC states that the safety and efficacy of sirolimus has not been established in liver transplantation.	This sentence should either be removed or amended to include everolimus as well as sirolimus whilst clearly stating that these are unlicensed therapies whose efficacy and safety had not been established at the time of writing of the NASH guidelines. Please also see further comments on sirolimus below.	To correctly reflect the recommendations in the NASH guidelines (within the already previously highlighted limitations).	No issue of factual accuracy identified as tacrolimus is introduced as an example, however the text has been amended for clarity. 'However, for example, the NASH guidance mention tacrolimus monotherapy and sirolimus as relevant therapies **for non-alcoholic steato-hepatitis patients undergoing liver transplantation**.'

Issue 5 Unlicensed Sirolimus Use

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg15 - The ERG's clinical advisor suggested that some currently receive sirolimus during first year of immunosuppressive therapy (not clear if this is monotherapy or in combination with other immunosuppressive agents). As stated in Issue 4, sirolimus does not have a UK license for use in liver transplantation. The following is quoted directly from the SPC: 'The safety and efficacy of Rapamune as immunosuppressive therapies have not been established in liver or lung transplant patients, and therefore such use is not recommended. In two clinical studies in *de novo* liver transplant patients, the use of sirolimus plus ciclosporin or tacrolimus was associated with an increase in hepatic artery thrombosis, mostly leading to graft loss or death. A clinical study in liver transplant patients randomised to conversion from a calcineurin inhibitor (CNI)-based regimen to a sirolimus-based regimen versus continuation of a	The comments on sirolimus should be amended to clearly state that it does not have a license in liver transplantation in addition to the passage already highlighting the significant potential safety issues with sirolimus use.	To ensure that it is clearly communicated that sirolimus therapy for liver transplantation is unlicensed.	It is the ERG's clinical advisor's opinion that 10-15% of all patients receive sirolimus instead of everolimus during first year of immunosuppressive therapy. For clarity, the text has been amended to include the use of an unlicensed indication. 'Clinical opinion sought by the ERG advised that about 10-15% of patients currently receive sirolimus, **although the therapy is unlicensed**, which like everolimus is an mTOR inhibitor, instead of everolimus during their first year of immunosuppressive therapy.'

CNI-based regimen 6-144 months post-liver transplantation failed to demonstrate superiority in baseline-adjusted GFR at 12 months (-4.45 ml/min and -3.07 ml/min, respectively). The study also failed to demonstrate non-inferiority of the rate of combined graft loss, missing survival data, or death for the sirolimus conversion group compared to the CNI continuation group. The rate of death in the sirolimus conversion group was higher than the CNI continuation group, although the rates were not significantly different. The rates of premature study discontinuation, adverse events overall (and infections, specifically), and biopsy-proven acute liver graft rejection at 12 months were all significantly greater in the sirolimus conversion group compared to the CNI continuation group'			

Issue 6 Clinical opinion with regard to current UK practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg15 - The ERG report contains the following sentence: 'Clinical opinion sought…advised that the about 10-15% of patients currently receive sirolimus…' before going on to state 'Use of sirolimus is significantly lower than everolimus….' The next paragraph goes on to say '….the ERG's clinical advisor explained that around 30% of patients receive tacrolimus monotherapy….and that about 70% of patients receive therapies including two agents…like mycophenolate (sic) acid or azathioprine in combination with reduced doses of tacrolimus.' There is clearly a significant lack of clarity here- the numbers stated sum to 115%, without the unquantified use of (unlicensed) everolimus.	It is suggested that all of this section is reviewed to convey the discussion with the ERG clinical adviser without the estimated proportions, which as stated convey a figure above 100%, or that the discussion is revisited so that a 'correct' estimate of the proportion of patients on the various therapy options is conveyed.	The estimates made in this section of the ERG report do not appear to make sense as they add up to over 100%- therefore clarification / rewriting is needed.	We are happy with the original wording. Amongst all patients that receive Tacrolimus, 30 % receive monotherapy and 70% receive a 2-agents therapy. Separately, 10-15% of all patients receive sirolimus according to the ERG's clinical advisor.

Issue 7 Use of the term ‘Mycophenolate Acid’

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg15 - The ERG report uses the term ‘mycophenolate acid’ This is also used on pages 17,18,25 ‘Mycophenolate Acid’ is incorrect usage- the correct wording if including acid is **mycophenolic acid**. The term ‘mycophenolate’ should only be used when referring to ‘mycophenolate mofetil’ or ‘mycophenolate sodium’	The ERG report should be amended to reflect the correct usage of the term mycophenolic acid when either salt presentation is being referred to and specify mycophenolate mofetil or mycophenolate sodium where appropriate.	To correctly implement the use mycophenolic acid, mycophenolate mofetil and mycophenolate sodium in the report as they should not be combined or used interchangeably as this could be misleading.	The report will be amended to reflect the correct use of the term’ mycophenolic acid’ on the relevant pages.

Issue 8 Specification of 'Mycophenolate Mofetil'

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg18 - The following statement is made in the report 'Therefore it seems that mycophenolate (sic) acid should have been used as the comparator drug….' As highlighted in clarification question A3, mycophenolate mofetil has been used throughout the submission as the mycophenolate sodium presentation of mycophenolic acid- Myfortic®- does not have a license for use in liver transplantation see section 4.1 of the relevant SPC (http://www.medicines.org.uk/emc/medicine/14917).	The ERG report should be amended to include the company justification as to why mycophenolic acid was not used as the comparator drug. Suggested wording could be: "The justification provided by Novartis on page 36 of their submission explained the choice to use mycophenolate mofetil specifically, as mycophenolate sodium (another presentation of mycophenolic acid) does not have a license for use in liver transplantation."	To make clear that there is a license variation between the presentations of mycophenolic acid, with only mycophenolate mofetil having a license in liver transplantation.	We are happy with the statement in the report as the clinical expert confirmed that, most UK clinicians will prescribe mycophenolic acid, as per scope. For clarification the text has been amended. '**however the company stated in the clarification document that mycophenolate sodium does not have a licence for use in liver transplantation.**'

