Dexamethasone intravitreal implant for diabetic macular oedema

STA REPORT

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List of Abbreviations

AE	Adverse event
AIC	Akaike information criterion
AUC	Area under the curve
BIC	Bayesian information criterion
BCVA	Best corrected visual acuity
BEV	Bevacizumab
BNF	British National Formulary
BRB	Blood retinal barrier
BRVO	Branch retinal vein occlusion
BSE	Better seeing eye
CC	Complications and morbidity
CEACs	Cost-effectiveness acceptability curves
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence internal
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CrI	Credible intervals
CRT	Central retinal thickness
CS	Company submission
CSMO	Clinically significant macular oedema
CV	Cardiovascular
DARE	Database of Abstracts of Review and Effects
DDS	Drug delivery system
DEX	Dexamethasone
DM	Diabetes mellitus
DMO	Diabetic macular oedema
DR	Diabetic retinopathy
EMA	European Medicines Agency
eMIT	Electronic market information tool
ERG	Evidence Review Group
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
FA	Fluocinolone acetonide
FAD	Final appraisal determination
FDA	US Food and Drug Administration
FEI	Fellow eye involvement
HbA1c	Glycosylated haemoglobin
HRG	Healthcare related group
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IOP	Intraocular pressure
ITT	Intention-to-treat
LAS	Laser
LOCF	Last observation carried forward

MIMS	Monthly Index of Medical Specialties
mITT	Modified intention-to-treat
NEI-VFQ	National Eye Institute Visual Functioning Questionnaire-25
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NMA	Network meta-analysis
NMB	Net monetary benefit
OCT	Optical coherence tomography
OSC	Optimized standard of care
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBM	Preference-based measures
PbR	Payment by results
PH	Public Health
PRN	Pro re nata
PSA	Probabilistic sensitivity analysis
PS DDS	Posterior segment drug delivery system
PSS	Personal social services
QALY(s)	Progression-adjusted life year(s)
QoL	Quality of life
QS	Quality standard
RAN	Ranibizumab
RCO	Royal College of Ophthalmologists
RCT	Randomized controlled trials
RR	Relative risk
RVO	Retinal vein occlusion
SAE	Serious adverse event
SD	Standard deviation
SMC	Scottish Medicines Consortium
SR	Systematic review
SPC	Summary of product characteristics
TA	Triamcinolone
TRSAE	Treatment-related serious adverse event
TTO	Time trade-off
UK	United kingdom
US	United States of America
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VFQ	Visual functioning questionnaire
VFQ-UI	Visual Functioning Questionnaire Utility Index
WSE	Worse-seeing eye
WTP	Willingness to pay
YAG	Yttrium aluminum garnet

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company for dexamethasone intravitreal implant (Ozurdex®, Allergan) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of dexamethasone intravitreal implant (referred to as dexamethasone hereafter) for treating diabetic macular oedema (DMO). Dexamethasone received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 24 July 2014 for the treatment of adult patients with visual impairment due to DMO, who are pseudophakic (have an artificial lens implant), or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. This indication was approved by the European Commission for a marketing authorisation on 24 August 2014.

The final scope was issued by NICE for this single technology appraisal (STA) prior to the CHMP positive opinion for dexamethasone and requested a broader population than that for which EU marketing authorisation for dexamethasone has been approved. The final scope requested, "people with diabetic macular oedema". The Evidence Review Group (ERG) notes that the company presented evidence for dexamethasone from six randomised controlled trials (RCTs [MEAD-010, MEAD-011, PLACID, 024, BEVORDEX and NCT00035906) in the company submission (CS). However, in terms of the actual populations in the six RCTs, none of them directly addressed the populations covered by the EU marketing authorisation for dexamethasone. All six RCTs had inclusion criteria designed to assesses broader populations to that of interest.

The inclusion criteria in terms of the prior treatment history for people included in the six RCTs differed from trial to trial. None of the trials directly addressed the populations considered insufficiently responsive to non-corticosteroid therapy or unsuitable for non-corticosteroid therapy. Subgroup data from the MEAD-010, MEAD-011, 024, PLACID and BEVORDEX studies were presented for the pseudophakic population and from the MEAD studies based on prior therapy use/treatment naive. The ERG notes that there is an absence of RCT data in the appropriate populations but is unable to comment further on the likely impact of using the whole population data as surrogate data for the populations for whom dexamethasone has EU marketing authorisation. The results presented in the CS are thus limited in their specificity for addressing the populations for whom dexamethasone has EU marketing authorisation.

The clinical trial data reported in the CS were based on trials of the dexamethasone 700 µg which has EU marketing authorisation for use in DMO. However, the ERG notes that two of the RCTs reported in the CS used treatment regimens that are not approved for use in the UK (BEVORDEX and 024). These two studies both allowed re-treatment with dexamethasone more frequently than the 6-month

minimum re-treatment period specified in the EU licence. The ERG thus does not consider these trials of relevance to the decision problem.

The comparators for this STA listed in the final scope issued by NICE are:

- Laser photocoagulation alone;
- Ranibizumab alone or in combination with laser photocoagulation;
- Fluocinolone acetonide intravitreal implant alone or in combination with laser photocoagulation;
- Bevacizumab (for people in whom ranibizumab and fluocinolone acetonide intravitreal implants are unsuitable) alone or in combination with laser photocoagulation.

The ERG notes that the company did not include data for fluocinolone acetonide in combination with laser photocoagulation or bevacizumab in combination with laser photocoagulation within the CS. The ERG also notes that the company included data for an additional comparator, watch and wait, within the submission. The company justified the inclusion of watch and wait as it is a comparator for dexamethasone in the people who are considered unsuitable for non-corticosteroid therapy, and for people who are considered insufficiently responsive to non-corticosteroid therapy in whom the fluocinolone acetonide implant is unsuitable. The company used a network meta-analysis (NMA) to provide data for some of the comparators in the CS where there were no head-to-head studies. The ERG has concerns over the validity of the results from the NMA due to the presence of both clinical and statistical heterogeneity within the network.

Regarding outcomes, data for best corrected visual acuity for both eyes (BCVA) was not specifically reported in the CS for any of the studies. In addition, the ERG notes that not all of the outcomes were covered within the CS for each of the six dexamethasone RCTs and data were not available for all of the outcomes in terms of the comparison of dexamethasone with each of the comparators in the NICE final scope. However, in terms of actual outcomes reported in the CS, the ERG considers the key clinical outcomes are reported in the CS although the ERG has concerns around the populations in which the outcome data are reported not addressing the EU licensed populations for dexamethasone in DMO.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company presented clinical effectiveness evidence on dexamethasone 700µg from six RCTs in the CS:

- MEAD-010 and MEAD-011: dexamethasone (6 monthly pro re nata [PRN]) versus sham;
- NCT00035906: dexamethasone (1 treatment only) versus observation;

- 024: dexamethasone (5 monthly) versus ranibizumab;
- PLACID: dexamethasone (6 monthly) + laser photocoagulation versus laser photocoagulation;
- BEVORDEX: dexamethasone (4 monthly) versus bevacizumab.

The two MEAD studies were identical in study design and provide the key data for dexamethasone in the CS although this is versus sham which was not a comparator of interest in the final scope issued by NICE. NCT00035906 limited treatment with dexamethasone to one dose and compared it with observation alone, which again was not a comparator listed in the final scope issued by NICE. However, based on the EU marketing authorisation for dexamethasone, the ERG considers observation and sham to be appropriate comparators for some of the populations for whom dexamethasone would be a treatment option. This is because observation and sham can be considered surrogates for watch and wait.

The ERG has concerns that 024 and BEVORDEX do not utilise the dexamethasone dosing regimen authorised in the UK; both utilise more frequent dexamethasone regimens than the EU marketing authorisation 6 monthly recommended minimum re-treatment period.

In view of the differences between each of the trials, with the exception of the MEAD studies, the ERG considers the company's decision to report each trial separately to be appropriate. The ERG notes that the company reported the MEAD studies separately, combined in a pooled analysis and also combined in a meta-analysis.

The ERG does not consider 024 or BEVORDEX to address the decision problem as they do not use the licensed treatment regimens for dexamethasone in the UK and so these studies are not discussed in detail in this report.

The MEAD studies and NCT00035906 were 3-armed RCTs, with one of the treatment groups being a lower dose of dexamethasone than that licensed for use in the UK (dexamethasone 350µg). The ERG thus does not consider data from this trial arm of relevance to this review and does not present or discuss the data in this report.

MEAD-010 contained 494 randomised patients (328 patients randomised to the two treatment arms of interest to this review) and MEAD-011 contained 554 randomised patients (373 patients in the two treatment arms of interest to this review). Both MEAD studies lasted for 36-39 months. PLACID enrolled and randomised 253 patients for 12-15 months planned follow-up, and in NCT00035906 there were 171 DMO patients randomised (although only 114 were randomised to treatment arms of interest to this review, i.e. dexamethasone 700µg or observation) and follow up was planned for 180 days. Efficacy analyses were based on the ITT (randomised) populations and safety analyses

comprised of people who received at least one dose of study medication with patients assigned to their randomised treatment group regardless of actual drug taken.

The ERG notes that the discontinuation rate is high in both the dexamethasone and sham groups in the MEAD studies (over 20% in each treatment arm) although lower discontinuation rates were observed in PLACID and NCT00035906. The ERG also notes that missing data in the MEAD studies were handled using last observation carried forward (LOCF) methodology and thus the high discontinuation rates could potentially confound the results of the trials. The ERG is unable to ascertain in which direction this bias might affect the results but that it is unlikely that the results presented would reflect the total population had discontinuations not occurred or patients been followed up post-discontinuation. In addition, the ERG notes that the discontinuation rate is nearly twice as high in the sham groups compared with the dexamethasone groups of the MEAD studies.

In the pooled MEAD analysis, dexamethasone resulted in a statistically significant increase in mean BCVA change from baseline and in the number of patients achieving both a ≥15 letter gain and a ≥10 letter gain from baseline compared with sham. However, from month 15 onwards in the MEAD studies, the improvement in BCVA provided by dexamethasone 700µg relative to sham was reduced and didn't recover until after 36 months. The ERG notes that this trend coincides with cataract adverse effects during the second year of the study in the dexamethasone group.

The company reported that there were no significant changes in contrast sensitivity or mean average NEI-VFQ-25 change (AUC approach) between dexamethasone and sham in the MEAD studies. However, dexamethasone resulted in a statistically significant greater reduction in mean CRT average change (AUC approach) compared with sham in MEAD-010, MEAD-011 and the MEAD pooled analysis.

The mean BCVA change from baseline, the proportion of patients achieving at least a 10-letter improvement in visual acuity at study end and the HRQL analyses in PLACID demonstrated no significant difference between dexamethasone + laser versus laser alone. In addition, there was no significant difference between dexamethasone and observation at day 180 in the proportion of DMO patients achieving at least a 10-letter improvement in visual acuity or at least a 15-letter improvement in visual acuity analyses in NCT00035906.

The most common ocular treatment-related adverse events (TRAEs) in the MEAD studies were cataract formation and raised IOP with dexamethasone, and conjunctival haemorrhage with sham although assessments of statistical significance weren't reported in the CS. Treatment-related IOP increase, cataract and vitreous haemorrhage all showed a statistically significant between-group

difference with more AEs in the dexamethasone + laser group compared with the laser alone group in PLACID.

In terms of subgroup analyses of relevance to the decision problem, the mean BCVA change from baseline with dexamethasone for the pseudophakic patients in the MEAD studies was statistically significant at all time points compared with sham. In addition, the pseudophakic patients in the dexamethasone group of the MEAD studies achieved a much greater improvement in BCVA compared to the whole trial ITT population (6.5 letters in the pseudophakic subgroup compared with 3.5 in the whole trial ITT population). This could be a result of the impact of cataract adverse effects in the phakic patients in the whole trial population.

There were fewer ocular AEs in the study eye in patients with a pseudophakic lens at baseline in the MEAD study who were randomised to dexamethasone compared with the whole study (ITT) population due to the absence of primary cataract AEs. The company reported that the most common ocular AE reported in the pseudophakic subgroup was IOP increase although fewer patients in the dexamethasone group (24.7%) experienced raised IOP compared with those in the dexamethasone group for the total MEAD (safety) population (36.0%).

Dexamethasone generally resulted in greater reduction in CRT and improvement in BCVA compared with sham in the PLACID subgroup analyses in people with prior laser or prior anti-VEGF therapy without prior steroid therapy.

Safety data suggest a similar safety profile for dexamethasone in the subgroup of patients with any prior treatment (including prior corticosteroid therapy) to that seen in the whole trial (safety) population of the pooled MEAD studies, with higher incidences of ocular adverse events in the dexamethasone group compared with the sham group.

The company also presented data in the CS from an NMA comprising of 11 RCTs (five dexamethasone RCTs and six RCTs for comparators with one additional trial included in the sensitivity analyses) in the CS. The comparisons considered in the NMA were:

- whole trial DMO population for trials reporting data on the proportion of patients achieving at least a 10 letter gain from baseline at 12 months or proportion of patients achieving at least a 10 letter loss from baseline at 12 months;
- subgroup analysis for those pseudophakic at baseline (in the absence of subgroup data the whole trial data were used);
- sensitivity analysis 1 (SA1): including the FAME trial for fluocinolone acetonide in the network that was excluded as it reported data for patients achieving a 15 letter improvement from baseline at month 12 rather than a 10 letter improvement (10 letter data were estimated for this analysis);

- sensitivity analysis 2 (SA2): using the outcome of 'gaining 15 or more letters at 12 months' (to assess the impact of using the 15 letter observed data for FAME instead of the estimated data in SA1).

There were clinical differences in the populations included in the RCTs in the NMA along with high levels of statistical heterogeneity within the NMA thus raising concerns to the ERG about the validity of the results from the NMA. The ERG also considers it important to highlight that the 95% credible intervals (95% CrIs) were quite wide for a large number of the RR estimates from the NMAs and the sensitivity analyses and thus there is a large amount of uncertainty around the efficacy estimates.

In terms of the base case NMA, bevacizumab 1.25mg PRN, DEX 700 plus laser PRN, laser PRN, ranibizumab 0.5mg + laser PRN and ranibizumab 0.5mg PRN were associated with a statistically significant lower risk of losing at least 10 letters compared with sham/no treatment. The same five treatments were also associated with a statistically significant risk of gaining at least 10 letters compared with sham. Dexamethasone alone was not associated with a statistically significant benefit in gaining or losing 10 letters over sham/no treatment.

The pseudophakic subgroup NMA both resulted in similar results for each intervention to the base case NMA. However, the RR of dexamethasone plus laser resulting in either a gain of at least 10 letters or a loss of at least 10 letters compared with sham/no treatment was no longer statistically significant in the pseudophakic subgroup analysis compared with the whole trial base case analysis.

The inclusion of FAME in the NMA (SA1) has had little effect on any of the efficacy estimates for the interventions included in the base case analysis. There was no statistically significant difference associated with either gaining or losing 10 or more letters with fluocinolone acetonide 0.2µg PRN compared with dexamethasone (DEX 700 PRN) [redacted]

The company reported in the CS that they conducted a pair wise meta-analysis synthesising data from MEAD-010 and MEAD-011 which they qualitatively compared with the results from the NMA for dexamethasone versus sham/no treatment and noted the results were different. The ERG notes that as only the MEAD trials inform this analysis in the NMA the results should be very similar. The ERG is thus concerned that the results of the NMA are substantially different from the meta-analysis and again brings into question the validity of the results from the NMA.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers that in terms of the actual populations in the six RCTs presented in the CS for dexamethasone, none of them directly addressed the populations covered by the EU marketing authorisation for dexamethasone. All six RCTs had inclusion criteria designed to assesses broader

populations to that of interest. The ERG thus considers that the results presented in the CS are limited in their specificity for addressing the populations for whom dexamethasone has EU marketing authorisation.

The ERG notes that two of the RCTs reported in the CS used treatment regimens that are not approved for use in the UK (BEVORDEX and 024). These two studies both allowed re-treatment with dexamethasone more frequently than the 6-month minimum re-treatment period specified in the EU licence. The ERG thus does not consider these trials of relevance to the decision problem.

In terms of the comparators, the ERG notes that the company did not include data for fluocinolone acetonide in combination with laser photocoagulation or bevacizumab in combination with laser photocoagulation within the CS. The ERG also notes that the company included data for an additional comparator, watch and wait, within the submission and that the company used an NMA to provide data for some of the comparators in the CS where there were no head-to-head studies. The ERG has concerns over the validity of the results from the NMA due to the presence of both clinical and statistical heterogeneity within the network.

Regarding outcomes, the ERG notes that not all of the outcomes were covered within the CS for each of the six dexamethasone RCTs and data were not available for all of the outcomes in terms of the comparison of dexamethasone with each of the comparators in the NICE final scope. However, in terms of actual outcomes reported in the CS, the ERG considers the key clinical outcomes are reported in the CS although the ERG has concerns around the populations in which the outcome data are reported not addressing the EU licensed populations for dexamethasone in DMO.

The ERG notes that missing data in the MEAD studies were handled using last observation carried forward (LOCF) methodology and thus considers that the high discontinuation rates in the MEAD studies could potentially confound the results of the trials. The ERG is unable to ascertain in which direction this bias might affect the results. The ERG is also concerned as to why the discontinuation rates in the dexamethasone arm of the MEAD studies were so high compared with discontinuation rates seen with dexamethasone in the other trials reported in the CS.

The ERG notes that whilst dexamethasone generally resulted in favourable efficacy outcomes compared with sham, clinically experts reported that they were not reflected in clinically significant changes in BCVA. In addition, from month 15 onwards in the MEAD studies the improvement in BCVA provided by dexamethasone 700µg relative to sham was reduced and didn’t recover until after 36 months. The ERG notes that this trend coincides with cataract adverse effects during the second year of the study in the dexamethasone group which must be considered when considering dexamethasone as a treatment option in phakic DMO patients.

The ERG acknowledges that the pseudophakic patients in the dexamethasone group of the MEAD studies achieved a much greater improvement in BCVA compared to the whole trial ITT population (6.5 letters in the pseudophakic subgroup compared with 3.5 in the whole trial ITT population). However, clinical expert's reported that this difference of 3 letters between the treatment groups may not represent a clinically meaningful change in BCVA to the patient. The ERG's clinical experts reported that a change of 5 or more letters is more likely to represent a clinically significant change to the patient.

In terms of the NMA, the ERG are concerned that the populations of the RCTS do not address the EU licensed populations for dexamethasone and in addition that there are clinical differences in terms of the baseline characteristics of the patients in the RCTs, i.e. a source of clinical heterogeneity. The company's statistical assessment of heterogeneity in the NMA suggest that there are high levels of statistical heterogeneity present and that the chosen model is a poor fit for the underlying data. The ERG is thus concerned about the validity of the results from the NMA. The ERG also notes that there is a considerable amount of uncertainty around some of the efficacy estimates from the NMA.

In addition, the pair wise meta-analysis from MEAD-010 and MEAD-011 which the company qualitatively compared with the results from the NMA for dexamethasone versus sham/no treatment resulted in substantially different efficacy estimates for this comparison. The ERG finds this to be another reason to be concerned about the validity of the results from the NMA.

1.4 Summary of cost effectiveness submitted evidence by the company

The company developed a *de novo* Markov model to investigate the cost-utility of dexamethasone as a treatment for DMO in adult patients with DMO and resulting visual impairment who were either:

- considered unsuitable for non-corticosteroid therapy;
- considered insufficiently responsive to non-corticosteroid therapy; or
- pseudophakic.

The main comparator in the analysis on patients with DMO who are considered unsuitable for, or non-responsive to non-corticosteroid therapy was 'watch and wait'. A scenario analysis considered fluocinolone acetonide for patients with DMO who are considered insufficiently responsive to non-corticosteroid therapy.

The main comparator in the analysis on patients with DMO who are pseudophakic was ranibizumab. A scenario analysis included bevacizumab, laser and watch and wait.

The model followed patient cohorts with DMO over a 15-year time horizon and estimated costs and QALYs associated with treatment of DMO and subsequent changes in patients' BCVA, as determined

by ETDRS letters. The model followed both eyes of each patient; BCVA changes in each eye were modelled independently. Treatment was modelled in both eyes (bilateral DMO) or in either the better-seeing eye (BSE) or worse-seeing eye (WSE) (unilateral DMO). Patients who were affected unilaterally at baseline might develop DMO in their fellow eye (fellow eye involvement, FEI) and move to bilateral treatment. The BSE and WSE of each patient were determined at baseline and fixed throughout the time horizon. The Markov model consisted of 6 visual acuity health states of 10 ETDRS letter increments each (except the mildest and the most severe health states). In every 3-month cycle of the model each eye might move up (improved vision) or down (worsened vision) by a maximum of one BCVA state, or the eye might remain in the same BCVA state (stable vision). Treatment for DMO influenced the probability of eyes affected with DMO transitioning between the BCVA states. Eyes without DMO were assumed to retain constant vision. All patients were at risk of death throughout the 15 years of the time horizon.

Treatment was provided for a maximum duration of 3 years. During this period, patients might discontinue treatment due to lack or loss of efficacy, adverse events, and other non-efficacy related reasons. Following treatment discontinuation it was assumed that patients received no further treatment. After discontinuation or end of treatment eyes affected with DMO transitioned between BCVA states according to natural progression. Patients in the cohort might experience five key adverse events requiring require medical or surgical intervention, comprising cataract, raised increased ocular pressure (IOP), retinal detachment, endophthalmitis and vitreous haemorrhage.

Efficacy data for each treatment were derived from the NMA conducted by the company; the pooled sham arm of the MEAD trials was used as a proxy for watch and wait, due to lack of more relevant data. The 12-month relative risks of improving vision (moving up one 10-letter state), worsening vision (moving down one 10-letter state) or maintaining stable vision (remaining in the same 10-letter state) for each treatment versus dexamethasone (which was used as baseline treatment) derived from the NMA were applied onto 3-month transition probabilities for dexamethasone, derived from the MEAD trials, over the duration of DMO treatment (maximum 3 years). Other clinical input parameters were obtained from key clinical trials for each treatment that were included in the NMA.

Health-related quality of life (HRQL) was assumed to depend on patients' visual acuity, as expressed by the BCVA states of each of their eyes. VFQ-UI, a preference based measure derived from the VFQ-25, a vision-specific quality of life measure, was used to value patients' HRQL. A regression model estimated utility values for each patient, based on the BCVA of patient's BSE and WSE. According to the regression model, both eyes contributed independently to the patient's utility, with the BCVA of the BSE having a higher impact than the BCVA of the WSE on the estimated utility.

The analysis adopted the perspective of the NHS and personal social services. Costs consisted of treatment costs, monitoring and test costs, costs of managing adverse events, and costs associated with severe vision loss incurred by patients in the most severe health states (BCVA ≤ 35 ETDRS letters). Unit costs were predominantly sourced from NHS reference costs 2012-13, MIMS, national unit costs of health and social care and other published literature. Resource use was informed by the key trials for each treatment included in the NMA and clinical expert opinion.

Results were presented for different discount rates in the price of ranibizumab and fluocinolone acetonide, because both drugs are subject to a confidential patient access scheme (PAS) and the exact details of the discounts in price were unknown to the company. In the base case results and the majority of scenario analyses, list prices and 50% discounts were used for both treatments.

In patients with DMO who are unsuitable for, or insufficiently responsive to non-corticosteroid treatment, the company estimated that dexamethasone dominated watch and wait (i.e. it was less costly and more effective) in both deterministic and probabilistic analysis. The probability of dexamethasone being cost-effective compared with watch and wait was 60.8% at a willingness-to-pay threshold of £20,000/QALY. In the scenario analysis that included fluocinolone acetonide, dexamethasone was cost-effective if no discount was applied to the price of fluocinolone acetonide (the latter was more costly and more effective than dexamethasone, with a deterministic ICER of £24,591/QALY). At a discount price of 20% or more, fluocinolone acetonide dominated dexamethasone.

In patients with DMO who are pseudophakic, the company estimated that dexamethasone was cost-effective compared with ranibizumab if the list price of ranibizumab was used; in this case, ranibizumab was more effective and more costly than dexamethasone with a deterministic ICER of £50,905/QALY and a probabilistic ICER of £89,531/QALY. The probability of dexamethasone being cost-effective compared with ranibizumab at list price was 75.6% at a willingness-to-pay threshold of £20,000/QALY. When a discount of ranibizumab of 30% or more was assumed, ranibizumab became cost-effective compared with dexamethasone. At a 50% discount price for ranibizumab, ranibizumab dominated dexamethasone in both deterministic and probabilistic analysis. The probability of dexamethasone being cost-effective under a 50% discount price for ranibizumab was 40.9%. In the scenario analysis that included bevacizumab, laser and watch and wait, dexamethasone was dominated by both laser and bevacizumab.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

Model structure

The ERG considers the model structure to be appropriate, consistent with the progression of the disease and reflective of patient presentation and treatment in clinical practice. Modelling transitions in BCVA states in each eye independently was an improvement over previous economic models assessing treatments for DMO, as it allowed a more realistic representation of patient experience and enabled a more accurate estimation of HRQL, as it considered the impact of each of the BSE and the WSE on HRQL separately. The economic model was well constructed and transparent; the ERG identified a few errors within the model, and a number of inconsistencies between the numbers reported in the company's submission and the electronic version of the model. However, the impact of these errors and inconsistencies on the results of the economic analysis was negligible.

The ERG feels that a major area of concern in the economic model structure lies in the company's assumption that the baseline distributions of BSE and WSE across BCVA states are independent from each other, especially considering that the BSE and WSE were fixed at initiation of treatment and throughout the model duration. The implication of this assumption is that the WSE has a non-trivial probability to be in a better BCVA state than the BSE at baseline, and potentially throughout the duration of the model. Considering that both eyes contribute to the patient's utility, with the visual acuity of the BSE having a greater impact than that of the WSE, this assumption may have introduced bias into the analysis. Moreover, the assumption that eyes could transition between BCVA health states by a maximum of one BCVA state per cycle did not appear to reflect trial evidence, as additional analyses requested by the ERG and undertaken by the company indicated.

Patient populations and interventions

The patient populations examined in the economic analysis appear to be reasonable and consistent with the licensed indications of dexamethasone for treatment of DMO. The interventions overall appear to be relevant. The ERG notes that, in principle, fluocinolone acetonide should be considered in the base case analysis of both DMO patients who are insufficiently responsive to non-corticosteroid therapy and those who are pseudophakic; however, the ERG acknowledges that the data analysis that was required in order to include fluocinolone acetonide in the base case analysis had considerable limitations. On the other hand, the ERG believes that laser should be included in the base case analysis of patients with DMO who are pseudophakic, as it comprises routine treatment in patients with DMO and CRT < 400 microns in NHS clinical practice.

Efficacy data on dexamethasone for patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy were taken from the whole DMO population in the MEAD trials. However, the ERG notes that the participants in the MEAD trials were not representative of these patient sub-groups examined in the economic analysis. Moreover, the ERG notes that efficacy data for pseudophakic patients with DMO were based on NMA outputs resulting

from a synthesis of data on pseudophakic and mixed DMO populations, as no (or very limited) data on pseudophakic patients were available for anti-VEGF and laser treatments.

The ERG notes that the use of sham as a proxy for watch and wait may have potentially led to the effect of watch and wait having been overestimated, and therefore the relative effect of dexamethasone versus watch and wait may have potentially been underestimated. This issue was reported by the company as an important limitation of their analysis; however, the ERG believes that the extent of underestimation of the dexamethasone effect is lower than the company claims.

Treatment effects

The ERG has major concerns with the application in the economic model of relative risks from the NMA (which synthesised 12-month efficacy data) onto 3-month baseline transition probabilities, over the maximum 3-year duration of all treatments. This application was based on the assumption that relative effects of all treatments considered in the NMA remain stable from initiation of treatment and up to 3 years of treatment duration; however, evidence from the MEAD trials suggests that this assumption is unlikely to hold, at least not in the whole DMO population (the assumption appears to be more consistent with evidence on pseudophakic patients treated with dexamethasone, but the available evidence did not allow assessment of its applicability in pseudophakic DMO populations receiving other treatments)..

Moreover, the ERG is concerned that the 'normalisation' of transition probabilities in the economic model, an approach adopted by the company in order to ensure that transition probabilities add up to 1, effectively resulted in the relative risks being consistently altered from their original values obtained from the NMA, thus potentially introducing bias into the analysis, the direction and magnitude of which were not possible to ascertain or predict.

Other clinical input parameters

The ERG notes that discontinuation rates in the model were derived by naïve synthesis of discontinuation trial data, i.e. the model utilised discontinuation data from treatment arms belonging to different trials, without any data synthesis; this method is inappropriate and may have introduced bias into the analysis.

Health-related quality of life

The ERG believes that the vision-specific preference-based measure used in the analysis (VFQ-UI) is appropriate for the purposes of this analysis; utilised measurements were obtained directly from patients with DMO participating in the MEAD trials. Utility in each patient was estimated using a regression model, which considered BCVA in the BSE and the WSE independently; the BSE contributed to a higher degree to the final utility compared with the WSE, which is in agreement with the perception that prevailed in the approaches for estimation of utilities in previous NICE TAs on

treatments of DMO. The economic model did not consider any disutility associated with treatment administration or adverse events, but the ERG estimates that their impact on the results of the analysis should be inconsequential.

Costs

The ERG believes that costs were overall appropriately captured in the company's submission. However, the ERG notes that the cost associated with severe vision loss (i.e. BCVA <35 letters) is likely to have been overestimated by the company, due to overestimation of the cost of residential care, which was one of its components. The company has utilised the unit cost of residential care provided by local authority. However, economic analyses in previous TAs have utilised the unit cost of private residential care, with views expressed that the private sector appears to be the main provider of residential care in the UK. The unit cost of private residential care is almost 50% lower than the unit cost of residential care provided by local authority. If private sector is the main provider of residential care, then use of the unit cost of local authority residential care by the company has seriously overestimated the cost associated with severe vision loss.

Analysis

The company carried out deterministic and probabilistic analyses as appropriate, and an extensive number of scenario and sensitivity analyses that aimed to explore the impact of the uncertainty in model input parameters.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths of the clinical analysis

The company presented data for dexamethasone from six RCTs within the CS that enabled comparisons of dexamethasone alone and dexamethasone plus laser with some of the comparators specified in the NICE final scope.

The key outcomes of clinical importance noted by the ERG's clinical experts were reported in the CS.

The company conducted subgroup analyses where they had sufficient data in the pseudophakic population which is of direct relevance to one of the populations in which dexamethasone has EU marketing authorisation. In addition, the company submitted additional data for the comparator watch and wait, which was not specified in the final scope issued by NICE.

NMAs were conducted by the company in accordance with the NICE DSU recommendations to enable an indirect comparison of dexamethasone with fluocinolone.

1.6.2 Weaknesses and areas of uncertainty in the clinical analysis

The EU marketing authorisation for dexamethasone restricts it's use to the treatment of adult patients with visual impairment due to DMO, who are pseudophakic (have an artificial lens implant) or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy and yet none of the dexamethasone RCTs in the CS are specific to these populations. The ERG thus considers that the efficacy of dexamethasone in these populations is associated with uncertainty, and in particular its relative efficacy in comparison with the other treatments of interest in the NICE final scope.

In addition, there is an absence of direct comparative data from RCTs comparing the EU licensed dosing regimen for dexamethasone with any of the comparators specified by NICE in the decision problem.

The results of the MEAD studies that provide the majority of evidence for dexamethasone within the CS are potentially flawed due to the high discontinuation rates across the trial arms and the use of a LOCF analysis to account for the missing data.

There were high levels of clinical and statistical heterogeneity associated with the NMA partly related to differences in the baseline characteristics of the studies included in the NMA. The ERG considers there to be substantial uncertainty in the results of the NMA and, in particular, a lack of face validity in the results for dexamethasone compared to sham/no treatment.

The absence of outcome data for some of the comparators in the NICE final scope, particularly the absence of outcome data for the relevant populations for this STA, i.e. those specified in the EU marketing authorisation for dexamethasone, make it impossible to fully assess the efficacy of dexamethasone in relation to the decision problem.

In addition, the safety and clinical efficacy data for dexamethasone in DMO are limited to a maximum of 39 months due to the duration of the included trials. The ERG consider this to be a further limitation of the data as no longer term data are available despite dexamethasone being available for treatment beyond three years.

1.6.3 Strengths of the economic analysis

- The model structure, which appears to be consistent with the progression of the disease and reflective of patient presentation and treatment in clinical practice.
- The modelling transitions in BCVA states that were estimated independently for each eye, allowing a more realistic representation of patient experience and enabling a more accurate estimation of HRQL, by considering separately the impact of each of the BSE and the WSE on HRQL.

- Utility data were collected from patients with DMO in the MEAD trials using a vision-specific preference-based measure, the VFQ-UI, which is relevant to people with DMO.
- The extensive scenario and sensitivity analyses exploring the impact of all input parameters on the cost effectiveness results.

1.6.4 Weaknesses and areas of uncertainty in the economic analysis

- The mismatch between the study population in the MEAD trials (which provided efficacy data for dexamethasone in the NMA that informed the economic model) and the licensed DMO populations that were considered in the economic models.
- The use in the economic analysis on pseudophakic patients of NMA outputs resulting from a synthesis of data on pseudophakic and mixed DMO populations.
- The use of sham as a proxy for watch and wait, which may have potentially led to the relative effect of dexamethasone versus watch and wait being underestimated, although the ERG believes that the extent of underestimation is lower than the company claims.
- The assumption that the baseline distributions of BSE and WSE across BCVA states are independent from each other, especially considering that the BSE and SWE were fixed at initiation of treatment and throughout the model duration; this may result in WSE having a non-trivial probability to be in a better BCVA state than the BSE at baseline, and potentially throughout the duration of the model.
- The application in the economic model of relative risks from the NMA (which synthesised 12-month efficacy data) onto 3-month baseline transition probabilities, over the whole 3-year duration of all treatments. To do this, the economic analysis assumed that relative effects of all treatments considered in the NMA remain stable from initiation of treatment and up to 3 years of treatment duration; evidence from the MEAD trials suggests that this assumption may not hold, at least not in the whole DMO population.
- The ‘normalisation’ of transition probabilities in the economic model, in order to ensure that transition probabilities add up to 1, which effectively resulted in the relative risks being consistently altered from their original values obtained from the NMA, thus introducing bias into the analysis, the direction and magnitude of which were not possible to ascertain or predict.
- The restriction of transitions by a maximum of one BCVA state per cycle, which, as further analyses (requested by the ERG and undertaken by the company) showed, does not reflect trial evidence.
- The naïve synthesis of discontinuation trial data in order to inform the model, which is inappropriate and may have introduced bias into the model.
- An overestimate of the cost associated with severe vision loss (i.e. BCVA <35 letters), due to overestimation of the cost of residential care.
- Lack of consideration of disutility associated with treatment administration and adverse events, although the ERG estimates that their impact on the results of the analysis should be inconsequential.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

At clarification, the ERG requested a number of analyses to be carried out by the company. In addition, the ERG conducted a number of model corrections and scenario analyses to investigate alternative parameters and assumptions within the model structure. The ERG considered deterministic results only due to time constraints, and also because the model results in the company submission were shown to be overall consistent between deterministic and probabilistic estimates.

Following ERG request, the company carried out an analysis for patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, using efficacy data for both watch and wait (sham used as a proxy) and dexamethasone from the MEAD trials. Moreover, no restriction of maximum one BCVA state up or down was imposed on eye movements in the model. The resulting ICER was £1,411,676/QALY. The company argued that this analysis was not appropriate as the sham effect in the MEAD trials was higher than expected due to trial design, resulting in an overestimation of the effect of watch and wait and an underestimation of the effect of dexamethasone. Therefore, the company argued that the analysis that utilised NMA outputs was more appropriate for the estimation of the cost effectiveness of dexamethasone relative to watch and wait.

The ERG notes that the relative effect between dexamethasone and sham (watch and wait) estimated in the NMA was informed directly and exclusively from the MEAD trials, as no other direct or indirect comparisons between the two interventions were made in the NMA. Therefore, the ERG considers that in principle, the results of the economic analysis between dexamethasone and watch and wait should be effectively the same, whether the relative effect is taken directly from the MEAD trials or from the NMA. The ERG attributes the discrepancy between the results of the two analyses to the following factors:

- The application of the relative risks derived from the NMA estimated using 12-month data, onto 3-month baseline transition probabilities in the economic model, from initiation of treatment and up to 3 years of treatment duration. This application was based on the assumption that relative effects of treatments were constant over the 3 years of treatment duration; however, as evidence from MEAD trials suggested, this assumption may not hold, as the relative effect between dexamethasone and watch and wait appears to be considerably reduced in the second year of treatment, and resumed towards the end of the third year.
- The normalisation of transition probabilities, an approach adopted by the company to ensure that the probabilities of each cohort in each model cycle summed up to 1, is likely to have introduced bias into the company's analysis, as it effectively resulted in the values of the relative risks obtained from the NMA being consistently altered across each health state and each 3-month cycle.

The ERG therefore feels that the company's base case economic analysis that utilised NMA data suffers from severe limitations and its results are unlikely to be robust. In contrast, the analysis that uses data directly from the MEAD trials appears to be more reflective of relative clinical effects between dexamethasone and sham, and is the one that ERG regards as the most appropriate for the estimation of the cost effectiveness of dexamethasone versus watch and wait in patients with DMO who are unsuitable for, or insufficiently responsive to non-corticosteroid therapy.

Nevertheless, the ERG estimated a revised deterministic base case ICER for the analyses based on the NMA outputs for all populations considered in the model. NMA was the only source of data for patients with DMO who are pseudophakic.

The ERG base case ICER incorporated all model corrections and the following scenarios:

- the numbers of total visits associated with treatment and monitoring of each treatment each year were amended to take into account that some re-treatment visits included monitoring visits;
- costs associated with IOP checks were removed from analysis, as IOP checks are performed within monitoring visits;
- the unit cost of local authority residential care was replaced by the unit cost of private residential care;
- the cost of depression, associated with severe vision loss, was updated using more recent data;
- the cost of medication for raised IOP was amended to take into account that generic prostaglandins comprise the more widely used pharmacological treatment for raised IOP;
- the cost of surgery for raised IOP was amended to take into account that trabeculectomy is the only surgical procedure relevant for raised IOP that is an adverse event of treatment in patients with DMO;
- 6 extra IOP visits were assumed for patients with DMO who were treated for raised IOP.

Following ERG corrections and amendments in the company's model data, the deterministic ICER of dexamethasone versus watch and wait in patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, became £22,049/QALY when NMA outputs were utilised; and £1,166,271/QALY when data from the MEAD trials for both dexamethasone and watch and wait (sham) were utilised, without transitions being restricted by one health state up or down.

In patients with DMO who are pseudophakic, ranibizumab at list price was not cost-effective compared with dexamethasone, but became cost-effective compared with dexamethasone when a 50% discount to its list price was assumed. Bevacizumab and laser both dominated dexamethasone.

1.8 Key issues

In summary, the ERG believes the key issues to be as follows:

Clinical:

- none of the dexamethasone RCTs in the CS are specific to any of the populations specified in the EU marketing authorisation for dexamethasone;
- absence of direct comparative data from randomised controlled trials comparing the EU licensed dosing regimen for dexamethasone with any of the comparators in the decision problem;
- absence of data for some outcomes for some of the comparators, particularly in the relevant populations for this STA, i.e. those specified in the EU marketing authorisation for dexamethasone;
- high discontinuation rates in the MEAD studies which provide the key data for dexamethasone alone in the clinical analyses (the direct comparison with sham/no treatment and with any other comparison facilitated by the NMA) ;
- limited long term data on the safety and clinical benefit of dexamethasone in DMO;
- high levels of clinical and statistical heterogeneity in the NMA which mean the ERG has strong reservations about how robust any conclusion based on the NMA might be.

Economic:

- According to the company's economic analysis, dexamethasone dominated watch and wait in patients with DMO who are unsuitable for, or insufficiently responsive to non-corticosteroid therapy; in the comparison with fluocinolone acetonide, dexamethasone was cost-effective if no discount was applied to the price of fluocinolone acetonide (the latter was more costly and more effective than dexamethasone, with a deterministic ICER of £24,591/QALY). At a 20% discount price, fluocinolone acetonide dominated dexamethasone.
- The company's analysis indicated that in patients with DMO who are pseudophakic dexamethasone was cost-effective compared with ranibizumab when the list price of the latter was considered, as ranibizumab was more effective than dexamethasone at an additional cost of £50,905/QALY (deterministic analysis) or £89,531/QALY (probabilistic analysis). When a discount of ranibizumab of 30% or more was assumed, then ranibizumab became cost effective compared with dexamethasone. Ranibizumab became the dominant strategy when a discount in its price of 50% or more was assumed. In a scenario analysis, dexamethasone was dominated by both laser and bevacizumab.
- The ERG's main criticisms of the economic analysis were:
    - The mismatch between the study population in the MEAD trials (which provided efficacy data for dexamethasone in the NMA that informed the economic model) and the licensed DMO populations that were considered in the economic models.
    - The assumption that the baseline distributions of BSE and WSE across BCVA states are independent from each other, especially considering that the BSE and WSE were fixed at initiation of treatment and throughout the model duration; this may result in

WSE having a non-trivial probability to be in a better BCVA state than the BSE at baseline, and potentially throughout the duration of the model.

  - The application in the economic model of relative risks from the NMA (which synthesised 12-month efficacy data) onto 3-month baseline transition probabilities, over the whole 3-year duration of all treatments. To do this, the economic analysis assumed that relative effects of all treatments considered in the NMA remain stable from initiation of treatment and up to 3 years of treatment duration; evidence from the MEAD trials suggests that the assumption may not hold, at least not in the whole DMO population.
  - The 'normalisation' of transition probabilities in the economic model, in order to ensure that these add up to 1, which effectively resulted in the relative risks being consistently altered from their original values obtained from the NMA, thus introducing bias into the analysis, the direction and magnitude of which were not possible to ascertain or predict.
  - The restriction of transitions by a maximum of one BCVA state per cycle, which, as further analyses (requested by the ERG and undertaken by the company) showed, does not reflect trial evidence.
  - An overestimate of the cost associated with severe vision loss (i.e. BCVA <35 letters), due to considerable overestimation of the cost of residential care.

