Single Technology Appraisal (STA)
Dexamethasone intravitreal implant for treating diabetic macular oedema [ID653]

Dear Ms Shergill,

The Evidence Review Group, BMJ Technology Assessment Group (BMJ-TAG), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 13 October 2014 by Allergan. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will address these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm on Friday 14 November 2014.**

Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Fay McCracken, Technical adviser, (fay.mccracken@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager, (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation
Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Individual trials

A1. **Priority question:** Please provide the clinical study reports for the NCT00036906 trial and BEVORDEX trials.

The clinical study report for BEVORDEX cannot be provided. This is an ongoing, investigator initiated study. The clinical study report is therefore not available and will not be the property of Allergan Limited when it is available.

The clinical study report for NCT00035906, otherwise known as DC103-06, is provided alongside this response document.

A2. Page 22, Table 15 (of the company submission). Please provide the baseline characteristics for the following subgroups in the MEAD-010 and MEAD-011 studies:
a) pseudophakic patients
b) phakic patients
c) treatment naive patients
d) patients who were not treatment naïve

Baseline characteristics for the pseudophakic subgroup of patients enrolled in MEAD-010 and MEAD-011 were presented in Appendix 21 of the company submission. Baseline characteristics for phakic patients, treatment naïve patients and patients who were not treatment naïve (treatment exposed) patients are provided in Appendix A2. Baseline characteristics for pseudophakic patients are also included in Appendix A2 for completeness.

A3. Please complete the table below to provide a breakdown of the number of patients at baseline in the full randomised population who were enrolled in MEAD-010 or MEAD-011 because they refused treatment or the investigator decided the patient would not benefit from laser treatment:

This level of detail regarding the eligibility criterion relating to treatment history was not collected in the individual clinical report files for patients enrolled in MEAD-010 or MEAD-011. Unfortunately, this table cannot therefore be completed.

A4. Please conduct a pair-wise meta-analysis of MEAD-010 and MEAD-011 for all outcomes reported in the submission and provide the meta-analysis files and results. Please compare the results of this meta-analysis with the pooled results for MEAD.

Pair-wise meta-analysis using a random effects model that calculates the within-trial differences to give a pooled summary estimate was conducted in R for clinical efficacy outcomes reported in the submission for the ITT populations of MEAD-010 and MEAD-011.
For continuous outcomes, the mean difference between DEX700 and sham treatment arms is calculated along with the between-group difference (p-value). For binary outcomes, an odds ratio for the event occurring in the DEX700 treatment arm vs. the sham treatment is calculated along with the between-group difference (p-value).

The forest plots presenting DEX700 vs. sham treatment comparisons from pair-wise meta-analysis are presented in Appendix A4. A summary of the pooled results presented in the submission and these pair-wise meta-analysis results are provided in Table 1.

Table 1: DEX700 vs. sham treatment comparisons from pooled and pair-wise meta-analysis of MEAD-010 and MEAD-011

	Pooled results		Pair-wise meta-analysis results	
	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Mean BCVA average change (AUC approach)	1.4 (0.2, 2.6)	0.023	1.54 (0.26, 2.81)	0.018
Mean BCVA change from baseline at study end	2.1 (-0.0, 4.2)	0.054	2.46 (0.33, 4.60)	0.024
Mean CRT average change (AUC approach)	-68.6 (-84.8, -52.4)	<0.001	-68.33 (-86.55, -50.12)	<0.001
Mean CRT change from	-54.2	<0.001	-56.08	<0.001

baseline at study end	(-81.1, -27.3)		(-84.88, -27.27)	
Mean NEI-VFQ-25 composite score average change (AUC approach)	-0.38 (-2.00, 1.23)	0.644	-0.24 (-1.96, 1.49)	0.788
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
BCVA improvement of ≥15 letters from baseline at study end	2.10 (1.39, 3.15)	<0.001	2.09 (1.39, 3.15)	<0.001
BCVA improvement of ≥10 letters from baseline at study end	1.82 (1.31, 2.52)	<0.001	1.82 (1.31, 2.52)	<0.001
Key: AUC, area under the curve; BCVA, best-corrected visual acuity; CI, confidence interval; CRT, central retinal thickness; DEX, dexamethasone; NEI-VFQ-25, National Eye Institute-visual function questionnaire-25.				

In the majority, the pooled results and pair-wise meta-analysis results are very similar. The biggest differences are observed in the mean BCVA change from baseline at study end and mean NEI-VEF-25 composite score average change (AUC approach) outcomes. This is perhaps unsurprising as the biggest between study differences are observed for these outcomes.

Of note, in pair-wise meta-analysis, DEX700 shows statistically significant superiority over sham treatment in mean BCVA change from baseline at study end analysis.

R code and data files for all pairwise meta-analysis models are provided alongside this response document.

A5. Please provide the per protocol results for the best corrected visual acuity outcomes reported in study 024 and an assessment of these in relation to the non-inferiority margins specified.

In per protocol analysis of the primary efficacy outcome, mean best-corrected visual acuity (BCVA) average change, [redacted] presented in Table 2.

Table 2: Mean BCVA average change from baseline during study 024, ETDRS letters (SD) – per protocol population

	DEX700 ([redacted])	RAN ([redacted])	DEX700 versus RAN		
			p-value	difference	95% CI
Mean BCVA at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean BCVA average change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					

Post-hoc analysis of secondary BCVA efficacy outcomes in the per protocol population [redacted] In per protocol analysis of the mean BCVA change from baseline [redacted] as presented in Table 3. In per protocol analysis of BCVA category change from baseline [redacted] as presented in Table 4. [redacted]

Mean BCVA average change (AUC approach) is based on observed data and thus the analysis presented in the submission is the only analysis of this outcome.

Table 3: Mean BCVA change from baseline in study 024, ETDRS letters (SD) – per protocol population

	DEX700 ([redacted])		RAN ([redacted])	
	Mean change	p-value	Mean change	p-value
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 2	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 4	[redacted]	[redacted]	[redacted]	[redacted]
Month 5	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 7	[redacted]	[redacted]	[redacted]	[redacted]
Month 8	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 10	[redacted]	[redacted]	[redacted]	[redacted]
Month 11	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

Table 4: BCVA category change from baseline in study 024 at Month 12, n (%) – per protocol population

	DEX700[redacted]	RAN [redacted]
≥15 letters improvement	[redacted]	[redacted]
≥5 and <15 letters improvement	[redacted]	[redacted]
No change (between -4 to +4 letters)	[redacted]	[redacted]
≥5 and <15 letters worsening	[redacted]	[redacted]
≥15 letters worsening	[redacted]	[redacted]
[redacted]		

Mixed treatment comparisons

A6. **Priority question:** Please provide working WinBUGS code files used for all mixed treatment comparisons (MTCs) (including sensitivity analyses) presented in the submission. Please provide the WinBUGS code files for the competing risks (mutually exclusive) model as well as for the baseline model, including the priors, initial values, and the formatted data.

WinBUGS code files for all MTC models are provided alongside this response document.

A7. **Priority question: Page 345** (of the company submission). Please clarify why 12-month data were used in the MTC and not data from any time point given that the relative risks estimated by the MTC were subsequently used to inform the economic model at 3-month cycles assuming constant relative risks.

Within the clinical evidence base identified for use in the MTC, BCVA letter gain or loss analysis was more commonly reported at 12-months, more than at any other time point. This was the primary efficacy analysis time point in five of the seven comparator trials used in the MTC models.

Of the trials meeting all other eligibility criteria applied to the systematic search results to identify the evidence base for MTC, the only trial with letter gain or loss analysis that did not report 12-month data but did report such data at a different time point was NCT00035906. As this trial assessed the clinical benefit of a single DEX700 implant, it is not considered of relevance to the comparative efficacy analysis of long-term effectiveness of DMO therapies evaluated in the economic modelling. Therefore, expanding the MTC data eligibility criterion from 12-months to any time point was not considered of value to the subsequent analyses.

A8. **Priority question:** As the relative risks used to inform the economic model are assumed not to change over time, there is no need to include only studies reporting 12-month data in the network. Please drop this criterion from included data and re-run the analysis using endpoint data from all the studies meeting the updated eligibility criteria for the MTC analysis (e.g. study NCT00035906 would now be included). Please provide updated WinBUGS files as specified in question A6.

As confirmed in the response to question A7, NCT00035906 is the only additional study meeting the requested updated eligibility criteria for outcomes of one or more of the following:

- Proportion of patients achieving at least a 10 letter gain from baseline

- Proportion of patients achieving at least a 10 letter loss from baseline

This study investigated the clinical efficacy of a single DEX700 treatment so is not explicitly comparable with any of the DEX700 treatment arms included in the MTC analysis presented in the submission. There is no benefit in including it as an additional treatment arm given that the outcomes of a single DEX700 treatment arm would not be relevant in the analysis of long-term effectiveness of DMO therapies in subsequent economic modelling. It could be considered equivalent to the DEX700 PRN treatment arm of the first six months of the MEAD trial programme, therefore data from NCT00035906 has been included in the requested update to the MTC analysis as an additional DEX700 PRN vs. sham/no treatment study. The fact that it is a single treatment trial should however be noted as a limitation of this update analysis. An additional limitation of this trial is that only 10-letter gain analysis is reported for the intent-to-treat population of all randomised patients so the proportion of patients losing at least 10-letters from baseline and the proportion of patients neither losing or gaining 10-letters from baseline is estimated within the MTC model.

The networks of evidence and forest plots presenting treatment comparisons from the updated MTC analysis are presented in Appendix A8. A summary of the original results and these updates results for the key comparisons taken from the relevant MTC models are provided in Table 5. Trends observed in the original results are mirrored in the requested analysis including study NCT00035906 with no effect on the overall conclusions of the MTC analyses.

Table 5: Original and updated MTC analysis outcomes for key comparisons

Comparison	Losing ≥10 letters, RR (95% CI)		Gaining ≥10 letters, RR (95% CI)	
	Original analysis	Requested analysis	Original analysis	Requested analysis
DEX700 PRN vs. sham/no treatment[a]	0.71 (0.41, 1.08)	0.72 (0.45, 1.02)	1.40 (0.92, 2.14)	1.39 (0.97, 2.01)
DEX700 PRN vs. bevacizumab[b]	18.75 (1.15, 1538.05)	21.42 (1.57, 1087.02)	0.41 (0.11, 0.95)	0.37 (0.11, 0.82)
Laser vs. DEX700 PRN[b]	0.64 (0.13, 2.66)	0.56 (0.14, 1.68)	1.27 (0.61, 3.39)	1.38 (0.73, 3.23)
Ranibizumab vs.	[redacted]	[redacted]	[redacted]	[redacted]

DEX700 PRN[b]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab + laser vs. DEX700 PRN[b]	[redacted]	[redacted]	[redacted]	[redacted]
Fluocinolone acetonide vs. DEX700 PRN[c]	0.64 (0.25, 1.54)	0.63 (0.27, 1.30)	1.39 (0.71, 2.72)	1.41 (0.80, 2.49)
Key: CI, confidence interval; DEX, dexamethasone; MTC, mixed treatment comparison; PRN, *pro re nata*; RR, relative risk **Notes**: [a]total population base case model; [b]pseduophakic population model; [c]total population sensitivity analysis model including FAME				

WinBUGS code files for the updated MTC models are provided alongside this response document.

A9. **Priority question: Page 185** (of the company submission). The additional eligibility criteria for the MTC analysis consider only interventions included in the scope as comparators. Please provide the full references of studies that were excluded from the network because of this criterion.

In total, 48 studies were excluded on the basis that the comparator arm utilised in the trial was not an active treatment included in the scope of the submission. The reference list for these studies is provided in Appendix A9.

Five of these studies are included in this reference list as they did not adhere to EU licence terms (or clinical practice in the case of bevacizumab) of loading dose requirements for anti-VEGF therapy. These trials were reviewed for potential inclusion in sensitivity analyses at the time of MTC planning but none reported letter gain or loss analysis at any time point that could be utilised. These studies are underlined in Appendix A9.

A10. Please provide justification and details of the mixed-treatment comparison model used for evidence synthesis. The competing risks model described in the NICE DSU Technical Support Document 2 is based on the assumption of constant hazards, which appears to be different to the model in the company submission.

The competing risks model referenced here is not the model upon which evidence synthesis was based. The model selected was the multinomial model that handles ordered categorical data that best fitted the efficacy outcome data. This model is described in the NICE DSU Technical Support Document 2[1] on pages 7-8 ("Ordered Categorical Data: Multinomial Likelihood and Probit Link (Appendix: Example 6)").

A11. Please provide the Deviance Information Criterion (DIC) and a comparison of the residual deviance with the number of unconstrained data points for each outcome when using a fixed and random effects model for the MTC.

Only a random-effects model was fitted to the data as there was no reason to believe *à priori* that the heterogeneity between studies would be zero. The trials are not homogenous in terms of trial design e.g. rescue therapy rules (see section 6.7.9 of the submission). Therefore a random-effects model was deemed a more appropriate choice as it incorporates a between-study heterogeneity parameter.

The DIC that assists with model selection was not therefore calculated and the residual deviance for each outcome when using a fixed model for the MTC is not available. A comparison of the residual deviance and the number of unique data points for the total population base case and pseudophakic population random effects model used for the MTC is provided in Table 37 of the submission. The same data is provided for the total population sensitivity analysis (including FAME) in Table 6.

Table 6: Between-study heterogeneity and model fit for total population sensitivity analysis (including FAME)

Between-study standard deviation (median; 95% CrI)	Total residual deviance (mean)	Number of unique data points
0.12 [0.01, 0.42]	68.2	50
Key: CrI, credible interval		

A12. Page 201 (of the company submission). Please justify why a binomial likelihood rather than a multinomial distribution (similar to the relative effects model) was used for the baseline model (sham/no treatment) in the MTC. Please also clarify how a dichotomous outcome (loss of at least 10 letters in best corrected visual acuity) was used in the baseline model to provide baseline probabilities for a multinomial distribution.