Issue 9 Tacrolimus trough levels in the Porayko study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg19 - Table 2 that summarises the dosages of drugs in the comparator studies for the potential renal function NMA states that in the study of Porayko et al that TAC trough levels were below 1.0ng/ml for the entire year. The above statement is incorrect- in the information reported in the study (Fig 2D), the trough levels of are below 1.0ng/ml in month 4 and month 12. Other months are not reported and levels for the first 4 weeks are above 1.0ng/ml.	The statement should be amended to state that trough levels were just below 1.0ng/ml at month 12, whilst being reported to be higher in the first 4 weeks- with only limited data being reported.	To correctly convey the information on tacrolimus dosing in the study.	Agreed. The text has been amended. 'TAC trough levels were maintained below 1.0 ng/mL **at month 12, whilst being reported to be higher in the first 4 weeks- with only limited data being reported**.'

Issue 10 ERG clinical expert on renal sparing effect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg19 - The ERG report summarises the discussion with a clinical expert- the first bullet states: 'When evaluating the benefit of EVR as a concomitant drug prescribed with a reduced dose of TAC and with regards to its renal sparing effect, EVR is likely to perform as good as MMF and AZA when given with reduced doses of TAC. This is because the renal sparing effect comes from allowing reduced doses of TAC (versus standard doses of TAC), therefore using EVR, MMF or AZA is likely to lead to the same renal outcomes. In this case, the cheaper drug is likely to be the most cost-effective therapy. That would be AZA.' There is no head-to-head evidence to support this statement particularly with regard to the speculation around renal function. The way this statement is framed in the ERG report could be misleading and does not have evidence to support it.	The point should be amended as follows: 'When evaluating the benefit of EVR as a concomitant drug prescribed with a reduced dose of TAC and with regards to its renal sparing effect, **it could be speculated that** EVR is likely to perform as **well** ~~good~~ as MMF and AZA when given with reduced doses of TAC. This is because the renal sparing effect comes from allowing reduced doses of TAC (versus standard doses of TAC)**;** therefore using EVR, MMF or AZA is likely to lead to the same renal outcomes. **However, this assumes that a similar reduction in TAC dose is possible with EVR, MMF and AZA for which there is no directly available evidence. In other words, *if* trough TAC levels were the same regardless of the concomitant drug, renal function could be preserved whilst maintaining adequate immunosuppression. This is clearly a speculative hypothesis.** ~~In this case, the cheaper drug is likely to be the most cost-effective therapy. That would be AZA.'~~	To make clear that this is a point of clinical opinion that would require evidence to support.	No issue of factual accuracy identified. We are happy with the original text as the report states that the points arose from discussion with our clinical expert.

Issue 11 ERG clinical expert on everolimus monotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg19- Following on from Issue 10, the next summary point discusses everolimus as a monotherapy regimen. Although the report states that the ERG is aware that the 'drug indication is not monotherapy…' the report goes on to state that 'disappointingly' not enough data exists to show the benefit of EVR monotherapy. There are two significant point of clarification that should be given emphasis as part of this point and everolimus monotherapy in the general: • The **license** for everolimus in liver transplantation requires it to be used in combination with reduced dose tacrolimus- therefore the submission is based on this combination. • The discontinuation of the TAC elimination arm in H2304 was on the advice of an independent data monitoring committee that ethically had to be	The point of discussion with the clinical expert should be reworded to reflect the fact that everolimus monotherapy is unlicensed and the fact that the tacrolimus elimination arm of the H2304 study was discontinued early on the advice of the independent data monitoring committee.	To clearly communicate the reasoning for the manufacturer submission focussing on the use of everolimus in combination with reduced dose tacrolimus.	No issue of factual accuracy identified. We are happy with the original text.

implemented. This is the reason why there is limited data for everolimus monotherapy			

Issue 12 Conclusions on the comparator set

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 20 - The ERG report concludes that the comparator set in the analysis is 'somewhat irrelevant' as it does not include 'reduced TAC monotherapy' and comparators that are not relevant 'from a clinical point of view'- AZA and MMF in combination with standard doses of TAC. This comment should be balanced with the facts that: • AZA and MMF in combination with calcineurin inhibitors are specifically referred to in the final scope from NICE. • The evidence base for a comparison versus 'reduced tacrolimus' monotherapy is limited and as highlighted in Table 2 of the ERG report- the definition of standard and	The ERG comments should be appended with the comments in the first column to ensure that a full, factual summary of the comparator issue is provided.	The amendments ensure that the ERG comments are balanced against the comparators postulated in the final NICE scope for this appraisal and the available evidence base.	No issue of factual accuracy identified. The ERG acknowledges that reduced TAC monotherapy is not part of the NICE scope, however the ERG considers it to be an extremely relevant comparator.

reduced dose tacrolimus varies between trials. Additionally, TAC monotherapy trials identified in the systematic literature review were classified by the study label- no trials were excluded on the basis of being defined by the study as reduced TAC monotherapy trials			

Issue 13 Comment on proportion of patients dead at year 40

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 21 and 101 In reference to the time horizon of the model, the ERG report states that 'Around year 40 of the analysis 100% of patients are virtually dead' The phrasing of this sentence is unclear- please see details of the proposed amendments.	For full factual clarity, this sentence should be amended to either state: 'By year 40 of the analysis, virtually all patients are dead.' or 'By year 40 of the analysis, 100% of patients are dead.'	The suggested phrasing should convey the point made by the ERG in a more effective and understandable manner.	No issue of factual accuracy identified, however the text has been amended for clarity. '**By year 40 of the analysis 100% of patients are dead**.'