- Following ERG corrections and amendments in the company's model data, the deterministic ICER of dexamethasone versus watch and wait in patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, became £22,049/QALY when NMA outputs were utilised.
- Following ERG corrections and amendments in an analysis carried out by the company following ERG request, which utilised data directly from the MEAD trials for both dexamethasone and watch and wait (sham) without imposing restrictions in movements between health states, the deterministic ICER of dexamethasone versus watch and wait in patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, became £1,166,271/QALY.
- In patients with DMO who are pseudophakic, following ERG corrections and amendments, ranibizumab at list price was not cost-effective compared with dexamethasone, but became cost-effective compared with dexamethasone when a 50% discount to its list price was assumed. Bevacizumab and laser both dominated dexamethasone.
- The key driver in the difference between the company's and the ERG results when the NMA outputs were used to inform the economic model was the unit cost of residential care used to estimate the cost associated with severe vision loss.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

In the Context section of the company's submission (CS; Section 2), the company provides an overview of the key complications of diabetes and focuses on the key aspects of diabetic macular oedema (DMO), the diabetic complication relevant to the decision problem. The CS includes details of the prevalence (Box 1), pathophysiology (Box 2), clinical consequences (Box 3) and prognosis of DMO (Box 4). In addition, the company presented an overview of the current resource use and costs of DMO (Box 5). The information presented in boxes is taken directly from the CS unless otherwise stated and the references have been renumbered.

Diabetes mellitus (DM) comprises of two main types; type 1 and type 2. The common defining feature of both types of DM is raised blood glucose (hyperglycaemia). Exposure to hyperglycaemia over time can lead to complications such as damage to blood vessels in the back of the eye resulting in proliferative diabetic retinopathy and DMO. The macula is a part of the retina and is responsible for central vision. Oedema is the excessive collection of fluid within the body. In DMO fluid accumulates in the macula. This is due to the resulting blood vessel damage from the effects of hyperglycaemia in diabetes. The accumulation of fluid in DMO may cause visual impairment and can lead to blindness.

Box 1. Prevalence of DMO

Diabetes mellitus (DM) is a chronic disease with rising prevalence of substantial magnitude. In the UK, the latest national prevalence estimate is 6-7%; amounting to ~3 million people, and it is estimated that this will rise to ~10% (5 million people) by 2025.[1-3] In England, current prevalence is estimated at 6.0% (2,703,044 people) and in Wales, current prevalence is estimated at 6.7% (173,299 people).[1] DMO is estimated to affect approximately 7% of all DM patients and can reportedly double the burden of disease management in this population.[4-6] Prevalence of sight loss, defined as central visual acuity <6/6, as a result of DMO is estimated at 2.8% of all DM patients in the UK.[4,7] DMO development is strongly associated with the duration of DM, with incidence increasing with lengthening duration.[8] It is estimated that almost all people with Type 1 DM and more than 60% of people with Type 2 DM experience retinopathy within 15–20 years of diagnosis.[9,10] and one in three people living with DM for 20 years or more develop DMO.[11] As such, DMO is likely to occur in older patients. Like with other complications, its development is also associated with the poor management of DM; DMO patients therefore often have a number of diabetic co-morbidities to manage.[6] DMO can affect either one or both eyes of the patient: termed unilateral DMO and bilateral DMO, respectively. DMO is the leading cause of blindness in the DM population, one of the leading causes of blindness in adults of working age, and the principal cause of visual impairment in individuals with diabetic retinopathy.[12-14]

Abbreviations used in the box: DM, diabetes mellitus; DMO, diabetic macular oedema.

Box 2. Pathophysiology of DMO

Inflammation is a central component of the multifactorial pathophysiology of DMO that causes blurring of vision through hyperglycaemic breakdown of the BRB, leading to a build-up of fluid (oedema) in the macular: the central part of the retina responsible for central vision. Such accumulation of fluid causes thickening and swelling that impairs the ability of photoreceptor cells in the macular to sense light, causing blurring of vision. The exact pathology of DMO remains unclear, but several pathways have been implicated in BRB damage to date. Alongside leukocyte accumulation, these include inflammatory processes such as increased VEGF levels and decreased pigment epithelium derived factor levels (pro-angiogenic factors), increased protein kinase C production, endothelial dysfunction and loss of retinal pericytes; resulting in vasoconstriction and hypoxia. [12,15-19]
Abbreviations used in the box: BRB, blood retinal barrier; DMO, diabetic macular oedema; VEGF, vascular endothelial growth factor.

Box 3. Clinical consequences of DMO

A number of studies report on the damaging effect of DMO on vision: limiting patients ability to perform everyday activities such as driving (UK licences require visual acuity ≥6/12), shopping, housework, meal preparation and using the telephone, which can challenge independent living and negatively affect patients' mental well-being (Barbeau et al. 2011;).[20-22] Additionally, the fear of losing sight or independence causes emotional distress for many patients, particularly in those with depressive disorder symptoms often linked to DM.[23,24] Quality of life (QoL) appears to systematically decline as vision impairment and severity of DMO worsen. Specifically, progression from unilateral to bilateral vision impairment and progression to vision-threatening stages from mild/moderate DMO are important factors in the reduction of patient QoL.[25,26] Moreover, limitation in physical and mental functioning due to visual impairment associated with DMO can compromise the patient's ability to successfully manage their DM and any co-morbidities. Patients with DMO report difficulties with reading nutrition and medication labels, testing blood sugar, self-administering medication and checking for wounds and sores.[27] Considering the patient is the key to successful disease management, this can have serious implications for the incidence of other diabetic complications and thus overall life expectancy. In a German study of 207 patients with diabetic retinopathy and DMO, patients on average stated that, if they did not have diabetic eye problems, their DM care would be better.[28] This is reflected in analysis of co-morbidities in DM patients with DMO that are shown to be significantly higher than in DM patients without DMO.[29,30]
Abbreviations used in the box: DM, diabetes mellitus; DMO, diabetic macular oedema; QoL, quality of life.

Box 4. Prognosis of DMO

DMO is a progressive disease that worsens with increased accumulation of fluid and proximity of the oedema to the fovea: the centre of the macular (centre-involving DMO).[17,19] It is estimated that the probability of losing two or more lines of visual acuity within 3 months is 4.5%[31] and nearly half of DM patients developing DMO will lose two or more lines of visual acuity within 2 years[32]; equivalent to 10 or more letters in the visual acuity score denoted according to vision impact presented in the MS Appendix 20.[33] If DMO is not effectively treated, it can therefore result in irreversible vision loss with DMO patients having a much higher likelihood of developing blindness (odds ratio = 8.6) compared with non-DMO patients with DM.[8,17,19] In patients with DMO, life expectancy is further reduced; they are reportedly at higher risk of macrovascular complications and mortality from cardiovascular (CV) disease and ischaemic heart disease than DM patients without DMO.[34-36] This is likely due to commonalities between pathogenic mechanisms of retinal microvascular abnormalities and cerebral microvascular abnormalities that subsequently result in macrovascular complications.[34,36,37]
Abbreviations used in the table: CV, cardiovascular; DM, diabetes mellitus; DMO, diabetic macular oedema.

Box 5. Resource use and costs of DMO

The annual resource use and cost per patient with DMO is estimated to be approximately twice as high as the per patient resource use and cost for DM patients without DMO.[5] One retrospective study of UK practice attempts to separate out additional costs solely related to DMO management through development of a multi-disease costing method.[4] Health and social care costs investigated included those associated with diagnosing, treating and managing DMO through screening, treatment, assessment, monitoring and consultation (that are typically borne by payers and patients), as well as downstream costs such as rehabilitation and residential care.[4] The overall cost of illness for DMO was estimated at £116,296,038, translating to ~£1,000 per year per patient (based on reported 2010 prevalence rates of 166,325 DMO patients in England) with direct healthcare costs related to hospital treatment estimated to account for the greatest proportion of the overall costs related to DMO.[4]
Abbreviations used in the table: DM, diabetes mellitus; DMO, diabetic macular oedema.

Based on expert clinical advice, the Evidence Review Group (ERG) considers the company's overview of the underlying health problem to be accurate.

2.2 Critique of company's overview of current service provision

The company's overview of current service provision included a summary of the relevant NICE technology appraisals and related guidelines (Box 6) along with a more detailed summary of the Royal College of Ophthalmologists (RCO) guidelines (Table 1). The CS also contained figures depicting the current UK treatment pathway for DMO (Figure 1) and the proposed position of dexamethasone in the treatment pathway (Figure 2). In addition, the company outlined the factors

relating to the estimated resource cost associated with dexamethasone use in DMO (Box 7) and estimated the number of patients in England and Wales who would be eligible for treatment with dexamethasone in this new indication (Box 8 and Table 2).

Box 6. Summary of the relevant NICE guidelines, NICE technology appraisals and other key guidelines in diabetes and DMO

NICE Guidelines

Type 1 diabetes: Diagnosis and management of Type 1 diabetes in children, young people and adults [CG15][38]

- *Type 2 diabetes: The management of Type 2 diabetes* [CG87][39]

NICE Guidance

- *Preventing Type 2 diabetes: risk identification and interventions for individuals at high risk [PH38]*[40]
- *Preventing Type 2 diabetes: population and community-level interventions [PH35]*[41]
- *Diabetes on adults quality standard [QS6]*[42]

NICE Technology Appraisals

- *Ranibizumab for the treatment of diabetic macular oedema [TA237]*[43]
- *Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237) [TA274]*[44]
- *Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema after an inadequate response to prior therapy [TA271]*[45]
- *Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (rapid review of technology appraisal guidance 271) [TA301]*[46]

Clinical Guidelines

- The Royal College of Ophthalmologists. *Diabetic Retinopathy Guidelines*. December 2012.[47]

Abbreviations used in the box: CG, clinical guideline; DMO, diabetic macular oedema; NICE, National Institute for Health and Care Excellence; PH, public health; QS, quality standard; TA, technology appraisal.

The ERG notes that there is currently no NICE guideline to specifically address management of DMO. However, the company presented a summary of the UK clinical guidelines developed by the RCO (Table 1).[47]

Table 1: Maculopathy recommendations from the Royal College of Ophthalmologists (December 2012) (taken from CS, Table 5)

CSMO	Centre-involving	Visual acuity	Phakic /pseudophakic	OCT	Treatment options
Yes	No		Either		Photocoagulation (**Level A**)

Yes	Yes	Normal, or minimally reduced by macular oedema (eg greater than 78 letters).	Either		Photocoagulation or observe if the source of leakage is very close to fovea and there are no other treatable lesions suitable or safe to laser (**Level C**)
Yes	Yes	VA in region of 78-24 letters (but eyes with better vision may under certain circumstances warrant treatment if oedema progressing and symptomatic)	Phakic	≥250µm central subfield thickness§	Intravitreal anti-VEGF treatment (*see comment below) with or without laser (**Level A**). For eyes unresponsive to other treatments, intravitreal fluocinolone implant may be considered, but bearing in mind the potential side-effects (**Level A**)
Yes	Yes	VA in region of 78-24 letters	Pseudophakic	≥250µm central subfield thickness§	Intravitreal anti-VEGF treatment*, OR Intravitreal triamcinolone (preservative – free) with or without adjunctive laser may also be considered. (**Level A**) OR intravitreal fluocinolone implant may be considered if available, and eye unresponsive to other treatments (**Level A**)
Yes	Yes	<24 letters	Pseudophakic	≥250µm central subfield thickness	Observation may be appropriate, especially if longstanding and no response to previous laser, or if considerable macular ischaemia. Otherwise may consider anti-VEGF treatment or intravitreal steroid after careful consultation and consent. (**Level B**)
Yes	Yes		Either	Vitreo-macular traction	Consider vitrectomy with/without adjunctive intravitreal anti-VEGF or steroid treatment (**Level C**)

Key: CSMO, clinically significant macular oedema; OCT, optical coherence tomography; VA, visual acuity; VEGF, vascular endothelial growth factor.

Notes: Anti-VEGF treatment regime: Initial loading phase of monthly injections for 4-6 months, followed by PRN phase with continued treatment until the macular is dry or until there is no further improvement.

* Monthly follow-up of patients undergoing anti-VEGF treatment with OCT scan and visual acuity assessment is required to decide on retreatments. If the patient has been stable off treatment for several monthly assessments, in Year 2 onwards the period between follow-up appointments may be increased gradually, ultimately to a maximum of 12-16 weeks as long as there are no other features requiring more frequent follow-up.

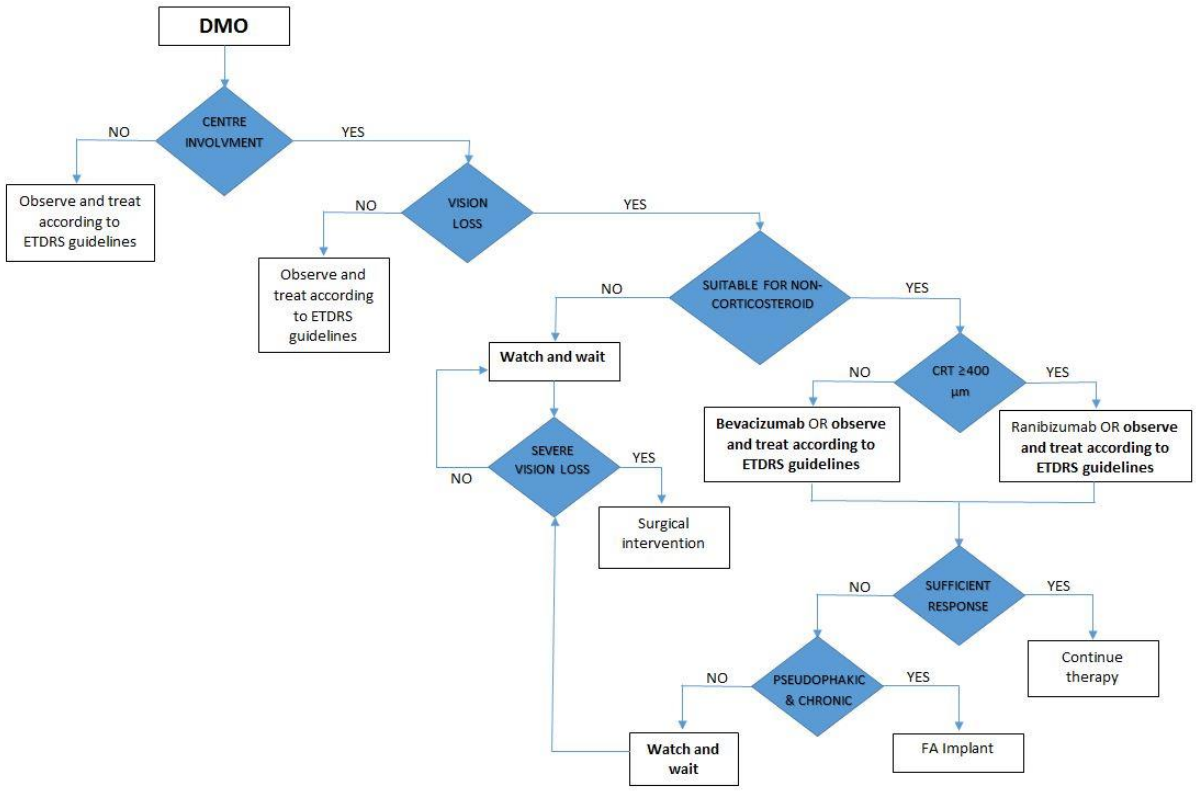
Patients unwilling or unsuitable for injections should be offered macular laser treatment if appropriate. (**Level A**)

§ - The NICE ACD refers to >400µm central retinal thickness in patients with DMO for whom ranibizumab may be considered. (http://guidance.nice.org.uk/TA/Wave23/41/Consultation/DraftGuidance). A final guidance is expected in February 2013 (http://guidance.nice.org.uk/TA/Wave23/41), if the NICE confirms this in final guidance (FAD), ranibizumab would be the anti-VEGF agent of choice for the subgroup of patients approved by NICE in England.

The ERG notes that since the publication of the RCO guidelines the FAD for TA237 has been published and this recommends ranibizumab as first line treatment for the subgroup of patients with DMO and a >400µm central retinal thickness.[48] Clinical experts to the ERG also confirmed this to now be part of the UK treatment pathway for DMO. The ERG also notes that, as reported by the company, the RCO guidelines recommend that all potentially suitable treatment options for an individual patient should be discussed with the patient concerned, and treatment tailored to meet the individual patient need.[47]

The company also presented an overview of the current DMO treatment pathway in the UK of relevance to the decision problem in the CS that was developed by the company in accordance with practicing UK ophthalmologists (Figure 1).

Figure 1: Current clinical pathway of care for DMO patients in the UK (reproduced from CS, Figure 2)



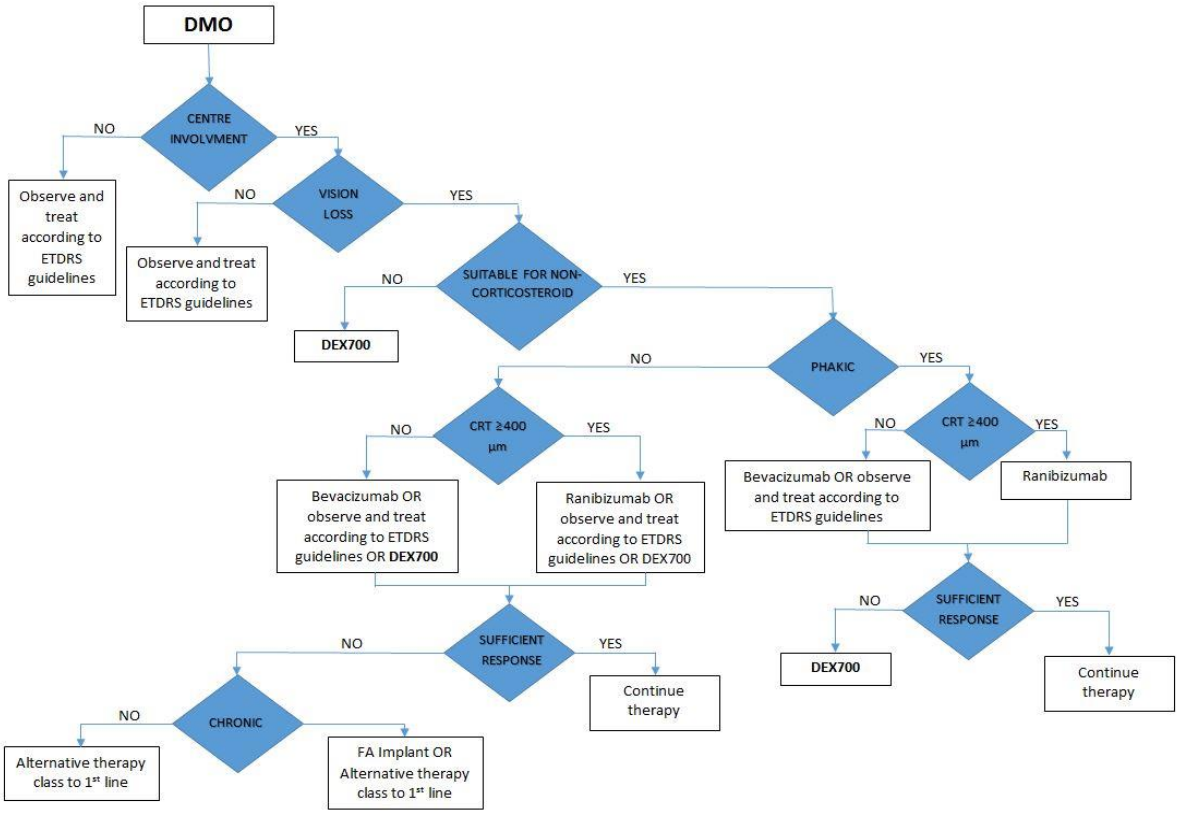
Key: CRT, central retinal thickness; DMO, diabetic macular oedema; ETDRS, Early Treatment of Diabetic Retinopathy Study.

The ERG consider it important to highlight that the Early Treatment Diabetic Retinopathy Study (ETDRS) was a key trial in DMO management as it firmly established laser photocoagulation as a treatment for diabetic maculopathy.[49] The company does not explicitly mention in their treatment

pathway what the "treat according to ETDRS guidelines" involves. The ERG considers that based on the ETDRS report number 2: Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema that the treatment under consideration at these steps in the company's treatment pathway would be laser photocoagulation.[50] In addition, clinical experts to the ERG report that bevacizumab is rarely used in UK clinical practice for treatment of DMO; ranibizumab and laser are the main treatment options currently used. Clinical experts also report that in some patients laser may be given in addition to other treatments etc. ranibizumab. However, the comparators and treatment options in DMO will be discussed in more detail in section 3.

The company's proposed changes to the UK treatment pathway with the introduction of the dexamethasone 700 implant are presented in Figure 2. These changes include the use of dexamethasone as a first line treatment option for pseudophakic patients or patients unsuitable for non-corticosteroid therapy, and dexamethasone as a second line treatment option in patients considered insufficiently responsive to non-corticosteroid therapy.

Figure 2: Potential clinical pathway of care for DMO patients in the UK with recommendation of DEX700 (reproduced from CS, Figure 3)



Key: CRT, central retinal thickness; DEX, dexamethasone; DMO, diabetic macular oedema; ETDRS, Early Treatment of Diabetic Retinopathy Study.

The CS states that broad spectrum antibiotics may also be required alongside dexamethasone therapy to manage the risk of eye infections. In addition, the CS reports that IOP may increase after intravitreal injection of a steroid such as dexamethasone and so topical IOP-lowering medicinal products may be prescribed where indicated. Clinical experts to the ERG report that these are not changes to the current treatment pathway as they would also be administered with other drugs in the current treatment pathway, e.g. the fluocinolone acetonide (FA) implant. The clinical experts also report that the broad spectrum antibiotics used would typically be topical and expected to be required for only one week post-implant procedure.

Box 7. Resource use

Administration of DEX700 is by intravitreal injection, conducted by a qualified and experienced ophthalmologist. The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) within a hospital setting. Monitoring for changes in IOP is recommended when treating with DEX700 and therefore a tonometry test is commonly conducted within 4-8 weeks of each injection. Monitoring for retreatment requires measurement of CRT with optical coherence tomography (OCT) and measurement of visual acuity in accordance with the SPC. Often the fundus of the eye is also observed through ophthalmoscopy. These tests will all be conducted within a single appointment, normally by a qualified ophthalmologist within a hospital setting. It is anticipated that assessment for DEX700 retreatment will be scheduled at intervals of 6 months or more from the last injection. Resource estimates are based on the Ozurdex® SPC and have been confirmed by practicing ophthalmologists with experience of DEX700 administration. Values are taken from NHS reference costs 2012/2013. All anticipated resource requirements are captured within the economic analysis discussed in section 5.
Abbreviations used in the box: CRT, central retinal thickness; DEX700, dexamethasone 700µg; OCT, optical coherence tomography; SPC, summary of product characteristics.

The CS reported that no additional infrastructure for the administration of intravitreal injections will be required to treat DMO in the UK. The company claims that “the introduction of DEX700 should in fact help to alleviate some of the strain on current infrastructure caused by frequent intravitreal injection treatment regimens” (CS, pg73). This is related to a potential reduction in visits for people being retreated with dexamethasone (6 monthly) compared to being retreated with an anti-VEGF (ranibizumab, should be administered once a month).

The company provided estimates for the number of patients in England and Wales with DMO who would be eligible for dexamethasone (Table 2), along with a description of how the estimates were obtained (Box 8).

Box 8. Description of how the company estimated the number of patients in England and Wales who would be eligible for treatment of DMO with dexamethasone

Prevalence of sight loss, defined as central visual acuity <6/6, as a result of DMO is estimated at 2.8% of all DM patients in the UK.[4,7] Applying this prevalence rate to the DM population in England and Wales as of 2013 (2,876,343)[1], 80,538 individuals are estimated to require treatment for visual impairment due to DMO. Clinician opinion is that approximately 25% of all DMO patients (~20,000) are considered insufficiently responsive to non-corticosteroid therapy (based on anti-VEGF response, given that laser monotherapy is rarely appropriate or beneficial and thus not commonly used in current clinical practice), and would be considered for treatment with DEX700. In addition, up to 35% of all DMO patients (~28,000) may be considered unsuitable for non-corticosteroid therapy according to ophthalmologists currently practicing across England and Wales (based on population definitions presented in the MS section 2.7 and detailed in the budget impact analysis presented in MS section 8 and MS Appendix 14) and would be considered for treatment with DEX700. Based on regulatory trial data (MEAD), it is estimated that approximately 21,000 DMO patients present with a pseudophakic lens and therefore are eligible for first-line treatment with DEX700. Bilateral DMO is observed in 36.4% of the MEAD DMO population, equating to an estimated ~94,000 eyes being potentially eligible for DEX700 therapy in England and Wales, though it should be noted that the injection of DEX700 into both eyes at the same time has not been studied and is not recommended, as is the case with alternative pharmaceutical treatment options for DMO.
Abbreviations used in the box: DEX700, dexamethasone 700µg; DM, diabetes mellitus; DMO, diabetic macular oedema; MS, manufacturer's submission; VEGF, Vascular endothelial growth factor.

Table 2: Estimated number of patients covered by DEX700 therapeutic indication in the marketing authorisation (reproduced from CS Table 4, pg45)

Population	**Percentage estimate of total DMO population**	**Percentage estimate of total DMO population that clinicians would consider treating with DEX700**	**Approximate patient number estimate**
Unsuitable for laser photocoagulation			
Centre-involving DMO	80%	-	-
DMO with associated visual impairment	30%	-	-
Unsuitable for anti-VEGF therapy			
Unable to attend appointments for DMO at least once a month e.g. working population, patients on	20%	12%	28,000

dialysis, prison population			
Pregnant women or women trying to conceive	2.5% (of females)	2.5% (of females)	
High-risk co-morbidities e.g. CV morbidity	≤5%	≤5%	
Vitrectomised eyes			
DMO with cystoid macular oedema			
Unsuitable for ranibizumab therapy			
CRT <400µm	85%	15%	
Insufficiently responsive to anti-VEGF therapy			
VA due to DMO where oedema is >300µm in any of the 5 central ETDRS zones OR In the opinion of the treating clinician there is potential for further visual improvement in oedema can be resolved further with alternative treatment	25%	25%	20,000
Pseudophakic patients	26.2%	26.2%	21,000
Abbreviations used in the table: CRT, Central retinal thickness; CV, Cardiovascular; DEX, Dexamethasone; DMO, Diabetic macular oedema; ETDRS, Early Treatment of Diabetic Retinopathy Study; VA, Visual acuity; VEGF, Vascular endothelial growth factor. Source: Appendix 14; section 10.14; Boyer et al. 2014[51]			

The clinical experts to the ERG have suggested that the estimate for the number of people unsuitable for laser therapy may have been overestimated by the company. The ERG also notes that some of the patients unsuitable for laser would be suitable for dexamethasone treatment according to the treatment algorithm (Figure 2) although the company does not specifically report any numbers for this population in Table 2. The ERG also acknowledges that the majority of patients unsuitable for laser would be considered for anti-VEGF and thus would also fall into one of the other categories in Table 2.

In addition to the details in Box 8, the company reported that the patient groups in Table 2 for whom dexamethasone would be a treatment option are not mutually exclusive and there is thus a possibility of variations in the estimates due to patient cross-over between the different populations. The CS reports that, "there will be some patients in the DMO population considered unsuitable for non-corticosteroid therapy that are also pseudophakic" (CS, pg46). The company thus highlights that the true number of eyes eligible for DEX700 in the UK will be less than the estimates presented in Table 2, i.e. less than 69,000 patients. The ERG also considers the company's inclusion of pregnant women in their estimates of people suitable for dexamethasone may be inappropriate given that dexamethasone is not licensed for general use in pregnant patients. The SPC instead states "Ozurdex

is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus".[52]

In summary, the ERG considers the company's overview of the current service provision and treatment pathway for DMO in the UK to be broadly accurate and agrees with the company's proposed positioning of dexamethasone in the treatment pathway based on the EU marketing authorisation. In terms of the company's estimate for the number of patients likely to be eligible for treatment with dexamethasone; the ERG was unable to validate the company's estimates as they were mostly based on clinical opinion. However, the ERG's clinical experts generally agree with the company's estimates apart from those for the number of patients unsuitable for laser.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the final decision problem issued by the National Institute for Health and Care Excellence (NICE; company's submission [CS], pgs 80-83), together with a brief description of the rationale for any deviation from the decision problem (Table 3). The ERG notes that the majority of the deviations from the decision problem are related to the restrictions for the use of dexamethasone in this indication that have been imposed by the EU marketing authorisation. Further details on these deviations are provided in Table 3.

Table 3. Summary of decision problem as outlined in the company's submission (reproduced from CS; pgs 80-83)

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Intervention	Dexamethasone intravitreal implant, alone or in combination with laser photocoagulation	Dexamethasone intravitreal implant, alone or in combination with laser photocoagulation	Not applicable
Population	People with DMO	Adult patients with visual impairment due to DMO, who are pseudophakic, or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy	In accordance with EU licence terms for use of DEX700 in DMO
Comparator(s)	Laser photocoagulation alone The following technologies alone or in combination with laser photocoagulation: Ranibizumab Fluocinolone acetonide intravitreal implant	Laser photocoagulation alone (for people who are pseudophakic) The following technologies alone or in combination with laser photocoagulation: Ranibizumab (for people who	In accordance with EU licence terms for use of DEX700 in DMO

	Bevacizumab (for people in whom ranibizumab and fluocinolone acetonide intravitreal implants are unsuitable)	are pseudophakic) Fluocinolone acetonide intravitreal implant (for people who are considered insufficiently responsive to non-corticosteroid therapy) Bevacizumab (for people who are pseudophakic and in whom ranibizumab and fluocinolone acetonide implants are unsuitable) Watch and wait (for people who are considered unsuitable for non-corticosteroid therapy and for people who are considered insufficiently responsive to non-corticosteroid therapy in whom the fluocinolone acetonide implant is unsuitable)	
Outcomes	The outcome measures to be considered include: best corrected visual acuity (the affected eye) best corrected visual acuity (both eyes) central foveal subfield thickness contrast sensitivity mortality need for cataract surgery adverse effects of treatment (including cataract formation and glaucoma) health-related quality of life, including the effects of changes in visual acuity	The outcome measures to be considered include: best corrected visual acuity (the affected eye) best corrected visual acuity (both eyes) central foveal subfield thickness contrast sensitivity mortality need for cataract surgery adverse effects of treatment (including cataract formation and glaucoma) health-related quality of life, including the effects of changes in visual acuity	Not applicable
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Not applicable

	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. The cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. The cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.	
Other considerations	If evidence allows, consideration will be given to subgroups according to: type of DMO (focal or diffuse, central involvement, ischaemic or non-ischaemic maculopathy) duration of DMO baseline visual acuity baseline central retinal thickness previous treatment history (including people who have received no prior treatment, and those who have received and/or whose disease is refractory to laser photocoagulation, ranibizumab or bevacizumab) prior cataract surgery Guidance will only be issued in accordance with the marketing authorisation.	Evidence is provided to allow consideration to be given to subgroups according to: previous treatment history (including people who have received no prior treatment, and those who have received and/or whose disease is refractory to laser photocoagulation, ranibizumab or bevacizumab) prior cataract surgery	In accordance with EU licence terms for use of DEX700 in DMO
Key: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; EU, European Union; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.			

3.1 Population

The final scope issued by NICE was for the whole population of people with DMO.[53] However, the company presents data only for certain subgroups of this population in line with the EU marketing authorisation for dexamethasone in DMO. These subgroups addressed within the CS are adult patients with visual impairment due to DMO, who are pseudophakic (have an artificial lens implant), or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. The ERG considers the company has selected the appropriate population to address within the CS and thus the

ERG agrees with the company's deviation from the population specified in the final scope issued by NICE.

The company consulted with practicing UK ophthalmologists to define people who may be considered unsuitable for non-corticosteroid therapy (Table 4).

Table 4: Patient populations considered unsuitable for non-corticosteroid therapy (adapted from CS, Table 6, pg 65)

Population	Rationale	ERG comments
Unsuitable for laser photocoagulation		
Centre-involving DMO	Clinical guideline recommendations due to safety concerns	Clinical experts report that laser may be given to some patients with centre-involving DMO to help manage and reduce its spread
DMO with associated visual impairment	Clinical guideline recommendations due to lack of evidence of vision restoration	Clinical experts report that laser may be given to some patients with visual loss as laser can improve vision in some of these patients.
Unsuitable for anti-VEGF therapy		
Unable to attend appointments for DMO at least once a month, e.g. working population, patients on dialysis, prison population	Demanding therapeutic regimen	Clinical experts report that working age people are likely to want the most effective treatment.
Pregnant women or women trying to conceive	Anti-VEGF mechanism of action may pose a risk to embryo-fetal development (including teratogenicity) and reproductive capacity	No comment
High-risk co-morbidities, e.g. CV morbidity	Systemic warnings of potential CV risk	Clinical experts report that many DMO patients will have associated CV co-morbidities as a result of their diabetes but this is unlikely to affect the treatment decision for DMO.
Vitrectomised eyes	Diminished effect due to reduced half-life	No comment
Unsuitable for ranibizumab therapy		
CRT <400µm	NICE restriction in England and Wales	Laser therapy would be a comparator for dexamethasone or considered prior to dexamethasone in some of the patients with CRT<400µm.
Abbreviations used in the table: CRT, central retinal thickness; CV, cardiovascular; DMO, diabetic macular oedema; NICE, National Institute of Health and Care Excellence; VEGF, vascular endothelial growth factor. Source: Appendix 14; section 10.14		

In addition to the people detailed in Table 4 whom could be considered unsuitable for non-corticosteroid therapy, there are some DMO patients that may refuse current therapeutic options for

reasons such as anxiety associated with laser treatment or regular intravitreal injections. The company reports that these patients could also be considered unsuitable for non-corticosteroid therapy.

Data from six dexamethasone randomised controlled trials (RCTs) are presented in the CS: MEAD-010[51,54], MEAD-011[51,55], 024[56], PLACID[57,58], NCT00035906[59,60] and BEVORDEX[61,62]. Three of these studies were phase III studies (MEAD-010, MEAD-011 and 024) and the remaining three studies were phase II studies (PLACID, NCT00035906 and BEVORDEX). MEAD-010 and MEAD-011 were identical in terms of study design, with MEAD-010 commencing prior to patient recruitment for MEAD-011.

In terms of the actual populations of the six RCTs, none of them directly addressed the populations covered by the EU marketing authorisation for dexamethasone. All six RCTs had inclusion criteria resulting in broader populations to that of interest. The EU marketing authorisation restricts the use of dexamethasone in DMO to people who are:

- pseudophakic; or
- insufficiently responsive to non-corticosteroid therapy; or
- unsuitable for non-corticosteroid therapy.

The differences between the data available in the six RCTs included in the CS and the populations specified in the EU marketing authorisation included that none of the six studies were exclusively in people who are pseudophakic (i.e. they all contained both phakic and pseudophakic patients).

The inclusion criteria in terms of the prior treatment history of patients included in the six RCTs differed amongst the trials and demonstrates how none of the trials directly address the population's considered insufficiently responsive to non-corticosteroid therapy or unsuitable for non-corticosteroid therapy. In the MEAD trials patients had to have had previous medical or laser photocoagulation therapy or to have refused or in the opinion of the investigator be unable to benefit from laser photocoagulation therapy. In 024 there were no restrictions based on previous treatments received. PLACID and BEVORDEX both required the oedema to be considered not amenable to laser photocoagulation therapy as stand-alone treatment. Finally, NCT00035906 had an inclusion criterion that required patients to have failed to respond to medical or laser therapy within the previous 90 days. In addition, NCT00035906 included patients with macular oedema from causes other than diabetes although the results presented in the CS were from the stratified subgroup of patients with DMO in NCT00035906.

The data provided in the CS for each of the six dexamethasone RCTs is based on the full trial populations, although subgroup data from the MEAD, 024, PLACID and BEVORDEX studies are also presented for the pseudophakic population and from the MEAD studies based on prior therapy

use/treatment naive. The ERG notes that this is a limitation of the available data but is unable to comment further on the likely impact of using the whole population data as surrogate data for the populations for whom dexamethasone has EU marketing authorisation. The results presented in the CS are thus limited in their specificity for addressing the populations for whom dexamethasone has EU marketing authorisation for. Specifically, the company reports that the following populations of interest to the decision problem are covered as part of the respective trials detailed below:

- Adult patients with visual impairment due to DMO who are considered insufficiently responsive to non-corticosteroid therapy: MEAD and NCT00035906;
- Adult patients with visual impairment due to DMO who are considered unsuitable for non-corticosteroid therapy: MEAD;
- Adult patients with visual impairment due to DMO who are pseudophakic: MEAD, study 024, PLACID, BEVORDEX and NCT00035906.

In the CS it was reported that all trials enrolled patients with centre-involving macular oedema and associated visual impairment. In addition, the CS reported that with the exception of NCT00035906, all patients enrolled in the trials were over the age of 18, i.e. all patients were adults. The ERG notes that the mean age of patients at baseline across the six dexamethasone trials was between 61 and 64 years. In addition, there were more males than females in the trials and more Caucasians than any other race. The inclusion criteria for visual acuity was between 34 and 70 ETDRS letters in five of the trials with the remaining trial, BEVORDEX allowing patients with severe vision loss (17 ETDRS letters) to also enrol. Central retinal thickness (CRT) was required to be over 250µm for inclusion in any of the trials and over 300 µm for inclusion in the MEAD [redacted] studies.

Patients with uncontrolled systemic disease, active glaucoma or a history of severe glaucoma were excluded from all six of the dexamethasone trials. However, patients with bilateral DMO could be enrolled in all of the trials although the way in which they were managed differed amongst the trials. Patients were not treated bilaterally in five of the studies: MEAD studies, 024, PLACID or NCT00035906. If both eyes were eligible for inclusion in the MEAD studies then the eye with shorter duration of macular oedema was selected; [redacted]; and in PLACID the eye with worse BCVA was selected. Patients were treated bilaterally in BEVORDEX although each eye was to receive a different randomised treatment.

In terms of applicability to the UK DMO population, clinical experts to the ERG consider each of the trials to have broadly representative populations. However, the ERG notes that only two of the six RCTs had UK based centres (MEAD-011 and 024) and that these only represented a small number of the total study centres in the trials. MEAD-010, like MEAD-011 and 024, had recruiting study sites

within multiple different countries across the world. The remaining three trials included study sites exclusively in the USA (NCT00035906), USA and Canada (PLACID), and Australia (BEVORDEX). In addition, the company highlights that the treatment naive subgroup of patients in MEAD would be likely to be managed differently today compared to when the MEAD studies were initiated. In current practice, the majority of the treatment naive patients presenting with the disease characteristics suitable for inclusion in the MEAD trials are likely to have received ranibizumab and thus not be treatment naive. The ERG considers that the subgroup analyses presented in the CS based on prior treatments received is thus useful in addressing this potential limitation of the MEAD trial data. However, the ERG considers that the treatment naive subgroup data does not address the population unsuitable for non-corticosteroid therapy as some of these patients would be suitable for ranibizumab in current clinical practice.

3.2 Intervention

The intervention that is the subject of this STA is dexamethasone intravitreal implant 700µg (Ozurdex®, hereafter referred to as dexamethasone), alone or in combination with laser photocoagulation. The company provides clinical evidence for both dexamethasone alone and dexamethasone in combination with laser in the CS which is in line with the final scope issued by NICE.[53]

Dexamethasone (Ozurdex) is an injectable intravitreal implant that delivers 700µg dexamethasone to the posterior segment of the eye through a solid polymer drug delivery system (DDS) over a period of 6 months or more. The dexamethasone implant initially releases a burst of dexamethasone to rapidly achieve a therapeutic concentration and then gradually releases the remaining total dose over several months. The DDS contains a material (copolymer, poly[lactic-co-glycolic] acid) which dissolves and degrades into CO_2 and water over time.[63,64] The dexamethasone implant remains in the vitreous for up to 270 days before fully dissolving.[52,65]

The intravitreal dexamethasone implant is a corticosteroid that has been shown to suppress inflammation by inhibiting fibrin deposition, capillary leakage and phagocytic migration of the inflammatory response, and thus is useful in the treatment of macular oedema.[52,59,63] Dexamethasone works as a glucocorticoid agonist binding to cytoplasmic glucocorticoid receptors and resulting in the reduced production of pro-inflammatory mediators that occur in diabetic macular oedema (DMO).[12,15-18,52,60]Dexamethasone can also resolve blood vessel dilation and altered flow as well as prohibiting exudation of fluids and leukocyte accumulation thus directly resolving macular oedema.[52,63,66]

Dexamethasone currently holds a marketing authorisation for the treatment of patients with macular oedema due to retinal vein occlusion (RVO) and for the treatment of patients with non-infectious

uveitis. The company reported that an application for extension of the authorisation for the dexamethasone 700µg implant to include DMO patients was submitted to the European Medicines Agency (EMA) on 21 June 2013.

Dexamethasone received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 24 July 2014 for the treatment of adult patients with visual impairment due to DMO, who are pseudophakic (have an artificial lens implant), or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. This indication was approved by the European Commission for a marketing authorisation on 24 August 2014. The CHMP rationale reported in the CS for the licence restrictions for dexamethasone use in DMO are summarised in Box 9.

Box 9. CHMP rationale for licence restrictions for dexamethasone use in DMO (CS, pgs 33-34)

The CHMP considered that the benefit–risk balance for DEX700 in the broad indication of treatment of adult patients with DMO was negative. They concluded that the treatment effect size observed in the overall population was too modest to warrant the increased risk of cataract.[16] The CHMP did, however, note improved results were seen in pseudophakic patients due to the absence of steroid-induced cataract events as a confounding factor for visual outcomes.[16] In addition, the CHMP considered that there was an unmet medical need for patients who are not suitable candidates for, or who do not respond adequately to other available DMO treatments, including laser photocoagulation and anti-VEGF inhibitor therapies. Patients enrolled in MEAD had previously received laser therapy or were not considered suitable candidates for such therapy. Whilst only a small proportion of patients from the MEAD trials programme had previously received anti-VEGF treatment, given the broader anti-inflammatory action of steroids compared with anti-VEGF agents, the CHMP felt it was reasonable to assume that steroids would be tried in patients with DMO who had not responded to anti-VEGF therapy, or who were unsuitable for monthly anti-VEGF injections, irrespective of lens status in current clinical practice. For patients considered insufficiently responsive to or unsuitable for non-corticosteroid therapy, the relative risk associated with DEX700 of cataracts and intraocular pressure (IOP) elevation (both of which are treatable) was considered justifiable compared to the far more serious risk of irreversible vision loss due to persistent DMO. Furthermore, the CHMP was of the opinion that there were some benefits in having the choice of a steroid treatment with a shorter duration of effect compared to the longer-acting steroid implant (fluocinolone acetonide), which was available for DMO treatment in many EU countries. The CHMP was therefore of the opinion that the benefits of DEX700 in the treatment of adult patients with visual impairment due to DMO who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for, non-corticosteroid therapy outweighed its risks and that the benefit–risk balance was favourable in this restricted population.[16]
Abbreviations used in the box: CHMP, Committee for Medicinal Products for Human Use; DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; EU, European Union; IOP, intraocular

pressure; VEGF, vascular endothelial growth factor.