A binomial likelihood using a probit link function was fitted to trials with a sham/no treatment arm only and considered only the lowest category of data (loss of 10 or more letters) because the probabilities of being in the other categories (stable and gaining 10 or more letters) are

estimated within the model. There is no need to model more than two categories for the baseline since we used a cut-off parameter (z) in the model which is not fixed but is estimated by the data in the model so that we can derive the probability of achieving other categories for a particular treatment. There is also a treatment effect parameter (d) which calculates the effects vs. sham/no treatment for a given category. Therefore, only the lowest category for the sham/no treatment arm is needed for the baseline model. This can be seen by the following code in the WinBUGS model:

```
T[j,k] <- 1 - phi(A + d[k] + z[j]),
```

where j is the category and k is the treatment arm.

A is the probability (on the probit scale) of being in the lowest category of vision for sham/no treatment and d[k] is the relative treatment effects for treatment k vs. sham/no treatment and z[j] is the cut-off for each of the three categories of vision, j. d[k] and z[j] are added to the mean probability of being in the lowest category of vision for sham/no treatment. As such, only the probability of losing 10 or more letters for the sham/no treatment arm is needed within the baseline model.

A13. Page 195 (of the company submission). Please clarify what assumptions have been made in order to split the proportion of patients not achieving a 10-letter improvement into a proportion of patients with 10-letter deterioration and a proportion of patients remaining stable in the BOLT trial in order to consider the data in the mixed-treatment comparison analysis.

There are three categories of vision (loss of 10 or more letters, stable, gain of 10 or more letters). Although BOLT only provides data for gaining 10 or more letters, the model allows us to borrow strength from the remaining trials within the model which report data for all three categories, and this allows us to estimate the cut-off points between categories. The proportions of patients in the loss and stable categories are estimated by the model by adding the treatment effect and the cut off to the probability being in the lowest category for the sham/no treatment arm (see the equation in response to A12).

A14. Page 214 and 215 (of the company submission). Please give more details on the mean multiplication factor of 1.989 that was estimated for sensitivity analysis 1 of FAME data, regarding its range and distribution across studies and interventions. Please also provide the assumptions made in order to estimate proportions of patients remaining stable and deteriorating by at least 10-letters for FAME, that were utilised in the mixed-treatment comparison model.

All trials within the clinical RCT evidence base that reported data for both ≥15 letter gain and ≥10 letter gain at 12 months were included in the calculation of the mean multiplication factor.

A relationship was established between ≥10 letter gain and ≥15 letter gain i.e. for each trial, a multiplying factor was calculated to get from ≥15 letter gain to ≥10 letter gain. The average (mean) of these individual multiplication factors was calculated to be 1.989. This overall mean multiplication factor was subsequently applied to the 15 letter gain data presented for the FAME study[2] to estimate the 10 letter gain data.

The ≥10 and ≥15 letter gain data and the resulting multiplication factor calculations are presented in Appendix A14. Of note, at the time of this analysis, BEVORDEX was only available in abstract form[3] in which only ≥10 letter gain data was presented. Therefore data from this trial was not included in the mean multiplication factor calculation.

Systematic review

A15. Page 89 (of the company submission). Please provide the rationale for excluding studies with treatment duration of less than 24 weeks from the systematic review.

Studies of less than 6 months duration were excluded from the DEX700 evidence base on the basis that the DEX700 implant provides dexamethasone treatment coverage for up to this period and therefore comparisons at earlier timepoints are inappropriate and do not help assess the benefit of DEX700 to the long-term management of DMO: the current unmet need to be assessed within the decision problem.

Furthermore, ophthalmologists practicing across England and Wales confirm that response to ranibizumab, the main alternative therapy option to DEX700, would not be assessed in clinical practice until at least the loading dose of three consecutive monthly injections have been given. This is the shortest conceivable response assessment time point of all potential comparators to DEX700. Of the excluded studies with treatment duration of less than 24 weeks, none that reported data at a time point of ≥12 weeks met all other eligibility criteria for inclusion in the MTC evidence base.

A16. Page 90, Figure 8 (of the company submission). Please provide the citations for the 34 studies excluded because the treatment duration was less than 24 weeks.

The reference list for citations excluded because the treatment duration of the studies reported was less than 24 weeks is provided in Appendix A16. Of note, four of these citations are associated with study NCT00035906 included in the clinical evidence base presented in the

submission. These citations are underlined in Appendix A16. Three report interim analysis and thus would have been excluded on this basis if ≥24 week data had have been reported. The fourth reports post-hoc analysis based on pattern of DMO as noted within the submission on page 92.

Section B: Clarification on cost-effectiveness data

B1. Priority question: Please provide the results for the base-case economic model for the comparisons between DEX700 and watch and wait using data from the pooled MEAD trials (that is, the DEX700 data as is plus the sham arm for watch and wait for the first 3 years of the model).

Please provide the Excel files and tabulated results for the following sub-analyses:

a. Use 3-month transition probabilities for watch and wait from the MEAD sham arm, using the assumption that improvement/worsening by at least 10-letters can only be achieved for the next health state up or down, respectively (this is the current modelling assumption)

Table 7: Results for DEX700 vs. watch and wait using MEAD data for the efficacy of both treatments, movements between health states restricted to a maximum of one state

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£12,091	5.7528			
DEX700 PRN	£20,413	5.7420	£8,322	-0.0108	Watch and wait dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

In this analysis both DEX700 and watch and wait are represented using patient-level data from MEAD, but movements between health states are restricted to a movement of a maximum of one health state up or down. DEX700 is dominated by watch and wait; however this analysis is not believed to be appropriate as we do not feel that the sham arm of the MEAD studies is representative of a true watch and wait strategy, instead we believe that the efficacy of watch and wait which was obtained from the MTC is more appropriate. This is discussed in further detail in the response to part b.

The excel model used to produce these results is “DMO_NICE_Oct2014_All DMO_No MTC.xlsb” and has been submitted separately on a CD.

b. Use the actual 3-month proportions of patients in each of the 6 health states for both DEX700 and W&W from the MEAD trials – in this case, no assumption of moving to adjacent health states is needed and the ACTUAL health states of patients, as observed every 3 months over the first 3 years, can be used.

Table 8: Results for DEX700 vs. watch and wait using MEAD data for the efficacy of both treatments, movements between health states unrestricted

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£13,607	5.7517			
DEX700 PRN	£21,241	5.7571	£7,635	0.0054	£1,411,676*

Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.
Notes: *DEX700 PRN vs. watch and wait.

In this analysis both DEX700 and watch and wait are represented using patient-level data from MEAD, and movements between health states are unrestricted (i.e. movements between all states are possible). DEX700 has a moderate incremental cost compared with watch and wait, and gains a small number of QALYs, resulting in a high ICER.
The excel model used to produce these results is “DMO_NICE_Oct2014_All DMO_No MTC_All movements.xlsb” and has been submitted separately on a CD.

In this comparison, the total QALYs for DEX700 and watch and wait increase and decrease respectively compared with the results seen in part a. This analysis demonstrates that the restriction of movements between health states to a maximum of one state up or down (which is necessary to utilise the network meta-analysis) biases against DEX700, in favour of watch and wait.

We do not believe that using data from the sham arm of the MEAD studies to represent watch and wait is appropriate. It is discussed in section 7.3.1 of the submission that the MEAD sham arm is likely to over-estimate the true efficacy of a watch and wait strategy. By the end of the studies 37.4% of sham patients had either discontinued from the studies due to lack or loss of efficacy or had been censored due to receipt of escape therapy.[4] Therefore throughout the study duration patients who were not responding to sham treatment were removed from the data set, leaving only a population which may be considered ‘super-responders’ and is not likely to represent what we would expect to observe with no active treatment in clinical practice. This interpretation is supported by clinical key opinion leaders in England who have described the sham results from MEAD as ‘atypical’ (S. Sivaprasad and Y. Yang, personal communication at the EURetina conference, 11-14 September, 2014).

This is illustrated by comparing outcomes in the MEAD sham arm with outcomes observed in natural history data from The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported by Mitchell *et al*.[5] (2012), as per Table 70 in the submission. A similar proportion of patients gained at least 10 letters from baseline; however a much lower proportion of patients lost at least 10 letters from baseline in the sham arm of MEAD compared with natural history (17% vs. 36%). This indicates that there was a much lower rate of visual decline in the sham arms of the MEAD studies compared with observed natural history data.

The sham arms of the MEAD studies are therefore not representative of a true "watch and wait" treatment arm, and the analysis using the network meta-analysis to estimate the relative efficacy of watch and wait compared with DEX700 is felt to be more appropriate. The base case network meta-analysis incorporates data from two additional studies[6, 7] which included a sham/no treatment arm and is therefore felt to be a more realistic representation of the true efficacy of a watch and wait strategy than the sham arm of the MEAD studies alone. However, this may still be an over-estimation of the true efficacy of watch and wait since the ETDRS study[6] allowed deferred laser treatment in the no treatment arm meaning that the study by Olk[7] (1986) is the only true no treatment arm within the network.

Given this, the results presented in the submission dossier, using the network meta-analysis are believed to be the most plausible representation of the true cost-effectiveness of DEX700 compared with a strategy of watch and wait.

c. For both DEX700 and watch and wait arms of the economic model, please estimate QALYs for the first 3 years using mean <u>utilities estimated directly from patients' responses on visual function questionnaire utility index</u>, instead of estimating these from the regression model reported in the company submission.

Two analyses have been presented in response to this question. The first analysis (Table 10) builds upon the modelling for the response to part b. of this question (i.e. using the patient-level data from MEAD to represent the efficacy of both DEX700 and watch and wait, with no restriction placed on the movements between the health states). The excel model used to produce the results of this analysis is "DMO_NICE_Oct2014_All DMO_No MTC_All movements_Utility update.xlsb" and has been submitted separately on a CD.

The second analysis (Table 11) builds upon the modelling for the response to question B4 (i.e. using the updated base case MTC to represent the efficacy of watch and wait, with movements between health states restricted to a maximum of one state). The excel model used to produce the results of this analysis is "DMO_NICE_Oct2014_All DMO_RevisedMTC_Utility update" and has been submitted separately on a CD.

Both analyses include the same update to the way utilities are applied within the economic model. Instead of applying the utility regression equation to the expected BCVA in each eye (calculated using the distribution of BCVA across the health states and the mean BCVA in each health state as described in section 7.4.11, pages 390-392 of the main submission), the mean utilities estimated directly from patients' responses to the VFQ-UI have been applied. The mean VFQ-UI score in each health state across pooled visits in MEAD, for the pooled population across the DEX700, DEX350 and sham treatment arms is summarised in Table 9.

Table 9: Distribution of VFQ-UI scores across pooled visits in MEAD (pooled DEX700, DEX350 and sham patients) (derived from Table 95 in the main submission)

	Patients treated in visit-defined BSE						
	Overall	**Health State 1**	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Patients treated in visit-defined WSE						
	Overall	**Health State 1**	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSE, better-seeing eye; DEX, dexamethasone; SD, standard deviation; VFQ-UI, Visual Functioning Questionnaire Utility Index; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File 2014[4]

These mean utility values in each health state for the BSE and for the WSE have therefore been applied within the economic model by applying the values for the BSE and WSE to the distribution of the BSE and WSE across the health states. This is achieved using simple multiplication of the proportion of BSE in health state 1 multiplied by the mean utility for the BSE being in health state 1, and so on. The whole person utility is therefore calculated as the utility in the BSE added to the utility in the WSE. This assumes that the patient has a utility associated with the level of vision in the BSE and a utility associated with the level of vision in the WSE, that these are independent of each other and that the BSE and WSE each account for 50% of the patients' vision, and hence 50% of the patients' utility.

Table 10: Results for DEX700 vs. watch and wait using MEAD data for the efficacy of both treatments, movements between health states unrestricted and with utilities based on the mean utilities estimated directly from patients' responses on visual function questionnaire utility index

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£13,607	6.7960			
DEX700 PRN	£21,241	6.8108	£7,635	0.00149	£513,797*

Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.
Notes: *DEX700 PRN vs. watch and wait.

Table 11: Results for DEX700 vs. watch and wait using the MTC for the efficacy of watch and wait, movements between health states restricted to a maximum of one health state and with utilities based on the mean utilities estimated directly from patients' responses on visual function questionnaire utility index

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£21,571	6.5962			
DEX700 PRN	£20,413	6.7702	-£1,158	0.1740	DEX700 PRN dominates

Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.

In both analyses the use of mean utility data for each health state in the BSE or WSE observed directly from the MEAD trials results in higher total and incremental QALYs than results using the utility regression analysis.

B2. Priority question: Page 386 to 388 and Appendix 18 (of the company submission). The submission reports a number of linear regression models that were tested in order to generate utility values based on visual function questionnaire utility index (with and without adverse events as independent variables) and EQ-5D.

Please provide details of all regression analyses undertaken, in line with the proposed checklist for statistical regression analyses published by Kearns et al. (http://www.nicedsu.org.uk/Regression-methods(2391678).htm), in particular:

a. the type of regression model used to analyse the data, any alternative models tested (e.g. Tobit models) and justification of your final choice;

b. the rationale for the choice of variables included in the model (it is noted that a regression analysis was carried out to determine the impact of raised intraocular pressure and of cataract but no other adverse events, of those included in the economic model, were considered);
c. the handling of missing data;
d. the results of any goodness-of-fit measures used to assess the model.

Methods:

Exploration of potential utility specifications proceeded in discrete steps, primarily correlating VFQ-UI outcomes with vision in the pooled sample of DEX700, DEX350 and Sham patients with and without covariate-adjustment for relevant patient characteristics. Analyses were performed on outcomes measured at baseline and pooled across all visits.

