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

Pro-forma Response

ERG report

Dexamethasone intravitreal implant for treating diabetic macular oedema [ID653]

You are asked to check the ERG report from BMJ-TAG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Monday 22 December** 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.

Issue 1 Pair wise meta-analysis synthesising data from MEAD-010 and MEAD-011 qualitatively compared with the results from the NMA were incorrectly reported in the submission and therefore in the ERG report

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>The ERG note their concern that the results of the NMA are substantially different from the meta-analysis which brings into question the validity of the results from the NMA on pages 14, 15, 147 and 321.

The point estimates were reported incorrectly in the submission with mean pseudophakic population data outcomes reported in error rather than median total population data outcomes.</td>
<td>We would kindly request the ERG to review their assessment of the comparability between the pair wise meta-analysis and NMA for MEAD-010 and MEAD-011 based on the corrected outcomes reported below:
<table>
<tr><th rowspan="2">Population</th><th colspan="2">NMA
(RR, [95% CrI])</th><th colspan="2">Direct pairwise meta-analysis
(RR, [95% CrI])</th></tr>
<tr><th>Lose 10+ letters</th><th>Gain 10+ letters</th><th>Lose 10+ letters</th><th>Gain 10+ letters</th></tr>
<tr><td>Total</td><td>0.71 [0.41, 1.08]</td><td>1.40 [0.92, 2.14]</td><td>0.72 [0.35, 1.25]</td><td>1.35 [0.77, 2.21]</td></tr>
<tr><td>Pseudophakic</td><td>0.47 [0.13, 1.14]</td><td>1.79 [0.88, 3.80]</td><td>0.46 [0.13, 1.07]</td><td>1.88 [0.93, 4.32]</td></tr>
</table>
</td>
<td>Mean pseudophakic population data outcomes reported in error in the submission.

The impact of this is significant as the face validity of the NMA is greatly improved when pair wise meta-analysis of the same population and data type are compared.</td>
<td>The ERG is unable to accept new data from the company as part of the factual error check of the ERG report. The errors identified by the company in the company's submission do not change the ERG's view on the validity of the NMA.</td>
</tr>
</table>

Issue 2 Influence of sham/no treatment on NMA outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 190-191 of the ERG report, the following comment is made: "The ERG would like to emphasise the fact that the estimated relative treatment effects for any pair of treatments included in a network are exclusively determined by the estimated relative effects reported in each of the trials that link, directly or indirectly, these treatments in the network, and are not influenced in any way by the absolute effects of these treatments within the network, as estimated by cumulating the absolute effects of the treatments that are observed in each of the individual trials." The NMA model approach resulted in relative risk estimates that were based on the absolute probability of losing ≥10 letters with sham/no treatment in line with the recommended model approach for such a data set in the NICE DSU (see submission, page number 201). This absolute probability is based on synthesised data from all trials (n=4) providing data for sham/no treatment. Relative risk estimates of DEX700 PRN vs. sham/no treatment are derived from this baseline probability and are therefore	We kindly request that the ERG reconsider this statement in light of this clarification.	Clarification of the use of the absolute probability, based on synthesised data from all trials providing data for sham/no treatment may impact the ERG opinion. This has some impact on the validity of utilising NMA analysis in the economic modelling (though we note the further concerns with the application of the NMA).	This is not a factual inaccuracy and therefor no change is required. According to the NMA model approach adopted by the company (which was developed by the NICE TSU), the relative effect of treatments was modelled in the form of log hazard ratios. The relative effect of dexamethasone versus sham (watch and wait) was exclusively informed by the MEAD trials. Subsequently, the company used additional code, also developed by the NICE TSU, to obtain absolute effects of each treatment, using the absolute probability of losing≥10 letters with sham/no treatment and the relative effects of each treatment versus sham/no treatment, as estimated in the NMA. The ERG agrees with the company that the estimation of absolute effects is affected by the baseline probabilities used, and therefore by the absolute probability of sham/no treatment which that was based on synthesised data from 4 trials. Finally, the company developed additional code to estimate relative effects between all pairs of treatments in the form of relative risks, using the estimated absolute probabilities. The ERG considers that this back-calculation of relative effects from absolute effects should result in similar relative effects to those that were originally estimated using the NMA model, which were exclusively informed by the MEAD trials (of course accounting for the difference between the types of outputs, i.e. there should be a difference between log hazard ratios, which were initially estimated using the

influenced by all trials with a sham/no treatment arm, not just those connected with DEX700 PRN.			MEAD data, and relative risks, which was the output produced by the company using the absolute effects). Some further discrepancies may exist due to the assumptions employed by the NMA model, which have been accumulated in each calculation step. The ERG argues that a change in the baseline probability between the MEAD trials and the 4 trials providing sham/no treatment data should not affect the relative effect of dexamethasone versus sham/no treatment which is informed by the MEAD trials. Further to that, the ERG notes that in Issue 1 above, the company demonstrates that the results of the NMA are comparable to the pair-wise meta-analysis of MEAD trials, which is consistent with the ERG's view.