Issue 14 Limitations of searches undertaken

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 22- A limitation of the searches undertaken is highlighted by the ERG stating that 'Any studies that evaluate the efficacy of EVR as a stand-alone intervention would be missed by this search' As stated in the description of Issue 11, the license for everolimus was known to be in combination with reduced dose tacrolimus due to the fact that only that arm of trial H2304 went forward to completion and that everolimus has a license for use in liver transplantation in combination with reduced dose tacrolimus in other countries. Therefore it could reasonably be inferred that searches should focus on combination use of everolimus as this was entirely concordant with the expected license.	A suggested amendment to the wording would be: 'Any studies that evaluate the efficacy of EVR as a stand-alone intervention would be missed by this search. However the expected license for everolimus in liver transplantation was only in combination with reduced dose tacrolimus therefore this could equally be considered appropriate and not a limitation.	This amendment demonstrates the fact that manufacturer chose to focus their submission on the licensed combination of everolimus and reduced dose tacrolimus.	No issue of factual accuracy identified, however the text has been amended for clarity. 'Any studies that evaluate the efficacy of EVR as a stand-alone intervention, would be missed by this search. However the expected license for everolimus in liver transplantation was only in combination with reduced dose tacrolimus any studies which might be useful for parametrisation of the model (for example) would be missed.'

Issue 15 Use of term 'Mycophenolic mofetil'

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg24 - The ERG report uses the term 'mycophenolic mofetil' 'Mycophenolic mofetil' is incorrect usage- the correct wording is **mycophenolate mofetil**. The term 'mycophenolic' should only be used when referring to 'mycophenolic acid'	The ERG report should be amended to reflect the correct usage of the term mycophenolate mofetil.	To correctly implement the use mycophenolic acid, mycophenolate mofetil and mycophenolate sodium in the report as they should not be combined or used interchangeably as this could be misleading.	The report has been amended to reflect the correct use of the term' mycophenolate mofetil'.

Issue 16 Presentation of Mycophenolic acid

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 24/25- With reference once more to the specification of mycophenolate mofetil, the ERG document contains the following text: 'After clarification, the company confirmed that mycophenolic mofetil was used in the submission instead of mycophenolic acid, originally defined in the scope. The company claims that there are two presentations of mycophenolic acid (mycophenolate mofetil and mycophenolate sodium) but that mycophenolate sodium is not licensed for use in liver	This section of text contains numerous factual errors and should be removed or completely re-written. The company 'claim' that mycophenolic acid has two presentations is not a 'claim' but a statement of fact. As previously stated, mycophenolate sodium does not have a license in liver transplantation and this is also factually correct. A clinician prescribing mycophenolate (sic) acid would likely be perceived to be a prescribing error and would require clarification, particularly if the patient had previously been stable on the mofetil presentation of mycophenolic acid. If a liver transplant patient was switched off-label to	To correctly communicate the reasons why the manufacturer submission chose to specify mycophenolate mofetil.	As per response of issue 8, the ERG acknowledge that mycophenolate sodium is not licensed for use in liver transplantation. However, clinical opinion sought by the ERG informed that in the UK most clinicians will prescribe mycophenolic acid.

transplantation (only for renal transplantation).Clinical opinion sought by the ERG informed that in the UK most clinicians will prescribe mycophenolate acid and that even though mycophenolate sodium and mofetil cannot be interchangeably used, the active component is the same and only a dose adjustment is necessary as 500mg mycophenolate mofetil = 360mg of mycophenolate sodium. Therefore, the ERG do not see a valid reason to specify the type of mycophenolate in the inclusion criteria, and the broad mycophenolate acid term could have been used instead.' Again, there are numerous occasions in this section where the ERG report has incorrectly used the term mycophenolate acid instead of mycophenolic acid (see Issue 7). The ERG report is also contradictory when it states that '…most clinicians will prescribe mycophenolate (sic) acid' and then goes on to state that the sodium and mofetil cannot be used interchangeably before then contending only a dose adjustment is necessary.	treatment with mycophenolate sodium, monitoring may be necessary to ensure that the patient remained stable- it is likely not to be as simple as adjusting the dose.		

Issue 17 Discussion of EPOCAL and PROTECT studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 27/28- The ERG report undertakes a brief review of two small studies that partially / fully investigate everolimus monotherapy. The reasoning for the inclusion of the review of these studies is that it is surmised that it would be 'useful to compare EVR monotherapy with EVR +rTAC' These studies were excluded from the manufacturer submission as they do not include the licensed combination of everolimus and reduced dose tacrolimus. Furthermore, neither study compares EVR monotherapy to EVR + rTAC which was the stated reasoning for the inclusion of the description of these two studies in the ERG report. Lastly, the concluding sentence that 'Both the EPOCAL and the PROTECT study (sic) show that EVR monotherapy is as effective as other treatments...' may not be	It is suggested that the discussion of the EPOCAL and PROTECT studies is removed as they are not relevant to the decision problem.	To accurately reflect the scope of the decision problem with respect to everolimus within its licensed indication and remove any potential confusion with discussion of non-licensed everolimus monotherapy.	The ERG are aware that everolimus monotherapy is not the drug indication, nonetheless we consider this to be an extremely relevant issue.

an appropriate closing statement given that, for example, only 43% or patients eliminated TAC in EPOCAL and there were high levels of discontinuation in both arms in PROTECT. As stated several times, the submission has focussed on the licensed combination of everolimus and reduced dose tacrolimus.			

Issue 18 Comparators in the NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 28 - The ERG report provides details of combination of treatments that were identified to enable a network of studies. To aid clarity, it would be helpful for the ERG report to note that the descriptions of the combinations stated are as described in the original study (i.e. a study that stated that it investigated reduced dose tacrolimus was described as such regardless of the actual dosage of tacrolimus investigated)	Inclusion of a note as described in the first column.	For the ERG report to completely report the approach taken in the manufacturers NMA.	No issue of factual accuracy identified. The ERG appreciate that the company reported the definitions of the combinations from the studies, however further interpretation should have been given on the heterogeneity of these definitions.