1. Descriptive analyses of unadjusted VFQ-UI values across and within the proposed model health states
    a. Baseline VFQ-UI in patients treated initially in the BSE/WSE
    b. Pooled VFQ-UI Scores across pooled visits in all patients
2. Scatter plots with fitted lines of the relationship between unadjusted VFQ-UI and BCVA:
    a. Unadjusted VFQ-UI vs BCVA in the BSE at baseline and across pooled visits
    b. Unadjusted VFQ-UI vs BCVA in the WSE at baseline and across pooled visits
3. Covariate-adjusted linear regression analyses of VFQ-UI scores at baseline, and covariate-adjusted linear mixed-effects analyses of VFQ-UI scores pooled across all visits – with patient, treatment arm, and study (MEAD-010 vs MEAD-011) included as random effects. Analyses were conducted in a step-wise fashion, controlling for
    a. BCVA only:
        i. BCVA in the BSE only
        ii. BCVA in the WSE only
        iii. BCVA in the BSE and BCVA in the WSE
    b. Additional demographic and disease characteristics
        i. BCVA in the BSE, BCVA in the WSE, age, and gender
        ii. BCVA in the BSE, BCVA in the WSE, age, gender and an indicator variable for patients with bilateral disease
        iii. BCVA in the BSE, BCVA in the WSE, age, gender and general health status (this model was exploratory because the *de novo* model health states are based on vision only and do not account for changes in patients' general health)
    c. Additional interaction term between BCVA in the BSE and BCVA in the WSE

The manufacturer's submission for TA237 was also criticized for not incorporating a disutility for patients suffering an ocular adverse event.[8] We therefore conducted additional exploratory analyses of the effect of adverse events on VFQ-UI outcomes. The final selection for the base-case

model was the covariate adjusted mixed-effects model was augmented with indicators for patients who experienced either elevated intraocular pressure (IOP; IOP elevation ≥10mmHg or IOP ≥30mmHg), cataract in the BSE or WSE, or cataract surgery. The specific adverse events of cataract, cataract surgery and elevated IOP, were selected specifically for inclusion as these are the well-known adverse events associated with intravitreal steroids as a class.

For linear regression analyses of baseline visit data, we report model coefficients, standard-errors, and p-values; and assess goodness of fit by the R-squared. For the linear mixed-effects analyses on pooled visit data, we report model coefficients, standard-errors, and p-values and assess goodness of fit using the Akaike information criterion (AIC), Bayesian information criterion (BIC) and AICC (AIC with correction for finite sample size). All analyses were conducted in SAS Version 9.3.

The EQ-5D was administered to patients at baseline in order to benchmark the overall quality of life of the patient population. Although the lack of sensitivity of the EQ-5D to changes in vision has been demonstrated, we conducted a sensitivity analysis that estimates the association between BCVA and utilities using data from the EQ-5D.

As a significant proportion of DMO patients have bilateral disease, our goal was a parsimonious utility specification that would incorporate vision, measured by best corrected visual acuity (BCVA), in both eyes (BSE and WSE) simultaneously. In line with the *de novo* model structure, that single equation would be used to calculate utilities in patients with unilateral disease (with appropriate assumptions on vision evolution in the unaffected eye), and in patients with bilateral disease.

Models other than the linear regression models described above were not investigated. Only observed data were included in these analyses (for both response and covariates); i.e. no adjustments or imputations for missing data were made. It was felt that this approach was justified because the aim of the analyses was to assess the association between visual acuity and utilities, not to measure a treatment benefit of a particular therapy.

Sample size

Nine hundred and thirty-two (932) patients receiving either DEX700, DEX350 or Sham had valid VFQ-UI scores at baseline (200 treated initially in the BSE and 732 treated in the WSE). In the pooled sample across all time-points, there were 9033 patient-visit VFQ-UI observations.

Results:

A summary of observed VFQ-UI and EQ-5D utilities in the MEAD studies were provided in the submission (section 7.4.3). The results of the regression analyses including goodness-of-fit statistics are presented in Table 12 to

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Table 15.

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Table 12: Covariate-adjusted linear regression of VFQ-UI scores at baseline

	Specifications								
Parameters	**Main model (BSE and WSE)**			**BSE only model**			**WSE only model**		
	Mean	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
BCVA_WSE	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
N		[redacted]			[redacted]			[redacted]	
R-square		[redacted]			[redacted]			[redacted]	

	Specifications														
	Main model + 1 covariate			**Main model + 2 covariates**			**Main model + 3 covariates**			**Main model + 4 covariates**			**Main model + 5 covariates**		
Parameters	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (Female vs. Male)				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO (Yes vs. No)							[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_BSE*BCVA_WSE										[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen Health - Excellent vs. Poor													[redacted]	[redacted]	[redacted]
Gen Health – Very Good vs. Poor													[redacted]	[redacted]	[redacted]
Gen Health - Good vs. Poor													[redacted]	[redacted]	[redacted]

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Gen Health - Fair vs. Poor													[redacted]	[redacted]	[redacted]
N		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
R-square		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	

Key: BCVA, best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; Gen, general; SE, standard error; WSE, worse-seeing eye.
Notes: Bold entries indicate p<0.05

Table 13: Covariate-adjusted mixed effects* analysis of VFQ-UI scores across all time points

	Specifications								
Parameters	**Main model (BSE and WSE)**			**BSE only model**			**WSE only model**		
	Mean	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
BCVA_WSE	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
N		[redacted]			[redacted]			[redacted]	
AIC		[redacted]			[redacted]			[redacted]	
BIC		[redacted]			[redacted]			[redacted]	
Likelihood Ratio test for Fit vs Main Model		[redacted]			[redacted]			[redacted]	

	Specifications														
	Main model + 1 covariate			**Main model + 2 covariates**			**Main model + 3 covariates**			**Main model + 4 covariates**			**Main model + 5 covariates**		
Parameters	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (Female vs. Male)				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Bilateral DMO (Yes vs. No)															
BCVA_BSE*BCVA_WSE															
Gen Health - Excellent vs. Poor															
Gen Health – Very Good vs. Poor															
Gen Health - Good vs. Poor															
Gen Health - Fair vs. Poor															
N															
AIC															
BIC															
Likelihood Ratio test for Fit vs Main Model															

Key: AIC, Akaike information criterion; BCVA, best-corrected visual acuity; BIC, Bayesian information criterion; BSE, better-seeing eye; DMO, diabetic macular oedema; Gen, general; SE, standard error; WSE, worse-seeing eye.
Notes: * Patient, Treatment and Study (010 vs 011) included as random effects; Bold entries indicate p<0.05

Table 14: Covariate-adjusted mixed effects* analysis of VFQ-UI scores adjusting for ocular adverse events

	Specifications								
Parameters	**Main model**			**Main model + cataract**			**Main model + cataract surgery**		
	Mean	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**
Intercept									
BCVA_BSE									
BCVA_WSE									
Cataract_BSE									
Cataract_WSE									
Cataract Surgery									

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N		[redacted]			[redacted]			[redacted]	
AIC		[redacted]			[redacted]			[redacted]	
BIC		[redacted]			[redacted]			[redacted]	
P-Value for Likelihood Ratio test of fit vs Main Model		[redacted]			[redacted]			[redacted]	
	Main model			**Main model + IOP change ≥10mmHg**			**Main model + IOP ≥30mmHg**		
Parameters	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IOP Change ≥10mmHg or IOP-Medication				[redacted]	[redacted]	[redacted]			
IOP ≥30mmHg or IOP-Medication							[redacted]	[redacted]	[redacted]
N		[redacted]			[redacted]			[redacted]	
AIC		[redacted]			[redacted]			[redacted]	
BIC		[redacted]			[redacted]			[redacted]	
P-Value for Likelihood Ratio test of fit vs Main Model		[redacted]			[redacted]			[redacted]	

Key: AIC, Akaike information criterion; BCVA, best-corrected visual acuity; BIC, Bayesian information criterion; BSE, better-seeing eye; DMO, diabetic macular oedema; Gen, general; IOP, intraocular pressure; mmHg, millimetres of mercury; SE, standard error; WSE, worse-seeing eye.
Notes: * Patient, Treatment and Study (010 vs 011) included as random effects; Bold entries indicate p<0.05

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Table 15: Covariate-adjusted linear regression of EQ-5D utility scores at baseline

	Specifications								
Parameters	**Main model (BSE and WSE)**			**BSE only model**			**WSE only model**		
	Mean	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
BCVA_WSE	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
N		[redacted]			[redacted]			[redacted]	
R-square		[redacted]			[redacted]			[redacted]	

	Specifications														
	Main model + 1 covariate			**Main model + 2 covariates**			**Main model + 3 covariates**			**Main model + 4 covariates**			**Main model + 5 covariates**		
Parameters	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**	**Mean**	**SE**	**P-value**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (Female vs. Male)				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO (Yes vs. No)							[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA_BSE*BCVA_WSE										[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen Health - Excellent vs. Poor													[redacted]	[redacted]	[redacted]
Gen Health – Very Good vs. Poor													[redacted]	[redacted]	[redacted]
Gen Health - Good vs. Poor													[redacted]	[redacted]	[redacted]

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Gen Health - Fair vs. Poor					[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
R-square	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	

Key: BCVA, best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; Gen, general; SE, standard error; WSE, worse-seeing eye.
Notes: Bold entries indicate p<0.05

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Table 12 presents the results of linear regression analyses of VFQ-UI scores at baseline. The primary specification [Main model] includes the vision in the BSE and WSE only. Two alternate specifications include the BCVA_BSE and BCVA_WSE separately. Remaining sensitivity analyses [Main + 1 covariate through Main + 5 covariates] include additional demographic and disease-related covariates. There were 932 patients with observed VFQ-UI scores at baseline.

With the exception of the variables measuring self-reported general health [Main + 5 covariates], adding additional covariates to the Main Model resulted in minimal increase in the R^2 (from 0.126 -0.142). In the Main model and sensitivity specifications Main + 1 covariate, - Main + 2 covariates and Main + 3 covariates, the coefficients on BCVA_BSE and BCVA_WSE were positive and statistically significant, with $\beta_{BCVA_BSE} > \beta_{BCVA_WSE}$. The magnitude of the estimated coefficients was also consistent across the four specifications. These findings are consistent with the published literature which has consistently demonstrated that visual functioning and quality of life is preferentially affected by vision in the BSE.[9] Alternate Model 1 which included only BCVA_BSE had a similar coefficient on BCVA_BSE (β=0.005) and R^2 compared with the Main Model; however, Alternate Model 2 which included BCVA_WSE only fit the data less well (R^2 of 0.064).

Adding the interaction term BCVA_BSE*BCVA_WSE in the Main + 4 covariates specification does not increase model fit as measured by the R^2 and the p-value for the interaction term.

Of interest, in these analyses the coefficient on age is consistently positive and statistically significant. This is at odds with the general perception (and published literature across multiple diseases) that age and general quality of life is negatively related.[10] One potential explanation is that patients who develop DMO at younger ages may have more severe disease (or underlying diabetes) – inducing a negative correlation between reported QoL and age. Although it should be noted that including direct measures of self-reported health [Main + 5 covariates] does not reduce the size of the coefficient on age. That said, the specification Main + 5 covariates was exploratory in nature as the economic model does not account for changes in the patients general health outside of improvements in vision measured by BCVA.

Table 13 reports the generalization of this approach to a mixed effects analysis on the pooled sample of VFQ-UI scores across all visits. There were 9028 pooled patient-visits with observed VFQ-UI scores and valid socio-demographic covariate measurements; and 9011 patient visits for the Main + 5 covariates specification.

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Similar to the regression model of VFQ-UI scores at baseline, the coefficients on BCVA_BSE and BCVA_WSE were stable across specifications; and positive and statistically significant, with $\beta_{BCVA_BSE} > \beta_{BCVA_WSE.}$. While the magnitude of the coefficients on BCVA_WSE was similar across the two sets of analyses (baseline and pooled-visits), the coefficients on BCVA_BSE decreased by about half in the mixed-effects analysis. Accordingly, the magnitude of the differential between the two coefficients β_{BCVA_BSE} and β_{BCVA_WSE} decreased by about 2/3 between the analyses conducted on outcomes and baseline, and the analyses conducted within the pooled sample.

Unlike the analyses of baseline outcomes, the statistical significance of the coefficients on BCVA_BSE and BCVA_WSE was maintained across all mixed effects specifications. These include the Main + 4 covariates specification with BCVA_BSE*BCVA_WSE interaction term (although the coefficient on the interaction term was small and not statistically significant), and Main + 5 covariates with terms measuring self-rated General Health. However, the counter-intuitive positive and statistically significant coefficient on age is consistently demonstrated in this analysis as well.

Of note, the AIC and BIC outcomes are smaller for the covariate-controlled analyses, and the likelihood ratio test statistic is significant. However, it is important to note that the coefficients on BCVA_BSE and BCVA_WSE do not change across specifications. Moreover, the only other consistent statistically significant coefficient in the models (age) does not vary across treatment because there is no vision-related mortality adjustment, i.e. the age profile is the same across treatment arms. Thus, for purposes of assessing differences in QALY gains between study arms, the most parsimonious model – the Main Model - was chosen as the base-case specification for estimating utilities.

Table 14 presents the results of linear mixed effects analyses of VFQ-UI scores controlling for concurrent ocular adverse events. The primary specification [Main model] includes the vision in the BSE and WSE only. Two alternate specifications include the BCVA_BSE and BCVA_WSE separately. Remaining sensitivity analyses [Main + 1 covariate through Main + 4 covariates] include additional terms for the occurrence of a cataract- or IOP-related event at the relevant visit. There were 9028 patient-visits with observed VFQ-UI scores and valid covariate measurements.