Dexamethasone now has regulatory approval from the EMA for the 28 EU member states plus Norway, Iceland and Lichtenstein for the treatment of adult patients with visual impairment due to DMO, who are pseudophakic, or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. In addition dexamethasone has regulatory approval from the US Food and Drug Administration (FDA) for the treatment of DMO. It is reported in the CS that dexamethasone was originally approved by the FDA in June 2014 as a treatment for DMO in adult patients who have an artificial lens implant (pseudophakic) or who are scheduled for cataract surgery (phakic). However, the FDA has recently approved dexamethasone for use in the general DMO population (29th September 2014) following the review of further clinical efficacy and safety data. No further details on these data were provided in the CS and so the ERG are unsure as to whether they have been provided within the CS.

In addition, dexamethasone is scheduled for a health technology appraisal by the Scottish Medicines Consortium (SMC) in December 2014 for use in the same DMO population as in this STA.

The company reported that patients receiving the dexamethasone implant should be instructed to self-administer broad spectrum antimicrobial drops daily for 3 days before and to continue them after each injection. In addition, if an IOP rise is detected post injection; topical IOP-lowering medicinal products may be prescribed. Patients are not otherwise routinely expected to require concomitant therapy alongside dexamethasone for treatment of their DMO.

3.3 Comparators

The comparators for this STA listed in the final scope issued by NICE are:

- Laser photocoagulation alone;
- Ranibizumab alone or in combination with laser photocoagulation;
- Fluocinolone acetonide intravitreal implant alone or in combination with laser photocoagulation;
- Bevacizumab (for people in whom ranibizumab and fluocinolone acetonide intravitreal implants are unsuitable) alone or in combination with laser photocoagulation.

The ERG considers that the company did not include data for fluocinolone acetonide in combination with laser photocoagulation or bevacizumab in combination with laser photocoagulation within the CS. In addition, the ERG notes that the company have restricted certain comparators to certain populations based on the restrictions in the EU marketing authorisation and the resulting likely position of dexamethasone in the treatment pathway for DMO. The company presented tables in the CS to detail the first-line and second-line comparators they considered appropriate for dexamethasone in each of the EU licensed DMO populations (Table 5 and Table 6).

Table 5. First-line comparators for dexamethasone in DMO (reproduced from CS, Table 7, pg 69)

Population	Comparator(s)	Licence restrictions	Clinical guideline restrictions	NICE restrictions	Justification
Adult patients with visual impairment due to DMO with a pseudophakic lens	Ranibizumab (± laser)	None	None	CRT ≥400µm	Established clinical practice in the NHS in line with clinical guideline recommendations. Licensed for use in DMO. Preferred first-line treatment option in England and Wales.
Adult patients with visual impairment due to DMO who are considered insufficiently responsive to non-corticosteroid therapy	Watch and wait	N/A	N/A	N/A	No alternative non-corticosteroid therapy licensed for use in the majority of patients considered insufficiently responsive to non-corticosteroid therapy.
Adult patients with visual impairment due to DMO who are considered unsuitable for non-corticosteroid therapy	Watch and wait	N/A	N/A	N/A	No alternative non-corticosteroid therapy licensed for use in patients considered unsuitable for non-corticosteroid therapy.
Abbreviations used in the table: CRT, central retinal thickness; DMO, diabetic macular oedema; NHS, National Health Service; NICE, National Institute of Health and Care Excellence.					

Table 6. Second-line comparators for dexamethasone in DMO (reproduced from CS Table 8, pg 70)

Population	Comparator(s)	Licence restrictions	Clinical guideline restrictions	NICE restrictions	Justification
Adult patients with visual impairment due to DMO with a pseudophakic lens	Laser photocoagulation	N/A	Centre-involving DMO Visual impairment	N/A	Historical clinical practice in the NHS in line with clinical guideline recommendations. Not commonly used as monotherapy since the introduction of pharmaceutical treatment options and the greater understanding of the limitations of its use.
	Bevacizumab (± laser)	N/A	None	N/A	Historical clinical practice in some hospitals within the NHS in line with clinical guideline recommendations. Not licensed for use in DMO. Declining in use since the introduction of licensed anti-VEGF agents for intraocular use. Only used to treat patients not eligible for licensed treatment options.
Adult patients with visual impairment due to DMO who are considered insufficiently responsive to non-corticosteroid therapy	Fluocinolone acetonide implant	Chronic DMO	None	Pseudophakic lens	Established clinical practice in the NHS in line with clinical guideline recommendations. Small patient group eligible for treatment. Viewed as a last-line treatment option as per the licence terms.
Abbreviations used in the table: DMO, diabetic macular oedema; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; VEGF, vascular endothelial growth factor.					

In summary, the company reported that the comparators they considered in the CS were:

- Laser photocoagulation alone (for people who are pseudophakic);
- Ranibizumab (for people who are pseudophakic) alone or in combination with laser photocoagulation;
- Fluocinolone acetonide intravitreal implant (for people who are considered insufficiently responsive to non-corticosteroid therapy) alone or in combination with laser photocoagulation;
- Bevacizumab (for people who are pseudophakic and in whom ranibizumab and fluocinolone acetonide implants are unsuitable) alone or in combination with laser photocoagulation;
- Watch and wait (for people who are considered unsuitable for non-corticosteroid therapy and for people who are considered insufficiently responsive to non-corticosteroid therapy in whom the fluocinolone acetonide implant is unsuitable) alone or in combination with laser photocoagulation.

The ERG notes that the company did not present specific clinical data to address all of these comparators in the CS. In particular, clinical data were not presented within the CS from the NMAs for either fluocinolone acetonide or bevacizumab or watch and wait in combination with laser. The ERG notes that some of the trials in the NMA allowed resue therapy with laser but the ERG does not consider this *ad hoc* use of laser to provide reliable clinical data for the respective therapy combination therapies.

The ERG considers the comparators for the pseudophakic and insufficiently responsive to non-corticosteroid therapy populations to be appropriate. In terms of the people unsuitable for non-corticosteroid therapy, the ERG considers that in addition to the comparators specified by the company, fluocinolone acetonide with or without adjuvant laser is also a potential comparator. However, the ERG also acknowledges that there are no direct head-to head trial data presented in the CS to address this particular population. The company presents a network meta-analysis (NMA) to address the comparison of dexamethasone with fluocinolone although all of the trials used in the network are not specifically in any of the populations specified in the dexamethasone EU marketing authorisation.

In terms of the comparisons presented in the CS of dexamethasone with laser, ranibizumab, bevacizumab and watch and wait, the company reports data from head-to-head trials as well as from a NMA. However, the ERG has concerns over both the dexamethasone dosing regimens used in the ranibizumab and bevacizumab trials as well as the comparability of the trials included in the NMA. Further details on the ERG's critique of the trials presented in the CS and the company's NMA are provided in Secion 4.

In summary, the ERG considers the company has included the key comparators requested in the NICE final scope within the CS along with the additional comparator, watch and wait. However, the ERG does not consider the comparison with ranibizumab or bevacizumab to be addressed appropriately within the CS due to the lack of both head-to-head and indirect comparable RCT data (the ERG has concerns over the heterogeneity between the trials in the company's NMA). In addition, the ERG has concerns about the lack of suitable subgroup data for the populations specified in the EU marketing authorisation for any of the comparators for dexamethasone specified in the NICE final scope.

3.4 Outcomes

The outcome measures to be considered according to the final scope issued by NICE are:

- best corrected visual acuity (the affected eye);
- best corrected visual acuity (both eyes);
- central foveal subfield thickness;
- contrast sensitivity;
- mortality;
- need for cataract surgery;
- adverse effects of treatment (including cataract formation and glaucoma); and
- health-related quality of life, including the effects of changes in visual acuity.

The company reported that they covered all outcomes requested in the NICE final scope within the CS. However, the ERG notes that not all of the outcomes were covered within the CS for each of the six dexamethasone RCTs and data were not available for all of the outcomes in terms of the comparison of dexamethasone with each of the comparators in the NICE final scope.

The primary outcome in the dexamethasone clinical trials varied but in general was either mean BCVA average change from baseline in the study eye or proportion of study eyes achieving at least a 10 letter improvement in BCVA.

In the NMA the outcomes used were: proportion of patients achieving at least a 10 letter gain from baseline at 12 months and proportion of patients achieving at least a 10 letter loss from baseline at 12 months. The company justified this outcome choice in the NMA with the following statement: "this is a clinically meaningful endpoint that can also be applied within the economic model to move patients between health states" (CS; pg185). Clinical experts to the ERG indicate that these outcomes are acceptable for addressing the efficacy of dexamethasone and are clinically meaningful measures of change in BCVA in the affected eye.

The secondary efficacy and safety endpoints of the six key trials presented in the CS varied across the trials but included change in BCVA at specified post-baseline time points, proportion of patients with improved or worsened vision, change in CRT at specified post-baseline time points, change in total leakage area at specified post-baseline time points along with safety and HRQL measures. Further details on the outcomes of each individual trial are provided in Section X.

The ERG note that BCVA assessments for the study eye were the most commonly reported vision outcomes in the RCTs in the CS and where assessed, BCVA in both eyes was generally assessed as a safety outcome in the clinical trials, but was not specifically reported for any of the clinical trials presented within the CS.

The ERG also notes that contrast sensitivity was reported only for the MEAD studies with no numerical data presented in the CS. The ERG considers that the need for cataract surgery is a subjective outcome and the company's reporting of cataract adverse effect is appropriate to address this outcome in the final scope issued by NICE. The HRQL data collected and reported from the RCTs was generally based on the NEI-VQ-25 vision specific QoL tool.

To summarise, given the available clinical data for dexamethasone, the ERG considers that the outcome data presented in the CS by the company are appropriate to address the outcomes listed in the final scope issued by NICE.

3.5 Timeframe

There was no specific recommendation on the treatment time frame specified in the final scope issued by NICE, and the duration of treatment varied across the six dexamethasone clinical trials from 1 dose of dexamethasone to a maximum of 39 months of treatment (administered ≥ 6 monthly as required). The ERG notes from discussion with clinical experts that treatment with dexamethasone could be expected to be continued for longer than 3 years in clinical practice. The ERG thus acknowledges that long-term safety and efficacy data for dexamethasone are limited by the trial durations.

The ERG notes that the company's NMA was based on 12-month outcome data. The ERG requested clarification on this decision when there were 3-year clinical trial outcome data available for dexamethasone. The company's response is presented in Box 10.

Box 10. Company's rationale for use of 12 month outcome data in the NMA (Company's response to clarification, A7, pg 6)

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.
Abbreviations used in the box: BCVA, best corrected visual acuity; DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; MTC, mixed treatment comparison; NMA, network meta-analysis.

Clinical experts to the ERG report that cataract adverse effect outcomes are most likely to occur after 12 months of dexamethasone therapy. The ERG note that this is consistent with the MEAD study data which suggested that cataract development was generally reported and treated in year 2 of dexamethasone treatment. The ERG and its clinical experts thus consider that the 3 year duration of the MEAD studies is suitable for capturing the key safety and efficacy outcomes associated with dexamethasone use. However, the ERG has concerns relating to the outcome data time point used in the NMA to inform the clinical efficacy of the treatments in the economic model. These concerns will be discussed further in Section 5.

3.6 Other relevant factors

The CS includes a section on equality issues where the company reports there are no equality issues (CS Section 3.1). The clinical experts to the ERG and the ERG agree with the company that there does not appear to be any major equality issues relating to dexamethasone use in DMO to be considered. In addition, the ERG is unaware of any ongoing Patient Access Scheme (PAS) application.

The ERG notes that the final scope issued by NICE specified that evidence permitting, consideration should be given to the following subgroups:

- type of DMO (focal or diffuse, central involvement, ischaemic or non-ischaemic maculopathy);
- duration of DMO;
- baseline visual acuity;
- baseline central retinal thickness;
- previous treatment history (including people who have received no prior treatment, and those who have received and/or whose disease is refractory to laser photocoagulation, ranibizumab or bevacizumab);
- prior cataract surgery.

The company presented subgroup data in the CS based on:

- previous cataract surgery i.e. pseudophakic (from the MEAD studies, 024, PLACID and BEVORDEX trials and also using the MEAD study data in the NMA);
- previous treatments received (from the MEAD studies).

However, the ERG notes that the CS did not contain data for dexamethasone in the following subgroups requested in the final scope issued by NICE:

- type of DMO (focal or diffuse, central involvement, ischaemic or non-ischaemic maculopathy);
- duration of DMO;
- baseline visual acuity;
- baseline central retinal thickness.

Clinical experts to the ERG indicated that these are clinically important subgroups, although the ERG acknowledges that data for these subgroups may not have been specifically collected in the dexamethasone clinical trials presented in the CS. In addition, the ERG notes that if data were available it is likely to have not been stratified at randomisation and thus would be *post hoc* non-randomised subgroup data. The ERG also notes that data for these subgroups would represent subgroup analyses of subgroups if they were performed in the licensed populations for dexamethasone, e.g. pseudophakic patient subgroup further split into subgroups based on type of DMO at baseline. The numbers in such analyses would be small and limited conclusions could be drawn from such analyses. The ERG thus considers the company's decision to omit subgroup analyses in these subgroups to be appropriate based on the available data. However, the clinical experts to the ERG suggest that subgroup analysis of the subgroups specified in the NICE final scope would be clinically useful, particularly subgroup analysis based on baseline CRT <400µm and ≥400µm.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review (SR) to identify published reports of trials relevant to the decision problem that is the focus of this STA. The aim of the SR was to identify evidence on the efficacy and safety of dexamethasone and relevant comparators for treatment of DMO. The interventions of interest were:

- Intravitreal dexamethasone 700µg;
- Laser photocoagulation (ETDRS guidelines);
- Intravitreal bevacizumab 1.25mg;
- Intravitreal ranibizumab 0.5mg;
- Intravitreal fluocinolone acetonide 0.2µg.

All interventions could be either used as monotherapy or in combination with other pharmaceutical or laser therapies. As discussed in Section 3, the final scope issued by NICE only required the treatments to be used as monotherapy or in combination with laser. The ERG notes that the studies included in the final review in the CS were consistent with the final scope issued by NICE. The ERG also notes that the final scope issued by NICE did not specify any specific doses or treatment regimens for any of the interventions. Clinical experts advised the ERG that the doses selected in the company's SR were the doses that would usually be used in the UK and where appropriate are consistent with the EU marketing authorisations. The ERG thus considers the interventions in the companys SR to be satisfactory for addressing the decision problem.

4.1.1 Description and critique of company's search strategy

The company reported that they conducted the searches to identify RCTs for the SR on 13th February 2014 and then updated the searches on 17th July 2014. The searches comprised of terms for diabetes AND macular oedema AND the interventions of interest (i.e. dexamethasone, laser photocoagulation, bevacizumab, ranibizumab and fluocinolone acetonide). In addition RCT and SR search filters were applied in the searches of MEDLINE, Embase and CINAHL. The ERG notes that the intervention search terms included triamcinolone acetonide and aflibercept although these were not specified as interventions of interest in the final scope issued by NICE or the company SR. The ERG considers the omission of both of these from the company's SR results to be appropriate as neither drug has EU marketing authorisation for use in DMO. In addition, clinical experts informed the ERG that neither triamcinolone acetonide nor aflibercept are currently routinely used in the UK for the management of DMO.

The databases searched by the company for RCT data, and time span of the searches are detailed in Table 7.

Table 7: The electronic databases searched to identify RCTs (reproduced from CS. Table 240, pg 541)

Database	Provider/interface	Coverage
Medline and Medline in Process & Other Non-Indexed citations	Ovid	1948–present
Embase	Ovid	1974–July 16
Cochrane Database of Systematic Reviews (CDSR)	Wiley Interscience	1996–present
Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Interscience	1898–present
Health Technology Assessment Database (HTA)	Wiley Interscience	1995–present
Database of Abstracts of Review of Effects (DARE)	Wiley Interscience	1995–present
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	EBSCO	1982–present

In addition, it is reported in the CS that the reference lists of SRs, meta-analyses and clinical guidelines identified during the searches were hand-searched to identify any further relevant studies. The unpublished data on file held by Allergan were also reviewed to identify further studies and data of relevance for the SR.

The company undertook searches of clinicaltrials.gov and selected relevant annual conference proceedings for the period of 2012-2013 or 2012-2014 for the purpose of identifying relevant on-going research. The conference proceedings searched were:

- 2012–2013 annual conference proceedings of the American Academy of Ophthalmology (AAO);
- 2012–2014 annual conference proceedings of the Association of Research in Vision and Ophthalmology (ARVO);
- 2012–2013 annual conference proceedings of the European Association for Vision and Eye Research (EVER);
- 2012–2014 annual conference proceedings of Controversies in Ophthalmology (COPHY);
- 2013 annual conference proceedings of the European Society of Retina Specialists (EURETINA).

It was not explained in the CS why some conference proceedings were only searched for certain years. The ERG speculates that it may be related to when in 2014 the annual conferences were

scheduled to take place as it is likely that not all would have been prior to the deadline for the CS for this STA.

In addition to the database searches for RCTs, the company conducted further database searches to identify non-RCT data to assist in addressing the review question. These searches were conducted on 18th July 2014 and were carried out in the same electronic databases as the searches for RCT evidence. The search terms used for the non-RCT searches comprised of terms for diabetes AND macular oedema AND dexamethasone. No restrictions were placed on date or study design. Further details on the search strategies used by the company for both the RCT and non-RCT evidence are presented in Appendix 9.1.

The company also reports that clinicaltrials.gov and the following conference proceedings were searched for non-RCT evidence:

- 2013 annual conference proceedings of the American Academy of Ophthalmology (AAO)
- 2013–2014 annual conference proceedings of the Association of Research in Vision and Ophthalmology (ARVO)
- 2013 annual conference proceedings of the European Association for Vision and Eye Research (EVER)
- 2013–2014 annual conference proceedings of Controversies in Ophthalmology (COPHY)
- 2013 annual conference proceedings of the European Society of Retina Specialists (EURETINA).

The ERG notes that the searches of conference proceedings were slightly more restricted by date for the non-RCT evidence compared with that for RCT evidence. However, the ERG considers the company's searches for both RCT and non-RCT evidence to be comprehensive in terms of addressing the decision problem.

4.1.2 Inclusion/exclusion criteria used in study selection

The company reported that two levels of study screening were conducted using the inclusion and exclusion criteria for the SR. The two levels of screening were conducted independently by two reviewers. Level 1 screening comprised of reviewing the abstracts of each identified reference. All references identified at level 1 as of potential relevance were retrieved in full text and the full texts were reviewed as part of the level 2 screening. It is reported in the CS that discrepancies between the two reviewers with regard to inclusion or exclusion of an article were resolved by a third reviewer. The final set of studies for the SR comprised of those articles that met all of the inclusion criteria and none of the exclusion criteria (Table 8).

Table 8: Eligibility criteria applied to systematic search results identifying the clinical evidence base of RCTs (reproduced from CS, Table 241, pg 551)

Inclusion criteria	Exclusion criteria
Population • Adult • Unilateral or bilateral DMO associated to DM • Pre-treated or treatment-naïve Interventions (one or more of the following) • Intravitreal dexamethasone 700ug • Laser photocoagulation (ETDRS guidelines) • Intravitreal bevacizumab 1.25mg PRN • Intravitreal ranibizumab 0.5mg PRN • Intravitreal fluocinolone acetonide 0.2ug • Monotherapy or combination pharmaceutical/laser therapy Comparators (one or more of the following) • Active therapy • Placebo • Sham treatment • No treatment Outcomes (one or more of the following) • BCVA change from baseline • BCVA improvement • BCVA worsening • Contrast sensitivity • Anatomical change from baseline • Safety and tolerability • Health related quality of life Study design • Randomised controlled trials Study duration • ≥6 months (24 weeks)	Population • Paediatric • Diabetic retinopathy patients without associated DMO • Macular oedema not associated to DM Interventions • Local corticosteroids • Local anti-VEGFs • Dosing regimens outside of UK licence terms/clinical practice Outcomes • Non-vision or anatomical related efficacy measures Study design • Prospective non-RCTs • Single arm trials • Observational studies Study duration • <6 months (24 weeks)
Abbreivations used in the table: BCVA, best corrected visual acuity; DM, diabetes mellitus; DMO, diabetic macular oedema; ETDRS, Early Treatment of Diabetic Retinopathy Study; PRN, as needed; RCT, randomised controlled trial; UK, United Kingdom; VEGF, vascular endothelial growth factor.	

The inclusion and exclusion criteria for non-RCT evidence had more restrictions than the RCT evidence review. The key differences were that the non-RCT evidence review limited the interventions to intravitreal dexamethasone 700ug monotherapy or combination with laser therapy. In addition, the study design restrictions for the non-RCT evidence limited inclusion to prospective non-RCTs, single arm trials and observational studies containing more than five patients with DMO.

The company reported that they did not attempt to limit the included studies based on the population for whom dexamethasone is restricted to in the EU marketing authorisation. The ERG considers this to be an acceptable decision as there were no directly relevant studies for any of these subpopulations of the DMO population for either dexamethasone or any of the comparator interventions specified in

the decision problem. The ERG notes that the company did limit study inclusion to studies over 6 months in duration. The company's justification for this decision was, "studies of less than 6 months duration were excluded 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" (CS, pg86). The ERG does not consider this to be an acceptable exclusion criteria as studies of shorter duration could still be of importance in assessing the short term safety of dexamethasone. In addition, this 6 month restriction could have resulted in the exclusion of potentially relevant studies of the comparators from the network meta-analysis as some of the comparators have shorter review and re-treatment periods, e.g. ranibizumab is typically 4-monthly. However, due to time constraints, the ERG is unable to comment further on the likelihood of missing studies and any potential impact this may have on the overall results.

4.1.3 Details of RCTs included in the review of clinical effectiveness

The company reported that combining the results of the original search and updated database search with the findings from the conference proceeding searches and other searches resulted in the identification of 4,441 potentially relevant citations.

These 4,441 citations comprised of 2,541 from the database searches, 1,891 from the conference proceeding searches and 9 from other sources.

Of the additional 9 citations, 7 were identified through confidential Allergan in house sources: 4 clinical study reports (MEAD-010, MEAD-011, PLACID, 024), the manuscript for the pooled MEAD data analysis[51], the protocol for BEVORDEX (Gillies *et al.* 2010[61]) and subgroup analysis of the ETDRS study to align patient with current practice[67]. The company reported that another citation (abstract presented at conference, 2011) was identified through reference review of an existing systematic review[68] and the 9th citation was identified through review of clinicaltrials.gov.[69]

After deduplication, there were a total of 3,400 articles which were assessed at level 1 (abstract screening) and 2,728 of them were excluded from further review. The remaining 675 citations were reviewed at level 2 as full text articles where available. Level 2 screening resulted in the identification of 65 RCTs in 90 publications for inclusion in the SR. Reasons for exclusion included non-RCT study design (n = 163), article not available (n = 5), post-hoc/pooled analysis (n = 46), study duration <24 weeks (n = 34), abstract only with not enough detail to assess study in full (n = 10), article unavailable (n = 5). Of the 65 RCTs meeting the eligibility criteria, 6 investigated the clinical efficacy and safety of dexamethasone 700µg (Table 9). The remaining 59 RCTS provided data on the comparators specified in the decision problem and thus contribute only indirect evidence. They will be discussed in Section 4.6.

Table 9: List of relevant dexamethasone RCTs identified by the systematic literature review (reproduced from CS, Table 11, pgs 93-94)

Trial number	Intervention	Comparator	Population	Study references
MEAD-010	Dexamethasone 700µg Dexamethasone 350µg	Sham	Adult patients with DMO (defined as clinically observable macular oedema involving the centre of the macular (fovea) associated with diabetic retinopathy) who have received prior medical or laser therapy or are deemed unsuitable for laser therapy (investigator opinion; patient refusal), with a baseline BCVA score between 34 letter and 68 letters and baseline CRT of ≥300 µm.	Boyer *et al.* 2014[51]; CSR 206207_010[54]
MEAD-011	Dexamethasone 700µg Dexamethasone 350µg	Sham	Adult patients with DMO (defined as clinically observable macular oedema involving the centre of the macular (fovea) associated with diabetic retinopathy) who have received prior medical or laser therapy or are deemed unsuitable for laser therapy (investigator opinion; patient refusal), with a baseline BCVA score between 34 letter and 68 letters and baseline CRT of ≥300 µm.	Boyer *et al.* 2014[51]; CSR 206207_011[55]
024	Dexamethasone 700µg	Ranibizumab 0.5mg	Adult patients with macular oedema involving the centre of the macular (fovea) due to diabetic retinopathy in at least one eye with a baseline BCVA score between 34 and 70 letters and baseline CRT of ≥300 µm with Spectralis (Heidelberg) or ≥275µm with Cirrus (Zeiss).	CSR 206207_024[56]
PLACID	Dexamethasone 700µg + laser photocoagulation	Sham + laser photocoagulation	Adult DM patients with retinal thickening results from diffuse DMO (defined as macular thickening involving the centre of the fovea that was evident on biomicroscopy or OCT) with a baseline BCVA between 34 and 70 letters and CRT of ≥275µm.	Callanan *et al.* 2013[58]; CSR 206207_012[57]
NCT00035906	Dexamethasone 700µg Dexamethasone 350µg	Observation	Adult patients with persistent macular oedema associated with diabetic retinopathy, uveitis, retinal vein occlusion, or Irvine-Gass syndrome, persisting at least 90 days after laser treatment or medical management by a physician. DMO subgroup: macular oedema persisting for 90 days after laser treatment or medical therapy with BCVA between 35 and 67 letters due to clinically detectable macular	Haller *et al.* 2010[60]; Kupperman *et al.* 2007[59]

			oedema due to diabetic retinopathy.	
BEVORDEX	Dexamethasone 700µg	Bevacizumab 1.25mg	Adult patients with a diagnosis of DM and DMO affecting the fovea in at least one eye who have received prior laser therapy or are deemed unsuitable for laser therapy (investigator opinion), with a baseline BCVA score between 17 and 72 letters and baseline central retinal thickness of ≥300 µm on spectral domain ocular tomography or >250 µm on time domain ocular tomography.	Gillies *et al.* 2010[61]; Gillies *et al.* 2010b[62]
Abbreviations used in the table: BCVA, best corrected visual acuity; CRT, central retinal thickness; DM, Diabetes mellitus; DMO, diabetic macular oedema; OCT, Optical coherence tomography; RCT, Randomised controlled trials.				

The ERG notes that the company reports only interim data are available for BEVORDEX at present, although they anticipate that the final analyses (24 month data) should become available within the next 12 months. The ERG also note that NCT00035906 was not exclusively in people with DMO although stratified subgroup data were presented in the CS for the people with DMO in NCT00035906.

The CS also reports that the search on clinicaltrials.gov identified 12 studies on dexamethasone that would potentially meet the eligibility criteria of the RCT and non-RCT systematic reviews although results of the studies have not been made available yet. The ERG has reviewed these 12 studies and considers that only 1 of them is likely to add further RCT-based data. The majority of the studies are observational studies, i.e. provide non-RCT data, and those that are RCTs mostly use dosing regimens that are not licensed in the EU in the second trial arm, e.g. dexamethasone 6 monthly versus 3 monthly. Further details of the 12 trials are presented in Appendix 9.2.

The ERG is not aware of any additional studies potentially relevant to this STA that have been omitted by the company.

4.1.4 Details of non-RCTs included in the review of clinical effectiveness

The company reported that the non-RCT searches of electronic databases identified a total of 396 potentially relevant articles which after removal of duplicates left 313 articles for review. In addition, there were 103 potentially relevant citations identified through the searches of the conference proceedings and one further citation (abstract presented at conference, 2010) obtained from the Allergan in house archives.[70]

A total of 417 articles were reviewed at level 1 (abstract) screening with 386 of them excluded from further review. Level 2 screening (full text where available) thus involved review of 31 articles of

which 10 studies in 11 publications met the inclusion criteria for the review of non-RCT evidence (Table 10). The company reported that of the 10 studies, only 9 reported data of relevance to the populations for which dexamethasone has EU marketing authorisation (detailed in Table 10).

Table 10: List of all non-RCTs identified by the systematic literature review (reproduced from the CS, Table 12 pgs 98-101)

	Study summary	Key endpoints	Results summary	Author conclusions	Justification for inclusion
Full publications identified in electronic database searches					
CHAMPLAIN (Boyer *et al.* 2011)[71]	Single-arm trial of DEX700 in patients with treatment-resistant DMO and a history of vitrectomy	Change from baseline in CRT and visual acuity up to week 26	Significant BCVA and CRT improvement throughout study	Treatment with dexamethasone intravitreal implant led to statistically and clinically significant improvements in both vision and vascular leakage from DMO in difficult-to-treat vitrectomized eyes and had an acceptable safety profile	Evidence for patients considered unsuitable for non-corticosteroid therapy
Medeiros *et al.* 2014[72]	Retrospective analysis of patients with refractory DMO treated with DEX700	Change from baseline in visual acuity and CRT up to 6 months	BCVA and CRT improvement at months 1 and 3 but worsening at Month 6	Intravitreal treatment with a dexamethasone implant safely reduced DMO and improved visual acuity in a difficult-to-treat patient population with long-standing refractory DMO	Evidence for patients considered insufficiently responsive to non-corticosteroid therapy
MOZART (Guigou *et al.* 2014)[73]	Retrospective analysis of patients with DMO treated with DEX700, 80% of which had received previous therapy	Change from baseline in visual acuity and CRT up to 6 months	BCVA and CRT improvement throughout study with a mean treatment interval of 5.4 months	Dexamethasone has an anatomical and functional effectiveness in the treatment of DMO. Outcomes for naive patients and lower CRT suggest that the duration of diabetes mellitus and previous treatments are negative factors of recovery. Side effects are rare and manageable. DEX700 seems to be a treatment for visual impairment due to DMO with a	Evidence for patients considered insufficiently responsive to non-corticosteroid therapy

				favourable safety profile. Patient follow-up must be adapted to half-life of the product with a control before M1 (intraocular pressure) and before M5 (DMO recurrence, BCVA)	
OCTOME (Mathew *et al.* 2014)[74]	Single-arm trial of DEX700 in patients with macular oedema secondary to retinal vascular diseases, 80% of which had DMO and at least 60% of which had received previous therapy	Change from baseline in visual acuity and CRT up to 6 months	Significant CRT improvement up to week 32, significant BCVA improvement up to week 20	DEX700 therapy has a rapid and dramatic effect on the macular for about 8 weeks followed by a sustained modest effect up to week 32. The optimal re-treatment time point is at 20 weeks.	Evidence for patients considered insufficiently responsive to non-corticosteroid therapy
Pacella *et al.* 2013[75]	Single-arm trial of DEX700 in patients with persistent DMO	Change from baseline in visual acuity and CRT up to 6 months	Significant BCVA improvement up to Month 4 with no change from baseline observed by Month 6. Significant CRT improvement up to month 3 with numerical improvement observed up to Month 6	The slow-release intravitreal dexamethasone implant, DEX700, produced significant improvements in best-corrected visual acuity and central macular thickness from the third day of implant in DMO sufferers, and this improvement was sustained until the third month	Evidence for patients considered insufficiently responsive to non-corticosteroid therapy
Zucchiatti *et al.* 2012[76]	Retrospective analysis of patients with persistent DMO treated with DEX700	Change from baseline in visual acuity and CRT up to 6 months	Significant BCVA improvement up to month 3 with no change from baseline observed by Month 6. Significant CRT improvement up to month 3 with numerical worsening from baseline observed at Month 6	In eyes with persistent DMO, DEX700 produces improvement in BCVA and CRT as soon as the first days after the injection. Such improvement is maintained until the fourth month	Evidence for patients considered insufficiently responsive to non-corticosteroid therapy
Poster presentations observed through conference proceeding searches					
Udaondo *et al.* 2013[77]	Single-arm trial in patients with	Change from	Significant BCVA and CRT	Intravitreal dexamethasone	

	treatment-naïve DMO	baseline in visual acuity and CRT up to 12 months	improvement up to Month 12	implant was well tolerated and effective in the management of DMO in this study	
Giralt *et al.* 2014[78]	Retrospective analysis of patients with refractory DMO treated with DEX700	Change from baseline in visual acuity and CRT up to 6 months	Significant CRT improvement up to Month 6 but no significant BCVA improvement over time	Intravitreal implant of dexamethasone appears to be promising in the short term, for improving retinal thickness more than visual acuity in eyes with chronic macular oedema unresponsive to other treatments. Randomised controlled trials with longer follow up are required to define optimum treatment regimens.	Evidence for patients considered insufficiently responsive to non-corticosteroid therapy
Gusson *et al*. 2013[79]	Single-arm trial in patients with DMO undergoing cataract surgery	Change from baseline in visual acuity and CRT up to 6 months	CRT improvement up to Month 4 with a return to baseline values observed at Months 5 and 6. BCVA improvement up to Month 6.	In this small case series, Dex-I avoided worsening of chronic DMO after cataract extraction and also improved foveal thickness for up to 4-5 months. Dex-I appears to be a good surgical adjuvant in these cases, but larger studies are necessary to confirm these data	Evidence for pseudophakic patients
Bonet-Fernandez *et al*. 2014[80]	Single-arm trial in patients with treatment-naïve or refractory DMO	Change from baseline in visual acuity and CRT up to 12 months	Maximum improvement in BCVA (greater in the treatment naïve group) and CRT observed at Month 2	We have achieved important VA improvements (greater in the naïve group) and OCT thickness in both groups with a satisfactory safety profile	Evidence for patients considered insufficiently responsive to non-corticosteroid therapy (refractory DMO group)
Abbreviations used in the table: BCVA, best corrected visual acuity; CRT, central retinal thickness; DEX700, dexamethasone 700µg; Dex- I, dexamethasone implant; DMO, diabetic macular oedema; OCT, optical coherence tomography; RCT, randomised controlled trial; VA, visual acuity.					

The non-RCT evidence is comprised of single arm prospective studies and retrospective observational studies in various patient populations. The studies vary in size (9–76 patients), duration (6–12

months), number of dexamethasone treatments permitted (1–3) and retreatment intervals (no restriction, ≥6 months). The company reported that there was a wide variety in the results of the non-RCT studies and that no strong conclusions could be made from the evidence. The non-RCT evidence was not used in the company's comparative clinical safety or efficacy analyses, or in the economic model.

The results of the 9 non-RCT studies were summarised in a narrative review in the CS. The ERG considers the company's use of the non-RCT evidence to be appropriate. The ERG does not consider the non-RCT evidence to add additional information to the RCT evidence presented in the CS to address the decision problem, and thus the ERG does not discuss the findings of the non-RCT studies further in this report. However, the results for the non-RCT review as reported in the CS are presented in Appendix 9.4and 9.5 for completeness.

4.1.5 Critique of data extraction

The company reported that the data extraction of the included trials was conducted by one reviewer using a pre-defined data extraction table. A second reviewer then verified the extracted data. The pre-defined data extraction table collected data on the basic characteristics of each selected study and the study results. The ERG considers the company's data extraction strategy to be acceptable.

4.1.6 Quality assessment

The company conducted a quality assessment for the trials included in the systematic review using criteria similar to the Cochrane risk of bias tool. A summary of the company's quality assessment for the six key trials presented within the CS are presented in Table 11 with the full quality assessment for each RCT presented in Appendix 9.3.

Table 11: Quality assessment results for RCTs (reproduced from the CS table 19, pgs 152-153)

	MEAD-010	MEAD-011	024	PLACID	NCT00035906	BEVORDEX
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Unclear	Yes
Were the groups similar at the outset of the study in terms of prognostic	Yes	Yes	Yes	Yes	Yes	Yes

factors?						
Were the care providers, participants and outcome assessors blind to treatment allocation?	Participants and outcome assessors. Not possible to blind care providers due to sham nature of control arm.	Participants and outcome assessors. Not possible to blind care providers due to sham nature of control arm.	Outcome assessors only. Not possible to blind participants and care providers due to differing nature of active treatment arms.	Participants and outcome assessors. Not possible to blind care providers due to sham element of control arm.	Outcome assessors only. Participants randomised to DEX were masked to the dose they received. Not possible to blind care providers due to the observation nature of the control arm.	Outcome assessors only. Not possible to blind participants and care providers due to differing nature of active treatment arms.
Were there any unexpected imbalances in drop-outs between groups?	Drop-out due to lack of efficacy higher in sham group.	Drop-out due to lack of efficacy higher in sham group.	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Yes	Yes
Source: Boyer *et al.* 2014[51]; Callanan *et al.* 2013[58]; CSR 206207-010[54]; CSR 206207-011[55]; CSR 206207-012[57]; CSR 206207-024[56]; Gillies *et al.* 2010[61]; Gillies *et al.* 2014b[62]; Haller *et al.* 2010[60]; Kupperman *et al.* 2007[59]						

The ERG considers the six dexamethasone RCTs to be of reasonable quality with the main areas of concern relating to the absence of participant blinding in several of the trials and the relatively high discontinuation rates in the MEAD studies.

In general, the ERG agrees with the company's overall quality assessment for each of the six trials.

4.1.7 Evidence synthesis

The company reports the data separately for each of the six dexamethasone trials in the CS. In addition, the data from the two MEAD studies are presented as a pooled analysis. In response to clarification, the company also provided data of the MEAD studies from a standard pair wise meta-analysis. Further details are presented in Section 4.3.

In terms of the comparison of dexamethasone with the other comparators of interest specified in the decision problem, the company reports results from a network meta-analysis. Further details of this analysis are presented in Sections 4.6 and 4.7.

4.2 Summary and critique of submitted clinical effectiveness evidence

The company presented clinical effectiveness data on dexamethasone from six phase II and III trials: MEAD-010, MEAD-011, 024, PLACID, NCT00035906 and BEVORDEX. These six trials are discussed in further detail below with a summary of the methods of each trial presented in Table 12.

Table 12: Comparative summary of methodology of the RCTs (reproduced from CS, Table 13, pgs 105-111)

Trial number	MEAD-010	MEAD-011	024	PLACID	NCT00035906	BEVORDEX
Location	59 study centres in 10 countries (Australia, Canada, Czech Republic, Germany, Israel, Philippines, Portugal, South Africa, Spain, USA)	72 study centres in 14 countries (Brazil, Canada, Colombia, France, Hungary, India, Italy, New Zealand, Poland, Singapore, South Korea, Taiwan, UK, USA)	57 study centres in 11 countries (Denmark, France, Germany, Israel, Italy, Netherlands, Portugal, South Africa, Spain, UK, USA)	48 sites in the USA and Canada	29 retina practices in the USA	7 study sites in Australia
Design	Multicentre, masked, randomised, sham-controlled, Phase III study designed to assess the efficacy and safety of 700µg and 350µg dexamethasone posterior segment drug delivery system in the treatment of patients with DMO.		Multicentre, open-label, randomised, Phase IIIb comparative study designed to assess if 700µg dexamethasone can be safely administered every 5 months and achieve improvement of visual acuity similar to ranibizumab in DMO.	Randomised, double-masked, sham controlled, Phase II clinical study to evaluate the safety and efficacy of the 700µg dexamethasone implant in combination with laser photocoagulation therapy in DM patients with diffuse DMO	Phase II randomised, prospective, multicentre, dose-ranging, single-masked controlled trial to evaluate the safety and efficacy of 700µg and 350µg dexamethasone drug delivery system in the treatment of patients with persistent macular oedema. DMO subgroup of interest to the decision problem.	Phase II, prospective, multicentre, randomised, single-masked clinical trial of sustained release intravitreal dexamethasone versus intravitreal injections of bevacizumab for diabetic foveal oedema.
Duration of study	36-39 months	36-39 months	12 months	12-15 months	6 months	24 months
Method of randomisation	A series of patient randomisation numbers were provided by a validated automated system. Sites used either the interactive voice response system or the interactive web response system to assign to each qualified patient a randomisation number. Patients were randomised in a 1:1:1 ratio.		An automated interactive voice response system/interactive web response system was used to randomise	The randomisation was stratified based on baseline BCVA in the study eye (≤49 or ≥50 letters). The randomisation	Patients were randomised using a 1:1:1 allocation generated by the study sponsor.	Patients were randomised using a series of serially numbered, opaque envelopes containing an assignment to 1

		patients in a 1:1 ratio. Randomisation was stratified by BCVA score at baseline (≥34 to ≤49 and ≥50 to ≤70).	schedule was computer generated and stored in a locked cabinet until the study ended. Patients were randomisation in a 1:1 ratio.		treatment arm. Treatment assignments were compiled using a list of computer generated pseudo-random numbers in permuted blocks of variable size. Randomisation was stratified by phakic or pseudophakic lens status and a history or vitrectomy or not.
Method of blinding	Patients were masked to the study treatments for the duration of the trial. Individuals collecting clinical data were masked to patient treatments. A central reading centre was used to evaluate ocular coherence tomography, fundus photographs and fluorescein angiography and the grader was masked from study treatments.	Individuals collecting primary efficacy (BCVA) data and evaluators at the reading center were masked to study treatment assignment for the duration of the trial. Patients and investigators were aware of the treatment assignment.	Both the patients and the study personnel who collected BCVA, OCT and FA data were masked to the patient study assignment.	Patients in the dexamethasone treatment groups were masked regarding the dose they had received. Key efficacy variables were collected and evaluated by personnel who were masked to patient study treatment.	BCVA examiner masked. Investigators, study coordinator, photographer, surgeon unmasked
Intervention(s) Comparator(s)	700µg dexamethasone posterior segment drug delivery system applicator system (DEX700) 350µg dexamethasone posterior segment drug delivery system applicator system (DEX350)	700µg dexamethasone posterior segment drug delivery system applicator system (DEX700) 0.5mg ranibizumab (RAN)	700µg dexamethasone posterior segment drug delivery system applicator system (DEX700) + modified ETDRS focal (direct/grid) laser photocoagulation (DEX	700µg dexamethasone posterior segment drug delivery system (DEX700) 350µg dexamethasone posterior segment drug delivery system	700µg dexamethasone posterior segment drug delivery system (DEX700) 1.25mg bevacizumab (BEV)

	Sham (needleless) applicator system (Sham)			+ laser) Sham implant + modified ETDRS focal (direct/grid) laser photocoagulation	(DEX350) Observation (no study treatment and no sham procedure)	
Treatment schedule	Patients received initial treatment on randomisation day (day 0). Starting from the Month 6 visit, patients were evaluated for retreatment eligibility every 3 months but the study treatment procedure was not to be performed more often than approximately 6 months. Patients were eligible for retreatment if retinal thickness in the 1mm central macular subfield by OCT was >175µm* or upon investigator interpretation of the OCT for any evidence of residual retinal oedema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the centre subfield).	Patients received initial treatment on randomisation day (day 0). Starting from the Month 6 visit, patients were evaluated for retreatment eligibility every 3 months but the study treatment procedure was not to be performed more often than approximately 6 months. Patients were eligible for retreatment if retinal thickness in the 1mm central macular subfield by OCT was >175µm* or upon investigator interpretation of the OCT for any evidence of residual retinal oedema consisting of intraretinal cysts or any regions of increased retinal thickening	Patients randomised to DEX700 received treatment at baseline, Month 5 and Month 10. Patients randomised to RAN received monthly treatment until maximum visual acuity was achieved (stable vision for 3 consecutive months). After suspension of treatment, monthly intravitreal injections were reinitiated if a decrease in vision due to DMO progression was observed and continued until maximum visual acuity was achieved again.	Patients received DEX700 or sham treatment on randomisation day (day 0). One month later all patients were treated with laser. Patients were evaluated for retreatment eligibility at study visits at months 4, 6 and 9. Patients were eligible for retreatment if retinal thickness in the 1mm central macular subfield by OCT was >250 µm; there was a minimum interval between treatments of at least 3 months for laser retreatment and 6 months for DEX implant of sham treatment; the patient was not at significant risk from retreatment and if the patient would benefit from	Patients received single treatment at randomisation.	Patients randomised to DEX700 received treatment at baseline. Starting from the Month 4 visit, patients were evaluated for retreatment every 6 weeks but the study treatment procedure was not to be performed more often than 4 months. Patients randomised to BEV received treatment at baseline, week 6 and week 12. Starting from the month 3 visit, patients were evaluated for retreatment eligibility every 6 weeks. At 24 weeks if persistence of macular oedema was observed, patients were evaluated for retreatment eligibility every 4 weeks. Patients were eligible for retreatment if CRT

	* retinal thickness threshold was reduced from >225 µm as of May 2010 in a protocol amendment based on investigator feedback that a more aggressive DMO treatment approach is adopted in current practice	(within or outside of the centre subfield). * retinal thickness threshold was reduced from >225 µm as of May 2010 in a protocol amendment based on investigator feedback that a more aggressive DMO treatment approach is adopted in current practice		retreatment. Patients could receive up to 3 additional lasers (at months 4, 7 and 10) and 1 additional DEX implant or sham treatment (at Month 6 and 9).		was >250µm on spectral domain or if VA was <79 letters.
Assessment schedule	Every 3 months	Every 3 months	Monthly	Months 1, 4, 6, 9, 12 & 15	Days 60, 90 and 180	Every 3 months
Escape therapy	None. Patients who required additional DMO in the study eye were considered study treatment failures and were withdrawn from the study based on when they last received study treatment.		Laser. Patients could receive laser treatment after Month 2 if they met the following criteria: visual acuity loss of ≥10 letters and/or CRT >320 µm and DMO present and >12 weeks since previous laser session.	None. Patients who required additional DMO in the study eye were withdrawn from the study based on when they last received study treatment.	Laser and/or pharmaceutical. Eyes that demonstrated a visual acuity loss of ≥15 letters could be treated with any other therapy (including laser and intravitreal triamcinolone) that the investigator deemed appropriate.	Laser. Patients could receive laser treatment if the study eye developed an area of focal oedema with circinate exudates that may benefit from laser treatment in the opinion of the investigator.
Primary outcomes	Mean BCVA average change (area under the curve approach).		Mean BCVA average change.	Proportion of patients who had at least a 10-letter improvement in BCVA from baseline at Month 12 in the ITT population of all randomised patients.	Proportion of eyes achieving at least a 10 letter improvement in BCVA at the day 90 follow-up visit.	The comparison of the proportion of eyes gaining 10 letters of visual acuity between the bevacizumab and dexamethasone implant arms after 104

					weeks.
Secondary outcomes	Proportion of patients with improvement of 15 or more letters from baseline; mean BCVA change from baseline; proportion of patients with improvement of 10 or more letters from baseline; proportion of patients with worsening of 15 or more letters from baseline; category distribution of BCVA change from baseline; mean CRT average change using an area under the curve approach; mean CRT change from baseline; proportion of patients at each diabetic retinopathy severity category; time to first diabetic retinopathy 3-step progression; time to first diabetic retinopathy 2-step progression; mean contrast sensitivity change from baseline; health related quality of life using the NEI VFQ-25; safety analysis	Mean BCVA average change (area under the curve approach); proportion of patients with improvement of 15 or more letters from baseline; mean BCVA change from baseline; proportion of patients with improvement of 10 or more letters from baseline; proportion of patients with worsening of 15 or more letters from baseline; proportion of patients with worsening of 10 or more letters from baseline; category distribution of BCVA change from baseline; CRT change from baseline; change from baseline in total leakage area; treatment exposure; HRQL; safety	Change in BCVA from baseline; change in retinal thickness in the central subfield by OCT; area of vessel leakage evaluated with fluorescein angiography; number of DEX implant or sham treatments; number of laser treatments; safety.	Proportion of eyes achieving a 15-letter improvement in BCVA, proportion of eyes achieving at least a 2- or 3- grade improvement in fluorescein angiographic leakage; change in central retinal thickness using OCT; safety.	Any change in visual acuity compared with the pre-injection levels; mean change in visual acuity compared with pre-injection level; number of laser treatments required for the treatment of macular oedema during the study; change in retinal thickness by OCT; patients satisfaction with treatment; safety. Safety outcomes include mean change in maximum diameter of foveal avascular zone; incidence and severity of ocular adverse events including severe loss of vision and thinning of neural retina; incidence and severity of non-ocular adverse events.