Issue 19 Number of UK Patients in H2304

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 31 - The ERG report incorrectly states the number of UK patients in trial H2304.	The actual number of UK patients in H2304 was [redacted], not as presented incorrectly in the ERG report	Correct information being provided by the ERG.	Typographical error corrected to [redacted] **in the UK**

Issue 20 Donor Risk Index

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 35 - The ERG report comments that the clinical expert stated that a 'donor risk index' would have provided a useful and unified measure for potential treatment modifiers. This is not entirely factually correct as there are two aspects two consider with regard to treatment modifiers - the modifiers related to the liver donor and the modifiers related to the organ recipient. A 'donor risk index' such as the one produced by the Cincinatti Children's Hospital Medical Center would only be applicable for the modifiers related to the donor and not the recipient (https://gastro.cchmc.org/calculators/donor-risk-index/).	The comment should be amended to state that a donor risk index would only consider treatment effect modifiers from the donor perspective and not the treatment effect modifiers related to the transplant recipient.	The amendment will clarify the utility of a 'donor risk index'.	No issue of factual accuracy identified. The ERG comment considers only the potential treatment modifiers related to the donor. The ERG don't claim that all treatment modifiers would be covered in a 'donor risk index'.

Issue 21 Validation of NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 38 -39 "The ERG found a significant limitation in the NMA presented by Novartis. Even though WinBUGS codes were included in the submission, these did not provide any relevant information. Whilst the codes presented reflect a standard NMA approach, these seem to have been either taken from other submission or from a theoretical exercise, as the data included in the codes do not relate to the submission data in any way. This poses a major limitation as the ERG could not verify which data were used for the analysis of specific outcomes. This represents a major concern as the ERG are not clear which studies have been included in the NMA analysis for the tBPAR outcome, due to lack of clarity and transparency in the submission." This statement links the justification of the limitation of not being able to run the WinBUGS codes with what the ERG	"The ERG was unable to re-run the analysis with the WinBUGS code presented and did not have sufficient time to request these at the clarification stages. The ERG was unclear with respect to one outcome: tBPAR for the studies included in the analysis after reviewing the information on studies in section 6.7.3 of the submission and the network diagrams presented by the manufacturer (studies included in Figure 23, Figure 24 and Figure 25 of the appendices)."	The company provided responses to all the clarification questions raised on the NMA providing further details of the methods and interpretation of the results. There was no statement at the clarification stages that the ERG was unable to run the WinBUGS codes. Novartis has all of the codes for this analysis and would of course have provided these again at the clarification stage to enable the ERG to run the analysis. The company had re-run the WinBUGS codes in the clarification stages in order to provide the leverage plots that were requested in the clarification questions. The manufacturer does not understand why the ERG requested more advanced diagnostics such as leverage plots for the NMA at the clarification stages when they had not attempted to re-run the base case analysis for the outcomes.	WinBUGS software for Bayesian analysis uses Markov chain Monte Carlo (MCMC) methods. Due to time constraints, we are not able to analyse the most recent Winbugs code received in this Factual inaccuracy check. The Winbugs code could not be run without the associated data in the first submission and the company should have provided all the relevant information as part of good reporting practice. In the clarification stage, the company state that they excluded some studies at the different follow-up but do not make it clear which were included in the results used in the model .

considers a ‘major concern’; with the lack of clarity of the studies included. These are two separate points of which the latter is factually inaccurate. The NMA data was provided in tables in the appendices and no issues were raised at the clarification stage with respect to WinBUGS codes.			

Issue 22 tBPAR NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG report
Pg 39- The ERG report comments that '…ERG are not clear which studies have been included in the NMA analysis for the tBPAR outcome…' In section 6.7.3 of the original manufacturer submission the study design, patient characteristics and the studies specifically feasible for each outcome in the NMA are reported. In this section under 'Outcomes' the studies are clearly reported for time to BPAR at 3 months, 6 months and 12 months. In addition, the manufacturer submission includes network diagrams in Appendix 14, of which figures 23, 24, 25 summarise the networks for acute rejection. Furthermore appendix 14 also provides the relevant data for each of the networks in tables 124-125. It should be made clear in the ERG report why the information noted above does not provide sufficient information about which studies were included	The quoted sentence should be amended to state that the manufacturer submission did provide network diagrams and data tables for the acute rejection outcome at various time points and then offer an explanation about why there was any possible lack of clarity. Similarly, the feasibility analysis section (6.7.3) in the original submission discusses all the feasible outcomes presented in the analysis.	To communicate that network diagrams and data tables were provided for the outcome under discussion.	No issue of factual accuracy identified. ERG are still not clear which studies have been included in the NMA analysis despite the network diagrams and data tables provided.

in the NMA analysis for tBPAR.			

Issue 23 NMA Leverage Plots Diagnostics

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 39- The ERG do not report that the manufacturer provided leverage plots of one outcome presented in the model, to aid further consideration of the NMA model selection. "Both random and fixed effects models were ran with the latter being preferred for most outcome measures. The company presented the Deviance Information Criterion (DIC) and upon the ERG request, the posterior mean of the deviance was also presented to ensure that the selected model's overall fit was adequate. These are presented in Table 8."	An additional sentence should be added to the end of the following paragraph on page 39. "Both random and fixed effects models were ran with the latter being preferred for most outcome measures. The company presented the Deviance Information Criterion (DIC) and upon the ERG request, the posterior mean of the deviance was also presented to ensure that the selected model's overall fit was adequate. These are presented in Table 8. **The manufacturer also provided leverage plots for BPAR in response to clarification."**	This should be added to reflect the additional work provided by the manufacturer to support the ERG at this point.	No issue of factual accuracy identified. The ERG report only comments on the DIC and posterior mean of the deviance, however the sentence has been added to aid clarity. '**The manufacturer also provided leverage plots for BPAR in response to clarification**.'