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For specification Main + 1 covariate, the patient was required to have a cataract recorded at the same visit (within the same visit window) as the VFQ-UI score was recorded. In contrast, for specification Main + 2 covariates, the patient could have had a cataract surgery event either in the same visit – or at the previous visit to that in which VFQ-UI score was recorded (i.e. within the prior 3 months, approximately). In both specifications Main + 1 covariate and Main + 2 covariates, the point estimates for the coefficients on the cataract-related adverse event measures are negative, but not statistically significant. The differences in AIC and BIC scores are minimal, and a likelihood ratio test shows no statistically significant differences in goodness of fit versus the main model.

Similar to specification Main + 1 covariate, in specifications Main + 3 covariates or Main + 4 covariates, the patient was required to have had the IOP-related event (change ≥10mmHg or level≥30mmHg), or concomitant IOP-medication, recorded within the same visit window as the VFQ-UI score. The coefficients on the IOP-related adverse events are negative but not statistically significant. Here too, the differences in AIC and BIC scores are minimal, and a likelihood ratio test shows no statistically significant differences in goodness of fit versus the main model.

Finally, for all specifications, the magnitude of the coefficients on BCVA_BSE and BCVA_WSE are unchanged from those in the Main Model. As a result, the decision was made to maintain the Main Model as they primary (base-case) specification. A crude assessment of the potential impact of including the utility terms for cataract and raised IOP is provided in the response to question B3 part b and demonstrates that the impact on the cost-effectiveness results of including these terms in the utility regression would likely be negligible.

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Table 15 presents the results of linear regression analyses of N=946 EQ-5D scores at baseline. The primary specification [Main model] includes the vision in the BSE and WSE only. Two alternate specifications include the BCVA_BSE and BCVA_WSE separately. Remaining sensitivity analyses [Main + 1 covariate through Main + 5 covariates] include additional demographic and disease-related covariates. There were 946 patients with observed VFQ-UI scores at baseline.

Compared with the analogous analysis of VFQ-UI scores at baseline, the R-squared of the linear models of the EQ-5D outcomes are lower. Moreover, in the Main Model, the coefficients on BCVA_BSE are lower for the EQ-5D analyses than the VFQ-UI analyses; and the coefficients on BCVA_WSE are both numerically smaller and statistically significant. After adjusting for socio-demographic covariates, the coefficient on BCVA_BSE is no longer statistically significant for Models Main + 2 covariates through Main + 4 covariates.

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B3. Priority question: Please comment on the following:

a. **Page 391, Table 100 and 101** (of the company submission). Using the reported regression model for visual function questionnaire utility index, the utility values range from 0.62 to 0.79, is this range reasonable and expected for a person with diabetic macular oedema?

We believe that the utility values produced by the regression equation for the visual function questionnaire utility index are reasonable and expected for a person with DMO. These utility values are calculated using a regression analysis, which was derived from a large number of observations within the MEAD clinical trials. Therefore these values were obtained directly from patients who had DM and DMO and are based on BCVA data, which varies widely over the course of the study.

Table 95 of the submission shows the range of observed utilities in patients whose study eye was the BSE or WSE of 0.54-0.74 and 0.63-0.78 when the study eye is categorised from the worst to the best health state (summarised in Table 9, question B1, part c). Based on these ranges, when considering the utility resulting from both eyes' vision being in the worst health state to both eyes' vision being in the best health state, a range of 0.62-0.79 is reasonable.

Previous NICE technology appraisals for DMO have included utility data from a number of sources.[8, 11] The committee for the most recently published technology appraisal in DMO (Fluocinolone acetonide, TA301) considered ICERs using three different publications,[12] Brown[13] (1999), Brown *et al*.[14] (2000) and Czoski-Murray *et al*.[15] (2009). None of these publications provided utility values specifically for vision loss due to DMO. The manufacturer's economic model for TA237 included a regression to predict EQ-5D scores based on data from the RESTORE study. This gave a range of utility values for the treated eye being in the worst to the best health state of 0.547-0.860.[16] The committee for the appraisal considered that given the population in RESTORE was treated in the WSE in the majority of cases, this range of utilities was broader than would be expected for this population.[16] The range of utilities for this appraisal is smaller than this range and hence is more appropriate.

Brown[13] (1999) measured utilities according to BSE visual acuity in a population of patients with impaired vision in at least one eye due to a variety of reasons. Brown *et al*.[14] (2000) measured utility in five visual acuity groups defined by the BSE in patients with age-related macular degeneration. Czoski-Murray *et al*.[15] (2009) used contact lenses to simulate bilateral visual impairment due to age-related macular degeneration (ARMD) in healthy participants. The values used in previous technology appraisals are summarised in Table 16, Table 17 and Table 18 for comparison.

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Table 16: Brown *et al*.[14] 2000

ETDRS letters	Utility
≥ 75	0.89
≥ 60 to < 75	0.81
≥ 50 to < 60	0.57
≥ 35 to < 50	0.545*
≥ 20 to < 35	0.52
<20	0.4
Key: ETDRS, Early Treatment Diabetic Retinopathy Study. **Notes:** *Estimated as mid-point between 0.52 and 0.57	

Table 17: Czoski-Murray *et al*.[15] 2006

ETDRS letters	Utility (TTO)
≥ 75	0.86
≥ 65 to < 75	0.813
≥ 55 to < 65	0.802
≥ 45 to < 55	0.77
≥35 to < 45	0.76
≥25 to < 35	0.681
<25	0.547
Key: TTO, time trade-off.	

Table 18: Brown[13] 1999

Snellen	Approx. ETDRS*	Utility
		0.89
20/30	75-80	0.84
20/40	70	0.8
20/50	65	0.77
20/70	55-60	0.74
20/100	50	0.67
20/200	35	0.66
20/300	25-30	0.63
20/400	20	0.54
Key: ETDRS, Early Treatment Diabetic Retinopathy Study. **Notes:** *Converted using Gregori *et al*.[17] 2010		

It is of note that the values in Table 16, Table 17 and Table 18 have previously been used to represent utilities based on the vision in the BSE only and hence are not directly comparable with the results of the regression analysis used within this submission which accounted for the level of vision in both eyes.

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The utility for clinical blindness (both eyes ≤35 letters) of [redacted] obtained from the VFQ-UI regression is reasonable in comparison with published values for the BSE having vision ≤35 letters; [redacted] is higher than the utility given by Brown *et al*.[14] (2000) but lower than the utility given by Brown[13] (1999) and Czoski-Murray *et al*.[15] (2009).

The utility for best vision (both eyes ≥75) of [redacted] is lower than published values in all cases, however the published utilities are not specifically accounting for the utility of vision loss due to DMO. The utility for patients with vision loss due to DMO may be expected to be lower than the utility for patients with the same level of vision loss due to another ocular morbidity due to the underlying impact of the patients' DM. Hence the value of [redacted] obtained for binocular good vision from the utility regression derived from VFQ-UI data obtained in the MEAD trials is felt to be appropriate.

b. **Appendix 18** (of the company submission). In the regression analysis that has considered the impact of adverse events, the respective coefficients were not statistically significant at the 5% significance level. However, these coefficients are larger than those related to worse-seeing eye and best-seeing eye, implying that adverse events have a higher impact on utility compared with worse-seeing eye and best-seeing eye. Is it reasonable to ignore the impact of adverse events on utility values from the economic model?

To include the impact of adverse events based on the regression equations presented in Appendix 18 within the economic model to determine the impact of including these on the results of the analysis would require significant re-programming of the model which is not feasible in the time available to respond to these questions. Therefore to attempt to answer this question a side calculation has been performed using the coefficients for cataract surgery and for increased intraocular pressure (IOP) ≥30mmHg or initiation of IOP medication, and the proportions of patients who experience each of these events.

The proportion of the total population experiencing cataract extraction is calculated as per Table 19

Table 19: Cataract extraction (as per Table 85 in submission, corrected in line with response to question C8 part b.)

	% Phakic			% phakic patients with cataract extraction			% total population with cataract extraction*		
Treatment	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
DEX700	75.50%	70.60%	55.62%	8.40%	19.17%	2.94%	6.3%	13.5%	1.6%
Watch and wait	75.50%	73.73%	72.01%	2.34%	2.34%	2.34%	1.8%	1.7%	1.7%
Fluocinolone acetonide	75.50%	75.50%	26.02%	0.00%	65.53%	41.98%	0.0%	49.5%	10.9%

Key: DEX, dexamethasone.
Notes: *Calculated as % phakic patients with cataract extraction multiplied by % phakic.

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Multiplying the % total population with cataract extraction by the coefficient for cataract surgery given in Table 262 of Appendix 18 in the submission (-0.0034), and assuming that this is applied for the cycle in which the cataract extraction is assumed (i.e. that the utility decrement lasts for a duration of 3 months or 0.25 years) gives the QALY decrements shown in Table 20. This demonstrates that the impact of including a utility decrement due to cataract extraction on the total QALYs is likely to be minimal. These values over-estimate the true decrement which would be applied within the economic model as these calculations do not account for discounting or mortality.

Table 20: QALY decrement due to cataract extraction

Treatment	QALY decrement				
	Year 1	Year 2	Year 3	Total	Difference: DEX700 vs.
DEX700	[redacted]	[redacted]	[redacted]	[redacted]	
Watch and wait	-0.000015	-0.000015	-0.000014	**-0.000044**	**-0.000139**
Fluocinolone acetonide	0.000000	-0.000421	-0.000093	**-0.000513**	**0.000331**
Key: DEX, dexamethasone.					

The proportion of the total population experiencing raised IOP ≥30mmHg or initiation of IOP medication is assumed to be as per Table 86 of the main submission (summarised in Table 21)

Table 21: Raised IOP (as per Table 85 in submission)

Treatment	Year 1	Year 2	Year 3
DEX700	12.10%	4.61%	1.15%
Watch and wait	0.00%	0.00%	0.00%
Ranibizumab	0.86%	0.00%	0.00%
Bevacizumab	9.52%	0.00%	0.00%
Laser	[redacted]	[redacted]	[redacted]
Fluocinolone acetonide	0.00%	4.80%	32.30%
Key: DEX, dexamethasone.			

Multiplying the % total population with raised IOP by the coefficient for raised IOP ≥30mmHg or initiation of IOP medication given in Table 262 of Appendix 18 in the submission (-0.0064), and assuming that this is applied for the duration of treatment (i.e. that the utility decrement lasts for a maximum duration of 3 years, consistent with the costing assumptions for IOP medication) gives the QALY decrements shown in Table 22. This demonstrates that the impact of including a utility decrement due to raised IOP on the total QALYs is likely to be minimal. Again these values over-estimate the true decrement, which would be applied within the economic model as these calculations do not account for discounting or mortality and not all patients will receive the utility decrement for the whole 3 year duration.

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Table 22: QALY decrement due to raised IOP

Treatment	QALY decrement				
	Year 1	Year 2	Year 3	Total	Difference: DEX700 vs.
DEX700	[redacted]	[redacted]	[redacted]	[redacted]	
Watch and wait	0.000000	0.000000	0.000000	0.000000	-0.003429
Ranibizumab	-0.000165	0.000000	0.000000	-0.000165	-0.003264
Bevacizumab	-0.001828	0.000000	0.000000	-0.001828	-0.001601
Laser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fluocinolone acetonide	0.000000	-0.000922	-0.006202	-0.007123	0.003694
Key: DEX, dexamethasone.					

Given these results, it is felt reasonable to ignore the impact of adverse events on utility values from the economic model as the impact of including them would be negligible.

B4. Priority Question: Please update the economic models using data from the updated MTC analysis as requested in priority question A8. Please provide updated Excel files and tabulated results.

Four excel models, updated to include the revised MTC analysis results, have been submitted separately on a CD. These are:

- "DMO_NICE_Oct2014_All DMO_RevisedMTC.xlsb"
  - DMO patients who are insufficiently responsive to non-corticosteroid therapy (base case excluding FAME)
  - DMO patients who are unsuitable for non-corticosteroid therapy
- "DMO_NICE_Oct2014_All DMO_incl.FAME_RevisedMTC.xlsb"
  - DMO patients who are insufficiently responsive to non-corticosteroid therapy (scenario analysis including FAME)
- "DMO_NICE_Oct2014_Pseudophakic_RevisedMTC.xlsb"
  - DMO patients who are pseudophakic (base case including ranibizumab only)
- "DMO_NICE_Oct2014_Pseudophakic_RevisedMTC_All_Tx.xlsb"
  - DMO patients who are pseudophakic (scenario analysis including ranibizumab, bevacizumab, laser and watch and wait)

The updated results are provided in Table 23, Table 24 and Table 25 for the base case in each patient population covered by the license for DEX700. The total costs and QALYs are marginally different from the values presented in the submission using the original MTC analysis; however the difference is very small and the conclusion of the analysis remains unchanged.

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Table 23: Base case results using updated network meta-analysis; DMO patients who are considered unsuitable for non-corticosteroid therapy

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£21,571	5.6785			
DEX700 PRN	£20,413	5.7420	-£1,158	0.0635	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Table 24: Base case results using updated network meta-analysis; DMO patients who are considered insufficiently responsive to non-corticosteroid therapy

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£21,571	5.6785			
DEX700 PRN	£20,413	5.7420	-£1,158	0.0635	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Table 25: Base case results using updated network meta-analysis; DMO patients who are pseudophakic

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab at list price					
DEX700 PRN	£15,720	5.0886			
Ranibizumab	£21,639	5.2119	£5,919	0.1233	£48,026*
Ranibizumab at 50% discount					
Ranibizumab	£14,920	5.2119			
DEX700 PRN	£15,720	5.0886	£800	-0.1233	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years. **Notes:** *Ranibizumab vs. DEX700 PRN.					

DEX700 remains cost-effective compared with ranibizumab in the population of patients with DMO who are pseudophakic up to a discount of 25% of the price of ranibizumab.

Table 26 and Table 27 provide updated results of scenario analysis including additional treatments included in the NICE scope within the economic analysis. The total costs and QALYs are marginally different from the values presented in the submission using the original MTC analysis; however the difference is very small and the conclusion of the analysis remains unchanged.