Issue 3 Review and re-treatment period of ranibizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is noted on page 58 of the ERG report that some of the comparators have shorter review and retreatment periods than dexamethasone and ranibizumab is given as an example with note that it is typically 4-monthly. Whilst the overarching message is correct, ranibizumab treatment is initiated with one injection per month until maximum visual acuity is achieved i.e. the patients are monitored monthly. Clinical trial data and expert opinion suggests	The 4-monthly reference should be removed from the example of ranibizumab.	According to clinical trial data and expert opinion, review and retreatment periods are not typically 4-monthly. The impact of this is significant when assessing the clinical benefit of dexamethasone in regard to capacity concerns and patient burden associated with the closer to monthly review and retreatment periods of anti-VEGF therapies.	The ERG thanks the manufacturer for highlighting this inaccuracy and has amended the text on page 58 accordingly.

many patients receive close to monthly treatment throughout the first year of ranibizumab therapy. Thereafter, monitoring and treatment intervals should be determined by the physician. Practicing ophthalmologists in the UK advised they would typically review bi-monthly. The 4-monthly reference in the ERG report does not reflect the SPC or clinical opinion.			

Issue 4 Description of dosing regimens of dexamethasone in PLACID and BEVORDEX

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Dexamethasone regimen is described as 6 monthly and 4 monthly for PLACID and BEVORDEX trials respectively on pages 11 and 72.	Dexamethasone regimen should be described as 6 monthly PRN and 4 monthly PRN for PLACID and BEVORDEX trials respectively.	Current description is in line with format for the 5 monthly continuous regimen adopted in study 024 so could be inferred as continuous treatment regimens which would be incorrect. The impact of this is minimal as this is not how the ERG has inferred the dosing regimen but should be corrected for clarification to new readers.	The ERG thanks the manufacturer for highlighting this inaccuracy and has amended the text on pages 11 and 72 accordingly.

Issue 5 Study referenced in description of subgroup analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
PLACID trial is referenced in the following paragraph on page 13 on the ERG report: "Dexamethasone generally resulted in greater reduction in CRT and improvement in BCVA compared with sham in the PLACID subgroup analyses in people with prior laser or prior anti-VEGF therapy without prior steroid therapy." This subgroup analysis was conducted on the MEAD trial population.	Paragraph should read: "Dexamethasone generally resulted in greater reduction in CRT and improvement in BCVA compared with sham in the MEAD subgroup analyses in people with prior laser or prior anti-VEGF therapy without prior steroid therapy."	Incorrect trial reference. The impact of this is minimal as the ERG are aware of the trial population on which this subgroup analysis was conducted but should be corrected for clarification to new readers.	The ERG thanks the manufacturer for highlighting this inaccuracy and has amended the text on page 13 accordingly.

Issue 6 Subgroup analysis: pseudophakic patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is stated that efficacy results for the pseudophakic subgroup of patients were only presented for the MEAD trial on page 109 of the ERG report. Post-hoc letter gain analysis of the pseudophakic population in PLACID was reported on page 178 of the submission.	This paragraph should be revised to reflect the submission where pseudophakic subgroup analysis was reported for both the MEAD and PLACID studies.	Pseudophakic population data reported for the PLACID trial in the submission. The impact of this is minimal as this subgroup analysis was conducted post-hoc on a small cohort of patients but should be corrected for clarification.	The ERG thanks the manufacturer for highlighting this inaccuracy and has amended the text on page 109 accordingly.

Issue 7 European marketing authorisation application

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 121 of the ERG report, it is stated that: "In addition, the company reported in the CS that the 10-letter improvement data were used as the primary outcome data from the MEAD studies in the European Marketing authorisation application."	The primary endpoint for the MEAD studies in Europe was the mean BCVA average change from baseline (AUC approach). This was therefore the primary outcome data from the MEAD studies in the European Marketing authorisation application. This sentence should therefore be removed.	Unclear as to where the confusion has arisen as it was not noted in the submission that the 10-letter improvement data were used as the primary outcome data from the MEAD studies in the European Marketing authorisation application. The impact of this is minimal as correct rationale for using 10-letter change in NMA is reported in the ERG report but this sentence should be removed for clarification.	The ERG thanks the manufacturer for highlighting this inaccuracy and has amended the text on page 121 accordingly.

Issue 8 Additional NMA conducted

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
As part of the clarification question responses, additional NMA was conducted on request of the ERG. This has been described as additional analysis that used the end point data from each of the studies excluded on the basis that they reported only 12-month data on page 123 of the ERG report. Studies were not excluded on the basis that they reported only 12-month data but rather were	Reference to the additional analysis should be amended to reflect that conducted.	Current description of the additional analysis conducted is incorrect. The impact of this is minimal as the ERG are aware of the details of the additional analysis conducted but this should be corrected for clarification to new readers.	The ERG thanks the manufacturer for highlighting this inaccuracy and has amended the text on page 123 accordingly.

excluded if they reported data at <12 months. In the event that data was only reported at >12 months, this would have been included but no studies reporting only >12 month data met all other eligibility criteria for inclusion in the NMA. The additional analysis conducted incorporated studies excluded from the original NMA on the basis that they only reported <12-month data.			