Issue 24 Sensitivity analysis/Scenario analysis for the NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 51- The last paragraph on page 51 of the ERG report is factually inaccurate. The manufacturer included all studies from the NMA SLR with the outcome available at the time point considered appropriate for the analysis and then ran scenario /sensitivity analysis to consider the impact on the results. The studies for each outcome included can be found in the network diagrams presented in the appendices. The results reported in the manufacturer submission refer to the full study set (those in the network diagrams for each outcome) not the sensitivity analysis referred to here by the ERG. “To increase compatibility, the	The ERG statement refers to sensitivity analysis rather than the base case analysis provided for each outcome by the NMA.	The response to clarification in question A17 were with respect to these sensitivity analyses and not the base case, which the ERG seems to have confused:	No issue of factual accuracy. The response to clarification in question A17 states that the absolute results were calculated using only the studies where all time points were measured. The company at no point state that this is a sensitivity analysis.

company decided to substantially reduce the amount of studies included in the estimation of different outcomes by dropping studies initially included in the NMA. Consequently, direct evidence was lost for specific time points thus reducing the overall sample size of the evidence base.”			

Issue 25 Scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 58- “Results of scenario analyses: The results presented by the company are extremely disappointing. No actual results were provided (neither in the submission or other documents) and Novartis simply reported that the only scenario which had an impact on BPAR free at 3 and 6 months was scenario 5 and that all other outcomes were insensitive to the scenario analysis.” The company was not asked to clarify at earlier stages and would have been happy to present these	Suggested amendment: “The results of the scenario analyses were not fully presented by the manufacturer, with only those results that impacted the model results were provided.”	The manufacturer presented all relevant scenario and sensitivity analysis to keep the submission to a manageable size.	No issue of factual accuracy. The ERG cannot request every elements of a full submission, The scenario analyses presented in the submission is extremely limited and should have been provided in the first place. In the circumstance that further information regarding scenario analysis had been available, it is unlikely that it would have had a major impact in the submission size.

results in more detail at the clarification stages if requested.			

Issue 26 Summary of Clinical Effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 59 - The ERG report provides the following summary with reference to trial H2304: 'Whilst graft loss or death seem to favour the TAC arm of the trial, the addition of tBPAR to the composite endpoint favours the EVR+rTAC arm.' To avoid any misinterpretation, it should be confirmed that when individual endpoints were considered e.g. death or graft loss, there was no statistical difference between the everolimus and control arms.	The summary should confirm that there was no statistical difference between the everolimus and tacrolimus control arms for either graft loss or death.	To correctly summarise the clinical outcomes of trial H2304	No issue of factual accuracy identified. It is not clear to the ERG that there was no statistical difference between the everolimus and control arms when individual endpoints were considered.

Issue 27 Model structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 61 and 94 - The ERG report quotes from the manufacturer submission as follows: '….a renal sub-model *was considered important because the treatment effect* **[survival of liver graft]** *has an impact on more than one aspect of a patients' health.'* The interpretation highlighted in bold inserted by the ERG is highly subjective and should be removed. The model structure was chosen as H2304 clearly demonstrated a statistically significant difference between treatment arms with regard to the preservation of renal function. As previously discussed elsewhere in the manufacturer submission (pg. 57) and in the ERG report (pg. 19) - this effect is most likely due to the reduction of tacrolimus dose that mitigates the adverse events of calcineurin inhibitors (e.g. tacrolimus) such as nephrotoxicity. This is the correct justification for use of a renal sub-model, not the unhelpful	The incorrect clarification added to the quote from the manufacturer submission should be removed.	To correctly convey the content of the manufacturer submission with regard to the presented justification of the model structure.	No issue of factual accuracy identified. For clarity, the added quote has been removed. 'a renal sub-model was considered important because the treatment effect has an impact on more than one aspect of patients' health.'

clarification inserted by the ERG which instead suggests that renal effect is due to survival of the hepatic graft.			

Issue 28 Comparator choice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 87 / 88 / 89- The ERG report again makes reference to the choice of comparators. To be factually representative, it should be confirmed that the comparators included were reflective of the final scope from NICE. Additionally, the comment with regard to MMF and AZA being used with concomitant doses of 'reduced TAC' should highlight the limitations of the evidence base for such comparisons, as previously discussed in Issue 10	ERG to confirm that the comparators included in the company submission were reflective of the final scope from NICE and that including comparisons with 'reduced dose TAC' may have had limited feasibility due to the limitations of the evidence base.	To correctly convey the issues with the choice of comparator for the company submission.	It is the ERG's opinion that reduced TAC monotherapy should have been included as a comparator due to its wide use in clinical practice.

Issue 29 TAC trough levels

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 106 - The ERG report makes observations about the average trough TAC levels in trial H2304. It should be noted that only considering average values does not present the full factual picture with respect to TAC levels- it is also relevant to have awareness as to what proportion of patients achieved the target trough levels. Considering only average levels could be skewed by extreme values.	The report should be amended to include the fact that the proportion of patients that achieved target trough levels is a relevant consideration.	To correctly discuss the issues related to trough TAC levels.	We are happy with the original wording. There is no other way of measuring TAC levels in a trial than using the mean of TAC trough levels. The only other option may be to use a weighted average, however this was not provided in the submission.

Issue 30 Clinical opinion on UK tacrolimus dosing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 106 - The ERG report quotes clinical opinion with regard to standard TAC regimen in the UK. It is not clear if this represents combination therapy with mycophenolate mofetil or azathioprine, or monotherapy.	The ERG report should clarify which immunosuppressive regimen is being considered with respect to the tacrolimus dosing suggested by the clinical adviser.	To ensure complete clarity on which immunosuppressive regimen is being considered in the advice from the clinician.	We are happy with the wording in the text since as stated in the submission on pg 127 and as in line with the Prograf SpC, standard TAC regimen is 5-20 ng/mL. The ERG report clearly compares the reduced TAC arm of the H2304 trial to standard TAC regimen in the UK.