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Table 26: Scenario analysis results using updated network meta-analysis; DMO patients who are considered insufficiently responsive to non-corticosteroid therapy (scenario analysis including fluocinolone acetonide)

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. baseline
	Cost	QALY	Cost	QALY		
Fluocinolone acetonide at list price						
DEX700 PRN	£20,413	5.7420				
Watch and wait	£21,512	5.6789	£1,100	-0.0631	DEX700 PRN dominates	-£17,433
Fluocinolone acetonide	£22,170	5.8255	£1,757	0.0834	£21,060*	£21,060
Fluocinolone acetonide at 50% discount						
Fluocinolone acetonide	£16,473	5.8255				
DEX700 PRN	£20,413	5.7420	£3,940	-0.0834	Fluocinolone acetonide dominates	-£47,226
Watch and wait	£21,512	5.6789	£5,040	-0.1465	Fluocinolone acetonide dominates	-£34,399

Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.
Notes: *Fluocinolone acetonide vs. DEX700 PRN.

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Table 27: Scenario analysis results using updated network meta-analysis; DMO patients who are pseudophakic (scenario analysis including bevacizumab, laser and watch and wait)

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. baseline
	Cost	QALY	Cost	QALY		
Ranibizumab at list price						
Laser	£7,818	5.1493				
Bevacizumab	£9,392	5.2391	£1,574	0.0898	£17,528*	£17,528
DEX700 PRN	£15,720	5.0886	£6,328	-0.1505	Bevacizumab dominates	-£130,206
Watch and wait	£19,384	4.9992	£9,992	-0.2400	Bevacizumab dominates	-£77,026
Ranibizumab	£21,639	5.2119	£12,247	-0.0273	Bevacizumab dominates	£220,930
Ranibizumab at 50% discount						
Laser	£7,818	5.1493				
Bevacizumab	£9,392	5.2391	£1,574	0.0898	£17,528*	£17,528
Ranibizumab	£14,920	5.2119	£5,528	-0.0273	Bevacizumab dominates	£113,522
DEX700 PRN	£15,720	5.0886	£6,328	-0.1505	Bevacizumab dominates	-£130,206
Watch and wait	£19,384	4.9992	£9,992	-0.2400	Bevacizumab dominates	-£77,026

Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.
Notes: *Bevacizumab vs. laser.

B5. Priority Question: Page 336-337 Table 71 and 71 (of the company submission).

a. Please clarify how each patient's pair of eyes was each assigned to health states 1 to 6 at baseline. Please report any underlying assumptions or state whether assignment of each eye to a baseline health state was made randomly, based on the baseline distributions of health states as reported on the tables.

The assignment of eyes to health states 1-6 at baseline was based on the distributions of health states reported in tables 71 and 72, without explicit modelling of correlation across eyes by health state (i.e. assuming vision in each eye is independent of vision in the other eye). For example, within the model the cohort of patients includes some patients with unilateral DMO in their BSE. For these patients their distribution of vision in the BSE is as per row 1 of data in Table 28, which reflects the baseline distribution of vision in the study eye for patients treated in the BSE, while the distribution of vision in the WSE (i.e. the fellow eye) is as per row 2 of data in Table 28, which reflects the baseline distribution of the vision in the non-study eye for patients treated in the BSE. This assumes that the overall vision

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experienced by the patient is equally influenced by the BSE and the WSE and means that for all patients within the cohort the distributions of vision in both the BSE and WSE are modelled, assuming that they are independent.

Table 28: Baseline distribution of vision across visual acuity states; All DMO patients (as per Table 71 of the main submission)

DMO status	Eye	Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
Unilateral DMO in the BSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
References: Allergan MEAD Data on File[4]

b. Please explain why the baseline distribution of best-seeing eye and worse-seeing eye in bilateral DMO was taken from respective DMO eyes in unilateral DMO and was not determined directly from data on the sub-group of patients with bilateral DMO.

The baseline distribution of vision in the BSE and WSE for bilateral DMO patients was taken from data from the study eye of MEAD, dependent on whether the study eye was the BSE or the WSE (which could include both unilaterally and bilaterally affected patients). The MEAD studies allowed only one eye to be treated within the study; therefore for patients who were affected bilaterally, only the study eye was treated in line with the study protocol. Given this, all analyses for the purposes of defining BCVA in the economic model were generated using study eye and non-study eye data (i.e. treated or non-treated), regardless of whether the patient was affected with DMO in one or both eyes.

Based on the suggested approach in the question here, a new analysis has been conducted to identify the proportion of eyes in each of the six visual acuity health states for patients with the following characteristics at baseline of the MEAD studies:

- Unilateral DMO in the BSE
  - BSE (study eyes)
  - WSE (non-study eyes)
- Unilateral DMO in the WSE
  - WSE (study eyes)

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    - BSE (non-study eyes)
- Bilateral DMO
    - BSE (study eye or non-study eye)
    - WSE (study eye or non-study eye)

Table 29 and Table 30 show the results of this analysis in the total DMO population for the DEX700 PRN treatment arm (in line with the data used in the submitted economic model) and for the pooled DEX700 PRN and sham treatment arms, to continue to address the point raised in question C19.

Table 29: Baseline distribution of vision across visual acuity states; all DMO patients (Taken from DEX700 data: new analysis by bilateral/unilateral status, including study eyes and non-study eyes)

DMO status	Eye		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
Unilateral DMO in the BSE	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File 2014[18]

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Table 30: Baseline distribution of vision across visual acuity states; all DMO patients (Taken from pooled DEX700 + sham data: new analysis by bilateral/unilateral status, including study eyes and non-study eyes)

DMO status	Eye		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
Unilateral DMO in the BSE	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File 2014[18]

These indicate that by determining the baseline BCVA distribution in the BSE and WSE for unilateral and bilateral patients separately the baseline distribution of vision is different to the baseline distribution assumed in the submitted economic model for the all DMO population.

Table 31 shows the impact of changing the baseline distribution of BCVA for the all DMO population in line with Table 30 (the original base case results are presented in Table 32 for comparison). Changing the baseline distribution impacts both the costs and QALYs, however DEX700 PRN remains highly cost-effective compared with watch and wait in the populations of DMO patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy. The economic model used to produce these results (DMO_NICE_Oct2014_All DMO_BL BCVA update.xlsb) has been submitted separately.

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Table 31: Base case results using baseline BCVA distribution as per Table 30; DMO patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£17,610	5.4357			
DEX700 PRN	£17,627	5.4944	£17	0.0587	£287*

Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.
Notes: *DEX700 PRN vs. watch and wait.

Table 32: Base case results in original submission; DMO patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£21,882	5.6764			
DEX700 PRN	£20,413	5.7420	-£1,469	0.0656	DEX700 PRN dominates

Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.

In the pseudophakic population the number of patients with unilateral DMO in their BSE was 10 in the DEX700 arm and 23 in the sham arm, therefore this analysis is based on a very small number of patients. Table 33 and Table 34 show the results of the new analysis in the pseudophakic DMO population for the DEX700 PRN treatment arm (in line with the data used in the submitted economic model) and for the pooled DEX700 PRN and sham treatment arms, to continue to address the point raised in question C19.

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Table 33: Baseline distribution of vision across visual acuity states; pseudophakic DMO patients (Taken from DEX700 data: new analysis by bilateral/unilateral status, including study eyes and non-study eyes)

DMO status	Eye		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
Unilateral DMO in the BSE	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File 2014.[18]

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Table 34: Baseline distribution of vision across visual acuity states; pseudophakic DMO patients (Taken from pooled DEX700 + sham data: new analysis by bilateral/unilateral status, including study eyes and non-study eyes)

DMO status	Eye		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
Unilateral DMO in the BSE	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File 2014. [18]

These indicate that by determining the baseline BCVA distribution in the BSE and WSE for unilateral and bilateral patients separately the baseline distribution of vision is different to the baseline distribution assumed in the submitted economic model for the pseudophakic DMO population.

Table 35 shows the impact of changing the baseline distribution of BCVA for the pseudophakic DMO population in line with Table 34 (the original base case results are presented in Table 36 for comparison). Changing the baseline distribution impacts both the costs and QALYs, improving the cost-effectiveness of DEX700 PRN compared with ranibizumab as DEX700 PRN remains cost-effective at higher discount to the price of ranibizumab in the population of DMO patients who are pseudophakic. The economic model used to produce these results (DMO_NICE_Oct2014_pseudophakic_BL BCVA update.xlsb) has been submitted separately.

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Table 35: Base case results using baseline BCVA distribution as per Table 30; DMO patients who are pseudophakic

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab at list price					
DEX700 PRN	£13,370	4.9370			
Ranibizumab	£20,565	5.0440	£7,195	0.1070	£67,245*
Ranibizumab at 50% discount					
DEX700 PRN	£13,370	4.9370			
Ranibizumab	£14,142	5.0440	£771	0.1070	£7,208*

Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.
Notes: *Ranibizumab vs. DEX700 PRN.

DEX700 PRN is cost-effective compared with ranibizumab at a willingness to pay threshold of £20,000 per QALY gained up to a discount of 39% to the price of ranibizumab.

Table 36: Base case results in original submission; DMO patients who are pseudophakic

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab at list price					
DEX700 PRN	£15,720	5.0886			
Ranibizumab	£21,724	5.2066	£6,004	0.1179	£50,905*
Ranibizumab at 50% discount					
Ranibizumab	£15,004	5.2066			
DEX700 PRN	£15,720	5.0886	£716	-0.1179	Ranibizumab dominates

Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.
Notes: *Ranibizumab vs. DEX700 PRN.

DEX700 PRN remains cost-effective compared with ranibizumab at a willingness to pay threshold of £20,000 per QALY gained up to a discount of 27% to the list price of ranibizumab.

c. Please explain why the distribution of eyes in unilateral DMO in the better seeing eye appears to be based on assumptions (rounded figures), and, if so, what these assumptions were.

The number of pseudophakic patients whose study eye was the BSE is 20 and the proportions of these patients whose study eye fell into each health state is a round number, as detailed in Table 37.

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Table 37: Baseline distribution of vision across visual acuity states; Pseudophakic DMO patients whose study eye was the BSE (as per Table 72 of the main submission)

DMO status	Eye	Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6	Total
Study eye = BSE; Study eye BCVA	Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	% of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
References: Allergan MEAD Data on File[4]

B6. Page 364, Table 90 (of the company submission). Please confirm that the proportion of 5.80% of vitreous haemorrhage for laser, reported to be from PROTOCOL has been applied to each year separately. Please clarify why for year 3 the model utilised data from year 2 using the last observation carried forward, when year 3 data (9 patients had intraocular pressure greater than 30mmHg in year 3) are available in Allergan 2014 (reference 201). Also, please confirm that figure 5.08% in year 3 is meant to be 5.80%.

We can confirm that the 5.80% is applied to laser in each year separately; this same proportion of patients experienced vitreous haemorrhage in Years 1 and 2 in the laser arm of the PROTOCOL I study.

In Year 3 of the PROTOCOL I study patients in the laser treatment arm were permitted to receive other treatments for DMO (including but not necessarily limited to ranibizumab and intravitreal triamcinolone) and remain in the study. Therefore the data for the laser treatment arm of PROTOCOL I in Year 3 was not felt to be appropriate for estimation of evidence for a laser monotherapy treatment arm, in this particular case as the rate of adverse events may have been confounded by the additional treatments permitted during Year 3. Last observation carried forward (LOCF) was used to extrapolate adverse event rates from Year 2 to Year 3 for laser monotherapy. Therefore the rate in Year 3 given in Table 90 of the submission should be 5.80% as per the rate in Year 2. This value is correct within the submitted economic model and so the results presented within the submission are correct.

We assume that the sentence "*Please clarify why for year 3 the model utilised data from year 2 using the last observation carried forward, when year 3 data (9 patients had intraocular pressure greater than 30mmHg in year 3) are available in Allergan 2014 (reference 201)*" should state 9 patients had vitreous haemorrhage in Year 3, rather than raised intraocular pressure given that the question refers to Table 90 which is for the rate of vitreous haemorrhage.

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B7. Page 331 (of the company submission). Please provide a rationale for using transition probabilities [for MEAD arms] based on observed data for a modified intention to treat (mITT) population, which included only patients who had at least one follow-up visit, instead of data from the ITT population .

The mITT population was used for all analyses of patient-level data to ensure that the model was based on data from patients with at least one follow-up observation so that there was at least some evidence of treatment effect. The transition probabilities were based on observed data (i.e. not using LOCF or any other extrapolation), therefore if this restriction to the population had not been made explicitly these patients would not have been included in the transition probabilities as they would not have had follow-up visits at both baseline and Month 3, both of which were required in order to be included within the estimation of the transition probability matrix for the first cycle. This restriction affected only a small minority of patients within the MEAD study (n=4 patients in the DEX700 PRN treatment arm).

B8. Please provide a rationale for not considering fluocinolone acetate in the economic analysis of pseudophakic patients with DMO (either in the base-case analysis or in a scenario analysis).

The comparison for the pseudophakic population has considered only first-line comparators (ranibizumab in the base case, with bevacizumab, laser and watch and wait included in scenario analysis). Fluocinolone acetonide is licensed for the treatment of vision impairment associated with chronic macular oedema, considered insufficiently responsive to available therapies and is therefore not licensed as a first-line therapy.[19]

We agree that in the population of pseudophakic patients, in a second- or third-line position fluocinolone acetonide may be considered a relevant comparator treatment, however this comparison has been covered by the scenario analysis comparison with fluocinolone acetonide in the population of patients with DMO who are considered insufficiently responsive to non-corticosteroid therapy. This sub-population may include patients who are pseudophakic and therefore covers all possible populations in which fluocinolone acetonide may be considered a relevant comparator to DEX700.