Issue 9 UK marketing authorisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the clinical issues section on page 148 of the ERG report, the UK marketing authorisation for dexamethasone is not described in full.	The first bullet point should be amended to: "UK marketing authorisation for dexamethasone restricts its use to the treatment of adult patients with visual impairment due to DMO, who are pseudophakic (have an artificial lens), or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy."	Incomplete bullet point. The impact of this is minimal as the ERG are aware of the full UK marketing authorisation but this should be corrected for clarification to new readers.	The ERG thanks the manufacturer for highlighting this inaccuracy and has amended the text on page 148 accordingly.

Issue 10 TRSAEs reported in NCT00035906

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 108 of the ERG report it	Sentence should be amended to reflect	Unconfirmed sentence.	The ERG thanks the manufacturer for highlighting

states that "….there were no incidences of TRSAEs associated with dexamethasone…" This is not strictly in line with what was reported in the submission.	submission content: "….there were no incidences of TRSAEs associated with intravitreal injection: retinal detachment or endophthalmitis…"	The impact of this is minimal as there was only one TRSAE potentially related to treatment reported in the NCT00035906 study and it is not confirmed that this was experienced by a patient with DMO. However, it is not confirmed that this was not experienced by a patient with DMO so sentence should be corrected for clarification.	this inaccuracy and has amended the text on page 108 to reflect the contents of CS reference 5: that there were no treatment related cases of retinal detachment or endophthalmitis in any group as the ERG considers the reporting of TRSAEs in the CS to be potentially misleading.

Issue 11 Incorrect number of citations reported during literature search process

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The number of citations reviewed at level 2 as full text articles in the RCT review is quoted as 675 on page 58 of the ERG report as a direct quote from the submission. This was a text error and should be 672 in line with the PRISMA presented as Figure 8 in the submission.	Sentence should be amended to reflect the correct number of citations taken through to level 2 screening: "The remaining 672 citations were reviewed at level 2 as full text articles where available."	Incorrect number referenced (as a result of the incorrect number referenced in the submission). The impact of this is minimal but should be corrected for clarification to new readers for whom the PRISMA may not be viewed in addition to the textual description of the literature search process.	The ERG is unable to accept new data from the company as part of the factual error check of the ERG report. The ERG agrees with the company that the impact of the error in the company submission is minimal.

Issue 12 Incorrect reporting of limitations of network meta-analysis including FAME study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report correctly cites from the CS that "*The network of*	We would kindly request the ERG to amend the sentence to	Current description of the limitation is incorrect.	The ERG is unable to accept new data from the company as part of the factual

evidence is based around 12-month data for all treatments; the FAME study only reports 24-month outcomes therefore this has been used in the absence of 12-month data" on page 181 and page 194; however this was an error in the reporting of the limitations within the CS which we would like to highlight. 12-month data from FAME was not reported in the text of the publication (whereas 24-month data was) and so the 12-month data was digitised from a line graph presented as a figure in the study publication. This is a limitation, as digitising is not 100% accurate and no uncertainty information were available from the figure.	reflect the different limitation of using the digitised data rather than using 24-month data instead of 12-month data: "The network of evidence is based around 12-month data for all treatments; the FAME study reports 12-month data only in the form of a line graph presented in a figure. The figure provided only the point-estimate and no uncertainty information. 12-month data were therefore digitised from the figure, a method of estimating data which is subject to error."	The impact of this is minimal as this was not the only listed limitation of the analysis, however should be corrected to ensure clarity for readers.	error check of the ERG report. The ERG agrees with the company that the impact of the error in the company submission is minimal.

Issue 13 Reporting of the number of additional treatments required in FAME

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state on pages 185-186 that the CS incorrectly uses LOCF for the number of treatments of fluocinolone acetonide in Year 3, when the Year 3 publication for the FAME study provides data for the number of injections received over 3 years which can be used to calculate the number in Year 3. We	Amend the additional number of injections received to the end of Year 3 to be 0.294 and the resulting number in Year 3 to 0.034 and amend scenario analysis B2 to reflect this change. (pages 186, 263, 297, 313, 443)	We believe the correction has been incorrectly reported and the report should be updated to reflect this. The impact of this is expected to be minimal as the change is 0.002 injections which will only impact the cost of treatment to a very small degree. (The cost of fluocinolone changes from	The publication (Campochiaro et al., Ophthalmol 2012; 119: 2125-32) reports on page 2128: "The percentage of patients that received 1, 2, or 3 study treatments at month 36 was […] 74.4, 21.6, and 4.0 in the low-dose group". Assuming that the 4.0% all had 3 injections, this gives an average of 1.296

are in agreement with this statement having reviewed the publication; however we believe that the revised figure should be 0.294 additional injections instead of the reported 0.296. The publication reports 76.1% with 1 injection, 18.7% with 2 injections and 5.3% with at least 3 injections (Table 1). Assuming the 5.3% all had 3 injections this gives an average of 1.294 treatments by our calculation.		£20,871, reported on page 451 to £20,843 when fluocinolone is at list price and the conclusion of the analysis is not changed).	treatments. The ERG agrees with the company that Table 1 provides different figures. However, the ERG notes that the retreatment figures provided in Table 1 for control and low dose fluocinolone acetonide are identical to those reported in Cunha-Vaz et al. (Ophthalmol 2014; 121: 1892-903) for patients with chronic DMO in the FAME trial. Therefore, the ERG decided to use the figures reported in the text and not in Table 1 (which appear to constitute factual errors in the published paper). The ERG does not consider the figure 0.296 to be a factual inaccuracy, therefore, no change was made in the ERG report.