Issue 31 Table 43 -Tacrolimus trough levels in NMA studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 113 - The ERG express concern on the MMF trial arms that were designated 'reduced TAC' As pointed out in Issue 18- in the base case analysis, the definitions for standard reduced dose TAC etc. are as per the definition given in the study- i.e. the company submission has not re-classified studies and used those of the authors of the studies. This applies to all studies quoted in this section by the ERG. Furthermore, it should be noted that the Porayko (1994) and McDiarmid (1993) studies are old and as noted in the McDiarmid study, were conducted before the best method for measuring FK-506 (tacrolimus) levels were established.	The clarifications noted in the first column should be included in this section to clarify the approach taken in the company submission.	To provide a representative comment on the approach taken in the company submission.	No issue of factual accuracy identified. Because different studies used different definitions for standard and reduced doses of TAC, they cannot be compared just by using the definitions. Further consideration should have been given on the profound impact of heterogeneity of these definitions.

Issue 32 Table 43- Tacrolimus trough levels in Porayko

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 114 - The comment made on the Porayko study in Issue 9 applies to this table.	As per Issue 9.	As per Issue 9.	Agreed. The text has been amended. 'TAC trough levels were maintained below 1.0 ng/mL at month 12, **whilst being reported to be higher in the first 4 weeks- with only limited data being reported**.'

Issue 33 Prograf Price

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 126- The ERG report notes that the company submission uses the price of Prograf (tacrolimus) to populate the model. For complete factual clarity, it should be noted that MHRA guidance requires tacrolimus to be prescribed by brand (http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON155756). Therefore, a market share weighted approach to determining the price may not be correct due to dosage variations between brands.	The ERG report should include the fact that MHRA guidance exists with respect to tacrolimus prescribing.	To ensure that the issues around tacrolimus prescribing are factually expressed.	The ERG comment concerns the choice of the brand for TAC. No justification was provided to use Prograf over another brand. Even if the MHRA guidance requires tacrolimus to be prescribed by brand, other brands than Prograf can be used as a continuous treatment by clinicians. Therefore the ERG chose to the average across all brand prices as a conservative choice.

Issue 34 MMF Dosing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 125- The ERG report comments that dose of MMF seems high (in discussion with the clinical adviser) The comment should reflect the fact that dose of MMF recommended in the SPC is 1.5g twice daily (3g per day) for liver transplant patients. http://www.medicines.org.uk/emc/medicine/1681.	This information should be added to the comment.	Communicates the recommended dose of MMF as per the current SPC.	No issue of factual accuracy identified. The ERG report the clinical advisor comments, however for clarity, the text was amended as follows: '**Although the MMF SPC recommends a dose of 3000mg per day**, the ERG's clinical advisor also mentioned that the doses of oral MMF seem high after 1 year, and that 1000 or 2000 (and not 3000) mg would reflect UK clinical practice more accurately for the 1 year post transplantation period.'

Economic model inaccuracies

Issue 35 Model stability

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 12 - The ERG were concerned with the 'lack of stability in the base case ICERs' as they were not able to replicate the same ICERs as reported in the submission. Novartis believe that this is an unfair criticism as the model type (patient simulation) means that small variations in the ICER would be expected. While the company recognises that more could have been done in the submission to detail the checks around this, external validation of the model by an external independent research group that ran diagnostics to determine the stability of the model results with 10,000 patients was performed and found that it was within plausible limits of acceptability.	A more fair critique would be: No evidence was presented in the submission as to model stability and no further clarification was sought at the clarification stage. As a result, the ERG is unable to determine if the model results are within an acceptable threshold of uncertainty around the estimates.	The company accepts that the submission did not adequately justify the number of patients used in the analysis, but does not agree with the interpretation by the ERG. By definition, patient simulation models are probabilistic in nature and therefore a static ICER would not be expected.	No issue of factual accuracy identified. We are happy with the original wording. The ERG found approximately 9% variation in the base case ICER when the model was ran without any changes. Therefore it is the ERG's opinion that the ICER is unreliable.

Issue 36 Discrepancy between NMA estimates and economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 70 - The ERG state that "Comparing Table 24 with Table 23 it can be noted that there is a discrepancy between the NMA estimates and the estimates used in the economic model." This is referring to the absolute decline in eGFR estimates from the NMA used to model renal function decline. The company would like to point out that there was extensive discussion and justification for the use of the standard TAC absolute estimate in the original submission, and in the clarification questions. Therefore, it is not accurate to refer to this as a discrepancy.	The company would like to amend the statement to state that: "The manufacturer provided a justification for the use of the absolute estimate for standard TAC in the economic model and not to assume the estimates for AZA + CIC and MMF + reduced TAC were the same as AZA + standard TAC and MMF + standard TAC."	There is no discrepancy between the NMA results and the economic model. The report goes on to quote the justification for the model inputs (last paragraph on pg. 70)	Page 70 Change made 'Although unclear, it seems that, the estimates for the decrease in eGFR at 12 months used in the comparator arms of the economic model (**Error! Reference source not found.**) are based on the estimate reported for standard TAC in the NMA (**Error! Reference source not found.**).'