This comparison was included as a scenario analysis only on the basis that IMS data demonstrated very little use of fluocinolone acetonide in clinical practice, a finding which has been confirmed by clinical key opinion leaders. This is likely due to the restrictions placed on the use of fluocinolone acetonide in England by the license (described above) and by NICE guidance (which further restricts use to the pseudophakic subgroup of patients).[12] In addition to this there are a number of major limitations in the data that are used to populate the network meta-analysis sensitivity analysis, which includes evidence from the FAME trial:

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- The network of 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
- The network of evidence is based around "all DMO patients", and for the majority of studies this includes some patients who are prior treated and some who are not; the FAME study included a patient population which was 100% prior treated
- The network of evidence considers (where possible) the probability of gaining at least 10 letters, losing at least 10 letters or gaining or losing less than 10 letters, in line with the vision state definitions within the economic model. The FAME study only reports data for the proportion of patients who gain at least 15 letters. This is a limitation for two reasons:
  - The study only reports the probability of gaining at least 15 letters, meaning that the probability of gaining at least 10 letters needs to be imputed
  - The study only reports one of the three outcomes of interest (gaining letters), meaning that the remaining two outcomes need to be imputed

Given these limitations, it is difficult to draw any meaningful conclusion from an analysis including fluocinolone acetonide.

B9. The economic model has used VFQ-UI for the estimation of QALYs instead of the EQ-5D.

a. Please provide quantitative and qualitative evidence that indicates that EQ-5D performs poorly in patients with DMO, as per NICE recommendations for submissions utilising an alternative utility measure (Guide to the methods for technology appraisal 2013, section 5.3.10).

Please refer to section 7.4.3 of the submission dossier for evidence that indicates that EQ-5D performs poorly in patients with visual morbidities.

Further to this, the validity of EQ-5D utility values for patients with DMO derived from RESTORE trial data have been disputed in a previous NICE technology appraisal.[16] The manufacturer's economic model for TA237 included a regression to predict EQ-5D scores based on data collected within the RESTORE study. This gave a range of utility values for the treated eye being in the worst to the best health state of 0.547-0.860. The committee for the appraisal considered that, given the population in RESTORE was treated in the WSE in the majority of cases; this range of utilities was broader than would be expected for this population.

b. Please provide more details on the methods used to generate the new utility index, their validity and an estimation of how use of the new measure may have affected the resulting utility values, as per NICE recommendations (Guide to the methods for technology appraisal 2013, section 5.3.10).

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Generic quality of life instruments like the EQ-5D and SF-36, which can be used to generate utilities for estimating quality of life for economic modelling, have been shown to be insensitive to changes in vision. In contrast, the condition-specific instrument, the NEI VFQ-25 is a non-preference based vision-specific quality of life measure which has been validated in a DMO population. However, the NEI VFQ-25 does not allow the direct estimation of utility weights. Therefore, utility values were derived from a preference-based scoring algorithm produced through direct valuation from the general population.

Kowalski *et al*.[20] (2012) used iterative Rasch analysis to identify a subset of six items from the NEI VFQ-25, which describe the impact of central and peripheral vision loss on daily functioning and well-being, was used to produce a health-state classification system, the Visual Function Questionnaire Utility Index (VFQ-UI).

An initial eight binocular visual-functioning health states were defined by the VFQ-UI. Then a general population health state valuation survey was administered to 607 members of the general population in the UK, Canada, Australia, and the US to elicit preference scores valued using time-trade off (TTO). Each participant was asked to value all eight health states. Using the resulting database of general population preferences, econometric modelling was used to create an algorithm (the VFQ-UI scoring algorithm), whereby a utility score could be estimated for any possible health state defined by the six NEI VFQ-25 items that comprise the VFQ-UI classification system.[21] Validation of the VFQ-UI outside of the development sample was performed using data from an interventional study that administered the NEI VFQ-25 to patients with vision loss due to intermediate or posterior uveitis.[22]

The development of the VFQ-UI classification system and algorithm was a multi-year research project sponsored by Allergan and conducted in collaboration with United BioSource Corporation and academic research groups, which included Professor John Brazier and Professor Ron Hays.

Details of the development and validation of the VFQ-UI algorithm have been published in the peer-reviewed literature.[20, 21] Use of the VFQ-UI algorithm for generating utilities has been evaluated and accepted by NICE in the submission for DEX700 in retinal vein occlusion, which received a positive recommendation.

The HRQL data used in the submission have a number of advantages that were not present in any identified study or in any previous economic evaluation for DMO. The majority of studies identified did not provide differential utility data for BSE and WSE patients. The utility data used in this analysis:

- Were obtained using methods which meet the NICE reference case, being valued using time-trade off (TTO) by members of the general public
- Are anchored between death and perfect health

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- Are based on the VFQ-UI, which is a vision-specific instrument measuring the effects of binocular vision on HRQL
- Provide utility data that map directly to the health states used in this model
- Allow estimation of utility impact based on both the WSE and BSE

To determine the impact of using utilities from the VFQ-UI compared with utilities from the EQ-5D (both measured within MEAD); scenario analysis was presented within the submission using a regression based on EQ-5D. This impacted the total QALYs gained by all treatments within the model; however consistent conclusions were reached for all analyses presented when either utility regression analysis was used. This suggests that the use of this utility measure does not have a large impact on the results of the economic evaluation.

B10. Page 330, Table 68 (of the company submission). Please provide a rationale for using LOCF from year 2 for patients receiving laser treatment in the model "DMO_NICE_Oct2014_Pseudophakic_All_Tx" when week 104 (17.6%), 128 (10.8%) and 156 (9.7%) data are available in Allergan 2014 (reference 201).

As discussed in the response to question B6, In Year 3 of the PROTOCOL I study patients in the laser treatment arm were permitted to receive ranibizumab on an as-needed basis and remain in the study.[23] This is because at the end of Year 2, patients receiving ranibizumab were shown to have significantly better outcomes compared with patients receiving sham + laser or intravitreal triamcinolone + laser. Therefore the data for the laser treatment arm of PROTOCOL I in Year 3 was not felt to be appropriate for estimation of evidence for a laser monotherapy treatment arm, in this particular case as the rate of laser treatments may have been confounded by the additional treatments permitted during Year 3 and patients may have received less laser than they would in practice because of these additional treatments.

B11. Page 37, Table 3 (of the company submission). The 'average cost of a course of treatment' row states that an average of 4.47 treatments over 3 years are expected. However, the 'anticipated average interval between courses of treatments' row in the same table states that patients will receive treatment at intervals of approximately 6 months. These statements seem to contradict each other. Please clarify the average number of treatments that a patient receiving DEX700 will have.

Additional DEX700 injections post initial treatment will be administered in accordance with retreatment criteria outlined in the summary of product of characteristics:

"Retreatment may be performed after approximately 6 months if the patient experiences decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening diabetic macular oedema."

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Some patients may therefore receive DEX700 approximately every 6 months. Others may still demonstrate treatment benefit at 6 months and thus will not receive DEX700 treatment at such frequent intervals.

The average cost of a course of treatment presented in Table 3 is based on the average number of DEX700 treatments received by patients in the MEAD trial programme over the 36 month treatment period from cumulative analysis that accounts for discontinuations every 3 months. This takes into account patients that were still experiencing treatment benefit 6 months after DEX700 administration and thus did not need receive retreatment at all available timepoints.

B12. Page 28, Table 2 (of the company submission). Please clarify the difference in total costs between dexamethasone and ranibizumab when ranibizumab is at a 50% discount.

The missing value from Table 2 for the incremental cost of DEX700 compared with ranibizumab when ranibizumab is at a 50% discount is £716.

Section C: Textual clarifications and additional points

C1. Page 409, Table 111 (of the company submission). Please explain why no intraocular pressure (IOP) checks have been applied to fluocinolone, as this is a corticosteroid and has the potential to raise IOP.

The resource use requirements for fluocinolone acetonide used within the economic model for this submission were assumed to be as per the manufacturer's submission for TA271, which did not include IOP checks.[11] This publication was felt to be an appropriate source for the resource use requirements for fluocinolone acetonide patients, and it was not felt appropriate to make an uninformed assumption that patients receiving fluocinolone would require the same degree of IOP monitoring as has been applied to DEX700. Further, the exclusion of this cost for fluocinolone acetonide patients is a conservative assumption against DEX700 in this comparison, and the inclusion of these costs would likely improve the cost-effectiveness of DEX700 compared with fluocinolone acetonide.

C2. Page 669, Table 260 (of the company submission). The ERG is able to verify the discontinuation due to adverse events (and other reasons) in month 23 *'Inp_Treatment'!AJ98* for bevacizumab in the model "DMO_NICE_Oct2014_Pseudophakic_All_Tx" based on Rajendram et al., 2012 (reference 200) which states 6 out of 42 patients discontinued the intervention in the bevacizumab arm during year 2. However, the ERG is unable to verify the 7.14% discontinuation rate used in years 3 to 5 in the references (Rajendram et al., 2012; Michaelides et al., 2010). Please clarify how a rate of 7.14% was estimated and the reference (with page number and/or table) used.

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Where patient-level data were available there was no clear pattern to discontinuation rates for treatments over the course of the clinical studies. Given this, LOCF was not felt to be an appropriate extrapolation measure for the rate of discontinuation from treatment. Discontinuation from treatment beyond the observed data has instead been estimated using the average rate across all observations (including zero observations). For bevacizumab there were two observations, Year 1: 0% (0/42 discontinuations), and Year 2: 14.29% (6/42 discontinuations).[24, 25] Therefore, the average discontinuation rate over all observations which is applied in Year 3 is (0%+14.29%)/2 = 7.14%.

C3. The ERG is unable to verify discontinuation due to adverse events (and other reasons) or lack or loss of efficacy for ranibizumab in the models ”DMO_NICE_Oct2014_Pseudophakic” and “DMO_NICE_Oct2014_Pseudophakic_All_Tx” based on the RESTORE references in Table 260 (Lang et al., 2004; Mitchel 2011; Schmidt et al., 2014).

a. Please clarify which reference (with page number and/or table) was used to estimate a discontinuation rate due to adverse events of:
   - 9.48% in month 11 ‘Inp_Treatment’!S97

The data for this input was taken from Mitchell *et al*.[26] (2011) Figure 2 (available in the online appendices). This figure demonstrated that 116 patients were enrolled in the study at baseline, and that during Year 1 of the study:

- 5 patients discontinued due to adverse events
- 1 patient discontinued due to abnormal laboratory values
- 4 patients discontinued due to withdrawal of consent
- 1 patient discontinued due to protocol deviation

These reasons for discontinuation from the study are considered to be covered by the terms “adverse events and other non-efficacy related reasons” and give a total of 11/116 = 9.48% patients who discontinued due to adverse events and other non-efficacy related reasons during Year 1 of the RESTORE study.

   - 6.02% in month 23 ‘Inp_Treatment’!AJ97

The data for this input was taken from Lang *et al*.[27] (2013) Figure 2 (available in the online appendices). Please note that the question states Lang *et al*. (2004) as the reference, however the references in Table 261 on page 679-670 of the submission are correctly stated as Lang *et al*. (2013). This figure demonstrated that 83 patients entered the extension study at the beginning of Year 2, and during Year 2 of the study:

- 1 patient discontinued due to adverse events
- 3 patients discontinued due to withdrawal of consent
- 1 patient discontinued due to missing information

This gives a total of 5/83 = 6.02% patients who discontinued due to adverse events and other non-efficacy related reasons during Year 2 of the RESTORE study.

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- 3.85% in month 35 'Inp_Treatment'!BA97

The data for this input was taken from Schmidt-Erfurth *et al*.[28] (2014) Figure 2 (available in the online appendices). This figure demonstrated that 83 patients entered the extension study at the beginning of Year 2, and during Years 2 and 3 of the study:

- 2 patients discontinued due to adverse events
- 3 due to withdrawal of consent
- 1 due to administrative problems
- 2 due to lost to follow up

This gives a total of 8/83 patients who discontinued due to adverse events and other non-efficacy related reasons during Years 2 and 3 of the RESTORE study. Accounting for the Year 2 data from Lang *et al*.[27] (2013) described above gives a total of (8-5)/(83-5) = 3/78 = 3.85% patients who discontinued due to adverse events and other non-efficacy related reasons during Year 3 of the RESTORE study.

- 6.45% in month 47 'Inp_Treatment'!BR97

In Years 4 and 5 the proportion of patients who discontinued from treatment due to adverse events and other non-efficacy related reasons was extrapolated as the average of all observations as LOCF was not felt to be an appropriate extrapolation measure for discontinuation (see response to question C2 for further detail). Therefore the rate applied in Years 4 and 5 was calculated using the data for Years 1 to 3 described above as (9.48%+6.02%+3.85%)/3 = 6.45%.

- 6.45% in month 59 'Inp_Treatment'!CI97

As above.

b. Please clarify which reference (with page number and/or table) was used to estimate a discontinuation rate, due to a lack or loss of efficacy of:
   - 0.86% in month 11 'Inp_Treatment'!S114

The data for this input was taken from Mitchell *et al*.[26] (2011) Figure 2 (available in the online appendices). This figure demonstrated that 116 patients were enrolled in the study at baseline, and that during Year 1 of the study:

- 1 patient discontinued due to unsatisfactory therapeutic effect

This gives a total of 1/116 = 0.86% patients who discontinued due to lack or loss of efficacy during Year 1 of the RESTORE study.

- 0.29% in month 47 'Inp_Treatment'!BR114

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During Years 2 and 3 of the RESTORE study there were no reported reasons for discontinuation which could be considered as discontinuation due to a lack or loss of efficacy (Schmidt *et al*.,[28] (2014) Figure 2; available in the online appendices).

In Years 4 and 5 the proportion of patients who discontinued from treatment due to a lack or loss of efficacy was extrapolated as the average of all observations as LOCF was not felt to be an appropriate extrapolation measure for discontinuation (see response to question C2 for further detail). Therefore the rate applied in Years 4 and 5 was calculated using the data for Years 1 to 3 described above as (0.86% + 0% + 0%)/3 = 0.29%.