Issue 14 Incorrect reporting of RRs calculated from non-normalised transition probability matrices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 203-204 the ERG present an analysis where they have back-calculated the RRs using the reported transition probabilities for DEX and for watch and wait (before normalisation of watch and wait transition matrices) and incorrectly state that the RR of worsening vision in states 2 and 3 are estimated to be lower than that in the NMA output. They additionally state that there are small errors in the RRs for other states and	We would appreciate if the ERG would amend the description of this analysis to remove the suggestion that there is a discrepancy between the calculated transition matrices and the RRs used to generate them and that there may be an	The ERG incorrectly suggests that there is a discrepancy and/or error in the economic model regarding the application of the RRs to the DEX transition matrices. This is not the case and so we would appreciate it if the ERG would revise their calculations and amend their discussion of the analysis in light of this. The impact of this is expected to be	The ERG thanks the company for highlighting the inaccuracy observed in the data reported in Tables 64 and 65. The ERG notes that this is not a factual inaccuracy, but rather the result of the approach adopted by the ERG in estimating the figures reported in the two tables. Nevertheless, the ERG recognises that the

other transitions which is due to rounding. The ERG have incorrectly applied their formula to back-calculate the RRs to the probabilities reported to only 2dp in the CS, rather than applying these to the actual numbers in the economic model. Using the rounded values does give errors in states 2 and 3 where the transition probabilities are small (state 2: [redacted] and state 3 [redacted]) however if the ERG were to calculate these within the economic model using the exact probabilities calculated in here, the RR for improving is 0.71 for all states, the RR of worsening is 1.42 for all states and the RR of remaining stable is 1.00 for all states, as expected from the NMA output). Further to this, Table 65 has also been calculated using the rounded probabilities rather than the actual probabilities in the model resulting in errors.	error in the estimated transition matrix for watch and wait prior to normalisation. Table 64 and Table 65 should be revised using the actual observed probabilities in the model rather than the rounded probabilities presented in the CS.	minimal as this was an exploratory analysis by the ERG which did not impact the outcomes of the economic model (the correct values are used in the economic model), however it may provide more confidence in the model calculations.	correction of the figures using more accurate data from the electronic version of the model rather than rounded data provided in the CS increases the reliability of the CS and the accuracy of the ERG report, and therefore has provided more accurately estimated figures in the two tables.

Issue 15 Correction to RRs reported for health state 6 in Table 65 and Table 67

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The RRs in health state 6 calculated by the ERG in Table 66 and Table 67 have been incorrectly reported as 0.00 for worsening and [redacted] for remaining stable in both tables.	In Table 66 the RR for worsening vision should be [redacted] and for stable vision should be [redacted]. In Table 67 the RR for worsening vision should be	The figures reported are incorrect and should be amended for the benefit of the reader. The impact of this is expected to be minimal as this was an exploratory analysis by the ERG which did not impact the outcomes of the economic model. The correct values are	The ERG thanks the company for highlighting this factual inaccuracy and has amended the report accordingly.

	[redacted] and for table vision should be [redacted].	used in the economic model.	

Issue 16 Incidence of cataract in MEAD

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG have stated on page 219 that there is a discrepancy between the cataract incidence calculated from the data provided [redacted] and the cataract incidence reported in the EMA assessment report (67.9%). The reason for this discrepancy is that the two analyses use different data: The ERG analysis uses the number of phakic patients who had cataract surgery in the study eye (Tables 12-21 of the CSRs). The EMA assessment used the proportion of patients experiencing cataract adverse events (Tables 12-20 of the CSRs). Please note, in this analysis the same patient may have had an adverse event on multiple occasions, and therefore could have been counted in more than one year. Yearly data should not	We would appreciate if the ERG would acknowledge that the reason for the discrepancy is that the estimates of the cataract incidence are not based on the same data and are therefore not comparable.	The evidence reported is misleading and should be amended for the benefit of the reader. The impact of this is expected to be minimal.	The ERG thanks the company for clarifying this issue. The ERG has amended the report accordingly.

therefore be used to calculate the total cataract incidence rate.			