Issue 37 Economic model critical appraisal checklists

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 87 / 88 / 89- The ERG provides three critical appraisal checklists for the *de novo* model. The company believes that the appraisal is unfair with respect to some dimensions and actually contradictory in some cases with the issues raised in this response. For example: *Example A:* Pg 87 - Item 1 of NICE decision problem checklist: 'Defining the decision problem' is marked as a tick and therefore clear. In contrast and contradictory: Pg 88 - Item 1 of the Drummond checklist: Has the correct patient group/population of interest been clearly stated? This is marked as a question mark with some concerns. The reviewer comment then refers to the trial population and considerable heterogeneity across the studies in the NMA. The decision problem for the model is	The critical appraisals are reconsidered following the issues of factual inaccuracy raised in this response with respect to the clinical evidence.	Provides clarity on the manufacturer response to questions.	Example A: The scope developed by NICE and the population of interest are two different aspects of the analysis. Example B: It is the ERG's opinion that reduced TAC monotherapy should have been included as a comparator due to its wide use in clinical practice. Furthermore, the study labels for TAC were not within the range in line with the Prograf SpC and as stated in the submission on Pg 127. Example C: No issue of factual accuracy identified. It is the ERG's opinion that the values obtained in the NMA analysis of the absolute results lack robustness. This is because of the heterogeneity of the standard TAC connector across the NMA studies.

clearly stated in the manufacturer submission. *Example B:* Pg 88 - Item 2 of the Drummond checklist: 'Is the correct comparator used?' With respect to the previous issues raised in this response the comparators were included in line with the NICE scope for the available evidence base. The study labels of the TAC arm were taken from those reported by the studies. *Example C:* Pg88 - Item 6 of Drummond checklist: 'Is the effectiveness of the intervention established?' The ERG states: "The effectiveness absolute values obtained for the NMA rely on a non-robust analysis." There is no explanation for this strong point and it was understood previously by the company that the ERG could not run the NMA analysis and therefore this would be difficult to judge. *Example D:* Pg 88 - Item 7 of Drummond checklist: 'Has a lifetime horizon			Example D: No issue of factual accuracy identified, however the ERG agrees that the comment regarding computational burden should be removed from this Item. The text has been updated to 'The time frame seems unnecessarily high, adding to the computational burden of the model.' This doesn't change the fact that the ERG believe that the time frame seems unnecessarily long considering that at around half of the 80-year time frame, 100% of patients are dead. '

been used for the analysis, if not has a shorter time horizon been justified?' A lifetime time horizon was used in the analysis and the question does not request a response on the computational burden. The company believes this requirement was clear and the ERG is answering another question about the computational burden of the model which is not relevant to this item on the checklist.			

Issue 38 Model starting point

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 95- The ERG states that "During the clarification process, the ERG asked the company to clarify at what point after transplantation the model begins. The company clarified that the model starts immediately (one day) post-transplant, as the use of comparator therapies begins at this time point." However, for the EVR + rTAC arm of the model, patients only start receiving treatment for 30 days after entering the model…."	Removing paragraph break.	Provides clarity on the manufacturer response to questions.	No issue of factual accuracy identified, however for clarity the paragraph break has been removed.

This paragraph spacing insinuates that Novartis did not clarify the latter part of this statement			

Issue 39 Mild Chronic Rejection state

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 97- The ERG states that "Clinical opinion sought by the ERG revealed that the state of mild chronic rejection seems somewhat vague and unfamiliar. Our clinical expert advisor did not see any valid (or justifiable) reason for patients only to progress to such state 1 year after transplantation." The company disagrees with this statement. The model was designed in line with discussion with two key clinical opinion leaders in England. These experts explicitly stated that most patients reside in a state of mild chronic rejection after 1 year after transplantation. However they also stated that definitions of this state vary.	This statement should be re-written to present a balanced clinical opinion on the mild chronic rejection state and reflect that Novartis had made it clear in the submission that this state was verified with clinical expert opinion.	To provide a balanced clinical opinion and represent the company justification in line with competing clinical opinions.	No issue of factual accuracy identified. We are happy with the wordings as it is the ERG's clinical expert's opinion that the definition of this state is unclear. Similarlythe two key clinical leaders consulted by the company stated that definitions of this state vary .

Issue 40 Links between hepatic and renal model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 97- The ERG state that “in the context of the decision problem faced in this submission, the ERG’s opinion is that a more interactive model linking hepatic and renal outcomes would be better suited.” The company do not disagree with this opinion, however it should be noted that evidence for the links between hepatic and renal outcome post-liver transplant is not clear, and the decision problem does not expressly link these two components of therapy. No concrete evidence was identified that would give the appropriate risk equations to model these linkages.	A more balanced view of the evidence would be more indicative of the problems with these linkages.	The language used insinuates that the company purposefully did not link these two components.	No issue of factual accuracy identified. The ERG only commented on the fact that the model chosen by the company is not as suitable as an interactive model that would link hepatic and renal outcomes in the scope of this submission.

Issue 41 3-month cycle length and half-cycle correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 100- The ERG state that they are "concerned that 3 month cycles could not capture all the relevant outcomes for the disease modelled as it seems that disease progression is faster in real life than in the model….Finally, from a methodological point of view, a 3 month cycle is a relatively long one, thus a half cycle correction should have been applied." The company worked closely with clinical KOLs to validate this model cycle length. Novartis' advisors considered this was appropriate and that it was unlikely to make a difference with shorter cycle length. The issue of half-cycle correction is a contentious one in the literature, and there are no agreed upon approaches in models with lifetime time horizons. The ISPOR Task Force report on State-Transition Modeling states: "A half-cycle correction should be applied to costs and effectiveness in the first cycle and in the final cycle **if**	This section should reflect the difference in opinion between the ERG and Companies' clinical experts as well as the debate within the literature on half-cycle correction.	To adequately reflect clinical opinion and the health economic methodological debate on the topic raised here.	The ERG acknowledge that the half-cycle correction would not solve the issue regarding the length of the cycle and the text has been removed. However, it is the ERG's clinical opinion that a 3-month cycle is a relatively long one.

not using a lifetime horizon.”			