Abbreviations used in the table: BCVA, best corrected visual acuity; BEV, bevacizumab; CRT, central retinal thickness; DEX, dexamethasone; DMO, diabetic macular oedema; FA, fluocinolone acetonide; HRQL, health-related quality of life; NEI-VFQ, National Eye Institute Visual Functioning Questionnaire-25; OCT, ocular computer tomography; VA, visual acuity.

Source: Boyer *et al*. 2014[51]; Callanan *et al*. 2013[58]; CSR 206207-010[54]; CSR 206207-011[55]; CSR 206207-012[57]; CSR 206207-024[56]; Gillies *et al.* 2010[61]; Gillies *et al*. 2014b[62]; Haller *et al*. 2010[60]; Kuppermann *et al.* 2007[59]

4.2.1 Detailed description of included RCTs

The six RCTs included in the CS providing clinical safety and/or efficacy data for dexamethasone 700µg compared the following:

- MEAD-010 and MEAD-011: dexamethasone (6 monthly *pro re nata* [PRN]) versus sham;
- NCT00035906: dexamethasone (1 treatment only) versus observation;
- 024: dexamethasone (5 monthly) versus ranibizumab;
- PLACID: dexamethasone (6 monthly) + laser photocoagulation versus laser photocoagulation;
- BEVORDEX: dexamethasone (4 monthly) versus bevacizumab.

The two MEAD studies were identical in study design and provide the key data for dexamethasone in the CS although this is versus sham which was not a comparator of interest in the final scope issued by NICE. NCT00035906 limited treatment with dexamethasone to one dose and compared it with observation alone, which again was not a comparator listed in the final scope issued by NICE. However, based on the EU marketing authorisation for dexamethasone, the ERG considers observation and sham to be appropriate comparators for some of the populations for whom dexamethasone would be a treatment option. This is because observation and sham can be considered surrogates for watch and wait.

The ERG has concerns that 024 and BEVORDEX do not utilise the dexamethasone dosing regimen authorised in the UK; both utilise more frequent dexamethasone regimens than the EU marketing authorisation 6 monthly recommended minimum re-treatment period. The final RCT, PLACID includes dexamethasone plus laser which was listed as an intervention of interest in the final scope issued by NICE.

In view of the differences between each of the trials, with the exception of the MEAD studies, the ERG considers the company's decision to report each trial separately to be appropriate. However, the ERG does not consider 024 or BEVORDEX to address the decision problem as they do not use the licensed treatment regimens for dexamethasone in the UK and so these studies are not discussed further in this report. However, the data from both trials are provided in Appendix 9.6 for information because they enable direct head-to-head comparisons of dexamethasone with ranibizumab and bevacizumab, two comparators of interest listed in the final scope issued by NICE. In addition, the MEAD studies and NCT00035906 were 3-armed RCTs, with one of the treatment groups being a lower dose of dexamethasone than that licensed for use in the UK (dexamethasone 350µg). The ERG thus does not consider data from this trial arm of relevance to this review and does not present or discuss the data in this report.

Population

MEAD-010 was conducted in 59 study centres in 10 countries, MEAD-011 was conducted in 72 study centres in 14 countries, PLACID was conducted in 48 sites in the USA and Canada and NCT00035906 was conducted in 29 sites in the USA. Only MEAD-011 contained patients from the UK. In terms of patient numbers in each of the studies, MEAD-010 contained 494 randomised patients (328 patients randomised to the two treatment arms of interest to this review) and MEAD-011 contained 554 randomised patients (373 patients in the two treatment arms of interest to this review). PLACID enrolled and randomised 253 patients, and in NCT00035906 there were 171 DMO patients randomised (although only 114 were randomised to treatment arms of interest to this review i.e dexamethasone 700µg or observation).

The patient selection criteria used for each of the studies are presented in Table 13. In general the inclusion and exclusion criteria were similar across the four studies. The ERG notes that restrictions based on prior use of corticosteroids varied notably between the MEAD and PLACID studies (3 months prior to study entry) compared with the NCT00035906 study (30 days prior to study entry).

Table 13: Eligibility criteria in the RCTs (reproduced from CS, Table 14, pgs 114-119)

Trial number	Inclusion criteria	Exclusion criteria
MEAD-010 MEAD-011	≥18 years; diagnosis of DM (Type 1 or 2); DMO in study eye defined as observable macular oedema involving the fovea associated with diabetic retinopathy with any of the following: prior medical therapy, prior macular laser (with the most recent laser at least 3 months prior to baseline), patient refused treatment or the investigator felt patient would not benefit from laser treatment; BCVA score 34-68 letters; retinal thickness ≥300µm by OCT; negative pregnancy test; written informed consent; written data protection consent; written documentation in accordance with state and country privacy requirements. Patients who had previously received intravitreal triamcinolone acetonide must have satisfied the following criteria: the	Uncontrolled systemic disease or current immunosuppressive diseases; initiation of medical therapy for DM or a change from oral hypoglycaemic agents to insulin within 4 months prior to baseline; HbA1c level >10%; renal failure requiring dialysis within 6 months prior to baseline; adjusted GFR <50ml/min. Any ocular condition which would have prevented a 15-letter improvement; presence of BRVO, CRVO, uveitis, pseudophakic cystoid macular oedema or any other condition that could contribute to macular oedema; presence of an epiretinal membrane or vitreoretinal interface changes. History of IOP elevation in response to steroid treatment; history of glaucoma or optic nerve head change consistent with glaucoma damage; OHT with IOP >23mmHg if taking no anti-glaucoma medications or IOP >21mmHg if taking 1 anti-glaucoma medications or taking 2 or more anti-glaucoma medications. Aphakia or presence of anterior chamber intraocular lens; active optic disc or retinal neovascularization; active or history of choroidal neovascularisation; presence of rubeosis iridis; active ocular infection in either eye; history of herpetic infection; presence of toxoplasmosis; presence of visible scleral thinning or ectasia; media opacity. Intraocular surgery within 90 days prior to baseline; history of central serious chorioretinopathy in either eye; history of pars plana vitrectomy; anticipated need for ocular surgery or laser within 1 year; history of use of intravitreal steroids other than TA; history of use of intravitreal bevacizumab, ranibizumab, pegaptanib within 3 months prior to baseline; periocular depot of steroids within 6 months prior to baseline; use of systemic

	intended dose for each injection was 4mg or less; the most recent dose was at least 6 months prior to the qualification/baseline visit; no treatment-related adverse event was seen that, in the opinion of the investigator, had the potential to worsen or reoccur with study treatment.	steroids (including dexamethasone) within 1 month prior to baseline; use of immunosuppressants, immunomodulators, antimetabolites and/or alkylating agents within 6 months prior to baseline; use of warfarin enoxaparin or heparin within 2 weeks prior to baseline; BCVA score <34 letters in the non-study eye; known allergy or hypersensitivity to the study medication; known allergy or hypersensitivity to the use of fluorescein or povidine iodine; contraindication to pupil dilation in either eye. Previous enrolment in a DEX PS DDS applicator system trial; patient planned extended absence away from immediate area of study centre; any condition that precluded patients ability to comply with study requirements; pregnancy, nursing or planning a pregnancy; current enrolment in an investigational drug or device study or participation in such a study within 30 days prior to baseline; condition or situation which put the patient at significant risk, may have confounded study results or interfered significantly with patient participation
PLACID	≥18 years old; Type 1 or Type 2 DM; mean retinal thickness ≥275 µm by OCT in the 1mm central macular subfield due to diffuse DMO (defined as macular thickening involving the centre of the fovea) not amenable to laser as stand-alone treatment (at screening); diffuse macular capillary bed leakage evident on FA; BCVA ≥35 and ≤70 letters using the ETDRS method at screening in the study eye.	Uncontrolled systemic disease; use of systemic corticosteroid within 12 weeks prior to baseline or anticipated use during the study; active ocular infection; glaucoma; history of IOP increase ≥10mmHg or to ≥25mmHg in response to corticosteroid treatment that required multiple IOP-lowering medication or laser or surgical treatment; history of presence of venous occlusive disease, uveitis, Irvine-Gass syndrome or any other condition other than diabetic retinopathy that could contribute to macular oedema; epiretinal membrane or vitreomacular traction that is primary cause of maular oedema; history of pars plana vitrectomy; active optic disc or retinal neovascularization; history of intravitreal corticosteroid use except dexamethasone of ≤4mg triamcinolone dosed at least 13 weeks prior to baseline; use of periocular corticosteroid within 26 weeks prior to baseline or topical nonsteroidal anti-inflammatory or corticosteroid within 4 weeks prior to baseline; active ocular infection of history or herpetic infection in eye or adnexa; aphakia or pseudophakia; any intraocular injection, surgery or laser within 13 weeks prior to baseline or anticipated need for ocular surgery during the study; any condition or disease would prevent a 10-letter improvement in BCVA; IOP >23mmHg if untreated or >21mmHg if treated with 1 medication; current treatment with 2 or more IOP-lowering medications; BCVA <34 letters at screening or baseline in non-study eyes
NCT00035906	≥12 years; macular oedema persisting for 90 days or more after laser treatment or medical therapy; BCVA 35-67 letters due to clinically detectable macular oedema.	Visual acuity worse than 20/200 in the study eyes; history of vitrectomy surgery in the study eye; use of systemic, periocular or intraocular corticosteroids within 30 days of enrolment; moderate or severe glaucoma in the study eyes; poorly controlled hypertension (defined as systolic pressure >160mmHg and/or diastolic pressure >90 mmHg); and poorly controlled DM (defined as HbA_{1c} level >13%).

Abbreviations used in the table: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; DEX, dexamethasone; DM, diabetes mellitus; DMO, diabetic macular oedema; ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, fluocinolone acetonide; GFR, glomerular filtration rate; HRQL, health-related quality of life; IOP, intraocular pressure; IVTA, intravitreal triamcinolone; OCT, optical coherence tomography; PS DDS, posterior segment drug delivery system; TA, triamcinolone; VA, visual acuity; YAG, yttrium aluminium garnet.

Notes: Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions

to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee Source: Boyer *et al*. 2014[51]; Callanan *et al*. 2013[58]; CSR 206207-010[54]; CSR 206207-011[55]; CSR 206207-012[57]; CSR 206207-024[56]; Gillies *et al*. 2010[61]; Gillies *et al*. 2014b[62]; Haller *et al*. 2010[60]; Kuppermann *et al.* 2007[59]

Randomisation was 1:1:1 in the MEAD studies and NCT00035906, and 1:1 in PLACID.

In PLACID the randomisation was stratified according to baseline BCVA in the study eye (≤49 or ≥50 letters). There was no mention of any stratification used in the MEAD or NCT00035906 studies. The baseline characteristics of the randomised patients in each of the studies are presented in tables below (Table 14 and Table 15)

Randomisation took place between February 2005 to June 2009 in the MEAD studies, October 2001 and September 2002 in NCT00035906 and PLACID was conducted between May 2007 and February 2010.

Table 14: Baseline characteristics of participants in the MEAD studies (reproduced from CS Table 15, pgs 122-123)

	MEAD-010			**MEAD-011**			**MEAD Pooled**		
	DEX700 (n=163)	DEX350 (n=166)	Sham (n=165)	DEX700 (n=188)	DEX350 (n=181)	Sham (n=185)	DEX700 (n=351)	DEX350 (n=347)	Sham (n=350)
Demographics									
Age, mean years (SD)	63.1 (8.0)	63.3 (9.0)	62.6 (9.1)	61.9 (8.6)	61.3 (9.3)	62.4 (9.9)	62.5 (8.3)	62.3 (9.2)	62.5 (9.5)
Male, n (%)	102 (62.6)	100 (60.2)	102 (61.8)	111 (59.0)	106 (58.6)	115 (62.2)	213 (60.7)	206 (59.4)	217 (62.0)
Caucasian, n (%)	138 (84.7)	140 (84.3)	134 (81.2)	96 (51.1)	94 (51.9)	99 (53.5)	234 (66.7)	234 (67.4)	233 (66.6)
Disease characteristics									
Duration of DM, mean years (SD)	17.2 (9.2)	16.2 (9.2)	15.3 (8.3)	15.9 (8.9)	15.5 (9.5)	16.4 (9.8)	16.5 (9.0)	15.8 (9.4)	15.9 (9.1)
Type 2 DM, n (%)	148 (90.8)	153 (92.2)	149 (90.3)	166 (88.3)	172 (95.0)	173 (93.5)	314 (89.5)	325 (93.7)	322 (92.0)
Baseline HbA1c, mean % (SD)	7.5 (1.1)	7.5 (1.1)	7.5 (1.1)	7.6 (1.2)	7.6 (1.2)	7.5 (1.0)	≤8%, n (%) 233 (66.4)	≤8%, n (%) 237 (68.3)	≤8%, n (%) 249 (71.1)
IOP in study eye, mean mmHg (SD)	15.3 (2.7)	15.8 (3.0)	15.4 (3.1)	15.4 (2.5)	15.5 (2.6)	15.2 (3.0)	15.3 (2.6)	15.6 (2.8)	15.3 (3.1)
≥ Severe DR, n (%)	62 (38.0)	65 (39.2)	68 (41.2)	89 (47.3)	86 (47.5)	81 (43.8)	151 (43.0)	151 (43.5)	149 (42.6)
Duration of DMO, mean months (SD)	24.0 (26.2)	24.9 (29.3)	27.2 (29.6)	23.2 (25.8)	25.5 (33.3)	24.8 (25.1)	23.6 (26.0)	25.2 (31.4)	25.9 (27.3)
Duration of	37 (22.7)	-	43	38	-	44	75	-	87 (24.9)

DMO ≥3 years, n (%)*			(26.1)	(20.2)		(23.8)	(21.4)		
Pseudophakic lens, n (%)	44 (27.0)	47 (28.3)	50 (30.3)	42 (22.3)	41 (22.7)	51 (27.6)	86 (24.5)	88 (25.4)	101 (28.9)
Baseline VA, mean letters (SD)	56.2 (10.05)	55.9 (9.6)	56.8 (8.1)	55.9 (9.8)	55.2 (9.7)	57.0 (8.8)	56.1 (10.0)	55.5 (9.7)	56.9 (8.7)
Baseline CRT, mean µm (SD)	436.7 (145.9)	457.4 (158.1)	468.7 (129.6)	486.0 (163.1)	475.4 (160.7)	453.7 (135.4)	463.0 (157.1)	466.8 (159.5)	460.9 (132.6)
CRT ≥400 µm, n (%)*	89 (54.6)	-	108 (65.5)	122 (64.9)	-	112 (60.5)	211 (60.1)	-	220 (62.9)
Study eye was BSE, n (%)	36 (22.1)	37 (22.3)	34 (20.6)	41 (21.8)	39 (21.5)	49 (26.5)	77 (21.9)	76 (21.9)	83 (23.7)
Bilateral DMO, n (%)	47 (28.8)	-	47 (28.5)	80 (42.6)	-	81 (43.8)	127 (36.2)	-	128 (36.6)
Treatment history for DMO in the study eye									
Treatment naïve, n (%)	40 (24.5)	40 (24.1)	38 (23.0)	64 (34.0)	58 (32.0)	51 (27.6)	104 (29.6)	98 (28.2)	89 (25.4)
Prior laser, n (%)	115 (70.6)	116 (69.9)	122 (73.9)	116 (61.7)	108 (59.7)	121 (65.4)	231 (65.8)	224 (64.6)	243 (69.4)
Prior anti-VEGF, n (%)	17 (10.4)	20 (12.0)	13 (7.9)	8 (4.3)	19 (10.5)	13 (7.0)	25 (7.1)	39 (11.2)	26 (7.4)
Prior steroid, n (%)	28 (17.2)	30 (18.1)	23 (13.9)	30 (16.0)	39 (21.5)	38 (20.5)	58 (16.5)	69 (19.9)	61 (17.4)

Abbreviations used in the table: BSE, best seeing eye; CRT, central retinal thickness; DEX350, dexamethasone 350µg; DEX700, dexamethasone 700µg; DM, diabetes mellitus; DMO, diabetic macular oedema; DR, diabetic retinopathy; HbA1c, glycosylated haemoglobin; IOP, intraocular pressure; NR, not reported; OCT, ocular computed tomography; RCT, randomised clinical trial; SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor.

Note: *analysed post-hoc due to licence/HTA restrictions on use of comparator therapies.

Source: Boyer *et al*. 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]; Clinical Story MEAD Final[81]

Table 15: Baseline characteristics of participants in PLACID and NCT00035906 (adapted from CS, Table 16, pgs 124-126)

	PLACID		**NCT00035906**		
	DEX + laser (n=126)	**Laser (n=127)**	**DEX700 (n=57)**	**DEX350 (n=57)**	**Observation (n=57)**
Age, mean (years (SD)	61.8 (11.1)	61.3 (9.3)	63.8 (11.6)	63.8 (10.2)	62.9 (12.0)
Male, n (%)	62 (49.2)	66 (52.0)	29 (50.9)	30 (52.6)	31 (54.4)
Caucasian, n (%)	82 (65.1)	73 (57.5)	43 (75.4)	41 (71.9)	41 (71.9)
Duration of DM, mean years (SD)	8.7 (13.9)	17.0 (13.0)	NR	NR	NR
Type 2 DM, n (%)	98 (77.8)	107 (84.3)	NR	NR	NR
Baseline HbA1c,	7.6 (1.4)	7.7 (1.2)	Median %:	Median %:	Median %:

mean % (SD)			7.6	7.3	7.3
IOP in study eye, mean mmHg (SD)	16.0 (3.1)	15.9 (2.7)	NR	NR	NR
Duration of DMO, mean months (SD)	22.4 (29.7)	28.2 (33.7)	Years, n (%): <0.5: 21 (36.8) 0.5-1.0: 15 (26.3) >1.0: 21 (36.8)	Years, n (%): <0.5: 16 (28.1) 0.5-1.0: 30 (52.6) >1.0: 11 (19.3)	Years, n (%): <0.5: 21 (36.8) 0.5-1.0: 13 (22.8) >1.0: 23 (40.4)
Duration of DMO ≥3 years, n (%)*	26 (20.6)	37 (29.1)	NR	NR	NR
Pseudophakic lens, n (%)	35 (27.8)	32 (25.2)	NR	NR	NR
Baseline VA, mean letters (SD)	57.6 (9.4)	57.8 (9.7)	54.7 (11.0)	54.4 (9.96)	54.4 (11.88)
Baseline CRT, mean µm (SD)	438.4 (133.9)	430.3 (131.2)	428.3 (155.9)	446.5 (123.7)	417.5 (126.8)
CRT ≥400 µm, n (%)*	70 (55.6)	64 (50.4)	NR	NR	NR
Study eye was BSE, n (%)	22 (17.5)	20 (15.7)	NR	NR	NR
Bilateral DMO, n (%)	74 (58.7)	83 (65.4)	NR	NR	NR
Treatment history for DMO in the study eye					
Treatment naïve, n (%)	48 (38.1)	42 (33.1)	NR	NR	NR
Prior laser, n (%)	78 (61.9)	84 (66.1)	35 (61)	34 (60)	29 (51)
Prior anti-VEGF, n (%)	2 (1.6)	7 (5.5)	NR	NR	NR
Prior steroid, n (%)	7 (5.6)	13 (10.2)	NR	NR	NR

Abbreviations used in the table: BEV, bevacizumab; BSE, best seeing eye; CRT, central retinal thickness; DEX350, dexamethasone 350µg; DEX700, dexamethasone 700µg; DM, diabetes mellitus; DMO, diabetic macular oedema; DR, diabetic retinopathy; HbA1c, glycosylated haemoglobin; IOP, intraocular pressure; NR, not reported; OCT, ocular computed tomography; RAN, ranibizumab; RCT, randomised clinical trial; SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor.

Note: *analysed post-hoc due to licence/HTA restrictions on use of comparator therapies.

Source: Callanan *et al*. 2013[58]; CSR 206207-012[57]; CSR 206207-024[56]; Clinical Story PLACID final[82]; Clinical Story 024 final[83]; Haller et al. 2010[60]; Gillies et al. 2014b[62]

The company reported that patient groups were similar at baseline both within and between these four dexamethasone trials although no measures of statistical significance were reported in the CS for any of the baseline characteristics. However, the ERG notes that based on the numerical data provided by the company, the treatment groups appear to be broadly comparable at baseline. The ERG considers it important to highlight that there were slightly more Caucasian and male patients in the trials compared to other races and female patients. The average age of patients was over 60 years and duration of DMO was around 2–3 years. There were just over a quarter of patients in the MEAD and

PLACID trials who were pseudophakic at baseline. The number of pseudophakic patients at baseline wasn't reported for NCT00035906. In terms of prior therapies, just over a quarter of patients study eyes in the MEAD and PLACID trials were treatment naive and over 60% had received prior laser therapy.

The ERG and its clinical experts consider the baseline characteristics of the MEAD, PLACID and NCT00035906 trials to be generally representative of the UK DMO population for whom treatment with dexamethasone would be considered.

Intervention and comparators

The intervention and comparators varied slightly between each of the trials with the exception of the MEAD studies which were identical in terms of study design. As discussed in Section 4.2, both MEAD and NCT00035906 included a third trial arm that comprised of a lower unlicensed dose of dexamethasone that is not discussed further in this report. Therefore only the trial arms of relevance to this review will be discussed below.

In the MEAD studies patients were randomised 1:1 to 700µg dexamethasone posterior segment drug delivery system applicator system (dexamethasone or DEX700) or a sham (needleless) applicator system (sham). Patients in the MEAD studies received their first study treatment on the day of randomisation (day 0). Patients were then followed up every 3 months and evaluated for retreatment eligibility from month 6 onwards every 3 months. However, re-treatment was not to be performed more frequently than every 6 months. Patients in the MEAD studies were thus eligible to receive a maximum of 7 dexamethasone or sham implants over the 36 to 39 month duration of the trials.

The criteria used to assess patient eligibility for retreatment were:

- retinal thickness in the 1mm central macular subfield by OCT was >175µm (this retinal thickness threshold was reduced from >225 µm as of May 2010 in a protocol amendment based on investigator feedback that a more aggressive DMO treatment approach is adopted in current practice); or
- investigator interpretation of the OCT suggesting evidence of residual retinal oedema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the centre subfield).

Rescue or escape therapies were not permitted in the MEAD studies and so any patients requiring additional treatment to dexamethasone (including laser) for DMO progression were withdrawn from the studies.

In PLACID patients were randomised 1:1 to 700µg dexamethasone posterior segment drug delivery system applicator system (dexamethasone) plus modified ETDRS focal (direct/grid) laser photocoagulation (dexamethasone + laser) or to a sham implant plus modified ETDRS focal

(direct/grid) laser photocoagulation (sham + laser). Patients received their first dose of dexamethasone or sham treatment on the day of randomisation (day 0). All patients were then treated with laser one month later. Patients were assessed for eligibility for re-treatment with their assigned study drug regimen at study visits at months 4, 6 and 9. The eligibility criteria for retreatment in PLACID was a retinal thickness in the 1mm central macular subfield as measured by OCT >250 µm. Laser treatment could not be administered more frequently than once every 3 months and once every 6 months for dexamethasone or the sham implant. These treatment restrictions resulted in patients being eligible to receive up to 3 additional lasers (at months 4, 7 and 10) and 1 additional dexamethasone implant or sham treatment (at Month 6 or 9). Patients in PLACID could thus receive a maximum of 2 dexamethasone or sham implants and 4 laser treatments over the 12 to 15 month duration of the trial.

In NCT00035906 patients were randomised 1:1 to receive 700µg dexamethasone posterior segment drug delivery system (dexamethasone) or observation (i.e. no study treatment was used). The patients in the dexamethasone arm of NCT00035906 received a single treatment at randomisation and then all patients were followed up for 180 days.

The ERG considers the treatment algorithm in the MEAD, PLACID and NCT00035906 studies to be consistent with how dexamethasone would be expected to be utilised in UK clinical practice. However, the ERG does not consider the concomitant use of laser in all patients in PLACID to be consistent with how laser would be used with dexamethasone in UK clinical practice. Clinical experts to the ERG report that whilst laser may be utilised alongside dexamethasone in UK clinical practice it would not be expected that all patients would require both laser and dexamethasone. Instead patients with DMO receiving dexamethasone would be assessed on an individual basis as to whether or not concomitant treatment with laser is required. It would be expected that concomitant laser would be used in a minority rather than a majority of DMO patients.

Outcomes

The primary efficacy endpoint in each of the trials along with the secondary and safety outcomes of relevance to the decision problem for this STA reported in the CS are detailed in Table 16. The ERG note that BCVA was measured using the ETDRS method in all four of the studies. The ERG consulted with clinical experts who have confirmed that the ETDRS method is a widely accepted method of assessing visual acuity in clinical trials. The ERG also notes that the BCVA outcome measures reported in the CS relate only to the study eye and there is no assessment of BCVA for both eyes reported within the CS for any of the RCTs.

The company highlights in the CS that the primary efficacy outcome for Europe in the MEAD trials was amended from the original primary outcome of the proportion of patients with a ≥15 letter gain at study end. The primary efficacy outcome used in Europe for the MEAD trials was mean BCVA

average change from baseline. However, the original primary endpoint remained in the US and was reported as a secondary outcome for Europe. The company rationale for this amendment in Europe was that it represented the current regulatory requirements and standard of care for DMO which had evolved over the period of time in which the MEAD studies were conducted. The ERG notes that data for both outcomes have been reported in the CS.

Table 16: Primary and secondary outcomes of the RCTs (adapted from CS, Table 17, pg 129-133)

Trial number	Primary outcome(s) and measures	Secondary outcome(s) and measures
MEAD-010 MEAD-011	The EU primary outcome was mean BCVA average change (AUC approach) from baseline through Month 36/39 (final analysis). Average change was measured using an AUC approach.	Key secondary outcome in the EU was the proportion of patients with improvement of 15 or more letters from baseline. Other secondary outcomes included change from baseline in BCVA at all post-baseline timepoints; proportion of patients with improving/worsening vision based on various categorisations; and contrast sensitivity. BCVA was measured using the ETDRS method. Contrast sensitivity was measured using the Pelli-Robson chart. Anatomical outcomes included the mean CRT average change (AUC approach); the change from baseline in CRT at all post-baseline timepoints; and the change from baseline in total leakage area at all post-baseline timepoints. CRT was assessed by OCT. Leakage area was assessed by fluorescein angiography. Patient reported outcomes were measured using the NEI VFQ 25 questionnaire. Throughout the course of the study, treatment exposure was recorded and all adverse events were monitored and reported, including seriousness, severity, action taken and relationship to study drug.
PLACID	The primary outcome was the percentage of patients who had at least a 10-letter improvement in BCVA from baseline at Month 12 in the intent-to-treat population of all randomised patients.	Secondary outcomes included the change in BCVA from baseline. BCVA was measured using the ETDRS method. Anatomical outcomes included the change from baseline in CRT at study end; and the change from baseline in total leakage area. CRT was assessed by OCT. Leakage area was assessed by fluorescein angiography. Throughout the course of the study, all adverse events were monitored and reported, including seriousness, severity, action taken and relationship to study drug.
NCT00035906	The primary outcome was proportion of eyes achieving at least a 10-letter improvement in BCVA at day 90.	Secondary outcomes included the proportion of eyes achieving a 15-letter improvement in BCVA. BCVA was measured using the ETDRS method. Anatomical outcomes included the change from baseline in CRT at post-baseline timepoints and proportion of eyes achieving at least a 2- or 3-grade improvement in leakage area. CRT was assessed by OCT. Leakage area was assessed by fluorescein angiography.

		Throughout the course of the study, all adverse events were monitored and reported, including seriousness, severity, action taken and relationship to study drug.
Abbreviations used in the table: AUC, area under the curve; BCVA, best corrected visual acuity; CRT, central retinal thickness; ETDRS, Early Treatment of Diabetic Retinopathy Study; DMO, diabetic macular oedema; OCT, ocular computed tomography; VA, visual acuity. Source: Boyer *et al*. 2014[51]; Callanan *et al.* 2013[58]; CSR 206207-010[54]; CSR 206207-011[55]; CSR 206207-012[57]; CSR 206207-024[56]; Gillies *et al.* 2010[61]; Gillies *et al.* 2014b[62]; Haller *et al*. 2010[60].		

In the MEAD and PLACID studies both patients and the study personnel who collected the safety and efficacy data were masked to the treatment assignment. In the MEAD studies each site had a masked treating investigator who administered the study treatment and performed post injection safety evaluations up to day 21 after each treatment. In NCT00035906 patients were only blinded to dexamethasone dose received, patients were otherwise aware of allocation to an intervention or observation group. However, the study personnel collecting and evaluating the efficacy data were masked to patient study group assignment and patients were informed not to discuss study treatment with the outcome assessors.

The OCT measurements of central retinal thickness and fluorescein angiograms were assessed at a central reading centre in each of the RCTs (MEAD, PLACID and NCT00035906) using standardized procedures and graders masked to study group assignment.

Safety parameters across the four trials were similar and included adverse events (AEs), IOP, biomicroscopic and ophthalmoscopic findings, and measures of diabetes control (HbA1c and glomerular filtration rate).

The ERG notes that BCVA both eyes was not specifically collected as an efficacy outcome for any of the RCTs and is not reported for any of the trials in the CS. In addition, contrast sensitivity was poorly reported in the CS with no numerical data presented. CRT data were not reported for PLACID and no numerical HRQL data were presented for PLACID. HRQL data were not collected in NCT00035906. However, the ERG considers that all remaining outcomes specified in the final scope issued by NICE for this STA were captured in the MEAD, PLACID and NCT00035906 trials and reported in the CS.

Subgroup analyses

The company reports in the CS that the pre-planned subgroup analyses in the MEAD trial programme included the following:

- Duration of DM;
- Duration of DMO;
- Baseline HbA1c;
- Prior laser treatment;

- Treatment-naïve patients;
- Lens status at baseline (pseudophakic versus phakic);
- Non-proliferative diabetic retinopathy (NPDR) severity at baseline;
- Country.

In addition, it is reported in the CS that post-hoc subgroup analyses in the MEAD trial programme were conducted and that these included analyses of the following:

- Lens status throughout the study;
- Cataract adverse event and extraction times;
- Baseline BCVA (≤55 letters and >55 letters);
- Baseline CRT (250-400µm and >400µm).

The company reported that the only pre-planned subgroup analyses in PLACID were related to BCVA category at baseline (≥34 to ≤49 letters and ≥50 to ≤70 letters) and in NCT00035906 pre-planned subgroup analyses based on cause of macular oedema were conducted.

In the CS, the company reports only numerical data for subgroup analyses for each trial based on treatment history in the study eye and lens status as these are considered of most relevance to the decision problem. The ERG is thus unable to comment on the results of any of the other subgroup analyses conducted in the four dexamethasone RCTs.

Follow-up

The follow-up of patients in the MEAD studies was planned to be between 36-39 months, in PLACID for 12-15 months and in NCT00035906 for 6 months.

Follow-up visits occurred every 3 months in the MEAD studies, with patients evaluated at each follow-up appointment for re-treatment but only receiving treatment if it was ≥6 months since the last treatment.

Follow-up in PLACID occurred at months 1, 4, 6, 9, 12 & 15 with patients evaluated for retreatment eligibility at the study visits at months 4, 6 and 9.

And finally, in NCT00035906 follow-up occurred at days 60, 90 and 180. All patients received only one treatment at baseline.

Clinical experts to the ERG report that as dexamethasone treatment is likely to be given for long term treatment of DMO, the trials with the longer duration of follow-up are most clinically useful, i.e. the

MEAD studies. However, the MEAD studies have a limited follow-up duration of 39 months and so longer term safety and efficacy data for dexamethasone in DMO are not available.

4.3 Description and critique of statistical approaches used in the RCTs

MEAD-010 and MEAD-011 were designed to evaluate the efficacy and safety of the dexamethasone intravitreal implant compared with sham for the treatment of DMO. NCT00035906 was designed to evaluate the efficacy and safety of dexamethasone compared with observation and PLACID was designed to evaluate the efficacy and safety of the combination therapy of dexamethasone and laser compared with laser alone.

The sample size calculation in the MEAD studies was based on the primary efficacy analysis of the BCVA average change from baseline in the study eye comparing dexamethasone and sham. The planned sample size was 170 patients per arm (510 patients total) to have a power of 80% (to detect a difference of 10% between the dexamethasone 700µg group and the sham group in the proportion of patients with ≥15-letter improvement in BCVA from baseline, assuming a 5% rate for sham and a 2-sided alpha level of 0.025. MEAD-010 achieved recruitment and randomisation of just under 170 patients per treatment arm (dexamethasone 700 µg: 163 patients and sham 165 patients) whereas MEAD-011 achieved just over 180 randomised patients per treatment arm (dexamethasone 700 µg: 188 patients and sham 185 patients).

The primary analysis of BCVA average change from baseline in the MEAD studies was performed using analysis of covariance (ANCOVA) with the treatment as a fixed effect and the baseline BCVA as a covariate. For patients with no post baseline BCVA assessment, the average change from baseline was 0.

Data from the MEAD studies were also pooled in an analysis presented in the CS with the rationale for this reported in a separate publication as, “because the studies were identical in design”. In addition, in response to a clarification question, the company provided the results for a meta-analysis of the MEAD studies. The pair-wise meta-analysis was conducted using data from the ITT populations of MEAD-010 and MEAD-011. A random effects model was used for all outcomes. For the continuous outcomes the mean difference between dexamethasone and sham treatment arm was calculated along with the between-group difference (p-value). For the dichotomous outcomes odds ratios were used as the summary statistic. The results of the meta-analysis are presented in Section 4.5.

In PLACID it was reported that the sample size was chosen based on an estimate that 30% and 14% of patients treated with dexamethasone plus laser photocoagulation and laser photocoagulation alone, respectively, would achieve at least a 10-letter improvement in BCVA from baseline at month 12. A

sample size of 105 patients in each treatment group was required for 80% power with 124 patients required in each treatment group to allow for the anticipated dropout rate of 15%. The study had 126 randomised patients in the dexamethasone + laser group and 127 in the laser group, and so it met its recruitment target.

In NCT00035906 it was estimated that a sample size of 255 patients (85 in each arm) was required to provide an 80% power to detect a 20% difference between the proportion of patients in the dexamethasone arm and the observation arm who achieved at least a 10-letter improvement in BCVA at day 90. This calculation was based on a 2-sided z test between 2 proportions, assuming a 10% outcome proportion in the observation group and a significance level of alpha equal to 0.025. In order to account for a dropout rate of 10%, a sample size of 285 patients (95 in each group) was planned for the study. NCT00035906 achieved randomisation of 105 patients in each group which is above the planned requirement for 95 patients per study group.

The ERG note that NCT00035906 was not conducted exclusively in people with DMO although the data presented in the CS is from the stratified subgroup of people with DMO in the study. The actual population of NCT00035906 was people with persistent macular oedema that had persisted for 90 days or more following laser or medical therapy. The underlying cause of the macular oedema could be diabetic retinopathy, central or branch retinal vein occlusion, uveitis, or Irvine-Gass syndrome. The patients in NCT00035906 were stratified at randomisation according to the underlying cause of macular oedema to balance any effect of underlying disease on treatment outcome. The ERG thus notes that the study size calculation for NCT00035906 was not powered to detect treatment effect differences for the DMO population.

The efficacy outcomes in the MEAD studies, PLACID and NCT00035906 were all evaluated in the intent-to-treat population defined as all randomised patients. Last-observation-carried-forward was used for imputation of missing values, except in the analyses of average change in BCVA and CRT from baseline (area under the curve [AUC] approach) and time-to-event data in the MEAD studies, which all used observed data. The analyses of efficacy parameters in PLACID were also performed for the modified ITT (mITT) population, defined as all randomized patients with diffuse macular capillary bed leakage at screening verified by the reading centre. Safety outcomes were evaluated in the safety population which was defined as patients who received at least one dose of randomised study treatment. Statistical analysis for all secondary outcomes was performed with a 2-sided alpha level of 0.05.

In general, the ERG considers the company's approach to the statistical analysis of the data in the dexamethasone RCTs to be appropriate. However, the ERG would like to highlight that the use of LOCF is only likely to be robust when patients have stable disease prior to discontinuing. This is

unlikely to be the case in the MEAD studies. The high discontinuation rate within the MEAD studies (x% dexamethasone vs x% sham) suggests that this is likely to have a substantial impact on the results. The ERG is unable to ascertain in which direction this bias might affect the results.

4.4 Summary statement

For this STA, six RCTs (MEAD-010, MEAD-011, PLACID, BEVORDEX, 024 and NCT00035906) were included in the clinical effectiveness section of the CS to provide clinical data on dexamethasone for the treatment of DMO. However, the ERG considers only four of the RCTs to be of direct relevance to the decision problem (MEAD-010, MEAD-011, PLACID and NCT00035906) because the remaining two studies used doses of dexamethasone that are not authorised for use in the UK. The ERG thus reports and critiques only the four RCTs deemed applicable to the decision problem in this report.

The ERG considers that the inclusion and exclusion criteria of the four RCTs were acceptable to address the each trial's objectives. In addition, the ERG notes that the baseline characteristics of the randomised populations of the trials appeared to be generally balanced between trial arms. Although no formal assessment was provided in the CS. However, the ERG and clinical experts have concerns regarding the applicability of the trials to the populations for which dexamethasone has EU marketing authorisation.

The interventions in the RCTs were dexamethasone 700µg intravitreal implant (MEAD studies and NCT00035906) or dexamethasone 700µg intravitreal implant plus laser photocoagulation (PLACID). The comparators varied across the trials. In the MEAD studies the comparator was sham, in PLACID it was laser alone and in NCT00035906 it was observation.

The ERG considers that the outcome data reported from RCTs appeared to be broadly consistent with the data collected in the trials. However, the ERG notes that BCVA both eyes requested in the NICE final scope was not reported in the CS for any of the trials.

In terms of follow-up and statistical data analysis, the ERG considers that the duration of follow-up in the RCTs was acceptable for the outcomes assessed. However, the ERG considers the high discontinuation rates in combination with the LOCF analysis has potentially introduced substantial bias into the results In addition, the ERG notes that treatment with dexamethasone may extend beyond 39 months in clinical practice and longer term safety and efficacy data for dexamethasone in DMO are not currently available although they would have been preferable.