- 0.29% in month 59 'Inp_Treatment'!CI114

As above

C4. The ERG is unable to verify the proportion of patients receiving fluocinolone and the proportion of patients discontinuing due to adverse events (and other reasons) in model "DMO_NICE_Oct2014_All DMO_incl.FAME " using the FAME references Campochiaro et al., 2011; Campochiaro et al., 2012; Cunha-Vas et al., 2013.

a. Please clarify which reference (with page number and/or table) has been used to estimate a proportion of 26% of patients receiving fluocinolone in the model for:
    - month 12 'Inp_Treatment'!Y61
    - month 24, 'Inp_Treatment'!AP61
    - month 26, 'Inp_Treatment'!BG61
    - month 48, 'Inp_Treatment'!BX61.

Campochiaro *et al*.[2] (2011) stated that during Year 2 of the FAME studies 21.3%, 1.9% and 0.3% of patients received 2, 3 and 4 injections respectively (Page 629, section: "*Repeated study treatments*"). This equates to an average of 0.26 additional treatments per patient during Year 2 of the study. The proportion observed in Year 2 was therefore fixed within the model to reach an average of 0.26 injections per patient. This input has been applied at the start of the Year (hence being applied in the Month 12 input, as the model begins with Month 0).

In Years 3 to 5 LOCF has been used, therefore it has been assumed that 0.26 additional injections were received at the start of each year (applied in Month 24, Month 36 and Month 48 within the model).

b. Please clarify which reference (with page number and/or table) was used to estimate a discontinuation rate of:
    - 20% due to adverse events for month 23, 'Inp_Treatment'!AJ97

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- 9% month 35, 'Inp_Treatment'!BA97
- 14.5% month 47, 'Inp_Treatment'!BR97
- 14.5% month 59, 'Inp_Treatment'!CI97

Campochiaro *et al*.[2] (2011) reported that out of 375 patients who entered the study 19.9% of patients failed to remain in the FAME studies until the Month 24 primary end-point (page 628). To enable uncertainty to be considered around this value, the number of patients was estimated as 19.9% x 375 patients, giving approximately 75 patients. This data was therefore entered in the model at the end of Year 2 (the Month 23 input within the model as the model begins with Month 0) as 75/375 patients (20.00%).

Campochiaro *et al*.[29] (2012) reported that out of 375 patients who entered the study 27.1% of patients exited the studies before the Month 36 visit (page 2126). To enable uncertainty to be considered around this value, the number of patients was estimated as 27.1% x 375 patients, giving approximately 102 patients who discontinued during the three years. The number of patients who discontinued during Year 3 was calculated as (102-75)/(375-75) = 27/300 patients who discontinued during Year 3. This data was therefore entered in the model at the end of Year 3 (the Month 35 input within the model as the model begins with Month 0) as 27/300 patients (9.00%).

The reasons for discontinuation given in both papers included withdrawal of consent, adverse events and death, but no reasons which could be considered as due to a lack or loss of efficacy and therefore all discontinuations were assumed to be due to adverse events and other reasons. It was not possible to disaggregate death from the other reasons for discontinuation.

In Years 4 and 5 the proportion of patients who discontinued from treatment due to a lack or loss of efficacy was extrapolated as the average of all observations as LOCF was not felt to be an appropriate extrapolation measure for discontinuation (see response to question C2 for further detail). Therefore the rate applied in Years 4 and 5 was calculated using the data for Years 2 to 3 described above as (20.00% + 9.00%)/2 = 14.5%.

C5. Please provide details on the methods of identification and selection for the following papers as data sources for the economic model, and the rationale for the data used:

a. Mulnier et al., 2006: mortality for patients with diabetes
b. Hirai et al., 2008: mortality attributable to DMO in patients with diabetes
c. Christ et al., 2008: mortality in people with severe loss of vision
d. Mitchell et al., 2012: natural progression of vision loss due to DMO
e. Colquitt et al., 2008: cost of severe vision loss

These studies were identified as references for these parameters which had been used and accepted in previous economic evaluations for DMO within the literature review conducted to identify published economic evaluations of treatments for DMO.

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C6. Page 397, Figure 65 (of the company submission). Please provide the references for the 3 'resource use' studies identified in the systematic literature review, the full text of which the company were unable to access.

The references for the three resource use studies which were identified in the systematic literature review which were unable to be accessed as full text articles are provided below:

- M. M. Hashir; M. I. Nazir; M. B. Pasha; M. F. Latif; M. Fatima; R. Faraz. 2008. Diabetic retinopathy. Medical Forum Monthly. 19, 14-25.

- J. N. Blustein; J. A. Gold; K. M. Miesbauer; C. L. Halvorsen. 1997. Diabetic Retinopathy Project. Wisconsin Medical Journal. 96, 60-61.

- -HAYES; -Inc. 2010, Intravitreal Dexamethasone Drug Delivery System (DDDS) for treatment of macular edema (Structured abstract). Health Technology Assessment Database.

C7. Page 520, reference 194 (of the company submission). The ERG is unable to differentiate between Table 03.1.4-1001 and Table 03.1.4-1019 in 'Allergan Inc. Clinical Story 024 Final. 2014'. Both tables are titled "Fellow Eye Occurrence in diabetic macular oedema and Receipt of Treatment During the Study". Please clarify the difference between these 2 tables and if Table 03.1.4-1019 has been used to estimate the % of DEX700 arm patients in MEAD who were affected unilaterally at baseline and developed fellow eye involvement over the study duration using the broad definition of diabetic macular oedema for the base case.

Reference 194 within the submission is for 'Allergan Inc. MEAD Economic Confidential Data. 2014', and not for 'Allergan Inc. Clinical Story 024 Final. 2014' as stated. This response therefore refers to the reference 'Allergan Inc. MEAD Economic Confidential Data. 2014', as this reference includes the tables which are referred to within the question.

Table 03.1.4-1019 is used in the base case analysis for the estimation of the proportion of DEX700 patients in MEAD who were affected unilaterally at baseline and who developed fellow eye involvement over the study duration, incorporating a broad definition of DMO as described on page 352 of the submission and below.

This analysis (Table 03.1.4-1019) gives a rate of 41.98% over 3 years and is based on the frequency of new incidences of "diabetic macular (o) edema", "diabetic neuropathy", "diabetic retinal (o) edema", "diabetic retinopathy", "macular degeneration", "macular oedema", "retinal degeneration" or "retinal neovascularisation".

The protocol of the MEAD studies allowed the use of escape therapy and the efficacy data were censored for the subsequent visits by carrying forward the last BCVA observation

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collected prior to the use of escape therapy forward throughout the study exit. The use of escape therapy was recorded as treatment for either DMO or DMO-related diagnosis.

A scenario analysis was therefore presented whereby the rate of fellow eye involvement is based on the specific fellow-eye occurrence of “diabetic macular (o) edema” recorded in the non-study eye during the MEAD study. This is derived from Table 03.1.4-1001 and gives a lower rate of 13.06% of DEX700 arm patients in MEAD who were affected unilaterally at baseline and developed fellow eye involvement over the study duration.

C8. Section 12.5.4.2, Table 12 to 21 and Table 14.6 to 3.5 (of the company clinical study reports).

a. Please clarify whether the data reported in the clinical study reports (number (%) of patients with cataract surgery in the study eye subgroup: phakic patients at baseline)) are cumulative?

Table 12-21 in section 12.5.4.2 of the clinical study reports provided for MEAD-010 and MEAD-011 only report cumulative data in the final row (Ever had). The data reported for each study visit are not cumulative and present the number of new patients with a phakic study eye at baseline that had cataract surgery in the study eye at each six month study visit.

Of note, one patient with a phakic study eye at baseline in each study received two cataract surgeries. The cumulative analysis presented in the final row (Ever had) therefore has one less patient than the total of new extractions at each visit reported in the previous rows.

b. In addition there is a discrepancy between the models and the submission, please clarify which value is the correct value to be used in the model and the reason for this difference.

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Parameter	Model reference	Submission reference
Cataract extraction rate DEX700 PRN: Year 1	'Inp_AE'!F15 8.40% =(9+13) / (117+145)	Page 360 Table 85 6.49%
Cataract extraction rate DEX700 PRN: Year 2	'Inp_AE'!G15 19.17% =(19+27) / ((117+145) - (9+13))	Page 360 Table 85 21.22%
Cataract extraction rate DEX700 PRN: Year 3 to 5	'Inp_AE'!H15 2.94% =(3+3) / ((117+145) - (9+3+19+27))	Page 360 Table 85 18.13%

This is an error in the report. The values in the model are correct.

C9. The cataract extraction rate for fluocinolone acetonide in year 2 is 65.53% based on "FAME: 154/235 phakic patients required cataract surgery to end of Year 2" in DMO_NICE_Oct2014_All DMO_incl.FAME 'Inp_AE'!I19. However, the ERG believes it is incorrect to estimate this rate based on the population from Campochiaro et al., 2012 with a duration of 36 months (188 out of 235 (80%) patients) and events from Campochairo et al., 2011 with a duration of 24 months (154 out of 375 (41%) patients). Please explain why these figures were used for the estimation of the final 65.53%.

The rate of cataract surgery should be applied to the phakic population only as pseudophakic patients already have an artificial lens. Campochiaro *et al*.[29] (2012) indicated that there were 235/375 phakic patients in the FAME studies at baseline. The number of events of cataract surgery in FAME to the end of Year 2 was 154 (Campochiaro *et al*.,[2] 2011) and to Year 3 was 188 (Campochiaro *et al*.,[29] 2012).These have therefore been used to calculate the proportion of phakic eyes which had cataract surgery in FAME during Years 1-2 and during Year 3, based on the number of phakic eyes at baseline.

These have been calculated as follows:

In Years 1-2 the rate of cataract surgery was calculated as the number of cataract surgeries in Years 1-2 divided by number of phakic patients at baseline = 154/235 = 65.53%. this rate is applied in Year 2.

In Year 3 the rate of cataract surgery was calculated as (the number of cataract surgeries in Year 3 minus the number of cataract surgeries in Years 1-2) divided by (the number of

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phakic patients at baseline minus the number of cataract surgeries in Years 1-2) = (188-154)/(235-154) = 41.98%

The rate of 41% given in Campochiaro *et al.*[2] (2011) is based on the whole population (375 patients) which includes some patients which are pseudophakic and hence not at risk of this adverse event; therefore this rate is an under-estimation of the true risk of cataract surgery which is applied only to phakic patients within the economic model.

C10. Page 340, Tables 74 and 75 and all Tables in Appendix 15 (of the company submission). Please confirm that these tables present 3-month transition probabilities for DEX700 AFTER the assumption that transitions may be made only to the adjacent health state up or down and thus are not representative of transition probabilities, as recorded in the MEAD DEX700 arm.

This is correct. These transition probabilities represent the 3-monthly transition probabilities after the assumption that transitions may be made only to the adjacent health states have been applied. The patient-level movements between the health states (number of patients) as recorded in the MEAD clinical trials (before this assumption is applied) are provided in the economic models on the sheet "*Sub 1*". The assumption to restrict the movements to the adjacent state only is applied on this sheet.

C11. Page 379 and 380 Figure 63 (of the company submission).

a. Please provide a rationale for the strict inclusion criteria (data relating to best-corrected visual acuity or adverse events, only patients with diabetic macular oedema) used for the identification of health-related quality of life studies.

Evidence was sought for the impact of visual impairment on HRQL for patients with DMO only as we feel that studies of the impact on HRQL of visual impairment due to other visual disorders may not accurately capture the true impact for a patient with DMO. This is due to the underlying DM, which may affect the HRQL of a patient with DMO in a way that would not be captured in HRQL studies for other visual disorders.

Further, given that HRQL data was collected within the MEAD clinical studies and was planned to be included within the *de novo* economic model to provide HRQL data for DMO patients, it was not felt that it would be necessary to extend the inclusion criteria to other visual disorders in order to identify relevant HRQL values for use within the *de novo* model.

b. Please also provide full references of the 6 studies the full text of which the company were unable to access, as stated in the flow diagram in Figure 63.

The references for the six HRQL studies which were identified in the systematic literature review which were unable to be accessed as full text articles are provided below:

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- Y. Shao; X. R. Li; Y. Shao; X. R. Li. 2008. [Effects of diabetic retinopathy on quality of life]. [Review] [Chinese]. Chung-Hua Yen Ko Tsa Chih [Chinese Journal of Ophthalmology]. 44, 660-663

- K. Emi; T. Oyagi; T. Ikeda; H. Bando; T. Okita; D. Kashimoto; S. Morita; N. Matsumura; K. Sawada; K. Sawada; E. Toyoda; C. Ueno; K. Emi; T. Oyagi; T. Ikeda; H. Bando; T. Okita; D. Kashimoto; S. Morita; N. Matsumura; K. Sawada; K. Sawada; E. Toyoda; C. Ueno. 2008. Influence of vitrectomy for diabetic retinopathy on health-related quality of life]. [Japanese]. Nippon Ganka Gakkai Zasshi - Acta Societatis Ophthalmologicae Japonicae. 112, 141-147

- E. Vodrazkova; S. Sefcikova; M. Helbich. 2012. Psychometric validation of Visual Function Questionnaire (NEI VQF-25) under local conditions in Slovakia, E.U. Ceska a Slovenska Oftalmologie. 68, 102-108

- E. Vodrazkova; S. Sefcikova; M. Helbich; E. Vodrazkova; S. Sefcikova; M. Helbich. 2012. [Psychometric validation of visual function questionnaire (NEI VQF-25) under local conditions in Slovakia, E.U]. [Slovak]. Ceska a Slovenska Oftalmologie. 68, 102-105

- P Mitchell. 2010. Restore trial of ranibizumab for diabetic macular oedema: 1-year findings. Clinical and Experimental Ophthalmology. 38, 12.