Issue 17 Reporting of Czoski-Murray utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 247-248 the ERG correctly reports that the company provided utility values from previous appraisals however they were unclear how the values from Czoski-Murray were estimated or sourced. This was an error in reporting by the company and the values reported as "Czoski-Murray" in Table 83 had been incorrectly labelled as such. The reported values were the values used in TA237 from the regression of EQ-5D values in RESTORE.	We would appreciate if the ERG would amend Table 83 presenting the values provided by the company to state that the values currently labelled Czoski-Murray were actually from TA237 as described.	We have incorrectly labelled the utility values presented and agree with the ERG's presentation of previous utility values in Table 84 as correct. The impact of this is expected to be minimal as the ERG have used the values they know to be correct in their scenario analysis.	The ERG is unable to accept new data from the company as part of the factual error check of the ERG report. The ERG agrees with the company that the impact of the error in the company submission is minimal.

Issue 18 Incorrect reference for Table 106 taken from company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The description for Table 106 (pages 278-281) states that the table was "*taken from CS, Table 116, pgs 317-425*". This is	Amend the reference to state pages 417-425 of the CS.	The reference is incorrect; correcting it would provide clarity for the reader. The impact of this is expected to be	The ERG thanks the company for highlighting this inaccuracy and has amended the report accordingly.

incorrect, the correct page reference is 417-425.		minimal.	

Issue 19 Footnotes for scenario 2 and 3 in Table 106 are misleading

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The footnotes to Table 106 (page 278-281) are incorrect for scenarios 2 and 3. Scenario 2 has a footnote of "*Not applicable to the population of DMO patients who were considered unsuitable for non-corticosteroid therapy*" and Scenario 3 has a footnote of "*Not applicable to the population of DMO patients who are considered insufficiently responsive to non-corticosteroid therapy*".	The footnote to Scenario 2 should read "Not applicable to the population of DMO patients who were considered unsuitable for non-corticosteroid therapy or who were considered insufficiently responsive to non-corticosteroid therapy" The footnote to Scenario 3 should be removed as this is applicable to all populations.	The footnotes included are incorrect; correcting them would provide clarity for the reader. The impact of this is expected to be minimal as the results presented for each scenario are presented in the correct populations.	The ERG thanks the company for highlighting these inaccuracies and has amended the report accordingly.

Issue 20 Results in Table 108 are inconsistent with the submitted economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that Table 108 (page 282) includes updated results of scenario 14 – 100% unilateral treatment in the WSE, claiming the results have come from the economic model.	We would appreciate if the ERG would revise their report to report the original results from the CS for scenario 14: 100% unilateral treatment in the	The results presented by the ERG are incorrect; correcting them would provide clarity for the reader. The impact of this is expected to be minimal as the corrected results would not	The ERG performed this scenario analysis on the model DMO_NICE_Oct2014_All DMO. The ERG set the value in cell F23 (baseline proportion of DMO patients treated bilaterally) on sheet "Con_Patient_Char" at zero (so that all

The results presented in Table 108 do not match those in the submitted version of the electronic model, the results presented in Table 148 of the CS do. The model in question is DMO_NICE_Oct2014_All DMO and the scenario in question is on sheet "Scenario Analysis" with the ICER in cell H189 (ICER £131,276) as reported in the CS.	WSE as these are the correct results.	change the conclusion of the analysis.	patients were treated unilaterally) and the value in cell F34 (proportion of unilateral patients treated in their BSE) on the same sheet at zero as well (so that all unilateral patients were treated in their WSE). The results produced on the "Results" sheet were those reported in Table 108 of the ERG report (page 282) and differed from those reported in Table 148 of the CS and also from the figure in cell H189 of the "Scenario Analysis" sheet of the model. Therefore, the ERG considers that there is no factual inaccuracy in Table 108.

Issue 21 Unable to replicate Table 128

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We have followed the calculations provided in Appendix 9.12 of the ERG report to verify the results presented for the additional analyses performed by the ERG, however we have been unable to replicate the analysis which produced the results in Table 128 as it is not clear which corrections and scenarios were applied to reach this result.	We would appreciate it if the ERG could include a clear description of the amendments made to the model used to give the results of analysis A4 in order that we may be able to reproduce the results in Table 128.	It is not clear how these results were reached and a clear explanation of the corrections and scenarios applied would aid understanding for the reader.	The ERG thanks the company for highlighting the inaccuracy in the figures reported in Table 128 and has amended the report accordingly. The calculations provided in Appendix 9.12 are correct, but the sentence above the table on page 448 providing calculations for analysis C14 should be omitted.

Issue 22 Discrepancy in fluocinolone results of Table 131

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We believe that the result obtained for fluocinolone acetonide in Table 131 is incorrect. We have followed the calculations provided in Appendix 9.12 applying these in the submitted model and replicated the results for DEX and watch and wait, however have obtained different results for fluocinolone acetonide. The results we have obtained are provided in Table 1 of the appendix to this proforma.	We would appreciate if the ERG would double-check that their updates applied to the model to obtain the results in Table 131 have been applied to the base case settings in the submitted economic model and to update their analysis if this is not the case.	We have been unable to replicate the results presented by the ERG, starting from the submitted model and applying the updates as detailed in Appendix 9.12. The impact of this is expected to be minimal as the differences between the results are small.	The ERG is unable to identify any factual inaccuracy in Table 131. The ERG has double-checked that the base case settings have been used, and that additional scenarios B1-B5 and C6-C12 have been applied, as described in Appendix 9.12. The results produced with the above settings are consistent with the results provided in Table 1 and therefore no corrections to the report have been made. The ERG notes that calculations are based on the figure 0.296 for additional injections for fluocinolone acetonide in Year 3, and not 0.294 that was the figure suggested by the company in Issue 13.