4.5 Summary of results of RCTs

4.5.1 Treatment compliance and discontinuations

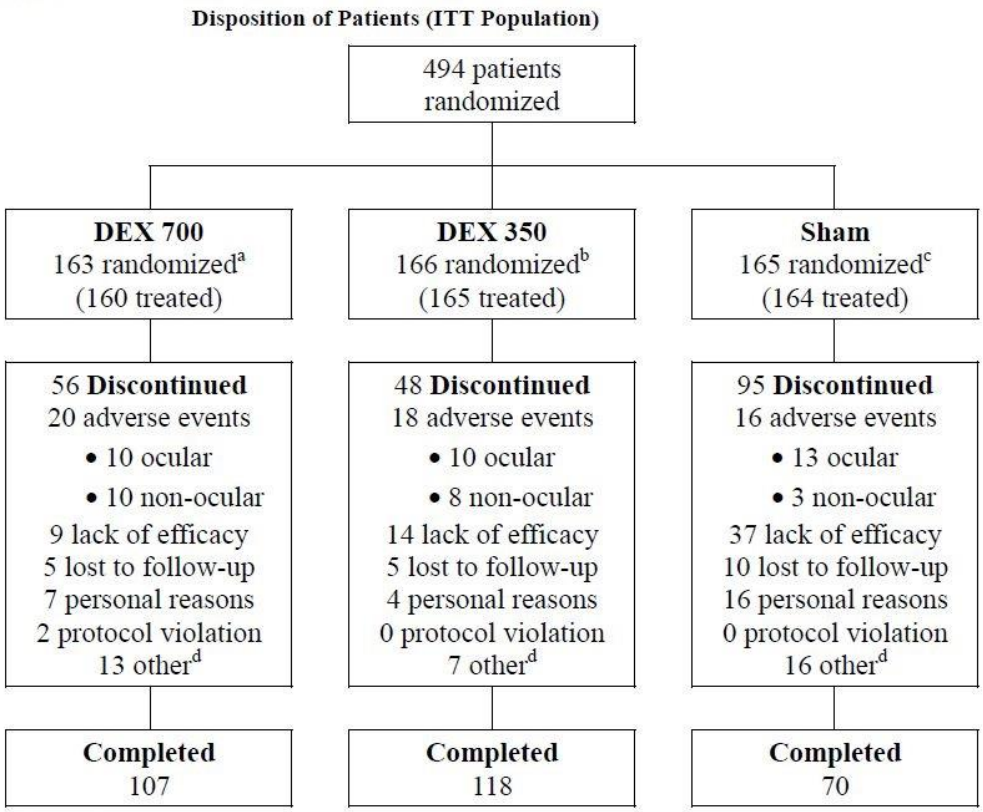
MEAD-010

There were 494 patients randomised to the three study arms of MEAD-010 resulting in an ITT population of 163 patients in the dexamethasone 700 µg group and 165 patients in the sham treatment group. In terms of the safety population, there were 160 patients in the dexamethasone 700 µg group and 164 patients in the sham group. The difference between the ITT and safety populations was thus small (3 patients in the dexamethasone arm and 1 patient in the sham arm) and as discussed in Section 4.3 was a result of patients whom did not receive any study medication being excluded from the safety analyses.

A total of 56 patients in the dexamethasone 700 µg group and 95 patients in the sham treatment group discontinued from the study. The ERG notes that the discontinuation rate is high in both groups and due to the LOCF analysis could potentially confound the results. In addition, the discontinuation rate is nearly twice as high in the sham group compared with the dexamethasone group. The main reason for discontinuation in the dexamethasone 700 µg group was adverse events (20 patients), with 10 being ocular and 10 being non-ocular. The main reason for discontinuation in the sham treatment group was lack of efficacy (37 patients). The ERG notes that there more discontinuations due to loss to follow-up (10 vs. 5) and personal reasons (16 vs. 7) in the sham group compared with the dexamethasone group. The company does not provide any justification for this imbalance in the CS.

The CONSORT diagram showing full details of the flow of patients during the MEAD-010 study is presented in Figure 3.

Figure 3: MEAD-010 CONSORT flow chart (reproduced from CS Figure 9, pg 144)



ITT = intent-to-treat

[a] Three patients (4368-4784, 4449-4268, and 8093-4766) were randomized to DEX 700 but never received treatment.

[b] One patient (4451-4278) was randomized to DEX 350 but never received treatment.

[c] One patient (4431-4098) was randomized to Sham but never received treatment.

[d] "Other" reasons for patient discontinuation included site closure, patient withdrawal of consent, poor compliance from patient, sponsor request, patient participation in other trial, etc

Source: CSR 206207-010[(54)]

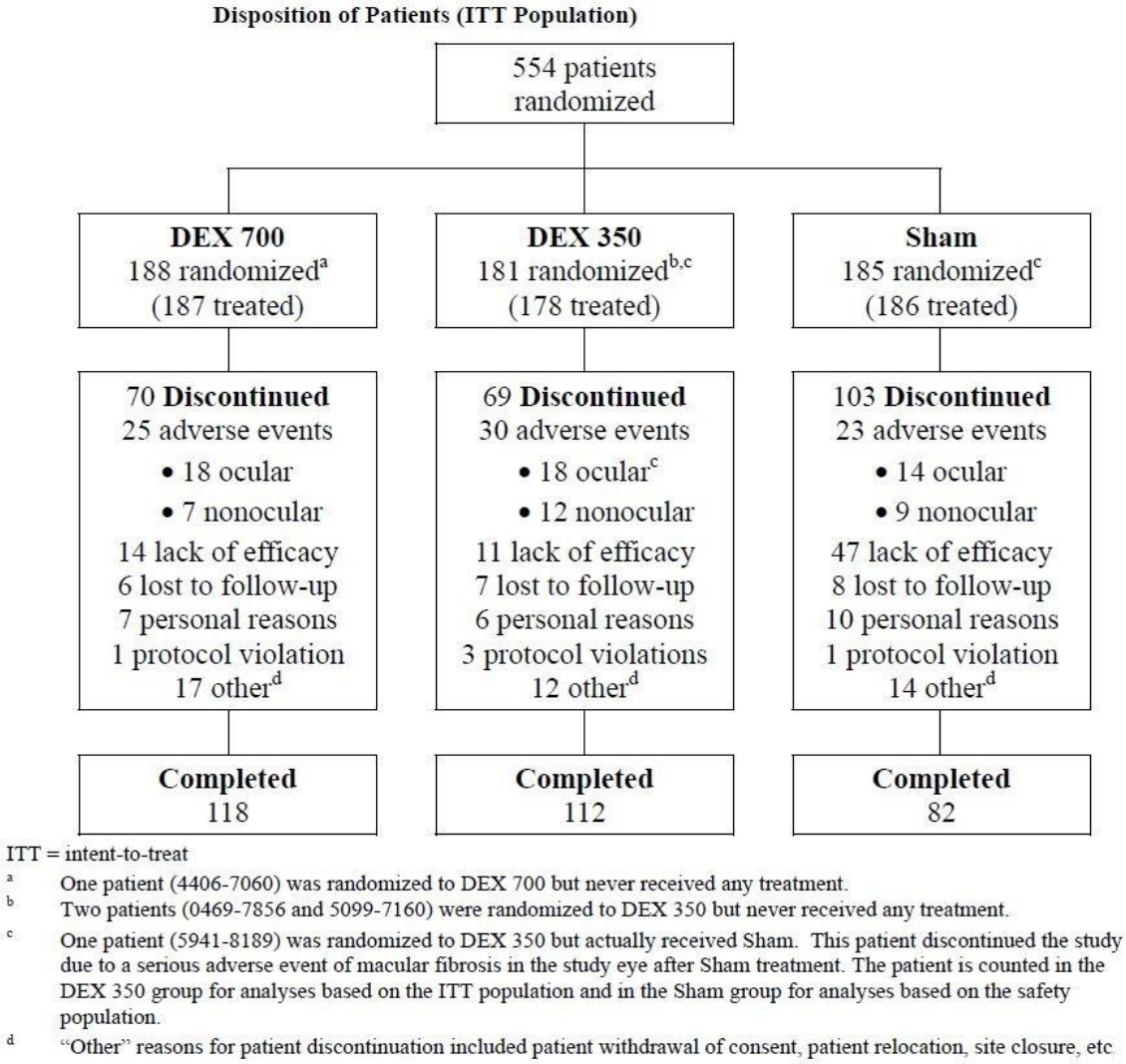
MEAD-011

There were 554 patients randomised in MEAD-011 resulting in an ITT population of 188 patients in the dexamethasone 700 µg group and 185 patients in the sham treatment group. In terms of the safety population, there were 187 patients in the dexamethasone 700 µg group and 186 patients in the sham group. The difference between the ITT and safety populations was 1 less patient in the dexamethasone arm (patient who received no study medication) and 1 additional patient in the sham arm)patient randomised to another treatment but actually received sham).

The reasons and treatment group allocation of patients discontinuing from MEAD-011 were similar to those in MEAD-010, i.e. more patients discontinued in the dexamethasone 700 µg group (70 patients) compared with the sham treatment group (103 patients). The main reason for discontinuation in the dexamethasone 700 µg group in MEAD-011 was adverse events (25 patients), with 18 being ocular and 7 being non-ocular. The main reason for discontinuation in the sham treatment group was lack of efficacy (47 patients). The ERG notes that the discontinuation rate is high in both groups and due to the LOCF analysis could potentially confound the results.

Full details on the flow of patients through the MEAD-011 study are presented in the CONSORT flow diagram, Figure 4.

Figure 4: MEAD-011 CONSORT flow chart (reproduced from CS Figure 10, pg 145)



Source: CSR 206207-011[55]

Treatment exposure in the MEAD studies

The company reported that the mean number of dexamethasone 700 µg treatments per patient in the safety population was 4.1 in the MEAD pooled analysis with <10% of patients receiving therapy every 6 months (Table 17). In terms of the timing of re-treatments over the 3-year study period, it was reported in the CS that approximately 80% of study retreatment's were administered between 5 to 7 months after the previous treatment: 39.9% were between 5 and 6 months, 41.7% were between 6 and 7 months, and 18.0% were after 7 months. The company reported that a treatment exposure-adjusted analysis demonstrated a mean injection rate over the 3-year study period of 5.1, and an injection rate of 1.7 per patient-year. The ERG notes that 40% of the re-treatments in the MEAD studies were given more frequently than the 6-month minimum re-treatment period specified in the EU marketing

authorisation for dexamethasone use in DMO. However, the ERG is unsure what proportion of the total population in the MEAD studies received non-EU-approved regimens of dexamethasone though and so is unable to determine the impact of this on the overall results of the MEAD studies.

Table 17: DEX700 treatment exposure across the MEAD trial programme (reproduced from CS, Table 41, pg 240)

	MEAD-010 (n=160)	**MEAD-011 (n=187)**	**MEAD pooled (n=347)**
Mean number of treatments	4.2	4.1	4.1
Total number of treatments, %			
1	12.5	12.8	12.7
2	16.9	14.4	15.6
3	10.6	11.8	11.2
4	9.4	14.4	12.1
5	13.8	14.4	14.1
6	27.5	23.5	25.4
7	9.4	8.6	8.9
Source: Boyer *et al*. 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]			

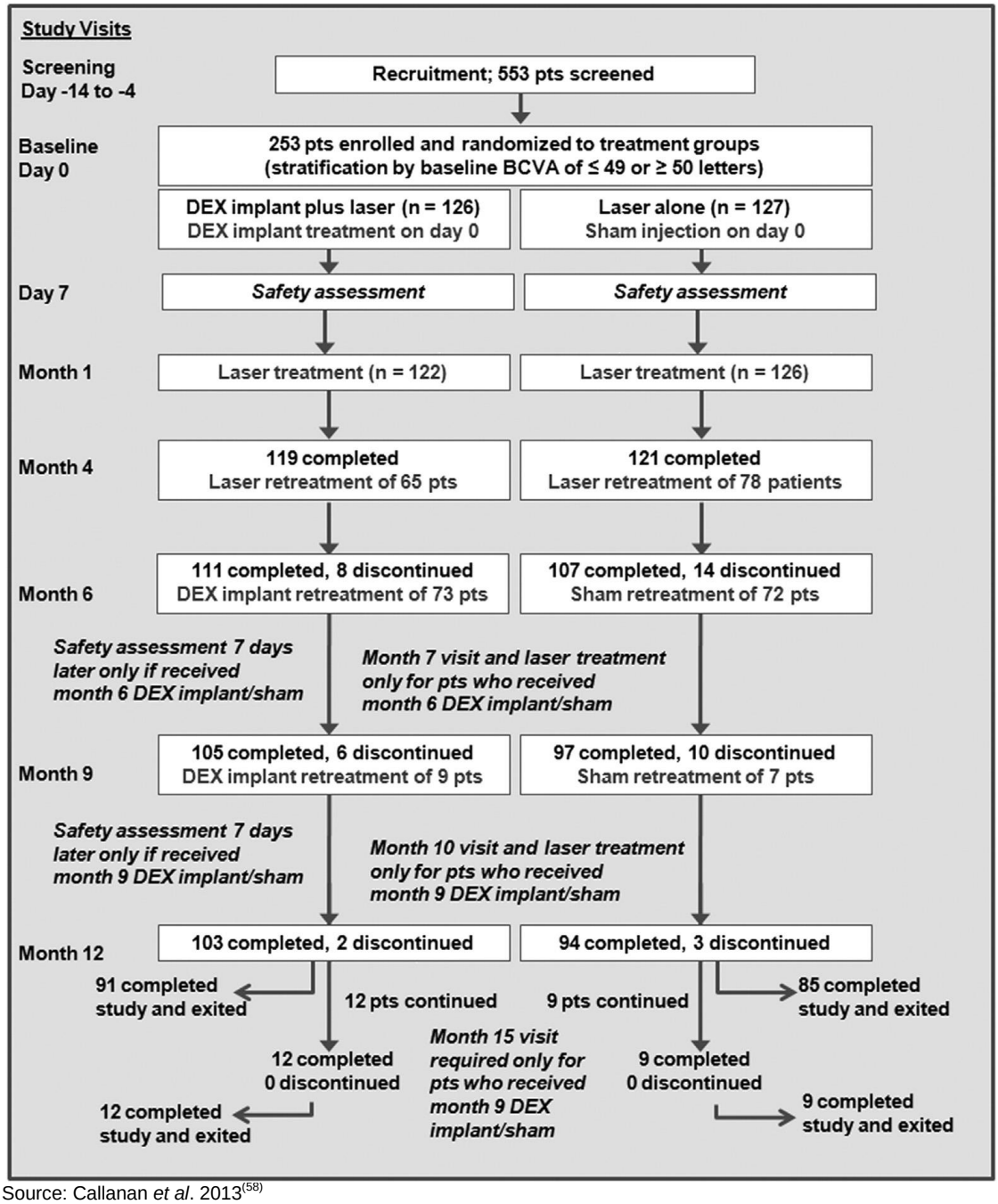
The company reported that the treatment exposure was similar for the subgroup of pseudophakic patients in the MEAD studies as for the full study population: the mean number of dexamethasone treatments per patient was 3.7 across the MEAD studies and the exposure-adjusted injection rate was 1.7 per patient-year.

PLACID

There were 253 patients enrolled and randomised in PLACID; 126 to dexamethasone 700 µg + laser and 127 to laser alone. Full details on the flow of patients through the study are presented in the CONSORT flow diagram, Figure 5.

Of the 126 patients in PLACID who were randomised to dexamethasone + laser, 73 patients (57.9%) received retreatment with dexamethasone at Month 6 and a further nine patients (7.1%) received retreatment at Month 9. In terms of the 35 pseudophakic patients randomised to dexamethasone + laser, 21 (60.0%) received retreatment with dexamethasone at either Month 6 or Month 9.

Figure 5: PLACID CONSORT flow chart (reproduced from CS Figure 12, pg 147)

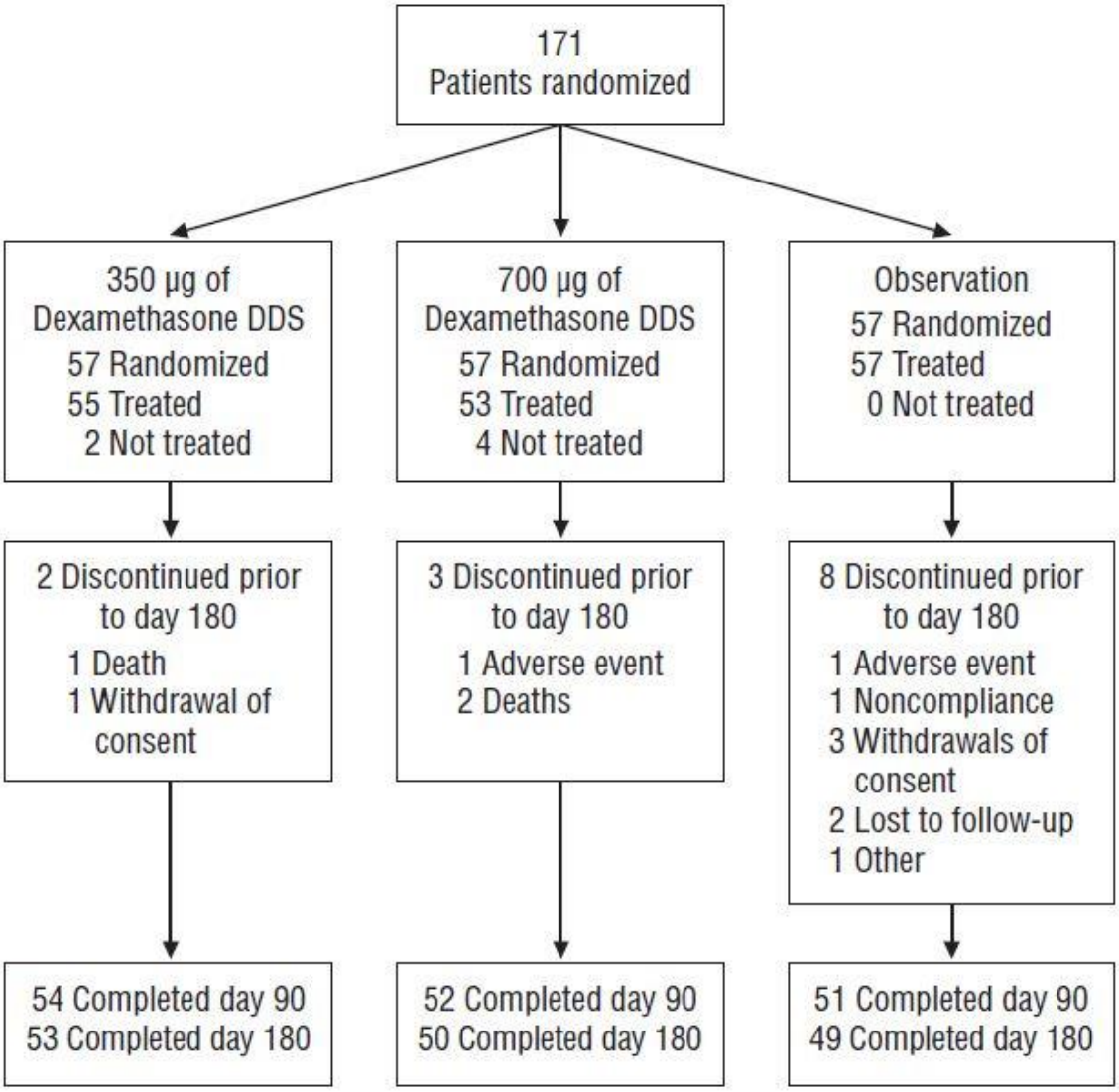


Source: Callanan *et al*. 2013[58]

NCT00035906

There were 171 patients with DMO randomised in NCT00035906; 57 to the dexamethasone 700µg group and 57 to the observation group (ITT population). For full details on the flow of patients during the study see Figure 6. In terms of treatment exposure, 53 patients in the dexamethasone group received the one dose of dexamethasone as planned in NCT00035906. There was no intervention provided in the observation group thus all 57 patients received the 'observation' intervention. The safety analyses for NCT00035906 thus comprised of 53 patients in the dexamethasone group and 57 patients in the observation group.

Figure 6: NCT00035906 CONSORT flow chart (reproduced from CS Figure 14, pg 149)



Source: Haller *et al*. 2010[60]

4.5.2 Treatment effectiveness results

It should be noted that the results presented in this section are for the whole trial populations in each of the dexamethasone RCTs and thus as discussed in Section 3 are not specific to any of the populations specified in the EU marketing authorisation for dexamethasone. The ERG thus considers it important that the whole trial population data in the following sections is interpreted with caution in relation to the decision problem; data from relevant subgroups of the RCTs are discussed in Sections 4.5.4 and 4.5.5.

MEAD studies

For the primary efficacy outcome of mean BCVA average change (AUC approach), dexamethasone resulted in a statistically significant increase in mean BCVA average change from baseline in MEAD-010 and the pooled MEAD analysis compared with sham. In MEAD-011 there was a trend favouring

dexamethasone over sham although the difference failed to reach statistical significance (Table 18). The company reported that this was fully investigated and accounted for in a post-hoc analysis of MEAD-011 and was a result of severe vision loss attributed to cataract (see Section 4.5.4 for further details). Clinical experts to the ERG suggest that whilst the mean BCVA change is statistically significant in the MEAD pooled analysis, it does not necessarily reflect a clinically significant difference. This is because the difference between the mean BCVA improvement in the dexamethasone group compared to the improvement in the sham group is less than one line on an ETDRS chart.

Table 18: Mean BCVA average change (AUC approach) from baseline in the MEAD trial programme, ETDRS letters (SD) (adapted from CS, Table 20, pg 155)

	DEX700	Sham	DEX700 vs. Sham p-value
MEAD-010	4.1 (8.3)	1.9 (7.7)	0.016
MEAD-011	2.9 (8.6)	2.0 (8.2)	0.366
MEAD Pooled	3.5 (8.4)	2.0 (8.0)	0.023

Abbreviations used in the table: AUC, area under the curve; BCVA, best corrected visual acuity; DEX700, dexamethasone 700µg; ETDRS, Early Treatment of Diabetic Retinopathy Study; SD, standard deviation.
Source: Boyer *et al.* 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]

Dexamethasone resulted in a statistically significant increase in the number of patients achieving both a ≥15 letter gain and a ≥10 letter gain from baseline compared to sham in each of the MEAD studies and the pooled analysis (Table 19). The ERG notes that this was the original primary efficacy outcome in the MEAD studies.

Table 19: Patients achieving a BCVA improvement of ≥15 letters or ≥10 letters from baseline at study end in the MEAD trial programme, n (%) (reproduced from CS Tables 21 and 22)

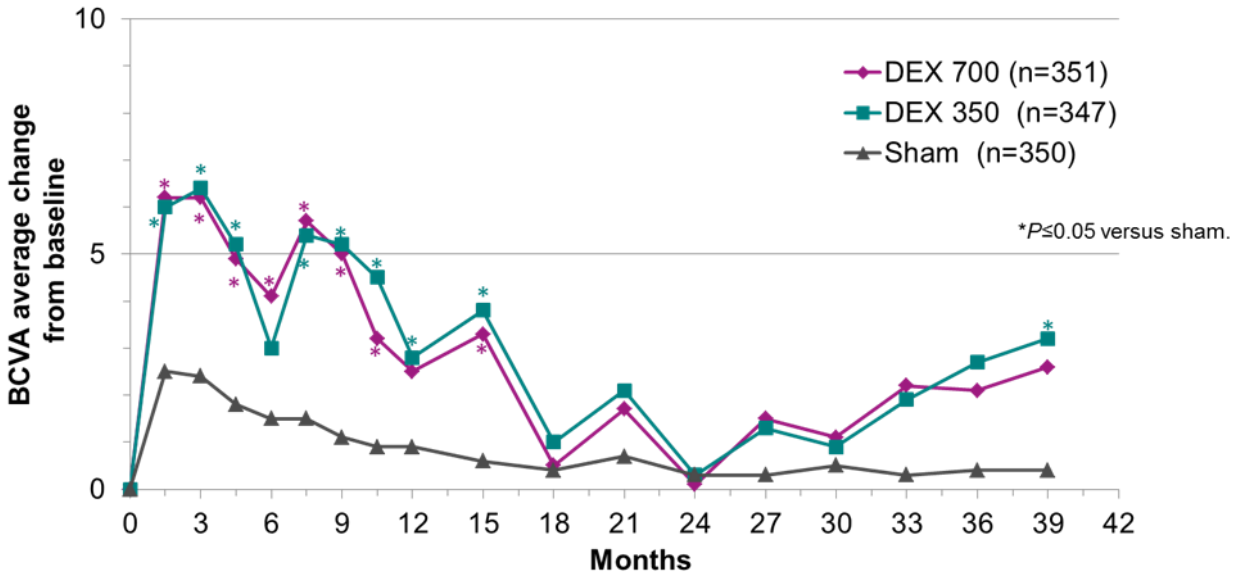
	DEX700	Sham	DEX700 vs. Sham p-value
Number of patients achieving a ≥15 letter gain from baseline			
MEAD-010	36 (22.1)	22 (13.3)	0.038
MEAD-011	42 (22.3)	20 (10.8)	0.003
MEAD Pooled	78 (22.2)	42 (12.0)	<0.001
Number of patients achieving a ≥10 letter gain from baseline			
MEAD-010	63 (38.7)	38 (23.0)	0.002
MEAD-011	65 (34.6)	46 (24.9)	0.040
MEAD Pooled	128 (36.5)	84 (24.0)	<0.001

Abbreviations used in the table: BCVA, best corrected visual acuity; DEX700, dexamethasone 700µg; ETDRS, Early Treatment of Diabetic Retinopathy Study; SD, standard deviation.
Source: Boyer *et al*. 2014[67], CSR 206207-010[121]; CSR 206207-011[123]; Summary of Clinical Efficacy[152]

Pooled analysis of the MEAD studies for mean change in BCVA from baseline at each study visit suggested a significantly greater improvement in BCVA with dexamethasone 700µg compared with

sham at most time points during the first 15 months of treatment. However, from month 15 onwards the improvement in BCVA provided by dexamethasone 700µg relative to sham was reduced and didn't recover until after 36 months (Figure 7). In Boyer *et al*. it is reported that this trend correlated with cataract adverse effects during the second year of the study in the dexamethasone group, which impaired their vision thus reducing the treatment effect of dexamethasone in terms of the vision related outcomes.[51] In addition, the company reported in the CS that the majority of cataract AEs occurred between months 12 and 24 of the MEAD studies. The ERG notes that the cumulative endpoint of mean BCVA average change (AUC approach) is impacted by the progression of lens opacification and primary cataract formation whereas the key secondary endpoint of patients with ≥15 letter gain from baseline at study end may be less impacted by cataract AEs if they are treated prior to study end; i.e. if the patients experiencing visual impairment as a result of cataract have undergone cataract surgery by 36 months then the potentially confounding effect of the cataract on the BCVA would no longer be present.

Figure 7: Mean BCVA change from baseline in the MEAD trial programme, ETDRS letters – pooled analysis (reproduced from CS, Figure 16, pg 157)



Key: BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study.
Source: Boyer *et al*. 2014[51]

The company reported that there were no significant changes in contrast sensitivity from baseline to study end for any treatment groups across the MEAD studies. No numerical data were presented in the CS to support this statement and so the ERG is unable to comment further on the effect of dexamethasone on contrast sensitivity.

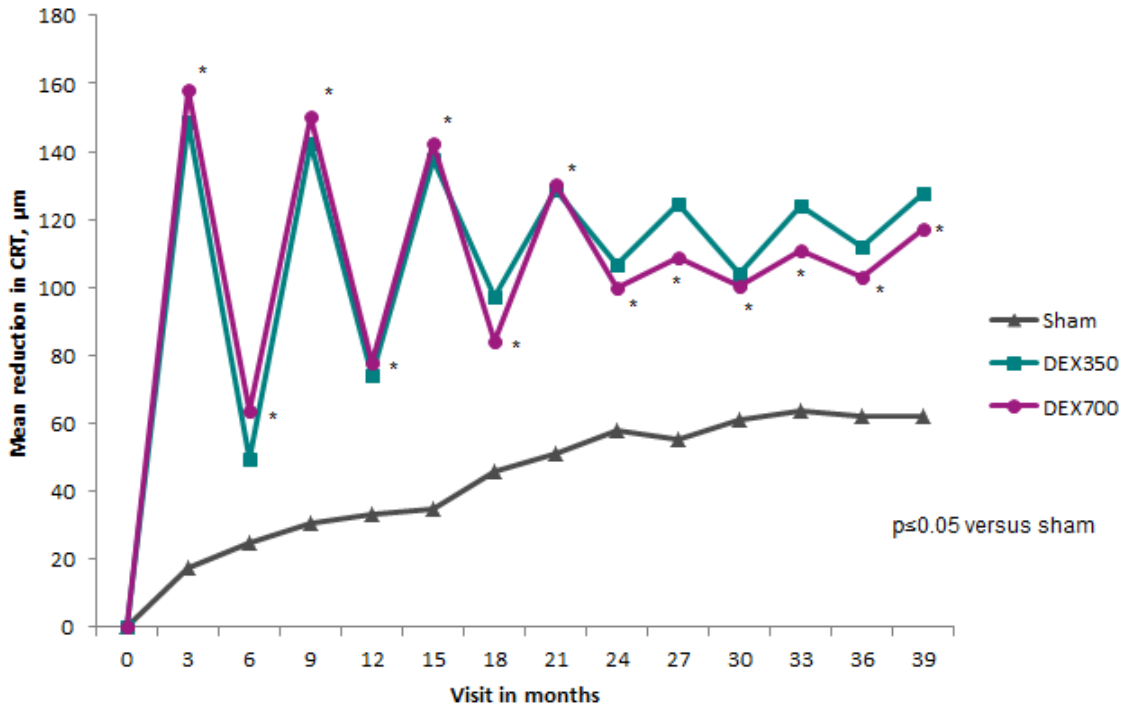
Dexamethasone resulted in a statistically significant greater reduction in mean CRT average change (AUC approach) compared with sham in MEAD-010, MEAD-011 and the MEAD pooled analysis

(Table 20). In addition the company reported that dexamethasone 700ug resulted in statistically significant superiority over sham for mean CRT change from baseline at each time point in MEAD-010, MEAD-011 and pooled MEAD analysis and at the study end points. However, data for only the pooled analysis were presented in the CS for this outcome (Figure 8).

Table 20: Mean CRT average change (AUC approach) from baseline in the MEAD trial programme, µm (SD) (adapted from CS, Table 25, pg 164)

	DEX700	Sham	DEX700 vs. Sham p-value
MEAD-010	-101.1 (119.2)	-37.8 (104.0)	<0.001
MEAD-011	-120.7 (145.6)	-45.8 (126.4)	<0.001
MEAD Pooled	-111.6 (134.1)	-41.9 (116.0)	<0.001
Abbreviations used in the table: AUC, area under the curve; CRT, central retinal thickness; DEX700, dexamethasone 700µg; SD, standard deviation. Source: Boyer et al. 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]			

Figure 8: Mean reduction in CRT from baseline in the MEAD trial programme, µm – pooled analysis (reproduced from CS Figure 20, pg 165)



Key: CRT, central retinal thickness; DEX, dexamethasone.
Source: Summary of Clinical Efficacy[84]

The National Eye Institute VFQ-25 tool (NEI-VFQ-25) which is a shortened version of the 51-item NEI VFQ field test version was used to assess HRQL in the MEAD studies. The NEI-VFQ-25 consists of 25 vision-targeted questions with the lowest and highest possible scores set at 0 and 100 points, respectively. In the CS it is reported that, "in the MEAD studies, treatment groups were

compared for the NEI-VFQ-25 composite score, as well as scores from 4 subscales selected for their close association with central visual acuity: general vision, difficulty with near vision activities, difficulty with distance vision activities, and mental health symptoms due to vision". The results of these analyses for the outcomes of mean average NEI-VFQ-25 change (AUC approach) and NEI-VFQ-25 change of minimal clinically important difference (MCID) at 36 months, where the MCID is defined as ≥10 point improvement, suggested no significant difference between dexamethasone and sham (Table 21).

Table 21: NEI-VFQ-25 change from baseline during the MEAD study period, pooled analysis (adapted from CS Table 26, pg 168)

	DEX700 (n=351)	**Sham (n=350)**	**DEX700 vs Sham p-value**
Mean average change (AUC approach) from baseline during the MEAD study period, NEI-VFQ-25 score			
Overall composite score	[redacted]	[redacted]	[redacted]
General vision	[redacted]	[redacted]	[redacted]
Difficulty with near vision	[redacted]	[redacted]	[redacted]
Difficulty with distance vision	[redacted]	[redacted]	[redacted]
Mental health symptoms due to vision	[redacted]	[redacted]	[redacted]
Patients with at least a10-point improvement in NEI-VFQ-25 score from baseline at month 36, n/N (%)			
Overall composite score	[redacted]	[redacted]	[redacted]
General vision	[redacted]	[redacted]	[redacted]
Difficulty with near vision	[redacted]	[redacted]	[redacted]
Difficulty with distance vision	[redacted]	[redacted]	[redacted]
Mental health symptoms due to vision	[redacted]	[redacted]	[redacted]
Abbreviations used in the table: AUC, area under the curve; NEI-VFQ-25, National Eye Institute-Visual Functioning Questionnaire; DEX700, dexamethasone 700µg. Source: [redacted]			

In the CS the company suggests that the HRQL data for the dexamethasone patients is being negatively impacted by progression of lens opacification and primary cataract formation.

In addition, the company provides data from a *post-hoc* analysis of the pooled MEAD data demonstrating that during the period between the development of a cataract and cataract surgery patients experienced minimal improvement in vision-related quality of life (QoL) with dexamethasone. However, after cataract surgery the vision-related QoL associated with dexamethasone use improved and was similar to the improvement reported by pseudophakic patients ([redacted]). The ERG considers it important to highlight that this additional QoL data is from a *post hoc* analysis and is for near-vision rather than for the overall composite NEI-VFQ-25 score; it should thus be interpreted with caution.

[redacted]

This figure has been redacted

Key: AUC, area under the curve; BCVA, best correct visual acuity; DEX, dexamethasone; VFQ-25, Visual Functioning Questionnaire-25.
Source: [redacted]

The company also reported in the CS that the patients that experienced at least a 10-letter improvement or at least a 15-letter improvement in BCVA demonstrated significant improvements in NEI-VFQ-25 near vision activity and distance vision activity subscales across multiple time-points for both the whole population and the pseudophakic population (numerical data reported in the CS).

In terms of mortality, the company reported in the CS that there were 9 deaths in the dexamethasone 700µg group and 5 in the sham treatment group across the two MEAD studies. It was also reported by the company that none of the deaths were due to ocular adverse events or considered by investigators to be related to treatment assignment. The ERG is thus unsure as to why there was an imbalance in deaths between the treatment groups.

Pair-wise meta-analysis results for the MEAD studies

In response to a clarification question the company conducted a pair-wise meta-analysis of MEAD-010 and MEAD-011 for the outcomes reported in the CS for the individual studies and presented the results of this meta-analysis compared with the pooled results for the MEAD studies (Table 22). The ERG considers the results of both the pooled analysis and pair-wise meta-analysis to be in keeping with each other.

Table 22: DEX700 vs. sham treatment comparisons from pooled and pair-wise meta-analysis of MEAD-010 and MEAD-011 (Company's response to clarification, Table 1, pg 3)

	Pooled results		**Pair-wise meta-analysis results**	
Continuous outcomes				
	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 baseline at study end	-54.2 (-81.1, -27.3)	<0.001	-56.08 (-84.88, -27.27)	<0.001
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
Dichotomous outcomes				
	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
Abbreviations used in the table: AUC, area under the curve; BCVA, best-corrected visual acuity; CI, confidence interval; CRT, central retinal thickness; DEX700, dexamethasone 700µg; NEI-VFQ-25, National Eye Institute-visual function questionnaire-25.				

PLACID

The analysis of the primary efficacy outcome, proportion of patients achieving at least a 10-letter improvement in visual acuity at study end in PLACID demonstrated no significant difference between dexamethasone + laser versus laser alone (Table 23). However, the ERG notes that treatment with dexamethasone + laser did result in a statistically significant improvement at months 1, 4, 7 and 9 compared with laser alone.

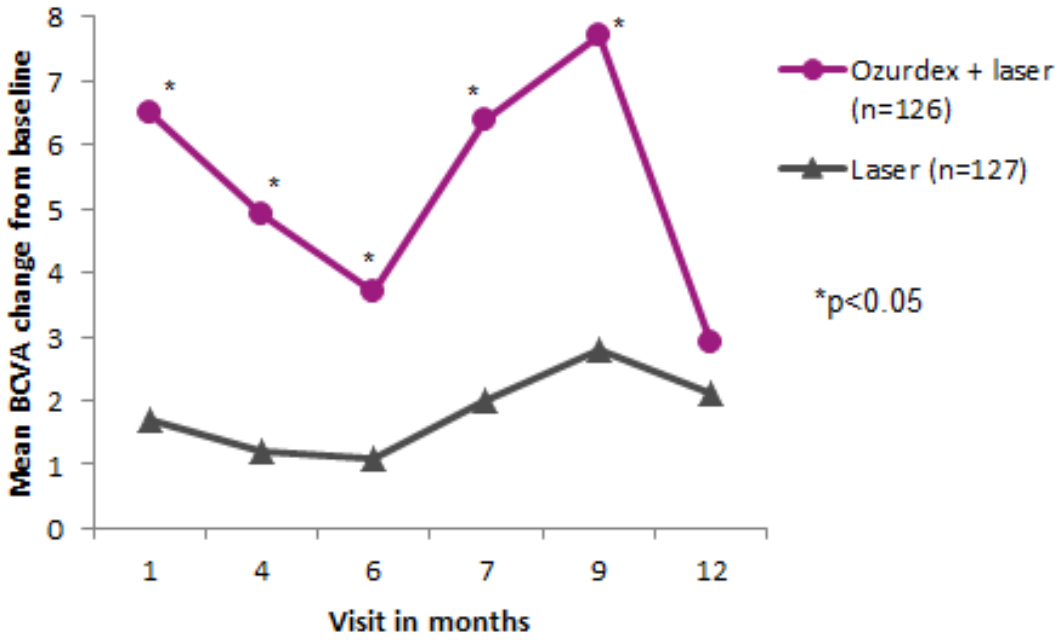
Table 23: Patients achieving a BCVA improvement of at least 10 letters from baseline at all time points in PLACID, n (%) (reproduced from CS, Table 31, pg 177)

	DEX700 + laser (n=126)	**Laser (n=127)**	**p-value**

Month 1	40 (31.7)	14 (11.0)	<0.001
Month 4	33 (26.2)	21 (16.5)	0.060
Month 6	28 (22.2)	22 (17.3)	0.326
Month 7 (1 month post retreatment)	28 (38.4)	14 (19.4)	0.014
Month 9	40 (31.7)	22 (17.3)	0.007
Month 12	35 (27.8)	30 (23.6)	0.453
Abbreviations used in the table: BCVA, best correct visual acuity; DEX, dexamethasone. Source: Callanan et al. 2013[58]			

The analysis of mean BCVA change from baseline analysis also demonstrated no significant difference at month 12 between dexamethasone + laser compared with laser alone (Figure 10). The ERG notes that at earlier time points the combination therapy demonstrated a statistically significant benefit over laser alone. In addition, the company reported that AUC analysis of the effect of treatment on the change from baseline BCVA over time demonstrated greater improvement in BCVA with dexamethasone + laser compared with laser alone over a 0 to 6 month period and 0 to 12 months (p<0.001; no further numerical data reported in the CS). Clinical experts to the ERG suggest that whilst the mean BCVA change is statistically significant up to 9 months, it does not necessarily reflect a clinically significant difference in BCVA.

Figure 10: Mean BCVA change from baseline in PLACID, ETDRS letters (reproduced from CS Figure 25, pg 178)



Key: BCVA, best correct visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study.
Source: Callanan et al. 2013[58]

The company reported in the CS that statistically significant differences were demonstrated in favour of dexamethasone + laser compared with laser alone after 1-4 months of initial treatment and retreatment for mean CRT. However, no numerical data were presented in the CS.

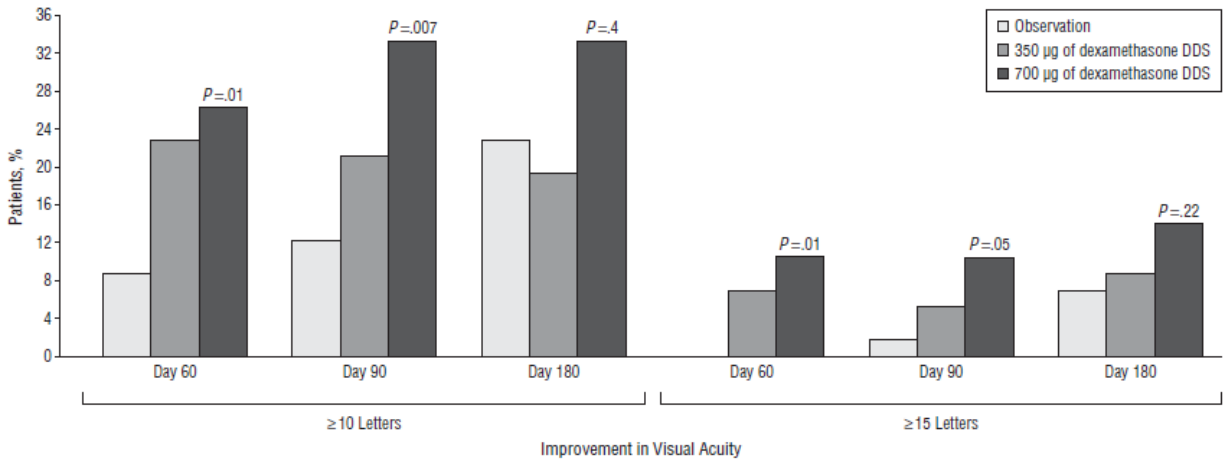
HRQL and visual-functioning were assessed in PLACID using the NEI-VFQ-25. It was reported in the CS that there was no significant difference between dexamethasone + laser compared with laser alone for HRQL. However, the company reported that the mean scores on several subscales for patients treated with dexamethasone + laser, increased during follow-up, reflecting improved vision-related quality of life. No numerical data were presented in the CS for HRQL in PLACID and so the ERG is unable to comment further on this outcome.

There were 6 deaths in total during PLACID with 2 of these in the dexamethasone + laser treatment group and 4 in the laser monotherapy group. The company reported that none of the deaths were due to ocular adverse events or considered by investigators to be related to treatment assignment.