- E. N. Cetin; Y. Bulgu; M. Zencir; A. M. Avunduk; V. Yaylali; C. Yildirim. 2012. Vision related quality of life in patients with diabetic retinopathy. Retina-Vitreus. 20, 213-217.

C12. Page 195 (of the company submission). Please explain what is meant by the ‘analysis windows’ reported in the submission.

‘Analysis windows’ refers to the range of days within which outcomes were candidates for allocation to a specific visit. Within each analysis window, the outcome of interest on the day closest to the target date for the visit was chosen. Analysis windows were constructed to be contiguous but mutually exclusive. Analysis windows were not required to be identical across studies as the follow-up visit frequency differed between trials. For MEAD-010, MEAD-011, study 024 and PLACID, the same analysis windows were used to generate outcomes for the MTC and economic modelling. An example of the analysis windows used, based on the MEAD trial programme, is presented in Table 38.

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Table 38: Analysis windows used to generate outcomes for the MTC and economic modelling

Window Number	Window Name	Target Day	Window Number	Window Name
1	Baseline[a]	<=1	<0	1
7	Month 3	90	2	134
9	Month 6	180	135	224
11	Month 9	270	225	314
13	Month 12	360	315	404
14	Month 15	450	405	494
15	Month 18	540	495	584
16	Month 21	630	585	674
17	Month 24	720	675	764
18	Month 27	810	765	854
19	Month 30	900	855	944
20	Month 33	990	945	1034
21	Month 36	1080	1035	1124
33	Month 39	1170	1125	1215
88	Out of Window		>1215	>1215
Key: MTC, mixed treatment comparison				

C13. Page 161 (Figure 18), page 166 (Figure 21) and page 169 (Figure 22) (of the company submission). Please explain the difference in the numbers of patients in each arm in the 'cataract surgery to last best-corrected visual acuity' analysis compared with the 'cataract adverse event to cataract surgery' analysis.

These post-hoc analyses are based on observed data. Therefore, only patients with a BCVA assessment post cataract surgery are included in Figure 18; only patients with a CRT assessment post cataract surgery are included in Figure 21; and only patients with a NEI-VFQ-25 assessment post cataract surgery are included in Figure 22.

C14. Page 349 (of the company submission). Beyond the study duration the discontinuation rates have been extrapolated using the average rate over the study duration applied in line with the relevant study cycle length". Please confirm that this applies only to studies with duration lower than 3 years, as the base-case analysis assumes treatment is terminated after 3 years so no discontinuation should be applied after that period.

Yes, this is correct. In the base case analysis this applies only to treatments with study duration less than 3 years: bevacizumab (BOLT; 2 year duration) and laser (PROTOCOL I; as laser patients were permitted to receive other treatments in Year 3 including ranibizumab and IVTA which could confound the data, as discussed in the response to question B6). In

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the base case analysis no treatment is assumed, and therefore no discontinuation is applied, beyond Year 3. However, in the scenario analyses increasing the treatment duration to 5 years this extrapolation applies to all treatments in Years 4 and 5, after which no discontinuation is applied.

C15. Page 100, Table 12 (of the company submission). Please provide an explanation for inclusion of the Udaondo et al 2013.

This table summarises all studies identified through systematic review of the non-RCT evidence base that met the eligibility criteria presented in Table 40 of the submission for completeness. The study reported by Udaondo et al.[30] at conference met these criteria and therefore was included in this table.

As was the case in the systematic review of RCT evidence, given that DEX700 is intended for use in various positions within the clinical pathway of care, no restrictions were placed upon the population in regard to treatment line. The study reported by Udando et al.[30] exclusively enrolled treatment naïve patients with DMO. In accordance with its indication for use in DMO, DEX700 may be used in treatment naïve DMO patients who are pseudophakic or who are considered unsuitable for non-corticosteroid therapy. The study reported by Udando et al.[30] did not report data for either of these populations and their inclusion could not be assessed from the information available in this conference presentation of results. The relevance of this study to the decision problem could not therefore be assessed and its inclusion in the non-RCT evidence presented could not be justified, as signified by the blank justification column in Table 12 of the submission.

C16. Page 229 to 238 (of the company submission). The flow chart of non-randomised control trials reports 10 studies meeting eligibility criteria but only nine appear to have been described. Please clarify the correct number and provide details of any missing studies.

Ten studies did meet the eligibility criteria of the non-RCT review but as outlined in Table 12 of the submission and summarised on page 234, one of these studies could not be considered relevant to the decision problem. This study, reported by Udando et al. 2013, was not therefore presented as part of the non-RCT evidence base summarised in section 6.8.

C17. Page 268 (of the company submission). Please provide the definitions used for ‘the expected levels of IOP elevation’ and ‘cataract’ in the adverse events.

No official definitions for ‘the expected levels of IOP elevation’ and ‘cataract’ reference made in the safety overview section (6.9.3) were pre-specified. This statement is based upon the well-known safety profile of intravitreal steroid therapies reported in the literature base and safety outcomes from pivotal clinical trials of DEX700 in other ophthalmological conditions.

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Ophthalmic corticosteroid exposure is known to be associated with the side effects of IOP elevation and cataract.[31-33]This safety profile is consistently observed in clinical trials of corticosteroid therapy in DMO[29, 33-35] and in clinical practice (see appendix 11 of submission).

Pivotal clinical trials of DEX700 in retinal vein occlusion (RVO) and uveitis demonstrated IOP elevation in up to 32.8% of study eyes.[36, 37] A similar level was therefore expected with DEX700 treatment of DMO as there is no clinical rationale or evidence to suggest the safety profile of DEX700 is not consistent across ophthalmological conditions.

Cataract adverse event rates in these trials were between 20-30% of phakic patients who did not present with cataract at baseline but these trials were only 6-12 months in duration.[36, 37] Clinical trials of other corticosteroid therapies in DMO demonstrate cataract adverse events are more common after 12 months of corticosteroid exposure.[29, 35] A higher level of cataract associated with DEX700 treatment was therefore expected in the MEAD trial programme than observed in the shorter trials of DEX700 use in RVO and uveitis as patients were followed for up to 39 months. Rates of cataract adverse events were not expected to exceed rates associated with alternative corticosteroid therapy use in DMO over similar periods (reported at approximately 80%)[29, 35]; therefore, the cataract adverse event rate in patients treated with DEX700 in the MEAD trial programme was expected to fall between 30-80%.

C18. Page 285, Table 58 (of the company submission). Please provide the criteria that would be used in clinical practice to select patients for whom DEX700 treatment would be suitable in terms of the patients “insufficiently responsive to laser” as provided for the other patient populations detailed in the table.

Criteria that would be used in clinical practice to select patients for whom DEX700 treatment would be suitable in terms of the patients “insufficiently responsive to laser” was not included in Table 58 of the submission as in clinical practice, response to laser for the treatment of DMO would not be independently assessed.

In current clinical practice, laser photocoagulation is not commonly used as a monotherapy for the treatment of DMO; rather, it is administered alongside pharmaceutical therapy when the oedema develops or progresses in a position or in a manner that physicians feel would benefit from laser treatment (see section 2.5 and appendix 11 of the submission). In light of this, response to laser would not be assessed independently of response to pharmaceutical treatment so it was not deemed appropriate to include such a population in Table 58.

Criteria that would be used in clinical practice to select patients for whom DEX700 treatment would be suitable in terms of the patients considered insufficiently responsive to non-corticosteroid therapy would therefore be based on criteria of the patients considered insufficiently responsive to anti-VEGF therapy. This population is included in Table 58 of the submission.

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C19. Please provide an explanation as to why the following baseline data have been extracted exclusively from the MEAD DEX700 arm and not from the mixed MEAD DEX700 and sham study sample:

a. Page 314 (of the company submission). The proportions of patients within the cohort who have unilateral diabetic macular oedema in the BSE or the WSE, or bilateral diabetic macular oedema at baseline.

Baseline data was taken from the DEX700 PRN treatment arm in order to reflect the characteristics of patients who were actually treated with DEX700 within the MEAD studies. The same baseline distribution was then applied to all treatments within the comparison for each population. Therefore, this is methodologically correct if we assume that the baseline characteristics of DEX700 patients are representative of a general DMO population. Table 39 shows the proportions of patients within the cohort who have unilateral diabetic macular oedema in the BSE or the WSE, or bilateral diabetic macular oedema at baseline by treatment arm in MEAD. This demonstrates that there is very little difference between the proportions observed in each of the DEX700, sham and pooled populations and therefore the choice to use the DEX700 data is not likely to have affected the results of the analysis.

Table 39: Proportions of patients within the cohort who have unilateral diabetic macular oedema in the BSE or the WSE, or bilateral diabetic macular oedema at baseline, by treatment arm

Population	Unilateral DMO in the		Bilateral DMO
	BSE	WSE	
All DMO			
DEX700	14.0%	50.0%	36.0%
Sham	15.0%	48.4%	36.6%
Total	14.5%	49.2%	36.3%
Pseudophakic			
DEX700	14.9%	48.6%	36.5%
Sham	14.5%	51.5%	34.0%
Total	14.7%	50.2%	35.1%

Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File 2014.[4]

b. Page 352 (of the company submission). The proportion of patients within the cohort who develop fellow eye involvement.

The reasons for choosing baseline data specific to the DEX700 treatment arm are discussed in the response to part a. Table 40 shows the proportions of patients within the cohort who had unilateral DMO at baseline and who developed DMO in their fellow eye during the study by treatment arm in MEAD. This demonstrates that there is a slight difference in the rate observed across the treatment arms and the pooled dataset; however the rate was highest in the DEX700 treatment arm (broad definition used in base case). Scenario analyses were

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presented within the submission using the lower rate (strict definition) and also including no fellow eye involvement. The rate of fellow eye involvement was shown to have limited impact on the results of the economic analysis with the conclusion of the analysis remaining unchanged in all populations even when no fellow eye involvement was assumed.

Table 40: Proportions of patients within the cohort who have unilateral diabetic macular oedema in the BSE or the WSE, or bilateral diabetic macular oedema at baseline, by treatment arm

Population	Proportion of patients with unilateral DMO at baseline who developed DMO in their fellow eye during the MEAD study	
	Broad definition of DMO	Strict definition of DMO
DEX700	41.98%	13.06%
Sham	34.23%	9.01%
Pooled	38.06%	11.04%
Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye. **Source:** Allergan MEAD Data on File 2014.[4]		

C20. Please confirm that the economic analysis used DEX700 as baseline treatment, and that the following references to sham as baseline treatment, should be amended:

a. Page 331, Table 69 (of the company submission): ("3-monthly probabilities [...] generated from the sham arm...")

Yes, this is a typographical error and should refer to DEX700.

b. Page 343 (of the company submission): "...the transition probabilities generated by applying the relative risks to the transition probabilities for watch and wait were normalised."

Yes, this is a typographical error and should refer to DEX700.

c. Page 364 (of the company submission): "transition probabilities [...] were based on watch and wait (sham) patients' transitions in the MEAD studies [...]. DEX700 and active comparator transition probabilities were calculated from these by applying relative risks [...] calculated from the network meta-analysis."

Yes, this is a typographical error and should refer to DEX700.

C21. Page 361, Table 86 (of the company submission). There is a discrepancy between the model "DMO_NICE_Oct2014_Pseudophakic_All_Tx" 'Inp_AE'!C39 and Table for the proportion of raised intraocular pressure in year 1 for laser treatment. The model uses a value of 1.02% whereas the submission presents a value of 0.01%.

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Based on Table 03.2.1-1077 in Allergan 2014 (reference 201), please confirm that 1.02% (3/293) is the correct value.

Yes, this is an error in the report. The value 1.02% used in the economic model is correct.

C22. Page 336, Table 71 (of the company submission). Please provide the missing footnotes for better-seeing eye and worst-seeing eye (1-4).

The relevant footnotes have been added below in Table 41 (table 71 of the main submission) and Table 42 (Table 72 of the main submission).

Table 41: Baseline distribution of vision across visual acuity states; All DMO patients (Table 71 in the main submission)

DMO status	Eye	Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
Unilateral DMO in the BSE	BSE[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE[3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE[4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE[3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: 1.Based on data for study eyes which were the BSE; 2. Based on data for non-study eyes which were the BSE; 3. Based on data for study eyes which were the WSE; 4. Based on data for non-study eyes which were the WSE.
References: Allergan MEAD Data on File[4]

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Table 42: Baseline distribution of vision across visual acuity states; DMO patients who are pseudophakic (Table 72 in the main submission)

DMO status	Eye	Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
Unilateral DMO in the BSE	BSE[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE[3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE[4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE[3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: 1. Based on data for study eyes which were the BSE; 2. Based on data for non-study eyes which were the BSE; 3. Based on data for study eyes which were the WSE; 4. Based on data for non-study eyes which were the WSE.
References: Allergan MEAD Data on File[4]

C23. Page 678, Appendix 19. Please clarify whether and if so how the discounting formula described was used, as it is not referred to in the text.

This discounting formula was not used within the economic model. This appendix has been included in error.

C24. Page 2 to 11. Please check and amend the page numbers in the list of tables as some of these appear to be incorrect.

The table list has been updated and is presented in Appendix C24.

C25. Page 89 and 90, Figure 8. There are some discrepancies in the text on page 89 compared with the details provided in the PRISMA diagram, Figure 8 on page 90. Please clarify which numbers are correct.

There is an error in the text on page 89 on the submission where the original search outcomes are summarised. It was stated that:

“After removal of duplicates, 1460 potentially relevant citations remained.”

This is based upon duplicate identification conducted within reference manager software but three further duplicates were identified manually. This sentence should therefore read:

“After removal of duplicates, 1457 potentially relevant citations remained.”

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The details provided in the PRISMA diagram correctly reflect this.

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