Issue 23 Discrepancy in watch and wait results of Table 131

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We believe that the result obtained for watch and wait in Table 133 is incorrect. We have followed the calculations provided in Appendix 9.12 applying these in the submitted model and replicated the results for all other interventions, however have obtained different	We would appreciate if the ERG would double-check that their updates applied to the model to obtain the results in Table 133 have been applied to the base case settings in the submitted economic model	We have been unable to replicate the results presented by the ERG, starting from the submitted model and applying the updates as detailed in Appendix 9.12. The impact of this is expected to be minimal as the differences between the results are small.	The ERG thanks the company for highlighting the inaccuracy in the figures reported in Table 133 and has amended the report accordingly.

results for watch and wait. The results we have obtained are provided in Table 2 of the appendix to this proforma.	and to update their analysis if this is not the case.		

Issue 24 Error in calculation instructions in Appendix 9.12 for scenario C7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The description of the change required to apply scenario 7 to the economic model states that cells C32:C36 in Inp_MRU should be changed from 2 to =IF('ERG analysis'!E9=TRUE,0,2); however the description of the scenario is to change the number of IOP visits to zero (only applicable for DEX). IOP visits for DEX are found in cells C32:G32 and so these are the cells in which the formulae should be replaced.	We suggest that the calculations reported for scenario C7 in appendix 9.12 are amended to reflect that it is cells C32:G32 which need to be changed in the Inp_MRU sheet.	The impact of this is expected to be minimal due to the small number of IOP appointments required and the low cost of these; however the current description is incorrect and misleading and those who are unfamiliar with the model may not be able to replicate this scenario based on these instructions.	The ERG thanks the company for highlighting the inaccuracy reported in the calculation sheet and has amended the report accordingly. The ERG confirms that the change in IOP visits from 2 to zero has been correctly applied in the electronic version of the model when running the additional analyses involving this scenario.

Issue 25 Discrepancies in results of Table 168

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We believe that the total cost obtained for DEX in scenario C2 of Table 168 is incorrect. We believe that the total cost should be £22,342 and the incremental cost	We would appreciate if the ERG would double-check that their updates applied to the model to obtain the highlighted results in Table	We have been unable to replicate all of the results presented by the ERG, starting from the submitted model and applying the updates as detailed in Appendix 9.12.	The ERG agrees with the company that in scenario 2 the rounded total cost for DEX is £22,342 (instead of £22,341 reported in Table 168); however, the incremental cost is £1,947, as reported in the table. The

therefore £1,948. It is likely that this is a rounding error in reporting. We also believe that the DEX total cost in scenario C12 of Table 168 is incorrect. We believe that the total cost should be £20,554 and the incremental cost therefore £1,328. We have followed the calculations provided in Appendix 9.12 applying these in the submitted model and replicated the results for all other interventions, however have obtained different results as discussed.	168 (scenarios C2 and C12) are correct.	The impact of this is expected to be minimal as the differences between the results are small.	ERG does not consider this negligible difference in the total cost for DEX due to number rounding a factual error and therefore no change has been made in the ERG report. The total and incremental cost figures for DEX in scenario C12 that are presented in Table 168 of the ERG report are £20,554 and £1,328, as suggested by the company, and therefore no correction is required.

Issue 26 Discrepancies in fluocinolone acetonide cost results of Table 169

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We believe that the cost results obtained for fluocinolone acetonide in Table 169 are incorrect, including the base case results which do not correspond with the results presented in Table 109 of the ERG report that have been correctly reported from the CS). We have followed the calculations provided in Appendix 9.12 applying these in the submitted model and replicated the results DEX and for	We would appreciate if the ERG would double-check that their updates applied to the model to obtain the results in Table 169 have been applied to the base case settings in the submitted economic model and to update their analysis if this is not the case.	We have been unable to replicate the results presented by the ERG, starting from the submitted model and applying the updates as detailed in Appendix 9.12. The impact of this is expected to be minimal as the differences between the results are small.	The ERG checked the submitted models and found that, in fact, the results for fluocinolone acetonide provided by the company are incorrect. This is because the economic model submitted by the company includes an error in the sheet “Inp_Treatment” as cell E25 should have the value of 1.75 (number of appointments for bilateral injections for fluocinolone acetonide) instead of the incorrect value of 1.50, which was the original value of the cell in the submitted

watch and wait, however have obtained different results for fluocinolone acetonide. The results we have obtained are provided in Table 3 of the appendix to this proforma.			model. Therefore, the ERG has added text before Table 109 in the ERG report, to note this issue.