NCT00035906

For the analysis of the primary efficacy outcome in NCT00035906: proportion of DMO patients achieving at least a 10-letter improvement in visual acuity, there was no significant difference between dexamethasone and observation at day 180 (Figure 11). However, dexamethasone was associated with a statistically significant improvement at days 60 and 90 compared with observation. This pattern of effect was also seen in the number of patients achieving at least a 15-letter improvement in visual acuity (Figure 11).

Figure 11: DMO patients achieving a BCVA improvement of at least 10 letters from baseline at all time points in NCT0035906, n (%) (reproduced from CS, Figure 27, pg 180)



Key: BCVA, best corrected visual acuity
Source: Haller et al. 2010[60]

It was reported in the CS that at Day 90, there was a mean decrease from baseline CRT of 132.3µm with dexamethasone (n=11) and an increase of 30.2µm in the observation group (n=19). This difference was based on observed data and was statistically significant, favouring treatment with dexamethasone (p<0.001). Day 180 data for this outcome was not reported in the publication cited by the company or in the CS.

There were two deaths in the dexamethasone 700µg group of the DMO subgroup of patients enrolled in trial NCT00035906 and no deaths in the sham arm. There were no details reported in the CS on the cause of these deaths and so it is unclear if they could be related to treatment exposure.

4.5.3 Safety and adverse events

MEAD studies

The company reported that dexamethasone was well tolerated in the MEAD studies with low discontinuation rates due to adverse events (AEs), low treatment-related serious AE (TRSAE) rates and no deaths deemed attributable to treatment (Table X). The company also reported that both discontinuations and adverse event rates were positively correlated with increased treatment exposure and that the overall incidence of AEs adjusted for treatment exposure time was similar among treatment groups although numerical data to support this were not presented in the CS.

There were more treatment-related adverse events (TRAEs) in patients treated with dexamethasone compared with sham in each of the MEAD studies and these TRAEs were mainly ocular in both treatment groups (Table 24). The ocular TRAEs that occurred in >2% of patients in either treatment group in the MEAD studies are presented in Table X.

Table 24: Safety profile across the MEAD trial programme, n (%) (adapted from CS Table 42, pg 242)

	MEAD-010		**MEAD-011**		**MEAD Pooled**	
	DEX700 (n=160)	**Sham (n=164)**	**DEX700 (n=187)**	**Sham (n=186)**	**DEX700 (n=347)**	**Sham (n=350)**

	MEAD-010		MEAD-011		MEAD Pooled	
	DEX700 (n=160)	**Sham (n=164)**	**DEX700 (n=187)**	**Sham (n=186)**	**DEX700 (n=347)**	**Sham (n=350)**
All adverse events	153 (95.6)	124 (75.6)	180 (96.3)	157 (84.4)	333 (96.0)	281 (80.3)
Ocular	142 (88.8)	97 (59.1)	172 (92.0)	131 (70.4)	314 (90.5)	228 (65.1)
Study eye	139 (86.9)	85 (51.8)	157 (84.0)	118 (63.4)	296 (85.3)	203 (58.0)
Non-study eye	82 (51.3)	66 (40.2)	116 (62.0)	91 (48.9)	198 (57.1)	157 (44.9)
Non-ocular	106 (66.3)	90 (54.9)	135 (72.2)	117 (62.9)	241 (69.5)	207 (59.1)
Treatment related AE	115 (71.9)	31 (18.9)	129 (69.0)	59 (31.7)	244 (70.3)	90 (25.7)
Ocular	115 (71.9)	30 (18.3)	129 (69.0)	59 (31.7)	244 (70.3)	89 (25.4)
Study eye	115 (71.9)	30 (18.3)	129 (69.0)	59 (31.7)	244 (70.3)	89 (25.4)
Applicator	46 (28.8)	18 (11.0)	60 (32.1)	34 (18.3)	106 (30.5)	52 (14.9)
Treatment	102 (63.8)	13 (7.9)	110 (58.8)	30 (16.1)	212 (61.1)	43 (12.3)
Non-study eye	0	0	0	0	0	0
Non-ocular	2 (1.3)	1 (0.6)	1 (0.5)	0	3 (0.9)	1 (0.3)
Serious AE	52 (32.5)	34 (20.7)	63 (33.7)	49 (26.3)	115 (33.1)	83 (23.7)
Ocular	11 (6.9)	5 (3.0)	22 (11.8)	11 (5.9)	33 (9.5)	16 (4.6)
Study eye	9 (5.6)	2 (1.2)	15 (8.0)	2 (1.1)	24 (6.9)	4 (1.1)
Non-study eye	3 (1.9)	3 (1.8)	12 (6.4)	9 (4.8)	15 (4.3)	12 (3.4)
Non-ocular	45 (28.1)	30 (18.3)	49 (26.2)	40 (21.5)	94 (27.1)	70 (20.0)
Treatment related SAE	4 (2.5)	1 (0.6)	12 (6.4)	0	16 (4.6)	1 (0.3)
Discontinuations due to AE	20 (12.5)	16 (9.8)	25 (13.4)	24 (12.9)	45 (13.0)	40 (11.4)
Deaths related to treatment	0	0	0	0	0	0

Abbreviations used in the table: AE, adverse event; DEX700, dexamethasone 700µg; SAE, serious adverse event.
Source: Boyer *et al.* 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]; Data on file – Summary of Safety[86]

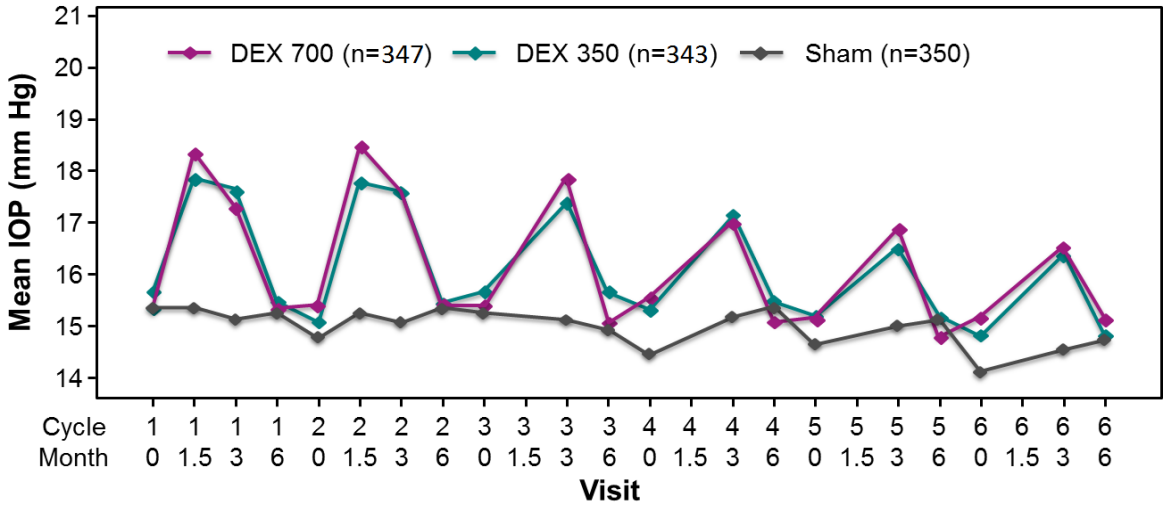
The most common ocular TRAEs with dexamethasone were cataract formation and raised IOP, and the most common ocular TRAE with sham was conjunctival haemorrhage (Table 25).

Table 25: Treatment-related ocular adverse events in the study eye that occurred in >2% of patients in any treatment group across the MEAD trial programme (adapted from CS Table 43, pg246)

	MEAD-010		MEAD-011		MEAD Pooled	
	DEX700 (n=160)	**Sham (n=164)**	**DEX700 (n=187)**	**Sham (n=186)**	**DEX700 (n=347)**	**Sham (n=350)**
IOP elevation	56 (35.0)	3 (1.8)	40 (21.4)	5 (2.7)	106 (30.5)	8 (2.3)
Cataract	44 (27.5)	7 (4.3)	57 (30.5)	14 (7.5)	101 (29.1)	21 (6.0)
Conjunctival haemorrhage	29 (18.1)	15 (9.1)	28 (15.0)	19 (10.2)	57 (16.4)	34 (9.7)
Cataract sub capsular	18 (11.3)	6 (3.7)	16 (8.6)	5 (2.7)	34 (9.8)	11 (3.1)
Cataract nuclear	10 (6.3)	3 (1.8)	5 (2.7)	4 (2.2)	15 (4.3)	7 (2.0)
Conjunctival hyperaemia	9 (5.6)	4 (2.4)	4 (2.1)	6 (3.2)	13 (3.7)	10 (2.9)
Eye pain	7 (4.4)	3 (1.8)	6 (3.2)	6 (3.2)	13 (3.7)	9 (2.6)
Conjunctival oedema	7 (4.4)	2 (1.2)	6 (3.2)	2 (1.1)	13 (3.7)	4 (1.1)
Vitreous haemorrhage	6 (3.8)	0	6 (3.2)	0	12 (3.5)	0
Vitreous floaters	6 (3.8)	0	4 (2.1)	1 (0.5)	10 (2.9)	1 (0.3)
Ocular hypertension	4 (2.5)	0	16 (8.6)	5 (2.7)	20 (5.8)	5 (1.4)
Lenticular opacities	3 (1.9)	0	5 (2.7)	0	8 (2.3)	0
Cataract cortical	1 (0.6)	2 (1.2)	5 (2.7)	5 (2.7)	6 (1.7)	7 (2.0)
Abbreviations used in the table: DEX700, dexamethasone 700µg; IOP, intraocular pressure. Source: Boyer *et al*. 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]; Summary of Safety[86]						

Raised IOP was reported in 36.0% of patients treated with dexamethasone in the MEAD studies pooled analysis although only 30.5% of these were deemed related to treatment (Table x). In terms of the magnitude of the rise in IOP, 27.7% of dexamethasone patients experienced an IOP rise ≥10mmHg at any visit during the MEAD study period; 32.0% experienced an IOP ≥ 25mmHg and 6.6% had an IOP ≥ 35 mmHg at any visit during the MEAD study period. The company reported that neither the incidence nor magnitude of IOP elevation increased over time with repeated dexamethasone treatments and that the IOP generally resolved after each injection (Figure 12).

Figure 12: Mean IOP by visit within the treatment cycle over the MEAD study period – pooled analysis (reproduced from CS, Figure 50, pg 244)



Key: DEX, dexamethasone; IOP, intraocular pressure.
Source: Boyer *et al.* 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]; Summary of Safety[86]

The company reported in the CS that 41.5% of the patients treated with dexamethasone required IOP-lowering medications in their study eye at some point during the MEAD studies. It was also reported in the CS that 7 patients (2.0%) randomised to dexamethasone developed glaucoma (this included open-angle glaucoma and angle-closure glaucoma) compared with 2 patients (0.6%) in the sham group of the MEAD studies. A total of 4 patients (1.1%) randomised to dexamethasone required surgical intervention to treat raised IOP: one patient required incisional surgery (trabeculectomy and iridotomy) to manage IOP elevation which was not considered related to treatment; one patient required incisional surgery to clear the aqueous outflow; one patient had an iridotomy for narrow angle glaucoma; and one patient had iridectomy due to cataract surgery. None of the patients in the MEAD studies required removal of the dexamethasone implant by vitrectomy to control IOP.

In terms of cataract AEs, a total of 67.9% of the phakic patients treated with dexamethasone in the MEAD pooled analysis (n=262) experienced a cataract adverse event compared with 20.4% of phakic patients randomised to sham (n=250) (Table 26). The company also reported in the CS that 85% of phakic patients presented with early lens opacification at baseline.

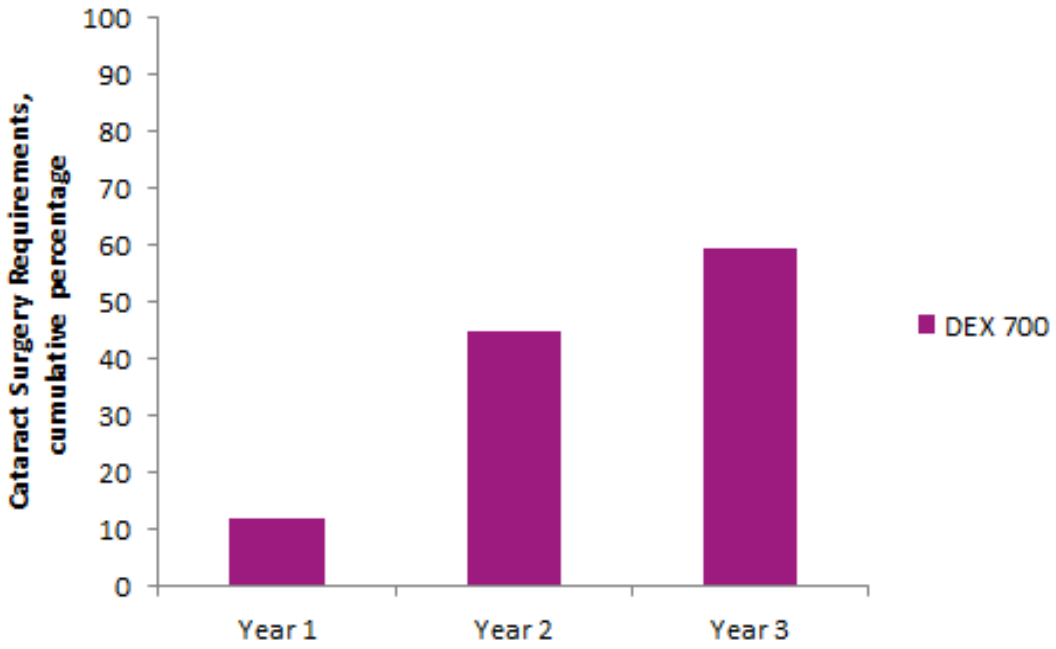
Table 26: Proportion of patients experiencing a cataract adverse event at any time during the MEAD study period, % - pooled analysis (reproduced from CS Table 44, pg 247)

	DEX700	Sham

MEAD-010	68.4	14.8
MEAD-011	67.6	25.2
MEAD Pooled	67.9	20.4
Abbreviations used in the table: DEX700, dexamethasone 700µg. Source: Boyer *et al*. 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]; Summary of Safety[86]		

The company reported that by the end of the MEAD studies, cataract surgery had been performed in 59.2% of the phakic patients treated with dexamethasone compared with 7.2% of the phakic patients randomised to sham (MEAD pooled analysis). The ERG also notes that over half of all the cataract extractions during the MEAD studies occurred within the second year of the studies (Figure 13).

Figure 13: Proportion of patients requiring cataract extraction across the MEAD study period, % - pooled analysis (reproduced from CS, Figure 51, pg 248)



Key: DEX, dexamethasone.
Source: Boyer *et al*. 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]; Summary of Safety[86]

PLACID

The safety results of PLACID suggested that both dexamethasone + laser therapy and laser alone were associated with low discontinuation rates due to AEs, no TRSAEs and no deaths attributed to treatment (Table 27). However, the ERG notes that dexamethasone + laser was associated with numerically more AEs and TRAEs compared with laser alone (Table 27).

Table 27: Safety profile in PLACID, n (%) (reproduced from CS, Table 53, pg 258)

	DEX700 + laser (n=125)	**Laser (n=127)**

All AEs	116 (92.8)	105 (82.7)
Ocular		
Study eye	92 (73.6)	74 (58.3)
Non-study eye	51 (40.8)	47 (37.0)
TRAE	52 (41.6)	24 (18.9)
Ocular	52 (41.6)	24 (18.9)
Study eye	52 (41.6)	24 (18.9)
Applicator	31 (24.8)	22 (17.3)
Treatment	30 (24.0)	NR
Non-study eye	0	0
Non-ocular	0	0
SAE	23 (18.4)	27 (21.3)
Ocular	1 (0.8)	0
Study eye	1 (0.8)	0
Non-study eye	0	0
Non-ocular	22 (17.6)	27 (21.3)
Treatment-related SAE	0	0
Discontinuations due to AE	9 (7.2)	12 (9.4)
Deaths related to treatment	0	0
Abbreviations used in the table: AE, adverse event; DEX, dexamethasone; SAE, serious adverse event; TRAE, treatment-related adverse event. Source: Callanan *et al*. 2013[58]; CSR 206207-012[57]		

The company reported in the CS that the most frequently reported ocular TRAEs (>2% in either treatment group) in the study eye in PLACID were IOP increase, conjunctival haemorrhage, cataract, eye pain, vitreous haemorrhage, vitreous floaters, subcapsular cataract, ocular discomfort and conjunctival oedema. Treatment-related IOP increase, cataract and vitreous haemorrhage all showed a statistically significant between-group difference with more AEs in the dexamethasone + laser group compared with the laser alone group. In terms of vitreous haemorrhage, this occurred in 4.8% (n=6) of people with dexamethasone + laser compared with 0% in the laser alone group (p=0.014). It was reported in the CS that all 6 reports of vitreous haemorrhage were mild in severity and that none required treatment.

Raised IOP deemed related to treatment was reported in 19.2% of patients treated with dexamethasone + laser compared with 0% of the patients treated with laser alone. IOP rises were all managed with non-surgical interventions such as topical IOP medications. A total of 15.9% of patients in the dexamethasone + laser group received IOP-lowering medications compared with 1.6% in the laser alone group.

In total, 22 patients (17.6%) treated with dexamethasone + laser therapy experienced a cataract adverse event compared with 9 patients (7.1%) treated with laser therapy alone. Treatment-related cataract in the study eye was reported in 8/91 phakic patients treated with dexamethasone + laser

(8.8%) compared with none of the 95 phakic patients treated with laser alone. The company reported in the CS that cataract surgery was performed in similar numbers of patients in both treatment arms: 6 patients in the dexamethasone + laser arm and 5 patients in the laser alone arm.

NCT0035906

The most common ocular adverse events reported in DMO patients enrolled in NCT0035906 were anterior chamber cell, anterior chamber flare and vitreous haemorrhage (Table 28). The company reported in the CS that there were no statistically significant between-group differences in the occurrence of any non-ocular adverse events and that there were no incidences of TRSAEs associated with dexamethasone although no numerical data were provided for these outcomes in the CS.

Table 28: Ocular adverse events reported in at least 10% of patients in any group at any time during NCT0035906, n (%) (reproduced from CS, Table 56, pg 264)

	DEX700 (n=53)	**Observation (n=57)**
Anterior chamber cell	14 (26.4)	1 (1.8)
Anterior chamber flare	11 (20.8)	5 (8.8)
Vitreous haemorrhage	12 (22.6)	3 (5.3)
Eye pain	5 (9.4)	2 (3.5)
VA reduced	9 (17.0)	6 (10.5)
Vitreous disorder	8 (15.1)	2 (3.5)
Increased IOP	5 (9.4)	0
Conjunctival haemorrhage	4 (7.5)	0
Maculopathy	4 (7.5)	1 (1.8)
Eye irritation	8 (15.1)	2 (3.5)
Vitreous floaters	9 (17.0)	0
Abnormal sensation in eye	8 (15.1)	2 (3.5)
Macular oedema	3 (5.7)	5 (8.8)
Eye pruritus	4 (7.5)	1 (1.8)
Retinal haemorrhage	6 (11.3)	12 (21.1)
Diabetic retinopathy	6 (11.3)	8 (14.0)

Abbreviations used in the table: AE, adverse event; DEX700, dexamethasone 700µg; IOP, intraocular pressure; VA, visual acuity.
Source: Haller *et al*. 2010[60]

IOP elevation to ≥25mmHg during the 180 day study follow-up period was reported in 13.2% of the dexamethasone safety population (n=53) compared with 0% of patients in the observation group. Eight patients (15%) in the dexamethasone safety population experienced an IOP increase of ≥10mmHg compared with one patient in the observation group. The company reported that all IOP rises were successfully managed with either observation or topical IOP lowering medication.

There was no significant difference in the number of cataract adverse events among the study groups in NCT00035906. There was also no between-group difference in the progression (at least 1-grade

increase on slit lamp examination) in any type of cataract However, no further details or numerical data were presented in the CS for these outcomes.

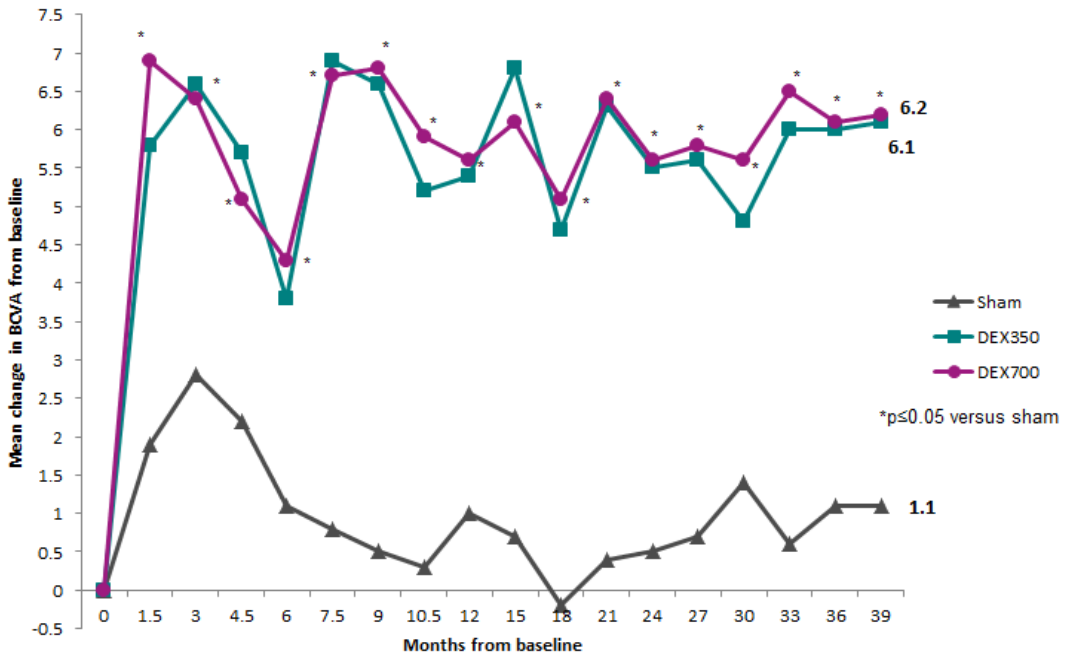
4.5.4 Subgroup analyses: pseudophakic patients

Efficacy results were presented for the pseudophakic subgroup of patients from only the MEAD studies, whereas safety results for this subgroup were presented from PLACID as well as the MEAD studies. There was no explanation provided in the CS as to why efficacy results weren't available from PLACID for pseudophakic patients. The ERG considers any data presented from NCT00035906 on pseudophakic patients would have been potentially misleading as they would have been based on very small numbers of patients.

[redacted]

The mean BCVA change from baseline with dexamethasone for the pseudophakic patients in the MEAD studies was statistically significant at all time points compared with sham (Figure 14 and Table 29).

Figure 14: Mean BCVA change from baseline for pseudophakic patients in the MEAD trial programme, ETDRS letters – pooled analysis (reproduced from CS, Figure 17, pg 159)



Key: BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study.
Source: Boyer *et al.* 2014[51]

Table 29: Mean BCVA average change (AUC approach) from baseline for pseudophakic patients in the MEAD trial programme, ETDRS letters (SD) (reproduced from CS, Table 23, pg 159)

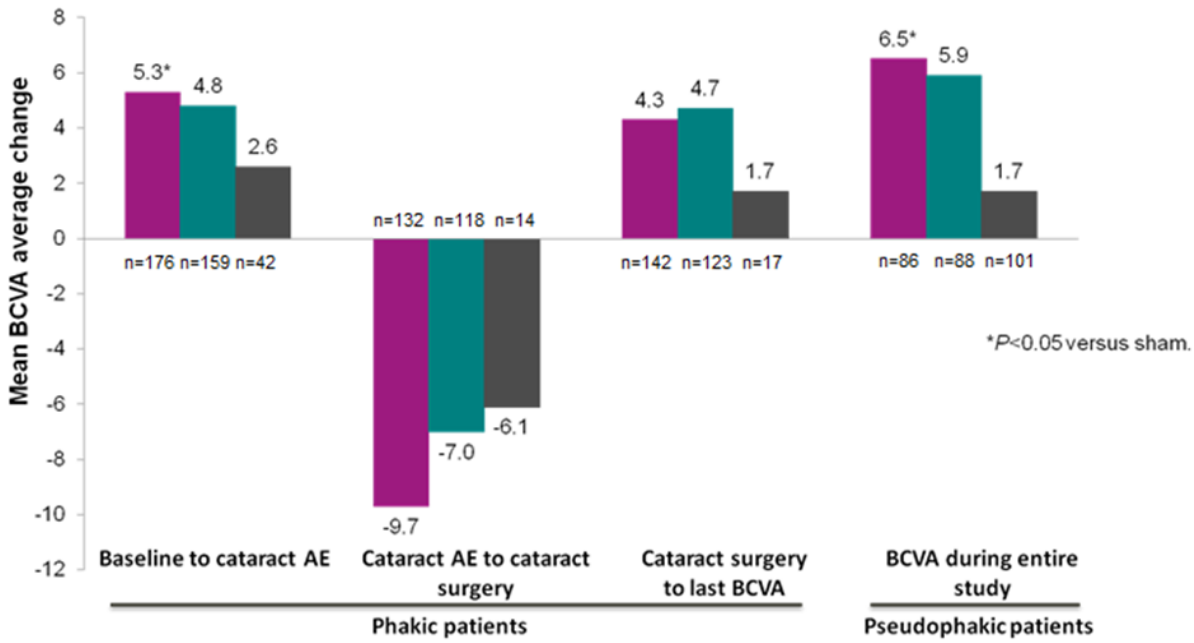
	DEX700	Sham	DEX700 vs. Sham p-value
MEAD-010	8.1 (8.0)	2.1 (7.2)	<0.001
MEAD-011	4.9 (7.9)	1.3 (7.0)	0.018
MEAD Pooled	6.5 (8.1)	1.7 (7.1)	<0.001

Abbreviations used in the table: AUC, area under the curve; BCVA, best corrected visual acuity; DEX700, dexamethasone 700µ; ETDRS, Early Treatment of Diabetic Retinopathy Study; SD, standard deviation.
Source: Boyer *et al*. 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]

Dexamethasone resulted in a more sustained treatment effect in terms of improvement in BCVA for the pseudophakic subgroup compared with the whole trial population. In addition, in terms of mean BCVA average change from baseline, the pseudophakic patients in the dexamethasone group of the MEAD studies achieved a much greater improvement in BCVA compared to the whole trial ITT population. In the MEAD pooled analysis, the mean BCVA average change for the dexamethasone group was 6.5 letters in the pseudophakic subgroup compared with 3.5 in the whole trial ITT population. The ERG's clinical experts advised that the pooled mean change in BCVA when compared with the sham group (improvement of 4.8 letters) may not be clinically significant. This could be a result of the impact of cataract adverse effects in the phakic patients in the whole trial population. The company reported in the CS that the proportion of pseudophakic patients achieving ≥15 letter gain from baseline at study end in the dexamethasone group was 23.3% compared with 22.2% in the whole trial population (ITT analysis). This suggests that the overall results in terms of improvement in BCVA in the MEAD studies were similar between the pseudophakic and whole trial populations.

The company reported in the CS that progression of lens opacification and primary cataract formation explains the observed difference in statistical significance of treatment effect across MEAD-010 and MEAD-011 in primary efficacy outcome analysis (as reported in Section 4.5.2). The company also reported that the proportion of patients with worsening of ≥30 letters from baseline at any visit as the result of cataract was 4.9 times higher in the dexamethasone group compared with sham in MEAD-011 but only 2.4 times higher in MEAD-010. A *post-hoc* analysis was reported in the CS to demonstrate the effect of cataract AEs on visual acuity with dexamethasone and how after cataract surgery, vision improved (Figure 15).

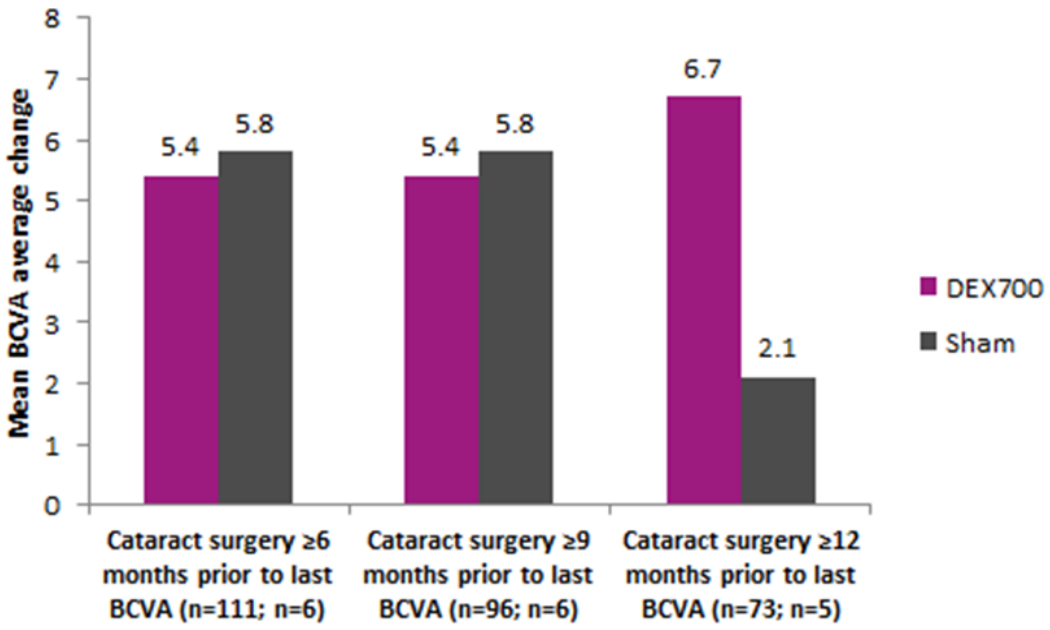
Figure 15: Mean BCVA average change (AUC approach) by lens status during the MEAD study period, ETDRS letters – pooled analysis (reproduced from CS Figure 18, pg 161)



Key: AE, adverse event; AUC, area under the curve; BCVA, best corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study.
Source: Boyer *et al.* 2014[51]

The company also reported results of an analysis of mean BCVA change by timing of cataract surgery in relation to the study end visit (Figure 16). The results of this analysis suggest those in the dexamethasone group who had ≥ 12 months follow-up post-cataract surgery had a greater improvement in BCVA from baseline compared with the sham group. In addition, the ERG notes that the patients who had ≥ 12 months follow-up post cataract surgery in the sham group experienced less improvement in BCVA compared to those who had <12 months follow-up; this may be a result of worsening of the DMO in the sham group compared with improvement in DMO in the dexamethasone group. The mean BCVA average change at study end for the phakic patients in both the dexamethasone and sham treatment groups who had cataract surgery and ≥ 12 months follow-up post-cataract surgery are similar to the results at study end for the pseudophakic patients.

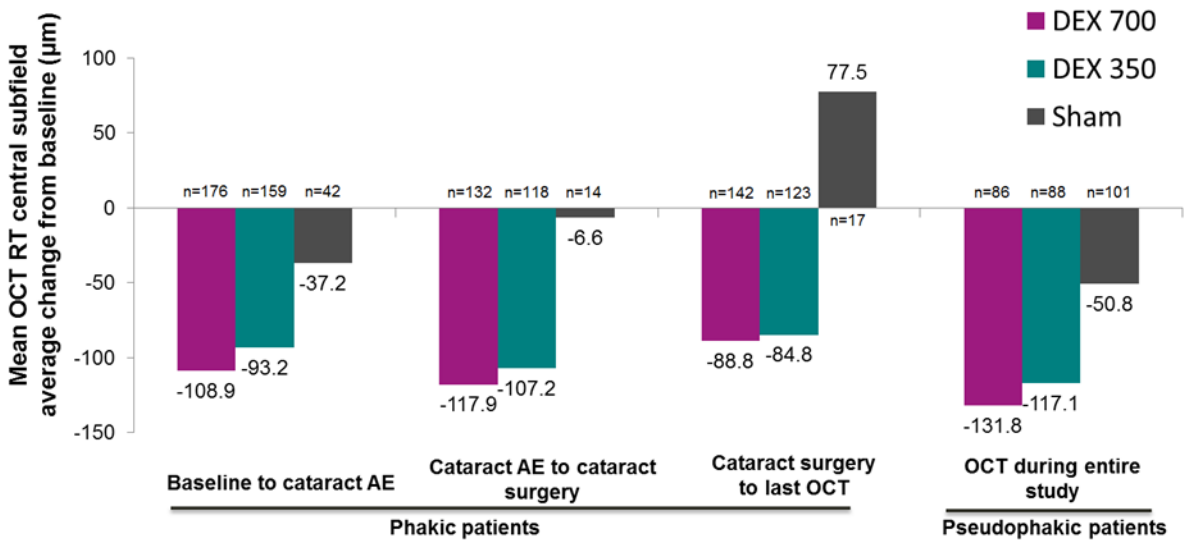
Figure 16: Mean BCVA average change (AUC approach) by timing of cataract surgery, ETDRS letters – pooled analysis (reproduced from CS Figure 19, pg 162)



Key: AUC, area under the curve; BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study; SD, standard deviation.
Source: BCVA by Cataract Surgery[87]

The mean CRT average change from baseline in the pseudophakic patients was -131.8µm in the dexamethasone group compared with -50.8 µm in the sham group (statistical significance not reported in the CS). The results for the whole trial (ITT) population whilst similar to the pseudophakic population results were slightly worse in each treatment group (-111.6 dexamethasone vs. -41.9 sham in whole trial compared with -131.8µm dexamethasone vs -50.8 µm sham in pseudophakics).

Figure 17: Mean average CRT change (AUC approach) by lens status during the MEAD study period, µm – pooled analysis (reproduced from CS, Figure 21, pg 166)



Key: AE, adverse event; AUC, area under the curve; (C)RT, (central) retinal thickness; DEX, dexamethasone; OCT, ocular computed tomography.
Source: Boyer *et al*. 2014[51]

Safety and adverse events in pseudophakic subgroup

The results of the analyses of the safety outcomes in the pseudophakic subgroup of the MEAD studies are presented in Table 30. Of particular note, there were fewer ocular AEs in the study eye in patients with a pseudophakic lens at baseline who were randomised to dexamethasone compared with in the whole study (ITT) population. This is a result of the absence of the primary cataract AEs seen in the phakic patients treated with dexamethasone in the whole study population.

Table 30: Safety profile across the MEAD trial programme, in pseudophakic subgroup, n (%) (reproduced from CS, Table 45, pg 249)

	DEX700 (n=85)	Sham (n=100)
All adverse events	91 (95.3)	86 (86.0)
Ocular – study eye	63 (74.1)	61 (61.0)
Non-ocular	61 (71.8)	66 (66.0)
Serious AE	31 (36.5)	36 (36.0)
Ocular – study eye	2 (2.4)	0
Non-ocular	28 (32.9)	31 (31.0)
Treatment related SAE	2 (2.4)	0
Ocular – study eye	2 (2.4)	0
Non-ocular	0	0
Discontinuations due to AE	11 (12.9)	13 (13.0)
Deaths related to treatment	0	0
Abbreviations used in the table: AE, adverse event; DEX700, dexamethasone 700µg; SAE, serious adverse event Source: Allergan EMEA Questions and Allergan Responses[88]		

The incidence of SAEs in the pseudophakic subgroup was similar in the dexamethasone group (36.5%) compared to the sham group (36.0%). The causes of the ocular SAEs seen in the two dexamethasone patients were vitreous adhesion and macular oedema. There was no difference in the number of discontinuations due to adverse events based on study treatment group: 13% of pseudophakic patients in each group discontinued due to an AE.

The ocular AEs occurring in >2% of pseudophakic patients are presented in Table X. The ERG note that the most common ocular AE reported was IOP increase although compared with the total study (safety) population fewer patients in the pseudophakic subgroup treated with dexamethasone (24.7%) experienced raised IOP compared with the total MEAD (safety) population (36.0%). The company reported that similar trends to the whole study (safety) population were observed in terms of the timing of IOP AEs suggesting there is no cumulative effect on IOP with dexamethasone re-treatments (no numerical data presented in the CS for the pseudophakic subgroup). It was reported in the CS that

IOP-lowering medication was prescribed to 32.9% of pseudophakic patients randomised to dexamethasone during the MEAD study period; this is lower than the number of patients in the dexamethasone group of the whole trial (safety) population who required IOP medication during the study (41.5%).

Table 31: Ocular adverse events in the study eye that occurred in >2% of patients in either the DEX700 or sham treatment group across the MEAD trial programme, pseudophakic subgroup, n (%) (reproduced from CS Table 46, pg 250)

	DEX700 (n=85)	**Sham (n=100)**
IOP increased	21 (24.7)	7 (7.0)
Conjunctival haemorrhage	16 (18.8)	17 (17.0)
Conjunctival hyperaemia	6 (7.1)	8 (8.0)
Cataract*	5 (5.9)	2 (2.0)
Macular fibrosis	4 (4.7)	3 (3.0)
Posterior capsule opacification	4 (4.7)	6 (6.0)
Visual acuity reduced	4 (4.7)	1 (1.0)
Ocular hypertension	4 (4.7)	2 (2.0)
Retinal neovascularisation	4 (4.7)	2 (2.0)
Vitreous floaters	4 (4.7)	2 (2.0)
Conjunctival oedema	4 (4.7)	0
Diabetic retinal oedema	4 (4.7)	2 (2.0)
Eye pain	3 (3.5)	5 (5.0)
Vitreous detachment	3 (3.5)	4 (4.0)
Macular oedema	3 (3.5)	3 (3.0)
Retinal haemorrhage	3 (3.5)	4 (4.0)
Eyelid ptosis	3 (3.5)	2 (2.0)
Dry eye	2 (2.4)	5 (5.0)
Retinal aneurysm	2 (2.4)	3 (3.0)
Conjunctivitis	2 (2.4)	2 (2.0)
Vitreous opacities	2 (2.4)	2 (2.0)
Corneal abrasion	2 (2.4)	4 (4.0)
Corneal erosion	2 (2.4)	2 (2.0)
Keratitis	2 (2.4)	1 (1.0)
Macular cyst	2 (2.4)	0
Pruritus	2 (2.4)	0
Uveitis	2 (2.4)	0
Retinal exudates	1 (1.2)	4 (4.0)
Blepharitis	1 (1.2)	8 (8.0)
Conjunctivitis allergic	0 (0.0)	4 (4.0)

Abbreviations used in the table: DEX700, dexamethasone 700µg; IOP, intraocular pressure.
Note: * adverse events identified as 'cataract' were secondary cataract.
Source: Allergan EMEA Questions and Allergan Responses[172]

The results of the safety and adverse events analyses in pseudophakic patients in PLACID are presented in Table 32. In comparison to the whole trial (safety) population of PLACID (Section 4.5.3), there were fewer events (%) for each of the safety outcomes reported in Table X in the pseudophakic subgroup. However, as or the whole trial (safety) population, dexamethasone + laser was associated with more adverse events compared to laser alone in the pseudophakic subgroup (85.7% vs. 75.0%).

Table 32: Safety profile in pseudophakic patients in PLACID, n (%) (reproduced from CS Table 54, pg 260)

	DEX700 + laser (n=35)	Laser (n=32)
All adverse events	30 (85.7)	24 (75.0)
Ocular adverse events in study eye	24 (68.6)	14 (43.8)
Ocular treatment-related adverse events in study eye	12 (34.3)	5 (15.6)
Abbreviations used in the table: DEX700, dexamethasone 700µg. Source: Clinical Story PLACID Final[82]		

In the CS it was reported that the most frequently reported ocular TRAEs in the pseudophakic subgroup were IOP increase, conjunctival haemorrhage, eye pain, vitreous haemorrhage and ocular discomfort (no numerical data presented in the CS). There was no significant between-group difference in ocular TRAEs in the pseudophakic subgroup. The company reported that IOP increase during PLACID was seen in four pseudophakic patients (study group not reported) and posterior capsule opacification in two pseudophakic patients (study group not reported).

4.5.5 Subgroup analyses: patients with prior treatment

The company presented the following subgroup analyses from the MEAD studies based on prior treatment exposure:

- any prior treatment;
- prior laser therapy;
- prior laser therapy and without prior steroid therapy;
- prior anti-VEGF therapy;
- prior anti-VEGF therapy without prior steroid therapy; and
- prior laser or prior anti-VEGF therapy without prior steroid therapy.

The ERG considers that the relevant subgroup from the EU marketing authorisation for dexamethasone that the subgroup analyses of patients with prior treatment could provide data, are those considered insufficiently responsive to non-corticosteroid therapy. The ERG thus considers only the three subgroup analyses in people without prior steroid therapy to be of relevance to the decision

problem: prior laser therapy and without prior steroid therapy (Table 33); prior anti-VEGF therapy without prior steroid therapy (Table 34); and prior laser or prior anti-VEGF therapy without prior steroid therapy (Table 35). The results of the remaining three subgroup analyses any prior treatment; prior laser therapy; and prior anti-VEGF therapy are presented in the appendices for additional information only (Appendix 9.8)

As discussed previously, the MEAD studies were not powered to detect statistical significant differences in any of the subgroup analyses. However, in each of the subgroups based on prior treatments received, dexamethasone generally resulted in greater reduction in CRT and improvement in BCVA compared with sham. However, the improvement in BCVA was modest and based on the ERG's clinical experts opinion, probably of no clinical significance.

Table 33: Efficacy in Patients with Prior Laser and Without Prior Intravitreal Steroid Therapy (reproduced from CS Table 264, pg 684)

	MEAD-010		**MEAD-011**		**Mead Pooled**	
Endpoint	**DEX 700**	**Sham**	**DEX 700**	**Sham**	**DEX 700**	**Sham**
Mean BCVA average change over 3 years, AUC approach (letters)						
BCVA ≥ 15-letter improvement from baseline at year 3/final visit (%)						
Mean BCVA change from baseline at year 3/final visit (letters)						
OCT retinal thickness at centre subfield mean average change over 3 years, AUC approach (µm)						

[a] Difference from sham p = < 0.05

[b] Difference from sham p = < 0.001

Abbreviations used in the table: AUC, area under the curve; BCVA, best corrected visual acuity; DEX700, dexamethasone 700 µg; OCT, optical coherence tomography

Note: The N value for the Sham group was 89 in Study 207207-011 and 192 in the pooled data for the OCT retinal thickness endpoint

Source: Tables 2107-4, 2107-5 and 2107-6

Table 34: Efficacy in Patients with Prior anti-VEGF and Without Prior Intravitreal Steroid Therapy (reproduced from CS Table 263, pg 683)

	MEAD-010		**MEAD-011**		**MEAD Pooled**	
Endpoint	**DEX 700**	**Sham**	**DEX 700**	**Sham**	**DEX 700**	**Sham**
Mean BCVA average change						

over 3 years, AUC approach (letters)						
BCVA ≥ 15-letter improvement from baseline at year 3/final visit (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean BCVA change from baseline at year 3/final visit (letters)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCT retinal thickness at centre subfield mean average change over 3 years, AUC approach (µm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Difference from sham p = < 0.05

Abbreviations used in the table: AUC, area under the curve; BCVA, best corrected visual acuity; DEX700, dexamethasone 700 µg; OCT, optical coherence tomography.