Issue 42 Probabilities vs. Rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 97-100- The ERG correctly point out that the model incorrectly uses probabilities from the NMA for tBPAR where these should have been converted to rates and back to probabilities. This was an oversight on the part of the company. As the report states later in this section, this is unlikely to have an impact on results and indeed, several test runs on the model using the correct method indicates that this is the case. If pointed out at clarification stage, results could have been provided to the ERG.	The ERG spend pages explaining this, though a one sentence ending states that this is not likely to have an impact on the results given the differences are so small. This section should be more balanced given the weight of the problem, as well as reflect that no questions on this were asked at the clarification stages. The company are happy to provide a corrected model and can confirm that the results from this model are similar to those presented in the submission.	The presentation of this problem in the report offers a skewed view of the size of the problem, implying it would have major impact when in fact it has little impact on the results.	No issue of factual accuracy identified. We are happy with the wordings as it is the duty of the ERG to shed some light on the submission's strengths and weaknesses.

Issue 43 Baseline eGFR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 112- The ERG states: “Even though the simulation in the economic model produced a baseline eGFR average level of 82 mL/min per 1.73 m2, the SD used is not justifiable.” The ERG correctly points out that the model uses the incorrect SD, however, as the range was taken directly from the CSR, it is unlikely to have an impact on the model and the wording used is quite strong.	This is an input error in the model and does not have a large impact on progression as the correct range from the CSR is used. This statement should reflect that this as a typo, and that the justification given in the submission is that this data is from the CSR.	The language used overstates the problem.	No issue of factual accuracy identified. We are happy with the wordings as it is the duty of the ERG to shed some light on the submission’s strengths and weaknesses.

Issue 44 NMA data use in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 113- The ERG states: “Upon the ERG’s request for further detail on how the company used the NMA data to obtain the estimates …. Novartis response to the ERG request for clarification is not really satisfactory as no additional information was provided by the company. Novartis simply presented the same results for which the ERG requested clarification and mentioned that these are the absolute results from the NMA….” The statement in the ERG report is very subjective, and the company believes it to be disingenuous. Novartis provided details of the NMA in the submission, as well as explanations of how the NMA outputs were used in the economic model. In the response to questions, Novartis supplied the absolute estimates and Credible Intervals along with a reference to the relevant section of the original submission dossier	Upon the ERG’s request for further detail on how the company used the NMA data to obtain the estimates, Novartis supplied the ERG with the absolute estimate tables and gave an explanation in Question A18, Question B5, and in the original submission.	The statement is not balanced as it states that we provided no additional information which is incorrect and misleading.	No issue of factual accuracy identified. It is the ERG’s opinion that the clarification was insufficient. The ERG were unable to replicate the NMA results due to a lack of transparency

where the use of these items was explained in more detail. If a more explicit question had been asked about specific details at the clarification stage, Novartis would have been happy to provide more information.			

Issue 45 Economic Model Scenario Analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 131- The ERG states: "The ERG could not find the scenario analysis in the Excel model…. This is particularly unsettling given that the face validity of the results is somewhat questionable." The statement from the ERG insinuates that Novartis was withholding information which was not the case. As the model is already sizable, different scenarios were saved as different versions of the model which would have been supplied upon request. Also, as previously described, Novartis do not agree that the face validity of the model is questionable.	A proposed statement on this would be: The ERG did not request or note that the additional scenario analyses were not included in the economic model and there was no request to the manufacturer to supply further information.	To provide a more balanced view of the scenario analyses.	No issue of factual accuracy identified. The manufacturer should have provided all the relevant information regarding the scenario analysis in the model submittedd in the first instance.

Issue 46 PSA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 132- The ERG states “Novartis ran a PSA using 1000 probabilistic simulations. In two different occasions the company reported that 5000 patients where used in the simulation and that 1000 were used in the simulation (as using 5000 patients supposedly produced the same results as 1000 simulations)” The ERG disagrees with the overall model approach, and gives reasons for this, some of which are discussed above. However, external validation of the model and an analysis of model results and distributional assumptions indicate that the model is producing stable results in the PSA. This information is available upon request.	The company believes this sentence should be deleted or re-stated as the point is not entirely clear. Suggested text is below. Novartis provided the results of a PSA using 1,000 simulations of 1,000 patients. The manufacturer states that this was chosen as the results of repeated PSA using these settings were found to produce similar results as a previous iteration of the PSA which ran 1,000 simulations with 5,000 patients. As model run time was long, the 1,000 simulations of 1,000 patients were chosen as a practicable solution, according to the manufacturer.	This amendment should be made as this statement is unclear.	For clarity, the following amendment has been made: ‘Novartis provided the results of a PSA using 1,000 simulations of 1,000 patients. According to the company, the results were stable at this level of simulation. The company tested a PSA using 1,000 simulations of 5,000 patients and claimed to have similar results. Therefore as the model run time was long, the 1,000 simulations of 1,000 patients were chosen as a practicable solution, according to the company.’

Issue 47 Grammatical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 51 Spelling of the word ‘expected’ is incorrect	Correct ‘eexpected’ to ‘expected’	To correct spelling	Typographical errors corrected
Pg. 77 Spelling of ‘Sullivan’ is incorrect	Correct ‘Sulivan et al, 2011’ to ‘Sullivan et al, 2011’	To correct spelling	
Pg. 91 Spelling of ‘SCR state’ is incorrect	Correct ‘SRS state’ to ‘SCR state’	To correct spelling	
Pg. 96 Spelling of ‘SCR state’ is incorrect	Correct ‘SR state’ to ‘SCR state’	To correct spelling and keep consistency with previous references to this state	
Pg. 97 Spelling of ‘SCR state’ is incorrect	Same as above	Same as above	
Pg. 100 Spelling of ‘stated’ is incorrect	Correct ‘sated’ to ‘stated’	To correct spelling	
Pg. 101 Spelling of ‘starting’ is incorrect	Correct ‘staring’ to ‘starting	To correct spelling	
Pg. 110 Grammar needs to be corrected in following sentence:	Change to: ‘However, two things should be **considered’**	To correct grammar	

‘However, two things should be consider’			