Issue 27 Discrepancies in fluocinolone acetonide cost results of Table 170

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We believe that the total cost obtained for watch and wait in scenarios C5, C11 and C12 of Table 170 are incorrect. We have presented revised results for these scenarios in Table 4 of the appendix to this proforma. We have followed the calculations provided in Appendix 9.12 applying these in the submitted model and replicated the results for all other interventions, however have obtained different results as discussed.	We would appreciate if the ERG would double-check that their updates applied to the model to obtain the results in Table 170 have been applied to the base case settings in the submitted economic model and to update their analysis if this is not the case.	We have been unable to replicate the results presented by the ERG, starting from the submitted model and applying the updates as detailed in Appendix 9.12. The impact of this is expected to be minimal as the differences between the results are small.	The ERG thanks the company for highlighting the inaccuracies reported in Table 170 and has amended the report accordingly. The ERG agrees with the company figures provided in Table 4 of the appendix for this proforma, except the results for scenario C12.

Issue 28 Editorial errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Some placeholders for data, section references, table references and box references not updated in the ERG report: Section reference missing on page 51 Discontinuation data missing on page 86 Table reference missing on page 102 Table reference missing on page 103 Table reference missing on page 104 Table reference missing on page 114 Table reference missing on page 115 Box reference missing on page 122 in text and in box label "Section 0" referred to on pages 157, 161 and 288 References missing and "Error! Reference source not found." In place on page 296	Placeholders to be updated as follows: Section reference on page 51 should be "…individual trial are provided in Section 4.5.2." Discontinuation data on page 86 should be "…(35.9% dexamethasone vs. 56.6% sham) suggests…" Table reference on page 102 should be "….and no deaths deemed attributable to treatment (Table 24)." Table reference on page 103 should be "…in the MEAD studies are presented in Table 25." Table reference on page 104 should be "….of these were deemed related to treatment (Table 25)." Table referenced on page 114 should be "….of pseudophakic patients are	Placeholders corrected. The impact of this is minimal but should be corrected for clarification to new readers.	The ERG thanks the company for highlighting these inaccuracies and has amended the report accordingly.

	presented in Table 31." Table referenced on page 115 should be "…each of the safety outcomes reported in Table 32." Box label of page 122 should be Box 11 and box referenced on page 122 should be "…random effects model is presented in Box 11." It is not clear what sections should be referred to in place of Section 0 It is not clear what references should be included in place of "Error! Reference source not found."		

Appendix: Supplementary tables

Table 1: Manufacturer results for analysis presented in Table 131 of the ERG report

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs baseline
	Cost	QALY	Cost	QALY		
Fluocinolone acetonide at list price						
Watch and wait	£15,171	5.6791	-	-	-	-
DEX	£16,601	5.7438	£1,431	0.0647	£22,105	£22,105
Fluocinolone acetonide	£20,156	5.8220	£3,554	0.0781	£45,496*	£34,897
Fluocinolone acetonide at 50% discount						
Watch and wait	£15,171	5.6791				
Fluocinolone acetonide	£15,220	5.8220	£49	0.1428	£344	£344
DEX	£16,601	5.7438	£1,382	-0.0781	Fluocinolone acetonide dominates	£22,105
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. *Fluocinolone acetonide vs dexamethasone						

Table 2: Manufacturer results for analysis presented in Table 133 of the ERG report

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER	ICER vs baseline (laser)
Laser	£6,831	5.1369				
Bevacizumab	£7,915	5.2359	£1,084	0.0990	£10,736*	£10,945
DEX	£12,841	5.0894	£4,926	-0.1465	Bevacizumab dominates	-£126,595
Ranibizumab (50% discount)	£13,556	5.2054	£5,640	-0.0305	Bevacizumab dominates	£98,134
Watch and wait	£14,799	4.9847	£6,883	-0.2512	Bevacizumab dominates	-£52,356
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. *Bevacizumab vs laser						

Table 3: Manufacturer results for analysis presented in Table 169 of the ERG report

Analysis	Intervention / Comparator	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
Base case	DEX700	£20,413	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,464	-0.0655	Dominated
	fluocinolone acetonide	£22,365	5.8214	£1,953	0.0794	£24,591
Model corrections						
B1: FEI rate set to	DEX700	£20,146	5.7438	-	-	-
	watch and wait	£21,520	5.6791	£1,374	-0.0647	Dominated