Note: The N value for the Sham group was 3 in Study 207207-011 and 9 in the pooled data for the OCT retinal thickness endpoint

Source: Tables 2107-1, 2107-2 and 2107-3

Table 35: Efficacy in Patients with Prior Anti-VEGF or Laser and Without Prior Intravitreal Steroid Therapy (reproduced from CS Table 265, pg 685)

	MEAD-010		**MEAD-011**		**MEAD Pooled**	
Endpoint	**DEX 700**[redacted]	**Sham**[redacted]	**DEX 700**[redacted]	**Sham**[redacted]	**DEX 700**[redacted]	**Sham**[redacted]
Mean BCVA average change over 3 years, AUC approach (letters)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA ≥ 15-letter improvement from baseline at year 3/final visit (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean BCVA change from baseline at year 3/final visit (letters)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCT retinal thickness at centre subfield mean average change over 3 years, AUC approach (µm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Difference from sham p = < 0.05

[b] Difference from sham p = < 0.001

Abbreviations used in the table: AUC, area under the curve; BCVA, best corrected visual acuity; DEX700, dexamethasone 700 µg; OCT, optical coherence tomography.

Note: The N value for the Sham group was 91 in Study 207207-011 and 195 in the pooled data for the OCT retinal thickness endpoint

Source: Tables 2107-7, 2107-8 and 2107-9

[redacted]Safety and adverse events data in the CS were not reported in the subgroup of patients who had received prior treatment without prior corticosteroid therapy. However, safety data were presented for the people who had received any prior therapy (i.e. including prior corticosteroid therapy [Table 36]). These data suggest a similar safety profile for dexamethasone in the subgroup of patients with any

prior treatment to that seen in the whole trial (safety) population of the pooled MEAD studies, with higher incidences of ocular adverse events in the dexamethasone group compared with the sham group.

Table 36: Safety profile of patients with any prior treatment, MEAD pooled, n (%)(reproduced from CS, Table 47, pg251)

	DEX700 (n=247)	Sham (n=261)
Ocular adverse events in the study eye	213 (86.2)	149 (57.1)
Non-ocular adverse events	169 (68.4)	153 (58.6)
Serious adverse events	84 (34.0)	66 (25.3)
Ocular study eye	17 (6.9)	2 (0.8)
Non-ocular	72 (29.1)	59 (22.6)
Treatment-related serious adverse events	12 (4.9)	0
Ocular	12 (4.9)	0
Non-ocular	0	0
Discontinuations due to adverse events	30 (12.1)	30 (11.5)
Adverse events associated with elevated IOP	94 (38.1)	12 (4.6)
Adverse events associated with cataract	128 (70.3)	36 (20.1)
Abbreviations used in the table: DEX700, dexamethasone 700µg; IOP, intraocular pressure. Source: Allergan EMEA Questions and Allergan Responses[88]		

4.5.6 Subgroup analyses: *a priori* subgroup analyses in MEAD studies

In the CS it was reported that dexamethasone resulted in a statistically significant greater improvement in mean BCVA average change (AUC approach) compared with sham in the following subgroup analyses:

- DM duration ≤15 years;
- DMO duration ≤1.5 years;
- patients with HbA1c ≤8%; and
- patients with severe non-proliferative diabetic retinopathy or worse at baseline.

In all other pre-planned subgroups, there was no statistically significant difference between dexamethasone and sham although dexamethasone resulted in numerically greater improvement in mean BCVA compared to sham. No numerical data were presented in the CS for any of the *a priori* subgroup analyses in MEAD studies

4.5.7 Summary of RCT results

- The primary results of the dexamethasone RCTs presented in the CS were for the whole trial populations and thus are not specific to any of the populations specified in the EU marketing authorisation for dexamethasone.

- The results of the MEAD studies are potentially flawed due to the high discontinuation rates across the trial arms and the use of a LOCF analysis to account for the missing data.
- In the pooled MEAD analysis, dexamethasone resulted in a statistically significant increase in mean BCVA change from baseline and in the number of patients achieving both a ≥15 letter gain and a ≥10 letter gain from baseline compared with sham.
- From month 15 onwards in the MEAD studies the improvement in BCVA provided by dexamethasone 700µg relative to sham was reduced and didn't recover until after 36 months. The ERG notes that this trend coincides with cataract adverse effects during the second year of the study in the dexamethasone group.
- The company reported that there were no significant changes in contrast sensitivity or mean average NEI-VFQ-25 change (AUC approach) between dexamethasone and sham in the MEAD studies.
- Dexamethasone resulted in a statistically significant greater reduction in mean CRT average change (AUC approach) compared with sham in MEAD-010, MEAD-011 and the MEAD pooled analysis
- The mean BCVA change from baseline, the proportion of patients achieving at least a 10-letter improvement in visual acuity at study end and the HRQL analyses in PLACID demonstrated no significant difference between dexamethasone + laser versus laser alone.
- There was no significant difference between dexamethasone and observation at day 180 in the proportion of DMO patients achieving at least a 10-letter improvement in visual acuity or at least a 15-letter improvement in visual acuity analyses in NCT00035906.
- The most common ocular TRAEs in the MEAD studies were cataract formation and raised IOP with dexamethasone, and conjunctival haemorrhage with sham.
- Treatment-related IOP increase, cataract and vitreous haemorrhage all showed a statistically significant between-group difference with more AEs in the dexamethasone + laser group compared with the laser alone group in PLACID.
- The mean BCVA change from baseline with dexamethasone for the pseudophakic patients in the MEAD studies was statistically significant at all time points compared with sham; and the pseudophakic patients in the dexamethasone group of the MEAD studies achieved a much greater improvement in BCVA compared to the whole trial ITT population (6.5 letters in the pseudophakic subgroup compared with 3.5 in the whole trial ITT population). This could be a result of the impact of cataract adverse effects in the phakic patients in the whole trial population.
- There were fewer ocular AEs in the study eye in patients with a pseudophakic lens at baseline in the MEAD study patients who were randomised to dexamethasone compared with the whole study (ITT) population due to the absence of primary cataract AEs.
- The most common ocular AE reported in the pseudophakic subgroup was IOP increase although fewer patients in the dexamethasone group (24.7%) experienced raised IOP compared with those in the dexamethasone group for the total MEAD (safety) population (36.0%).

- Dexamethasone generally resulted in greater reduction in CRT and improvement in BCVA compared with sham in the subgroup analyses in people with prior laser or prior anti-VEGF therapy without prior steroid therapy
- Safety data suggest a similar safety profile for dexamethasone in the subgroup of patients with any prior treatment (including prior corticosteroid therapy) to that seen in the whole trial (safety) population of the pooled MEAD studies, with higher incidences of ocular adverse events in the dexamethasone group compared with the sham group.

4.6 Description and critique of the multiple treatment comparison

4.6.1 Methods

The company conducted network meta-analyses (NMAs) to provide relative treatment effect estimates between dexamethasone and the various comparators specified in Section 4.1.2 for efficacy endpoints. The same searches used to identify trials were used as those described above in Section 4.1.1. However, additional inclusion/exclusion criteria were applied for the NMAs in terms of the outcomes of interest. For trials to be included in the NMA, they were required to report outcome data for one of the following two outcomes:

- proportion of patients achieving at least a 10 letter gain from baseline at 12 months; or
- proportion of patients achieving at least a 10 letter loss from baseline at 12 months.

The company's rationale for selecting these outcomes for the NMA is presented in Box 11.

Box 11. Company rationale for the choice of outcomes in the NMA (CS pg 185)

The proportion of patients achieving at least a 10-letter improvement or worsening in BCVA from baseline at month 12 was chosen as this is a clinically meaningful endpoint that can also be applied within the economic model to move patients between health states.
Abbreviations used in the box: BCVA, best corrected visual acuity; NMA, network meta-analysis.

The ERG notes that the company included a sensitivity analysis for the outcome of proportion of patients achieving at least a 15 letter gain from baseline at 12 months in the CS. The ERG also notes that a 15-letter improvement in BCVA was the primary efficacy outcome in the MEAD studies although the 10-letter improvement was reported as a secondary outcome. In addition, the company reported in the CS that the 10-letter improvement data were used as the primary outcome data from the MEAD studies in the European Marketing authorisation application. The clinical experts to the ERG agree with the company that a 10-letter improvement or worsening in BCVA is a clinically meaningful change in visual acuity. However, the ERG is not sure as to what the most appropriate time point to assess this outcome within the NMA is. The ERG does not consider the 12 month timeframe to be appropriate for use in the economic model; the rationale for this is discussed in Section 5. However, the ERG notes that the majority of the clinical trials used in the company's NMA

report this outcome data at 12 months. The ERG notes that based on the efficacy findings for dexamethasone in the whole trial population, 12 month data may bias the results against dexamethasone because of the impact of cataract adverse effects on the visual acuity. Data at 12 months in the pseudophakic subgroup would be unaffected by this potential confounder.

The same methods used for study appraisal, study inclusion, data extraction and quality assessment the systematic review of RCTs described in Section 4.1 were used in the NMA trial selection process. Treatment arms from multi-arm trials that did not include a comparator of interest were not included in the analyses as per the eligibility criteria. Sham treatment and no treatment arms were assumed to be the same in the NMA and were thus pooled in the NMAs. The ERG has concerns as to the impact the pooling of sham and no treatment arms may have had on the efficacy estimates from the NMA as the absence of blinding in the no treatment arms could have impacted the results. However, the ERG notes that had the company not assumed equal efficacy for sham and no treatment then it would not have been possible for the company to conduct the NMA as this assumption creates the only link in the network between the dexamethasone MEAD studies and the rest of the network.

The BCVA data from each of the trials was split into the following three categories:

- worsening, defined as loss of 10 or more letters at 12 months;
- stable, defined as loss or gain of <10 letters at 12 months; and
- improvement, defined as gain of 10 or more letters at 12 months.

The stable vision group for each trial was calculated by subtracting the total number of patients from the number of patients losing 10 or more letters and the number of patients gaining 10 or more letters.

The company conducted the NMAs in WinBUGS (version 14) (MRC Biostatistics Unit, Cambridge, UK), using R (version 3.1.1) as an interface. All NMA results reported in the CS were from random effects models. The company's justification for the choice of the random effects model is presented in Box X.

Box X. Company's justification for the choice of the random effects model for the NMA's (Compan''s response to clarification, A11, pg 8)

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. Therefore a random-effects model was deemed a more appropriate choice as it incorporates a between-study heterogeneity parameter.

The relative risk (RR) and probability of being in each of the three groups of vision were estimated using Markov Chain Monte Carlo (MCMC) methods. The WinBUGs model used a multinomial

likelihood with a probit link function to estimate the relative treatment effects. The multinomial model that was used was able to account for trial data where only one of the categories of vision was reported. A binomial likelihood using a probit link function was fitted to the trials with a sham/no treatment arm and it considered only data for the outcome of loss of at least 10 letters. The ERG notes that for one of the sensitivity analyses conducted in the CS (sensitivity analysis 2 [SA 2]) a binomial likelihood with a logit link function model was used. The company reported, and the ERG can confirm, that the models used were in-line with the recommendations in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[89]

A subgroup analysis was conducted to assess the impact of being pseudophakic at baseline on the efficacy outcomes. However, not all trials reported suitable subgroup data or even lens status at baseline. The ERG notes that the treatments where lens status is mostly likely to be expected to influence efficacy results is the corticosteroid therapies, i.e. dexamethasone and fluocinolone acetonide. The dexamethasone studies in the network all reported pseudophakic subgroup data apart from BEVORDEX. Total population data was used in the absence of pseudophakic subgroup data from the studies not reporting pseudophakic subgroup data as the company deemed it to be, "a reasonable representation of the estimated treatment effect in such patients" (CS, pg 193). Whilst subgroup data from each trial would have been preferable, the ERG agrees with the company's approach in the absence of such data from the non-corticosteroid therapy trials.

The company also conducted two sensitivity analyses for the NMA. These were as follows:

- Sensitivity analysis 1 (SA1): including the FAME trial for fluocinolone acetonide in the network. In order to do this the company estimated data for 10 letter improvement from the data reported for patients achieving a 15 letter improvement from baseline at month 12. The method used to calculate this data were clarified by the company during the clarification question stage and the company's response is reported in Box 12.
- Sensitivity analysis 2 (SA2): using the outcome of 'gaining 15 or more letters at 12 months'. The company conducted this analysis to assess the impact of using the 15 letter observed data for FAME instead of the estimated data in SA1 for the proportion of patients achieving a 10 letter improvement from baseline at month 12 data affected the results.

Box 12. The company's explanation for how the 10 letter improvement data were calculated for FAME (Company's response to clarification, A14, pg 10).

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 study2 to estimate the 10 letter gain data.

Of note, at the time of this analysis, BEVORDEX was only available in abstract form3 in which only ≥10 letter gain data was presented. Therefore data from this trial was not included in the mean multiplication factor calculation.

In addition, in response to clarification question A8, the company conducted an additional analysis that used the end point data from each of the studies excluded on the basis that they reported only 12-month data. The company reported in the response to clarification question A7 that only one study was excluded from the base case NMA for this reason (NCT00035906). The company conducted an updated analysis including the end-point data from NCT00035906, a study with 6-month outcome data for dexamethasone versus observation and provided the results (Section 4.7.5).

4.6.2 Outcomes reported in the NMAs

The clinical outcomes reported from the NMAs in the CS were:

- loss of 10 or more letters at 12 months; and
- gain of 10 or more letters at 12 months.

These outcomes were reported for the base case analysis, the pseudophakic subgroup analysis and SA1.

The outcome of gaining at least 15 letters at 12 months was assessed and reported for SA2.

4.6.3 Studies included in the analyses

In total 11 trials met the inclusion criteria for the NMA (Table 37). These 11 trials included five of the dexamethasone RCTs presented in the CS (MEAD-010, MEAD-011, study 024, PLACID and BEVORDEX) and an additional six RCT's for other comparators. The dexamethasone NCT00035906 trial was excluded from the NMA because it did not report outcome data at 12 months.

The eleven trials provided clinical evidence for all relevant comparators apart from fluocinolone acetonide. The key RCT (FAME) providing evidence for fluocinolone acetonide was excluded because it didn't report 10-letter BCVA data.[90] However, the company decided that due to the absence of direct evidence for dexamethasone versus fluocinolone acetonide, they would include FAME in a sensitivity analysis of the NMA to enable an indirect comparison of dexamethasone with fluocinolone acetonide. The inclusion of FAME in the NMA required 10-letter data that was estimated from the 15-letter analysis data from FAME. Further details on the method used to calculate 10-letter data for FAME are reported in Section 4.6.1.

Table 37: Summary of the trials used to conduct the NMA's for the base case total population and pseudophakic subgroup (reproduced CS, Table 35, pg 194)

No. of trials	Trial Reference	Treatment Arm 1	Treatment Arm 2	Treatment Arm 3
1	024	DEX 700 CNT	Ranibizumab 0.5mg PRN	
1	BOLT	Bevacizumab 1.25mg PRN	Laser PRN	
1	PLACID	DEX 700 + laser PRN	Laser PRN	
1	BEVORDEX	DEX 700 PRN ≥4 month intervals	Bevacizumab 1.25mg PRN	
2	ETDRS (Hornberger SG) Olk	Laser PRN	Sham/No treatment	
2	MEAD-010 MEAD-011	DEX 700 PRN	Sham/No treatment	
3	PROTOCOL I RESTORE REVEAL	Ranibizumab 0.5mg + laser PRN	Ranibizumab 0.5mg PRN	Laser PRN
Abbreviations used in the table: CNT, continuous; DEX700, dexamethasone 700µg; PRN, *pro ne rata*				

In terms of the dexamethasone treatments in the NMA, the company kept each different treatment regimen as a separate treatment with in the network. The ERG agrees with this decision as several of the regimens involve the use of dexamethasone outside the EU marketing authorisation. The ERG considers the only dexamethasone treatments relevant to the decision problem from the NMA to be the DEX 700 PRN regimen (hereafter referred to as dexamethasone), and the DEX 700 + laser PRN regimen (hereafter referred to as dexamethasone plus laser). Results for all treatments are presented below but discussion will focus on these two treatments along with the comparator treatments.

Network diagrams for each of the following NMAs reported in the CS are presented below:

- total population base case NMA;
- pseudophakic subgroup analysis;
- SA1: inclusion of FAME in the network; and
- SA2: using the outcome of 'gaining 15 or more letters at 12 months'.

In summary, the studies included in each of the NMAs were the same studies in the base case analysis and pseudophakic subgroup analysis, one additional study in SA1 (FAME), and one less study in SA2 compared to SA1 (Olk et al).[91] In the updated analysis presented in response to clarification question A8, NCT00035906 was included in the networks as an additional study (alongside the MEAD studies) providing data on the comparison of DEX 700 PRN compared with Sham/no treatment. The ERG notes that NCT00035906 compared one dose of DEX 700 with observation and so technically is

different to the MEAD studies where re-treatment as required with DEX 700 was allowed. However, the ERG also notes that NCT00035906 reports outcome data at 6 months and thus based on the EU marketing authorisation only one dose of DEX 700 would be allowed within the study time frame.

Figure 18: Network of evidence for trials included in the total population base case network meta-analysis of worsening of at least 10 letters, worsening/improvement of less than 10 letters and improvement of at least 10 letters at 12 months (reproduced from CS Figure 29, pg 194)

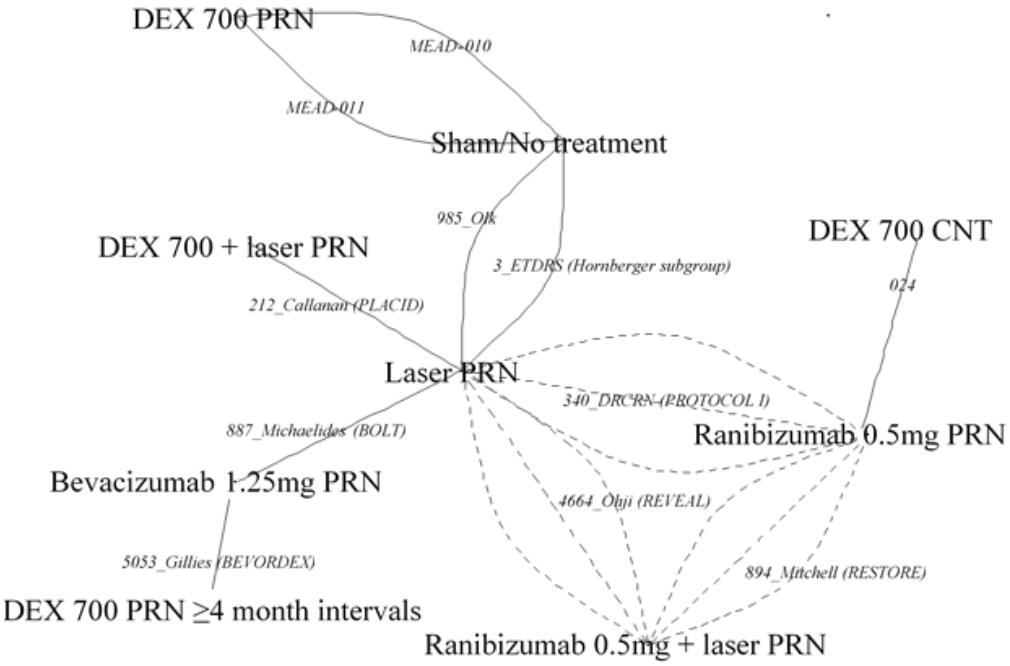
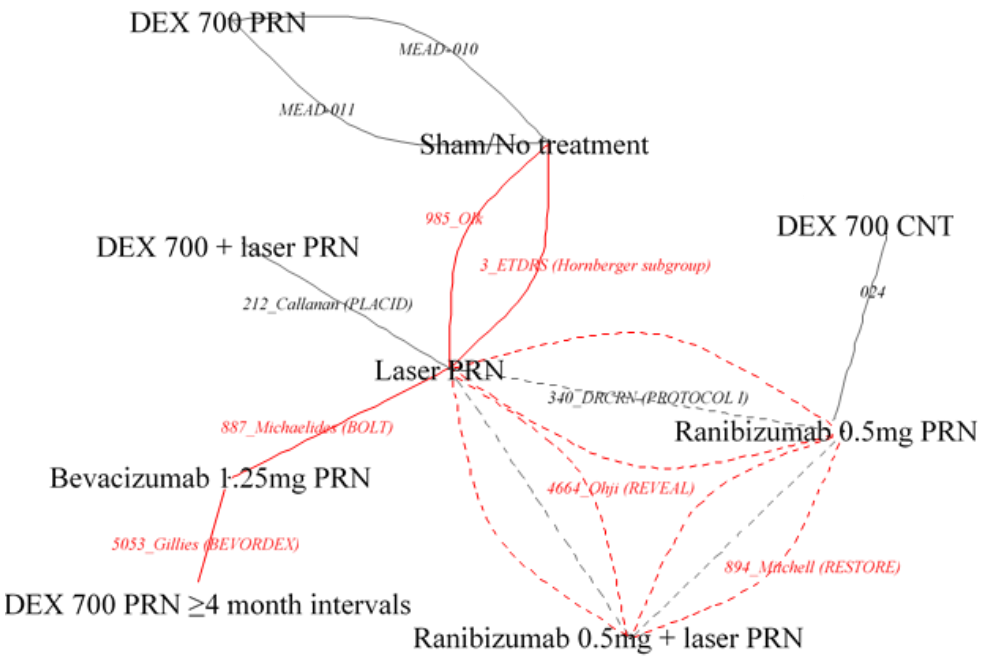


Figure 19: Network of evidence for trials included in the pseudophakic network meta-analysis of worsening of at least 10 letters, worsening/improvement of less than 10 letters and improvement of at least 10 letters at 12 months (reproduced from CS Figure 30, pg 195)



Note: red lines represent the absence of pseudophakic population data and so total population data is used in the network meta-analysis of this subgroup

Figure 20: Network diagram for SA1 (total population analysis including FAME) (reproduced from CS Figure 39, pg216)

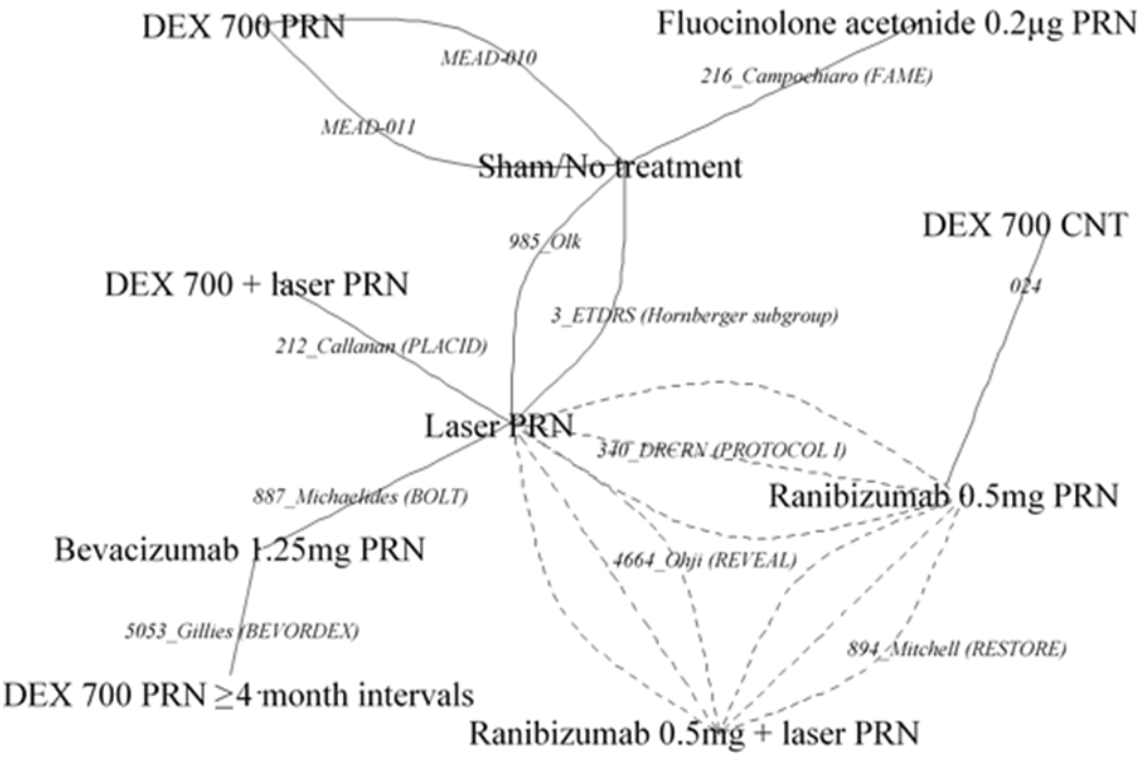
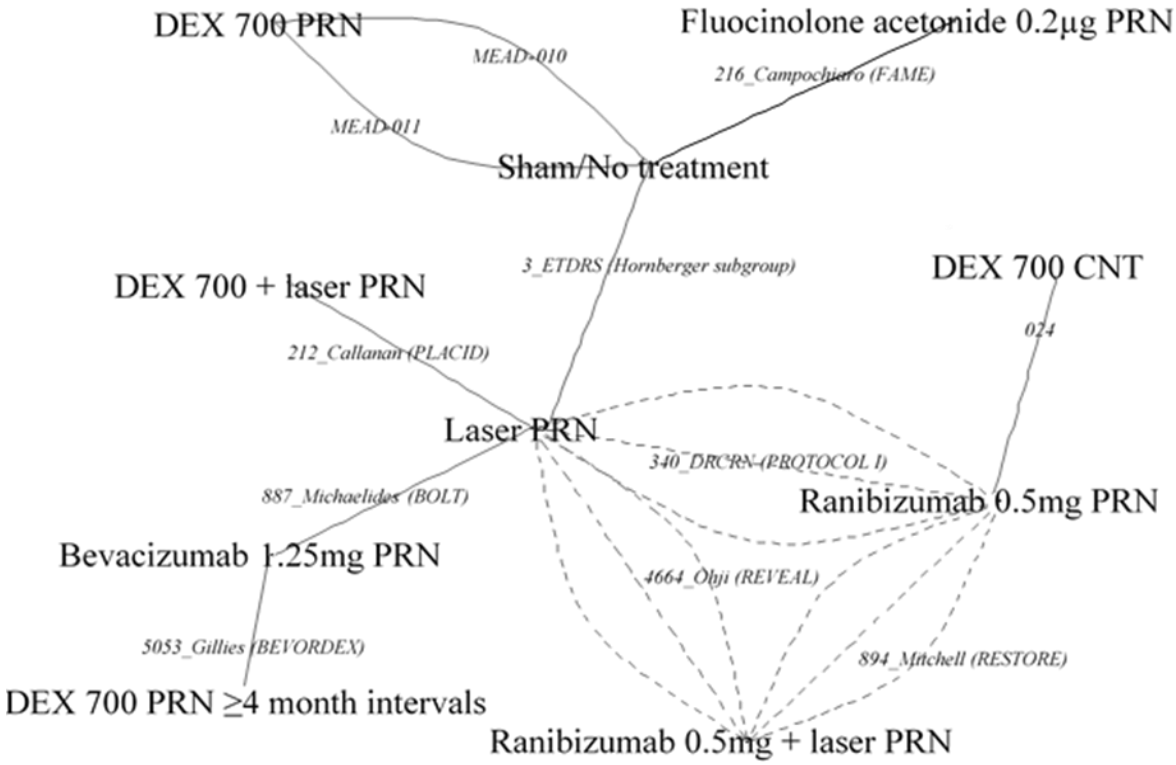


Figure 21: Network diagram for SA2 (proportion of patients achieving at least a 15-letter improvement in BCVA from baseline at 12 months) (reproduced from CS Figure 44, pg 222)



The ERG considers it important to highlight that the BOLT trial only reported data for the proportion of patients achieving a 10 letter improvement from baseline at 12 months and not data for worsening of 10 letters at 12 months. The company reported in the CS that the WinBUGs model used the proportion of patients not achieving a 10 letter improvement from baseline at 12 months in BOLT as a combined proportion of patients achieving a 10 letter worsening from baseline at month 12 and patients demonstrating a change in vision within a 10-letter range.

A summary of the six RCTs included in the NMA for the dexamethasone comparators and the FAME study used in the sensitivity analyses is presented in Table 38 along with a summary of the company's quality assessment for each of the studies.

Table 38: Key characteristics of comparator trials meeting the eligibility criteria for inclusion in NMA analysis and the FAME trial used in sensitivity analysis (reproduced from CS Table 33)

Trial number	Design summary	Patient population	Intervention (n)	Comparator (n)	Escape therapy	Primary outcome	Risk of bias
BOLT (Michaelides *et al*. 2010)[92]	RCT Phase II Single-blind	Adult patients with type 1 or 2 DM and centre involving CSMO who have received at least 1 prior macular laser therapy and no anti-VEGF treatment within the past three months. A baseline BCVA between 35 and 69 ETDRS letters and baseline CMT or ≥270µm	Bevacizumab 1.25mg PRN (n=42)	Laser PRN (n=36)	None	Mean BCVA change at 12 months	Low
ETDRS (Hornberger *et al.* 2006)[67]	RCT	Adult patients with macular oedema and mild to moderate diabetic retinopathy in at least one eye.	Laser PRN (n=144)	No treatment + deferred laser (n=293)	Deferred laser in no treatment arm	BCVA change of at least 15 letters from baseline each year	Unclear
FAME (Campochiaro *et al.* 2011)[90]	RCT Phase III Double-blind	Adult patients with DMO who have received at least 1 prior macular laser treatment with BCVA between 19 and 68 letters and mean foveal thickness of at least 250µm	Fluocinolone acetonide 0.2µg/day (n=375) Fluocinolone acetonide 0.5µg/day (n=393)	Sham (n=185)	Laser Pharmaceutical	BCVA change of at least 15 letters from baseline at 24 months	Low
OLK (Olk, 1986)[91]	RCT	DMO (defined as having two or more disc areas of retinal thickening and involving the centre of the macular) with BCVA less than 20/32 and better than 20/200	Laser PRN (n=82)	No treatment (n=78)	None	BCVA change from baseline at 12 months	Unclear
PROTOCOL I (DRCRN, 2010)[93]	RCT Phase III Double-blind	Adult patients with retinal thickening due to DMO with BCVA between 24 and 78 letters and CRT at least 250µm in the central subfield	Ranibizumab 0.5mg + laser PRN (n=187) Ranibizumab 0.5mg PRN + deferred	Sham injection + laser (n=293) Intravitreal triamcinolone 4mg + laser (n=186)	Deferred laser in ranibizumab monotherapy arm	Mean change in BCVA at 12 months	Low

			laser (n=188)				
RESTORE (Mitchell *et al*. 2011)[94]	RCT Phase III Double-blind	Adult patients with visual impairment due to focal or diffuse DMO in one eye and not other causes, with BCVA letter score between 39 and 78 and HbA1c at least 10%	Ranibizumab 0.5mg PRN (n=116) Ranibizumab 0.5mg + laser PRN (n=118)	Laser PRN (n=111)	None	Mean average change in BCVA over 12 months	Low
REVEAL (Ohji *et al.* 2012)[95]	RCT Phase III Double-blind	Adult patients with visual impairment due to focal or diffuse DMO in at least one eye who are eligible for laser treatment in the opinion of the investigator, with BCVA between 78 and 39 letters and HbA1c of at least 10%	Ranibizumab 0.5mg PRN (n=133) Ranibizumab 0.5mg + laser PRN (n=132)	Laser PRN (n=131)	None	Mean average change in BCVA over 12 months	Unclear
Abbreviations used in the table: BCVA, best corrected visual acuity; CRT, central retinal thickness; CSMO, clinically significant macular oedema ; DM, diabetes mellitus; DMO, diabetic macular oedema; ETDRS, Early Treatment of Diabetic Retinopathy Study; NMA, network meta-analysis; PRN, *pro ne rata;* RCT, randomised controlled trial; VEGF, vascular endothelial growth factor.							

Key differences between the clinical trials in the network included the use of escape therapy (e.g. deferred laser) and differences in standard clinical practice due to the wide variation in date when the trials were conducted. In terms of escape therapy, the ranibizumab monotherapy arm in PROTOCOL I and the no treatment arm in ETDRS both allowed deferred laser as required which was similar to in the dexamethasone 024 and BEVORDEX RCTs. FAME allowed non-study pharmaceutical or laser therapy at the investigators' discretion which confounds the efficacy results associated with fluocinolone acetonide. With regards to the variation in standard practice, the ETDRS and study by Olk et al. (hereafter referred to ask the Olk study) were both conducted before the year 2000, whereas the remaining studies were all conducted post-2000. The company reported in the CS that the ETDRS and Olk study are likely to contain patients unrepresentative of the equivalent populations today in which laser or no treatment would be considered treatment options. This is partly due to improvements in the management of diabetes and the diagnosis of DMO. It is also partly due to the introduction of alternative treatments for DMO such as ranibizumab. The company reported that they included the Olk and ETDRS studies in the NMA because they were 'essential' to the network. The company attempted to reduce this clinical heterogeneity in the NMA by using data from a specially designed post-hoc analysis of the ETDRS data using a selected patient cohort that they considered to be most similar to the DMO patients in the more recent RCTs. The population inclusion criteria for the post-hoc analysis included DMO patients with central macular thickening and baseline BCVA between 23-73 letters.

The baseline characteristics of the patients in the seven comparator trials included in the NMAs or sensitivity NMAs are presented in Table 39. The ERG note that there were differences in a number of the patient characteristics at baseline between the different trials, e.g., duration of DMO, visual acuity, previous treatment history and lens status at baseline. The ERG is unable to comment on the likely direction of effect of these differences for each comparator in the network due to the lack of baseline data for all characteristics for each of the trials.

Table 39: Baseline characteristics of the patients in the seven comparator trials included in the NMA's or sensitivity NMA's (reproduced from CS Table 34)

	ETDRS (n=448)	BOLT (n=80)	FAME (n=560)	Olk (n=160)	PROTOCOL I (n=668)	RESTORE (n=345)	REVEAL (n=396)
Demographics							
Age, mean years	59.3	64.2	62.5	Median: 64	Median: 63	63.5	61.1
Male, n (%)	212 (47.3)	55 (68.8)	323 (57.7)	NR	382 (57.2)	201 (58.2)	NR
Caucasian, n (%)	NR	39 (48.8)	396 (70.7)	NR	467 (69.9)	NR	NR
Disease characteristics							
Duration of DM, mean years (SD)	NR	14.1	20.9	Median: 14	Median: 17	14.3	NR
Type 2 DM, n (%)	NR	72 (90.0)	510 (98.1)	58 (36.3)	602 (90.1)	302 (87.5)	(98.7)
Baseline HbA1c, mean % (SD)	HbA1c <7: 18.5%	7.6	7.8	NR	Median: 7.3	NR	7.5
Duration of DMO, mean months (SD)	NR	NR	45.0	NR	NR	21.5	NR
Pseudophakic lens, n (%)	NR	13 (16.3)	204 (36.4)	6 (3.8)	NR	NR	NR
Baseline VA, mean letters (SD)	61.5 (10.5)	55.2	54.0	NR	≥20/63: 59.4% ≤20/80: 40.6%	63.5	58.6
Baseline CRT, mean µm (SD)	NR	494.0	456.1	NR	Median: 382	418.5	421.9
Bilateral DMO, n (%)	NR	NR	NR	NR	275 (41.2)	NR	NR
Treatment history for DMO in the study eye							

	ETDRS (n=448)	BOLT (n=80)	FAME (n=560)	Olk (n=160)	PROTOCOL I (n=668)	RESTORE (n=345)	REVEAL (n=396)
Treatment naïve, n (%)	448 (100)	NR	0	NR	253 (37.9)	182 (53)	NR
Prior laser, n (%)	0	NR	560 (100)	15 (9.4)	375 (56.1)	162 (47)	NR
Prior anti-VEGF, n (%)	0	NR	0	NR	69 (10.3)	0	NR
Prior steroid, n (%)	0	NR	0	NR	97 (14.5)	0	NR

Abbreviations used in the table: CRT, central retinal thickness; DM, diabetes mellitus; DMO, diabetic macular oedema; NMA, network meta-analysis; NR, not reported; SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor.
Source: Campochiaro *et al*. 2011[90]; DRCRN, 2010[93]; Hornberger *et al*. 2006[67]; Michaelides *et al*. 2010[92]; Mitchell *et al*. 2011[94]; Ohji *et al.* 2012[95]; Olk *et al*. 1986[91]

4.6.4 Heterogeneity

The company presented details of the between-study standard deviation for the base case and pseudophakic subgroup analysis as a measure of the between study heterogeneity in the CS with similar data provided for SA 1 in the company's response to clarification questions (Table 40). The results for all three NMAs suggest the presence of statistically significant differences in the between study standard-deviations (Table 40).

The company also presented a comparison of the mean total residual deviance with the number of unique data points within the base case analysis, the pseudophakic subgroup NMA and the SA 1 NMA. For all three models, the total residual deviance is substantially higher than the corresponding number of data points suggesting the models are a relatively poor fit.

Table 40: Between-study heterogeneity and model fit for base case total population and pseudophakic subgroup (adapted from CS Table 37 and Company's response to clarification Table 6)

Analysis	Between-study standard deviation (median; 95% CrI)	Total residual deviance (mean)	Number of unique data points
Base Case (total population)	0.11 [0.01, 0.41]	66.1	48
Pseudophakic subgroup	0.22 [0.02, 0.63]	61.7	48
SA 1 (including FAME)	0.12 [0.01, 0.42]	68.2	50
Abbreviations used in the table: CrI, credible interval; SA, sensitivity analysis			

The ERG is concerned that the models used for each of the NMAs conducted by the company are based on a heterogeneous network of trials, as indicated by the between study standard deviation and so relatively poor model fit, and thus the results of the NMAs may be unreliable. The ERG thus advises that all results from the NMAs are interpreted with caution.

The company reported in their response to clarification questions that, "the DIC that assists with model selection was not calculated" because the random effects model was selected *a priori* for all the NMA outcomes. The residual deviance for each outcome when using a fixed model for the NMA was thus not available so the ERG are unsure as to whether a fixed effects model may have provided a better fit to the data compared with the actual random effects models used by the company for the NMAs.

4.7 Results of the NMAs

4.7.1 Whole population, base case NMA results

The results of the base case NMAs were reported in the CS as relative risks where results which are greater than 1 indicate that the treatment under observation has a greater probability of gaining or losing at least 10 letters at 12 months compared with the reference treatment. For the outcome of

losing at least 10 letters, a favourable point estimate is an RR of less than 1. For the outcome of gaining at least 10 letters, a favourable point estimate is an RR of greater than 1. The ERG considers it important to highlight that the 95% credible intervals (95% CrIs) were quite wide for a large number of the RR estimates from the NMAs and the sensitivity analyses and thus there is a large amount of uncertainty around the efficacy estimates. In addition, the ERG had concerns around the comparability of the trials linking dexamethasone with the other treatments in the network and the poor fit of the models to the datasets. The ERG thus considers that the results reported from the NMAs should be interpreted with caution.

The results of the whole population base case NMA for the outcome of losing at least 10 letters is presented in Figure 22and the results for gaining at least 10 letters are presented in Figure 23. The ERG note that in comparison with sham/no treatment, all treatments have an RR of less than 1 for losing at least 10 letters and an RR of greater than 1 for gaining at least 10 letters. The treatments of interest that were associated with a statistically significant lower risk of losing at least 10 letters compared with sham/no treatment were bevacizumab 1.25mg PRN, DEX 700 plus laser PRN, laser PRN, ranibizumab 0.5mg + laser PRN and ranibizumab 0.5mg PRN. The same five trials were also associated with a statistically significant risk of gaining at least 10 letters (bevacizumab 1.25mg PRN, dexamethasone + laser, laser PRN, ranibizumab 0.5mg + laser PRN and ranibizumab 0.5mg PRN). Dexamethasone alone was not associated with a statistically significant benefit in gaining or losing 10 letters over sham/no treatment.

4.7.2 [redacted]

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4.7.3 Pseudophakic subgroup NMA results

The results of the pseudophakic subgroup NMA for the RR of losing at least 10 letters are presented in Figure 24and for the RR of gaining 10 or more letters are presented in Figure 25. All treatments in the analysis have a RR of less than 1 compared with sham/no treatment for losing at least 10 letters

with bevacizumab 1.25mg PRN, laser PRN, ranibizumab 0.5mg + laser PRN and ranibizumab 0.5mg PRN all resulting in a statistically significant reduction in the risk of losing at least 10 letters compared with sham/no treatment. All treatments in the network also had an RR greater than 1 compared with sham/no treatment with the same four treatments resulting in a statistically significant RR for losing at least 10 letters. Dexamethasone and dexamethasone + laser resulted in no significant difference for either gaining or losing at least 10 letters compared with sham/no treatment.

**[redacted]

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The base case NMA for the total population and the pseudophakic subgroup NMA both resulted in similar results for each intervention. However, the RR of dexamethasone plus laser resulting in either a gain of at least 10 letters or a loss of at least 10 letters compared with sham/no treatment was no longer statistically significant in the pseudophakic subgroup analysis compared with the whole trial base case analysis.

The RR of dexamethasone compared with sham/no treatment was lower for the pseudophakic subgroup [redacted] than for the total population (RR=0.71) although both were statistically non-significant. In addition, the RR of dexamethasone gaining 10 or more letters vs sham/no treatment are higher for the pseudophakic subgroup (RR=1.79) than for the total population (RR= 1.40). These results are in keeping with the results of the MEAD studies where the pseudophakic subgroup had greater improvements in visual acuity compared with the whole trial populations.

4.7.4 Results of SA1

The results for SA1 are presented in Figure 26. The inclusion of FAME in the NMA has had little effect on any of the efficacy estimates for the interventions included in the base case analysis. In terms of the efficacy of fluocinolone acetonide, it resulted in a statistically significant RR of losing 10 or more letters compared with sham/no treatment [redacted]). Fluocinolone acetonide 0.2µg PRN was also associated with a statistically significant RR of gaining 10 or more letters compared with sham/no treatment [redacted]There was no statistically significant difference associated with either gaining or losing 10 or more letters with fluocinolone acetonide 0.2µg PRN compared with dexamethasone (DEX 700 PRN) [redacted]

However, the ERG consider it important to note that there was a higher proportion of pseudophakic patients enrolled in FAME compared with the proportion enrolled in the MEAD studies and so the efficacy estimates of dexamethasone vs fluocinolone acetonide from the NMA may be biased towards favouring fluocinolone acetonide.