23.77%	fluocinolone acetonide	£22,176	5.8220	£2,029	0.0781	£25,978
B2: Re-treatments for fluocinolone not based on LOCF	DEX700	£20,413	5.7420	-	-	-
	fluocinolone acetonide	£20,857	5.8214	£444	0.0794	£5,590
	watch and wait	£21,877	5.6765	£1,020	-0.1449	Dominated
B3: Cataract extraction to amended ERG figures	DEX700	£20,837	5.7420	-	-	-
	watch and wait	£21,874	5.6765	£1,037	-0.0655	Dominated
	fluocinolone acetonide	£22,365	5.8214	£1,528	0.0794	£19,241
B4: Cost of fluorescein angiography at £144	DEX700	£20,633	5.7420	-	-	-
	watch and wait	£22,137	5.6765	£1,504	-0.0655	Dominated
	fluocinolone acetonide	£22,580	5.8214	£1,948	0.0794	£24,528
B5: Vitreous haemorrhage cost at £989 & retinal detachment cost at £1,080	DEX700	£20,302	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,574	-0.0655	Dominated
	fluocinolone acetonide	£22,365	5.8214	£2,063	0.0794	£25,980
All model corrections	DEX700	£20,674	5.7438	-	-	-
	fluocinolone acetonide	£20,898	5.8220	£224	0.0781	£2,865
	watch and wait	£21,778	5.6791	£880	-0.1428	Dominated
Additional scenario analyses						
C1: Annual probability of FEI of 55.28%	DEX700	£22,267	5.7294	-	-	-
	fluocinolone acetonide	£23,727	5.8174	£1,460	0.0880	£16,580
	watch and wait	£24,330	5.6583	£603	-0.1591	Dominated
C2: Probability of deterioration of vision increased to 5.5%; improvement 3.5% and stable 91%	DEX700	£22,342	5.7287	-	-	-
	fluocinolone acetonide	£23,582	5.8073	£1,240	0.0786	£15,784
	watch and wait	£24,284	5.6648	£702	-0.1426	Dominated
C3: Discontinuation set at zero	DEX700	£21,511	5.7394	-	-	-
	fluocinolone acetonide	£22,380	5.8275	£869	0.0881	£9,856
	watch and wait	£25,171	5.6536	£2,791	-0.1739	Dominated
C4: HR of mortality 3.5 for DMO vs. general population	DEX700	£18,948	5.2991	-	-	-
	watch and wait	£19,782	5.2388	£834	-0.0603	Dominated
	fluocinolone acetonide	£21,410	5.3721	£2,462	0.0730	£33,726

C5: NA	-	-	-	-	-	-
C6: Monitoring visits are incorporated into treatment visits	DEX700	£20,179	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,698	-0.0655	Dominated
	fluocinolone acetonide	£22,331	5.8214	£2,152	0.0794	£27,101
C7: IOP checks removed from model	DEX700	£19,989	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,888	-0.0655	Dominated
	fluocinolone acetonide	£22,365	5.8214	£2,376	0.0794	£29,928
C8: Private residential care at £532 per week	watch and wait	£14,443	5.6765	-	-	-
	DEX700	£16,436	5.7420	£1,994	0.0655	£30,424
	fluocinolone acetonide	£20,800	5.8214	£4,363	0.0794	£54,953
C9: Cost of depression at £2252	DEX700	£20,778	5.7420	-	-	-
	fluocinolone acetonide	£22,509	5.8214	£1,731	0.0794	£21,800
	watch and wait	£22,560	5.6765	£51	-0.1449	Dominated
C10: Mean cost of raised IOP (medication) at £88.77	DEX700	£20,376	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,501	-0.0655	Dominated
	fluocinolone acetonide	£22,340	5.8214	£1,964	0.0794	£24,734
C11: Mean cost of raised IOP (surgical) at £1273	DEX700	£20,417	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,460	-0.0655	Dominated
	fluocinolone acetonide	£22,424	5.8214	£2,007	0.0794	£25,282
C12: Add 6 extra IOP visits for those with raised IOP	DEX700	£20,521	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,356	-0.0655	Dominated
	fluocinolone acetonide	£23,040	5.8214	£2,519	0.0794	£31,772
C13: NA	-	-	-	-	-	-
Abbreviations used in the table: Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; FEI, fellow eye involvement; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure; NA, not applicable.						

Table 4: Manufacturer results for analysis presented in Table 170 of the ERG report

Analysis	Treatment	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
C5: Bilateral treatment with anti-VEGF 75% 1	laser	£8,361	5.1368	-	-	-
	bevacizumab	£9,191	5.2377	£830	0.1010	£8,219
	DEX700 PRN	£15,720	5.0886	£6,529	-0.1491	Dominated
	ranibizumab	£21,549	5.2066	£12,358	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,632	-0.2553	Dominated

admin visit						
C11: Mean cost of raised IOP (surgical) at £1273	laser	£8,364	5.1368	-	-	-
	bevacizumab	£9,402	5.2377	£1,038	0.1010	£10,285
	DEX700 PRN	£15,724	5.0886	£6,322	-0.1491	Dominated
	ranibizumab	£21,724	5.2066	£12,322	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,421	-0.2553	Dominated
C12: Add 6 extra IOP visits for those with raised IOP	laser	£8,404	5.1368	-	-	-
	bevacizumab	£9,447	5.2377	£1,043	0.1010	£10,330
	DEX700 PRN	£15,826	5.0886	£6,379	-0.1491	Dominated
	ranibizumab	£21,728	5.2066	£12,281	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,376	-0.2553	Dominated
Abbreviations used in the table: Abbreviations used in table: CS, company submission; DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; FEI, fellow eye involvement; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure; NA, not applicable.						