[redacted]

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[redacted]

[redacted]

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4.7.5 Results of SA2

The results of SA 2 are presented as ORs (Figure 28) rather than RRs. The results of ORs and RRs are not directly comparable. However, the ERG notes that the results for fluocinolone acetonide versus sham/no treatment demonstrate the same direction of effect in SA1 and SA2 although in SA1 there is a statistically significant difference favouring fluocinolone acetonide, whereas in SA2 the difference

is not statistically significant. In SA 2 fluocinolone acetonide (0.2µg PRN) has statistically non-significant higher odds of gaining 15 or more letters vs. sham/no treatment

[redacted]

[redacted]

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4.7.6 Results of updated NMA in response to clarification

The results of the updated NMA conducted in response to clarification question A8 which involved including NCT00035906 in the network (updated analysis) were compared with selected results from the other NMAs conducted by the company reported in Sections 4.7.1 to 4.7.3 (original analysis) and are presented in Table 41. The original analyses used in the comparisons in Table 41 by the company appear to have been selected based on the populations for which they would be considered a comparator for dexamethasone; i.e. bevacizumab and ranibizumab in the pseudophakic population NMA subgroup analysis. However, the ERG considers some of the analyses not reported in Table 41 would also be suitable for comparison with the updated analysis results although the ERG considers the key analyses for the pseudophakic subgroup have been presented. In addition, as discussed in Section 4.6 the ERG has general concerns with the NMAs in terms of the trials included, heterogeneity and model fit. The ERG does not consider the results of the updated analysis to improve the reliability of the estimates for the efficacy of dexamethasone with any of the comparators in the NMAs. The ERG does however note that the results of the updated analysis are similar to the original analysis results.

Table 41: Original and updated NMA analysis outcomes for key comparisons (Company's response to clarification, Table 5)

Comparison	Losing ≥10 letters, RR (95% CI)		Gaining ≥10 letters, RR (95% CI)	
	Original analysis	Updated analysis	Original analysis	Updated 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. 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)

Abbreviations used in the table: CI, confidence interval; DEX, dexamethasone; 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

4.8 Comparison of MEAD results with NMA results

The company reported in the CS that they conducted a pair wise meta-analysis synthesising data from MEAD-010 and MEAD-011 which they qualitatively compared with the results from the NMA for dexamethasone versus sham/no treatment. The company did not provide details of the data used in the pair wise meta-analysis and so the ERG is unable to validate the results of the analyses. However, the ERG note that the RR from the pair wise meta-analysis of losing 10 or more letters was [redacted] which is different to the RR from the NMA of 0.71 (95% CrI [0.41, 1.08]). In addition, the RR for gaining at least 10 letters at 12 months from the pair wise meta-analysis is [redacted] which differs from the NMA RR of 1.40 (95% CrI [0.92, 2.14]). The ERG is concerned that the point estimates are different between the two analyses (particularly for losing 10 or more letters) and that the uncertainty around the estimates from the NMA is substantially reduced compared to the meta-analysis. As the only the MEAD trials inform this analysis in the NMA they should be very similar. As such the ERG is concerned that the results of the NMA are so different from the meta-analysis but unfortunately has not had the time to investigate this more completely. However it does bring into question the face validity of the results from the NMA and the ERG has strong reservations about how robust any conclusion based on them might be.

4.9 Conclusions of the clinical effectiveness section

4.9.1 Summary of clinical results

- The primary results of the dexamethasone RCTs presented in the CS were for the whole trial populations in each of the RCTs and thus are not specific to any of the populations specified in the EU marketing authorisation for dexamethasone.
- The results of the MEAD studies are potentially flawed due to the high discontinuation rates across the trial arms and the use of a LOCF analysis to account for the missing data.
- In the pooled MEAD analysis, dexamethasone resulted in a statistically significant increase in mean BCVA average change from baseline and in the number of patients achieving both a ≥15 letter gain and a ≥10 letter gain from baseline compared with sham.
- From month 15 onwards in the MEAD studies the improvement in BCVA provided by dexamethasone 700µg relative to sham was reduced and didn't recover until after 36 months. The ERG notes that this trend coincides with cataract adverse effects during the second year of the study in the dexamethasone group.
- The mean BCVA change from baseline, the proportion of patients achieving at least a 10-letter improvement in visual acuity at study end and the HRQL analyses in PLACID demonstrated no significant difference between dexamethasone + laser versus laser alone.
- The most common ocular TRAEs with dexamethasone in the MEAD studies and dexamethasone + laser in PLACID were cataract formation and raised IOP.

- The mean BCVA change from baseline with dexamethasone for the pseudophakic patients in the MEAD studies was statistically significant at all time points compared with sham; and the pseudophakic patients in the dexamethasone group of the MEAD studies achieved a much greater improvement in BCVA compared to the whole trial ITT population. This could be a result of the impact of cataract adverse effects in the phakic patients in the whole trial population.
- There were fewer ocular AEs in the study eye in patients with a pseudophakic lens at baseline in the MEAD study patients who were randomised to dexamethasone compared with the whole study (ITT) population due to the absence of primary cataract AEs.
- The most common ocular AE reported in the pseudophakic subgroup was IOP increase although fewer patients in the dexamethasone group (24.7%) experienced raised IOP compared with those in the dexamethasone group for the total MEAD (safety) population (36.0%).
- Safety data suggest a similar safety profile for dexamethasone in the subgroup of patients with any prior treatment (including prior corticosteroid therapy) to that seen in the whole trial (safety) population of the pooled MEAD studies, with higher incidences of ocular adverse events in the dexamethasone group compared with the sham group.

4.9.2 Clinical issues

- UK marketing authorisation for dexamethasone restricts it use to the treatment of adult patients with visual impairment due to DMO, who are pseudophakic (have an artificial lens implant);
- None of the dexamethasone RCTs in the CS are specific to any of the populations specified in the EU marketing authorisation for dexamethasone;
- Absence of direct comparative data from RCTs comparing the EU licensed dosing regimen for dexamethasone with any of the comparators specified by NICE in the decision problem;
- The results of the MEAD studies that provide the majority of evidence for dexamethasone within the CS are potentially flawed due to the high discontinuation rates across the trial arms and the use of a LOCF analysis to account for the missing data;
- High levels of clinical and statistical heterogeneity in the NMA and so the ERG has strong reservations about how robust any conclusion based on them might be;
- Absence of data for some outcomes for some of the comparators in the decision problem, particularly the absence of outcome data for the relevant populations for this STA i.e. those specified in the EU marketing authorisation for dexamethasone;
- Limited long term data on the safety and clinical benefit of dexamethasone in DMO.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and a *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© EXCEL-based economic model. Table 42 summarises the location of the key economic information within the company's submission (CS).

Table 42. Location of relevant information within the company's submission

Information	Section (CS)
Systematic review of published economic evaluations	7.1, pg286
De novo analysis	7.2, pg307
Population	7.2.1, pg307
Model structure	7.2.2, pg312
Technology	7.2.7, pg325
Re-treatment and discontinuation	7.2.8, pg326
Clinical parameters and variables	7.3, pg331
Measurement and valuation of health effects and adverse events	7.4, pg371
Resource identification, valuation and measurement	7.5, pg394
Sensitivity analysis	7.6, pg416
Results	7.7, pg429
Validation	7.8, pg492
Subgroup analysis [not applicable]	7.9, pg493
Interpretation of economic evidence	7.10, pg494
Strengths and weaknesses of economic evaluation	7.10.3, pg495
Appendix 10: Search strategy for cost-effectiveness studies	10.10, pg583
Appendix 11: Quality assessment of cost-effectiveness studies	10.11, pg597
Appendix 12: Search strategy measurement and valuation of health effects	10.12, pg624
Appendix 13: Resource identification, measurement and valuation	10.13, pg638
Appendix 14: Key opinion leader input	10.14, pg647
Appendix 15: Supplementary efficacy data	10.15, pg666
Appendix 16: Disaggregated discontinuation data	10.16, pg669
Appendix 17: Scenario analysis: Additional mortality due to severe vision loss	10.17, pg671
Appendix 18: Supplemental utility data	10.18, pg672
Abbreviation used in table: CS, company's submission.	

5.2 Summary of the company's key results

In the base-case analysis, the company presented deterministic and probabilistic results for the comparisons of dexamethasone 700µg intravitreal implant *pro re nata* (DEX700 PRN) versus watch and wait (for patients with DMO who are considered unsuitable for, or insufficiently responsive to, non-corticosteroid therapy), and versus ranibizumab injection (for patients with DMO who are

pseudophakic). For the latter, two analyses were provided: one that used the list price of ranibizumab, and another that assumed a 50% discount in the price of ranibizumab, because ranibizumab is subject to a confidential patient access scheme (PAS) and the exact details of the discount in ranibizumab's price are unknown to the company. A 50% discount was chosen to represent the most pessimistic results for dexamethasone and allow the committee to select the ICER that most closely represents the true cost to the NHS. In scenario analyses, further comparisons were made with fluocinolone acetonide implant (for patients with DMO who are considered insufficiently responsive to non-corticosteroid therapy) and with bevacizumab, laser photocoagulation and watch and wait (for patients with DMO who are pseudophakic). A summary of the ICERs presented by the company in the base case analysis is provided in Table 43, for ease of reference.

Table 43. Summary of the ICERs presented by the company for the base case analysis

DEX700	ICER	Probability of cost effectiveness*
Population: patients with DMO who are considered unsuitable for non-corticosteroid therapy **Comparator: watch and wait**		
ICER – Deterministic	DEX700 dominates (less costly, more effective)	Not applicable
ICER – Probabilistic	DEX700 dominates (less costly, more effective)	60.8%
Population: patients with DMO who are considered insufficiently responsive to non-corticosteroid therapy **Comparator: watch and wait**		
ICER – Deterministic	DEX700 dominates (less costly, more effective)	Not applicable
ICER – Probabilistic	DEX700 dominates (less costly, more effective)	60.8%
Population: patients with DMO who are pseudophakic **Comparator: ranibizumab**		
A. Using the list price for ranibizumab		
ICER – Deterministic	£50,905** (DEX700 less costly, less effective)	Not applicable
ICER – Probabilistic	£89,531** (DEX700 less costly, less effective)	75.6%
B. Assuming 50% discounted price for ranibizumab		
ICER – Deterministic	Ranibizumab dominates	Not applicable
ICER – Probabilistic	Ranibizumab dominates	40.9%
Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio * Probability of dexamethasone considered as being cost-effective at a threshold of £20,000/QALY versus relevant comparator ** ranibizumab vs dexamethasone		

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic review of the economic literature to identify cost-effectiveness studies of therapies used in the treatment of vision impairment due to DMO. The search was carried out in February 2014 and updated in July 2014. Searches were performed in Medline and Medline In-Process and other non-indexed citations, Embase, Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Review and Effects (DARE), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and EconLit.

Search terms captured the condition of interest (DMO), a range of interventions (dexamethasone, aflibercept, bevacizumab, ranibizumab, trimacinolone acetonide, fluocinolone acetonide and laser photocoagulation) and used filters for economic evaluation studies based on SIGN recommendations. No date or language limits were applied. Relevant NICE guidance was identified and included within the description of identified studies. Further details of the search strategy are provided in the company submission (Appendix 10, pages 583-97). All search strategies developed by the company for identification of relevant economic evidence, data on health related quality of life (HRQL) and resource use and costs are presented in Appendix 9.9.

Studies were included in the review if they were a cost-effectiveness analysis evaluating a treatment for the management of vision impairment due to DMO. Studies were excluded if they were not a cost-effectiveness analysis, they were a cost-effectiveness analysis in an indication other than DMO or they were a cost-effectiveness analysis in DMO but did not evaluate a treatment for the management of DMO (e.g. diagnostic testing for DMO). Studies were also excluded if they met the inclusion criteria but were available as an abstract only, as this was deemed to be insufficient evidence for inclusion in the review.

After removing duplicates, the company identified a total of 202 citations in the initial search and nine citations in the update. Following review of these citations, the company identified seven relevant studies, and through an additional search, two relevant NICE technology appraisals. The quality assessment for each study was provided in the company submission (Appendix 11, pages 597-624). Methods and results of all studies have been summarised in tables in the company submission (Tables 59 and 60, respectively; pages 290-306). A summary of the company's overview of the economic models developed for the NICE Technology Appraisals is provided in Box 13.

Box 13. Overview of economic models developed for the NICE Technology Appraisals NICE TA237[43]/TA274[44] (ranibizumab for DMO) and TA271[45]/TA301[46] (fluocinolone acetonide for DMO), adapted from CS, Table 59.

NICE TA271 /TA301
Population: Patients with chronic DMO (original base case) and patients with chronic DMO and a pseudophakic lens (PAS submission scenario)

Intervention: Fluocinolone acetonide intravitreal implant (FA)

Comparators: 'Optimised standard of care' (OSC) (based on the FAME trial)[90]

Laser photocoagulation (LAS) (based on DRCR PROTOCOL B trial)[93]

Time horizon: 15 years

Cycle length: 3 months

Discounting: 3.5% per year

Model structure and assumptions:

Model included 13 BCVA-defined health states (defined by 5-letter increments in the treated eye) and death.

No distinction between treatment in the BSE or the WSE; bilateral treatment assumed for 35% of patients in the OSC group with a lower proportion in the FA group reflecting contraindication based on raised IOP.

In Years 1-3 distribution of patients across BCVA-defined health states taken directly from the FAME trials; beyond Year 3 Markov structure, with transition probabilities extrapolated from the last 4 quarters of the FAME trials. Patients receiving further FA treatment at Month 36 were assigned a probability of improving by 5 letters in each cycle; patients not receiving a further FA treatment at Month 36 and patients receiving OSC or LAS were assigned a probability of worsening by 5 letters in each cycle.

Utilities: Assigned to each BCVA-defined health state; utility data taken from Brown *et al.* (2000)[96], extrapolated to fit the model health states; 25% QALY uplift applied to bilateral patients; no utility decrement for side effects.

Re-treatment & rescue therapy: One FA implant assumed every 3 years; re-treatment at Month 36 if a patient had gained at least 5 letters. Withdrawal rates from FAME applied to calculate an adjusted re-treatment rate, applied equally across BCVA-defined states. Patients in FA and OSC arms could receive LAS and other therapies (triamcinolone, ranibizumab, bevacizumab and dexamethasone) based on rates observed in FAME.

Costs: treatment acquisition and administration costs, costs of treatment for adverse events and annual cost of blindness for patients whose treated-eye BCVA fell below 35 letters.

Amendments based on ERG request for clarification:

Use of utility data from Heintz *et al.* (2012)[97]; response rate amended using a 10-letter re-treatment criterion.

Patient access scheme submission:

Use of utility data from Brown *et al.* (1999)[98], Brown *et al.* (2000)[96] and Czoski-Murray *et al.* (2009)[99]. Assumption that changes in vision for patients treated in WSE had 30% of the HRQL impact of same change in vision from treating BSE; 20% treated in BSE, 40% treated in WSE and 40% treated bilaterally.

NICE TA237/TA274

Population: Patients with DMO; average age at baseline 63 years; baseline VA not reported.

Intervention: ranibizumab monotherapy (RAN), ranibizumab + laser (RAN+LAS)

Comparator: laser monotherapy (LAS)

Time horizon: 15 years

Cycle length: 3 months

Discounting: 3.5% per year

Model structure, input parameters and assumptions:

Patients assigned a starting BCVA between 75 and 36 letters. Health states defined by BCVA in the treated eye in increments of 10 letters (0-25; 26-35; 36-45; 46-55; 56-65; 66-75; 76-85 and 86-100). Transition probabilities taken from the RESTORE trial[94] in Year 1. In Year 2 vision assumed to remain constant based on DRCR.net PROTOCOL I.[93] In Year 3 onwards probability of improving or deteriorating based on natural history. Mortality data for general population adjusted using a relative risk for death of people with clinically significant DMO compared with people with DM but without DMO.

Utilities: Assigned to each health state based on EQ-5D data from RESTORE using linear regression. No utility decrement assumed for adverse events.

Treatment patterns: In line with RESTORE, 7 RAN injections assumed in Year 1, with a stopping rule for patients with BCVA >76 letters (no treatment costs). In Year 2, 3 additional injections for RAN and 2 additional injections for RAN+LAS in line with DRCR PROTOCOL I. Two and one laser treatments assumed in Years 1 and 2, respectively; no treatment assumed after Year 2.

Costs: Treatment acquisition and administration costs, costs of treating adverse events (cataract, endophthalmitis, retinal detachment and vitreous haemorrhage), costs of monitoring and costs of severe vision loss (applied to people whose treated eye was <35 letters).

Revised analysis based on appraisal consultation document (including first patient access scheme submission):

Revised model considered treatment in BSE only. Higher relative risk of mortality was applied to account for higher risk of mortality in DM population relative to general population.

Stopping rule removed so that patients were treated with RAN in all health states. Additional treatment beyond Year 2 was assumed; 2 injections of RAN in Year 3 and 1 injection in Year 4; 1 LAS treatment in Years 3 and 4. Vision assumed to remain stable in Years 2-4, with natural history applied from Year 5.

Scenario analysis whereby bilateral treatment was simulated for 35% of patients by doubling costs of RAN and treatment administration. Cost of severe vision loss decreased; 25% uplift in QALYs applied.

Subgroup analysis in patients with central foveal thickness >400µm added.

Revised patient access scheme submission:

Approximated ICER for treatment of both eyes calculated by multiplying ICER from BSE model by 1.5; utility values from Czoski-Murray *et al.* (2009)[99] applied in the base case.

Number of RAN injections amended to 7, 4 and 3 in Years 1-3, respectively, with no further injections.

Reduced time horizon of 10 years was adopted.

Abbreviations used in table: BCVA, best corrected visual acuity; BSE, better-seeing eye; DM, diabetes mellitus; DMO, diabetic macular oedema; ERG, evidence review group; FA, fluocinolone

acetonide; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure; LAS, laser; NICE, National Institute for Health and Care Excellence; OSC, optimised standard of care; QALYs, quality-adjusted life yeas; RAN, ranibizumab; WSE, worse-seeing eye.

ERG comment

The ERG considers that the search terms used by the company to identify economic evaluations were comprehensive and appropriate and that the inclusion and exclusion criteria were appropriate given the decision problem for this STA. For completeness, the ERG reviewed the two related NICE appraisals (TA271/301 and TA237/274) and found no additional cost-effectiveness studies included in their submissions. Moreover, ad-hoc searches indicated that it is unlikely that any relevant cost-effectiveness analyses have been omitted.

5.4 Summary and critique of the company's submitted economic evaluation by the ERG

5.4.1 NICE reference case checklist

Table 44 and Table 45 summarise the ERG's quality assessment of the company's economic evaluation.

Table 44 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for a base case analysis, with reference to the NICE scope outlined in Section 3; Table 45 summarises the ERG's appraisal of the quality of the company's *de novo* economic model using the Philips checklist[100].

The ERG's main criticisms of the cost-effectiveness analysis were:

- The mismatch between the study population in the MEAD trials (which provided efficacy data for dexamethasone in the NMA that informed the economic model) and the licensed DMO populations that were considered in the economic models.
- The use in the economic analysis on pseudophakic patients of NMA outputs resulting from a synthesis of data on pseudophakic and mixed DMO populations.
- The use of sham as a proxy for watch and wait, which may have potentially led to the relative effect of dexamethasone versus watch and wait being underestimated, although the ERG believes that the extent of underestimation is lower than the company claims.
- The assumption that the baseline distributions of BSE and WSE across BCVA states are independent from each other, especially considering that the BSE and SWE were fixed at initiation of treatment and throughout the model duration.

- The application in the economic model of relative risks from the NMA (which synthesised 12-month efficacy data) onto 3-month baseline transition probabilities, over the whole 3-year duration of all treatments. To do this, the economic analysis assumed that relative effects of all treatments considered in the NMA remain stable from initiation of treatment and up to 3 years of treatment duration; evidence from the MEAD trials suggests that this assumption may not hold, at least not in the whole DMO population
- The 'normalisation' of transition probabilities in the economic model, in order to ensure that these add up to 1, which resulted in the relative risks being effectively and consistently altered from their original values obtained from the NMA, thus introducing bias into the analysis, the direction and magnitude of which were not possible to ascertain or predict
- The restriction of transitions by a maximum of one BCVA state per cycle, which, as further analyses (requested by the ERG and undertaken by the company) showed, does not reflect trial evidence
- The naïve synthesis of discontinuation trial data in order to inform the model, which is inappropriate and may have introduced bias in the model
- An overestimate of the cost associated with severe vision loss (i.e. BCVA <35 letters), due to overestimation of the cost of residential care
- Lack of consideration of disutility associated with treatment administration and adverse events, although the ERG estimates that their impact on the results of the analysis should be inconsequential

These criticisms are described in greater detail in the subsequent tables.

Table 44. NICE reference case checklist for a base case analysis

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Broadly yes, although the ERG notes the scope was finalised before the agreed EU licence terms for use of DEX700 in DMO; hence the company limited consideration from 'DMO patients' to 'adult patients with visual impairment due to DMO, who are pseudophakic, or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy', which was narrower than the population defined in the scope. The population in the MEAD trials was not necessarily representative of patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy. Analysis on pseudophakic patients was based on data from a mixed (phakic and pseudophakic) population for a number of drugs.
Comparator(s)	Alternative therapies routinely used in the NHS	Broadly, yes. The company addressed all four comparators listed in the scope, however: • Combination therapies were not considered due to either lack of relevant evidence (regarding bevacizumab + laser and fluocinolone acetonide + laser) or due to evidence suggesting lack of clinical and cost effectiveness (in the technology appraisal of ranibizumab for the treatment of DMO, ranibizumab + laser was dominated by ranibizumab monotherapy) • Watch and wait was used as the main comparator for patients

		with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, which was not included in the scope. • Ranibizumab, bevacizumab and laser were not included in the analysis on DMO patients who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy • Fluocinolone acetonide was used only in a scenario analysis in patients who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy • Fluocinolone acetonide was not included in the analysis on pseudophakic patients with DMO; bevacizumab abd laser were used only in a scenario analysis in this population In addition, the combination of DEX700 with laser was not considered as the marketing authorisation for dexamethasone in patients with DMO is based on monotherapy.
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-utility analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes; the ERG notes that the time horizon selected (15 years) was long enough to capture the costs and consequences associated with DMO treatment and was consistent with previous cost-effectiveness studies identified in the systematic review undertaken by the company.
Synthesis of evidence on outcomes	Systematic review	Yes; a systematic review and NMA of efficacy data was carried out. However, the ERG notes that only 12-month data were used to inform the NMA which resulted in the exclusion of potentially relevant studies. Moreover, the application of NMA data on the model required making the assumption that relative effects remain stable over time, which does not appear to hold, and also required 'normalisation' of values which resulted in relative risks obtained from the NMA being consistently changed over time, which has introduced bias in the analysis. No synthesis of discontinuation data was attempted; raw trial arm data from different trials were utilised in the model.
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes, but EQ-5D data was obtained from the MEAD trials at baseline and was used only in scenario analysis; however, EQ-5D does not appear to be appropriate for the study population. A condition-specific preference-based measure (the VFQ-UI) which has been derived from NEI VFQ-25, was used instead to describe health states associated with visual impairment.
Benefit valuation	Time-trade off or standard gamble	Yes; TTO.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes; preference scores for the VFQ-UI have been elicited using TTO from 607 members of the general population in the UK, Canada, Australia and the USA.[101]

Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes; the company carried out deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses
Abbreviations used in the table: CEACs, cost-effectiveness acceptability curves; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ERG, evidence review group; HRQL, health-related quality of life; NEI-VFQ, National Eye Institute Visual Functioning Questionnaire-25; NICE, National Institute for Health and Care Excellence; OWSA, one-way sensitivity analysis; QALYs, quality-adjusted life yeas; TTO, time trade-off; VFQ-UI, Visual Functioning Questionnaire Utility Index.		

Table 45. Philips checklist[100]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated
S2: Statement of scope/perspective	Clearly stated (UK NHS)
S3: Rationale for structure	Clearly stated; the company described in detail clinician input derived at the advisory board meetings (CS; Appendix 14).
S4: Structural assumptions	The structural assumptions were transparent. The ERG had concerns about the validity of the following structural assumptions: • The baseline distributions of BSE and WSE across BCVA states were independent from each other (CS, pg336) • movements were restricted to improving or worsening by a maximum of one visual acuity state per cycle (CS; pg337) • patients were only at risk of FEI by the end of Year 1 or Year 2 (CS; pg351) During clarification the ERG asked the company to perform an analysis where the movements between health states were unrestricted using the actual 3-year MEAD trial data. The ERG also explored the impact of increasing the risk of FEI beyond year 2. The results from these analyses are presented in Section 0.
S5: Strategies/ comparators	The main comparators in the base case for DMO patients who are considered unstable for or insufficiently responsive to non-corticosteroid therapy and for DMO patients who are pseduophakic were watch and wait and ranibizumab, respectively. Fluocinolone acetonide was only included as a comparator ina scenario analysis for the population of DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; laser and bevacizumab were only included as comparators in scenario analysis for the population of DMO patients who are pseudophakic. The company assumed a maximum duration of treatment of 3 years in the base case. The ERG is concerned that the company has underestimated the duration of treatment in UK clinical practice if treatment continues until a patient is no longer responsive. The company provided a scenario analysis extending the duration to 5 years, but restrictions on the

	available data limited the validity of this analysis.
S6: Model type	Appropriate; cost-utility analysis.
S7: Time horizon	Appropriate: a 15 year horizon was applied within the model. The ERG notes that the time horizon selected was sufficient to capture the costs and consequences associated with DMO treatment and is consistent with the time horizons applied in previous cost-effectiveness studies identified in the company's systematic review.
S8: Disease states/pathways	Appropriate; the ERG notes that the health states correspond to those applied in previous cost-effectiveness studies identified in the company's systematic review.
S9: Cycle length	Appropriate; the ERG considers three months to be a reasonable cycle length to capture the consequences of modelled events and is consistent with the cycle lengths applied in previous cost-effectiveness studies identified in the company's systematic review.
Data	
D1: Data identification	Clinical efficacy data for dexamethasone were taken from the pooled MEAD trials. The company carried out a systematic review for the identification of comparator efficacy data. The company's literature searches for cost-effectiveness analyses, resource use and cost, and utilities were clearly described. However, the ERG notes that the company's inclusion criteria were too restrictive for the HRQL search. Some data were derived from studies identified as data sources in previous economic evaluations of treatments for DMO. The rationale for the selecting of data from studies non-systematically identified was not consistently described. Clinical expert opinion was used to inform parameters such as resource use and was elicited from an advisory board meeting (CS; Appendix 14).
D2: Pre-model data analysis	The company conducted a NMA to obtain the relative risks of improving or worsening vision, which were used to inform the model. The NMA utilised exclusively 12-month data, ignoring studies that did not report such data, and ignoring endpoint data in studies with longer time horizon. Details of pre-model data analysis relating to utilities were lacking from the CS; however, relatively comprehensive details were provided at clarification.
D2a: Baseline data	Baseline data were taken from the MEAD clinical trials which were representative of patients with DMO in the general population. 3-month data on patients treated with dexamethasone, collected over the 3-year duration of the MEAD trials, were used as baseline.
D2b: Treatment effects	Treatment effects for the economic model were estimated from a NMA. The ERG is concerned that 12-month treatment effects were applied across all cycles in the economic model, from initiation of treatment and up to 3 years of treatment duration, based on the assumption that relative effects are stable over time; this assumption, as evidence suggests, may not hold. Moreover, the economic model 'normalised' transition probabilities, effectively altering the values of relative risks obtained from the NMA. This issue, which is likely to have introduced bias in the economic analysis, is discussed further in Section 5.4.6.2. No synthesis of discontinuation data was performed. Discontinuation data taken from different trials were combind by 'naïve' synthesis. The ERG notes that "sham" data has been used as a proxy for non-treated (watch and wait) patients. This is likely to have overestimated the effect of watch and wait and, therefore, underestimated the relative treatment effect of dexamethasone.
D2c: Costs	The company used the latest source of data where possible (NHS Reference Costs 2012/13; MIMS [accessed July 2014] and Unit Costs for Health and Social Care 2012/13). The company used list prices for drugs included within the base case and performed scenario analysis varying the discount applied to ranibizumab and fluocinolone acetonide to take into account the agreed PAS available to the NHS (agreed price was unknown to the company). The ERG notes that NICE recommends use of eMIT to establish costs for drugs which

	receive a discount; the ERG carried out an analysis in which the cost reported in eMIT for latanoprost (a generic prostaglandin administered to patients with increased IOP) was applied within the model, instead of the list price reported in MIMS that was utilised by the company. The ERG regards the costs applied to residential care to be overestimated and inconsistent with previous NICE TAs for the treatment of DMO; the ERG carried out an analysis using alternative costs reported in Curtis 2013. The results of all additional analyses presented in Section 6.
D2d: Quality of life weights (utilities)	Utility data used in the model were based on VFQ-UI data obtained from MEAD trial participants. VFQ-UI is a vision-specific preference-based measure, derived from NEI VFQ-25. The company performed linear regression analyses on VFQ-UI and EQ-5D data from MEAD, using BCVA in WSE and BCVA in WSE as independent variables. This resulted in the development of an algorithm for the estimation of whole person utility from the BCVA in both the BSE and the WSE. The ERG had the following concerns around the utility data used in the model: • no details on the regression models tested, the process for the identification of the regression model selected, and the model fit were provided in company submission; these, however, were provided during clarification • regression analysis showed that the impact of adverse events on utility was non-significant; however, the VFQ-UI is a vision-specific measure and has not been designed to capture potential adverse events from treatment • no disutility due to treatment administration was considered, although its impact on the results is estimated to be relatively small During clarification the ERG asked the company to estimate QALYs for the first 3 years of the model using mean utilities estimated directly from patients' responses on the VFQ-UI, instead of estimating these from the regression model reported in the company submission. The results from this analysis are discussed in Section 6, however the copany's approach was not appropriate, as argued by the ERG.
D3: Data incorporation	Appropriate; the company clearly described how data were used in the model, all sources were referenced and copies of referenced papers were provided. Standard distributions were used for different outcomes (e.g. the gamma distribution for costs). The ERG notes a small number of errors within the model, the impact of which was generally small.
Assessment of uncertainty	
D4a: Methodological	Appropriate analytical methods were used, and were supported with sensitivity and scenario analyses to test the robustness of the chosen base case approach.
D4b: Structural	Different structural assumptions were not assessed.
D4c: Heterogeneity	Appropriate, the company presented results for each sub-population of DMO patients separately.
D4d: Parameter	Appropriate; uncertainty was assessed through deterministic and probabilistic sensitivity analysis.
Consistency	
C1: Internal consistency	The model appeared to be mathematically sound with no obvious inconsistencies. The company reported that the model quality assured by a health economist with experience in model validation. The ERG performed a number of checks, all of which indicated that the model functions as expected. A few errors were identified by the ERG, which did not have any significant impact on the results.
C2: External consistency	External consistency was discussed with clinical experts at the advisory board meetings (CS; Appendix 14). The results of the model were as expected.
Abbreviations used in table: BCVA, best corrected visual acuity; BSE, better-seeing eye; CS, company submission; DMO, diabetic macular oedema; ERG, evidence review group; FEI, fellow eye involvement; HRQL, health-related quality of life; MIMS, Monthly Index of Medical Specialities; NEI-VFQ, National Eye Institute Visual Functioning Questionnaire-25; NICE, National Institute for Health and Care Excellence; NMA, network meta-	

analysis; QALYs, quality-adjusted life yeas; TAs, technology appraisal's; VFQ-UI, Visual Function Questionnaire Utility Index; WSE, worse-seeing eye.

5.4.2 Model structure

The company's *de novo* model comprises a cohort Markov model that follows patients with DMO over a 15-year time horizon and models costs and QALYs associated with treatment of DMO and subsequent changes in patients' BCVA. The model follows both eyes of each patient; BCVA changes in each eye are modelled independently. Treatment may be modelled in both eyes (bilateral DMO) or in either the better-seeing eye (BSE) or worse-seeing eye (WSE) (unilateral DMO). Patients within the cohort who are affected unilaterally at baseline may develop DMO in their second eye, termed fellow eye involvement (FEI) and move to bilateral treatment. The BSE and WSE of each patient are defined at baseline and fixed throughout the time horizon. As illustrated in Figure 29, the Markov model consists of 6 visual acuity health states of 10-letter increments each, except the two extreme states, i.e. the mildest and the most severe; the definition of each health state is shown in Table 46. Each eye with DMO may transition between the 6 BCVA states every 3 months, which is the cycle length of the model. In each 3-month cycle the eye may move up (improved vision) or down (worsened vision) by a maximum of one BCVA state, or the eye may remain in the same visual acuity health state (stable vision). Treatment for DMO influences the probability of transitioning between the BCVA states. Eyes without DMO are assumed to retain constant vision. All patients are at risk of death throughout the model time horizon. A half-cycle correction has been applied in the model.

Figure 29. Model structure – visual acuity states (reproduced from CS, figure 54)

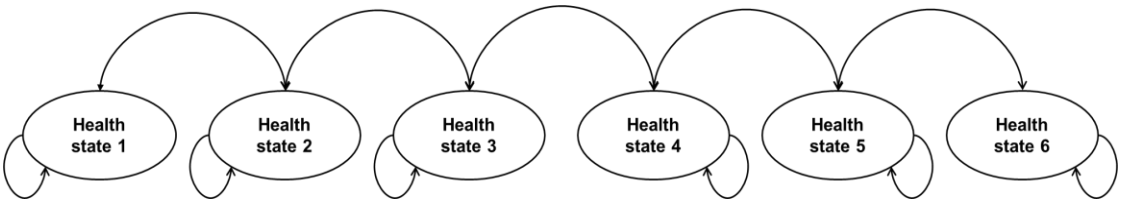


Table 46: Visual acuity health state definitions (reproduced from CS,Table 61)

	Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
ETDRS letters	≤35	36–45	46–55	56–65	66–75	≥76
Approximate Snellen equivalents at 6m/20ft	≤6/60	6/60–6/38	6/38–6/24	6/24–6/15	6/15–6/10	≥6/10
	≤20/200	20/200–20/125	20/125–20/80	20/80–20/50	20/50–20/32	≥20/32

	Legal blindness if BSE				20/40 in BSE is the legal threshold for driving	
Abbreviations used in table: BSE, better-seeing eye; ETDRS, Early Treatment Diabetic Retinopathy Study. Source: Gregori *et al.* (2010)[102]						

The model assumes a maximum duration of treatment of 3 years in the base case; the company's rationale for this assumption and the ERG critique of it are discussed in Section 0. At any time during treatment patients within the cohort may discontinue from treatment for one of two independent reasons:

- Lack (or loss) of efficacy of treatment;
- Adverse events and other non-efficacy related reasons (e.g. withdrawal of consent, lost to follow-up, protocol violation, personal reasons, etc.).

Discontinuation from treatment was modelled to reflect the high discontinuation rates that were observed within the MEAD trials (where 22.5% of patients in the pooled dexamethasone arms discontinued from the study due to adverse events and other non-efficacy related reasons, 4.3% discontinued due to lack or loss of efficacy of treatment and 9.8% were censored due to receipt of an off-protocol treatment). People discontinuing from treatment cannot be assumed to receive the costs and efficacy of treatment within the economic model. The economic model therefore assumed that, following discontinuation, patients receive no further treatment and subsequently their affected eye(s) transition(s) through the BCVA states at a rate consistent with the natural history of vision in patients with DMO. The company expressed the opinion that modelling an explicit next line of treatment following discontinuation would address a different decision problem, i.e. assessment of an optimal sequence of treatments for DMO; therefore, it was decided the assumption of no treatment received following discontinuation was most appropriate for the decision problem addressed by their economic analysis.

The model also considered five key adverse events of interest that may require medical or surgical intervention, comprising cataract, raised increased ocular pressure (IOP), retinal detachment, endophthalmitis and vitreous haemorrhage. Incorporation of adverse events in the model is discussed further in Section 5.4.8 of this report.

Visual acuity health states were based on a 10-letter change in BCVA on the ETDRS eye chart because, according to the company, this 10-letter change is often used as a measure of visual acuity in clinical trials of interventions for DMO. It was argued that a gain or loss of 10 letters may be

associated with a clinically significant change in the health-related quality of life (HRQL) of the DMO population. Severe vision loss (defined as BCVA ≤ 35 letters within the model) in both eyes was considered clinical blindness and was associated with increased costs and mortality (discussed in relevant sections below).

The 3-month cycle length of the Markov model was selected to be consistent with the visit schedule in the MEAD trials, which are the main source of efficacy and resource use data for dexamethasone.

The economic model was structured and populated using a number of simplifying assumptions:

- Patients within the cohort who were affected bilaterally from baseline (or who developed FEI) were assumed to receive the same treatment, at the same frequency and achieve the same level of efficacy in both eyes. This assumption was justified by supporting evidence on 18 DMO patients who were treated bilaterally with ranibizumab and showed a symmetrical functional response, defined as an increase in BCVA of at least 5 letters on the ETDRS scale, in 72% of patients.[103] Based on this evidence, it was assumed that a symmetrical response would be seen with any treatment for DMO.
- The BSE and WSE were defined at baseline and fixed throughout the time horizon. The company acknowledged that, in reality, changes in BCVA through progression of DMO or through the treatment of DMO may cause the eyes to change status; the BSE may become the WSE (due to disease progression) or the WSE may become the BSE (due to efficacy of treatment) and the true effect of treatment may not be accurately captured; however, it was argued that this simplifying assumption is consistent with previous economic modelling on DMO.
- Movements between health states were restricted to a maximum of one BCVA state in each 3-month cycle. Therefore, any improvement or worsening in the data that was greater than one BCVA state, was restricted to a movement of only one state. This assumption was necessary to enable the Markov model to be informed by the output of the network meta-analysis (NMA), which will be further discussed in Section 5.4.6.2, given the level of reported information within the trial source publications. The company argued that in order to allow movement of more than one BCVA state in the model would require evidence on the proportion of patients who gained or lost at least 20 letters, which is not a widely reported outcome in study publications. The company acknowledges that this assumption constitutes a limitation of the analysis, as it does not allow capturing the proportion of eyes that would gain or lose a high number of letters and would therefore move up or down by more than one BCVA states. This assumption, according to the company, may have introduced bias, as it may have under-estimated treatment effect for treatment with better (more extreme) visual acuity outcomes. Conversely, it may have inflated the treatment effect for treatments with poorer (more extreme) visual acuity outcomes. Nevertheless, the company expressed the view that making this assumption of a movement up or down by a maximum of one BCVA state was the most robust approach to populating the Markov model with NMA outputs, and was consistent with the assumption used in the economic model developed for the NICE TA for aflibercept for the treatment of central retinal vein occlusion.[104]

- FEI might occur only at the end of Year 1 or Year 2. This assumption was made to prevent the need for further sets of health states to be modelled for the fellow eye. It was claimed that this assumption was validated against the MEAD clinical data, in which the majority of incidences of FEI occurred during Years 1 and 2. Furthermore, the company was advised by clinical experts that this was a reasonable assumption and that if the second eye was going to develop DMO, it would likely do so within 2 years of the first eye developing DMO.
- Upon development of DMO in the fellow eye, the same treatment as received in the first eye was assumed to be given for a period of up to 3 years starting from this point. Treatment in the fellow eye was assumed to be initiated at the end of the year in which the eye developed DMO. For example, if a patient within the cohort was affected unilaterally at baseline in their BSE, and their WSE developed DMO during Year 1, it was assumed that the BSE would receive treatment during Years 1-3 and the WSE would receive treatment during Years 2-4, provided that the patient did not discontinue from treatment. The newly affected eye was assumed to receive treatment at the rate expected in Year 1, and to receive the efficacy of treatment associated with Year 1.
- In the case of bilateral DMO at baseline or FEI, the model assumed that the patient, rather than each eye, was at risk of discontinuation; in the case of FEI, since the initially affected eye was at risk of discontinuation as observed in Year 2 (or 3) while the newly-affected eye was at risk of discontinuation as observed in Year 1, the patient risk of discontinuation was calculated using the formula for the probability of either eye discontinuing, assuming that the probabilities are independent:

$$P(A \cup B) = P(A) + P(B) - (P(A) \times P(B))$$

- If a patient discontinued from treatment and then developed FEI, both eyes received the transition probabilities associated with eyes with DMO which discontinued from treatment.
- The model tracked whether the initially affected eye was the BSE or the WSE for the purposes of assigning utilities. Resource requirements were assumed to be the weighted average of the resource use associated with the year of treatment each eye is receiving.
- Eyes without DMO retained constant vision (unless they developed FEI); the company acknowledged the fact that patients with diabetes mellitus (DM) are at a higher risk of ocular comorbidities such as diabetic retinopathy, cataracts and glaucoma, so eyes without DMO may still be likely to experience a decline in vision. However, the company argued that all patients within the cohort, regardless of the DMO treatment received, had the same probability of having unilateral DMO and experienced the same risk of ocular comorbidities in their fellow eye, hence any vision loss resulting from ocular comorbidities other than DMO would affect all cohorts equally; therefore non-consideration of the negative effect of ocular comorbidities on vision should not impact on the model outcomes.
- Each patient was assumed to be phakic or pseudophakic in both eyes where both eyes were affected with DMO.

ERG comment

Following consultation with clinical experts, the ERG considers the model structure (including the main health states and the cycle length) to be appropriate, consistent with the progression of the

disease as reflected in changes in vision acuity and the availability of 3-month clinical data from the MEAD trials, respectively; modelling BCVA changes in each eye independently allowed a more realistic representation of patient experience and in theory enables more accurate estimation of HRQL, as it considers the impact of each of the BSE and the WSE on HRQL separately, as it will be discussed in Section 5.4.10. Consideration of unilateral DMO and potential subsequent FEI or bilateral DMO from baseline is consistent with the presentation and progression of DMO in clinical practice.

Clinical expert opinion was that the definition of health states using 10-letter increments is reasonable and that a 10-letter change reflects clinically significant change; the assumption that each eye can only transition between adjacent health states in every 3-month cycle was also considered reasonable for simplification purposes and broadly reflective of clinical changes observed in patients with DMO in routine practice. However, during clarification the ERG requested the company to perform additional analyses using the actual MEAD data for watch and wait, assuming restricted movements (**analysis A3**) and unrestricted movements (**analysis A4**). The results, presented in Section 6.1.1, indicate that this assumption does not hold and has underestimated the efficacy of DEX700 relative to watch and wait in terms of QALYs gained.

Treatment discontinuation is an important aspect of any therapy, and the ERG believes its inclusion in the model structure increases the model's face value. The ERG finds reasonable the company's justification for assuming no further treatment for patients who discontinue the initiated treatment and the progression of vision according to the natural history of the disease, as modelling further lines of treatment would divert the focus of the original decision question and would likely introduce uncertainty in the model, in terms of the efficacy of the next line of treatment (people who have discontinued a previous treatment are likely to be different from treatment naïve patients and data specific to people discontinuing a previous treatment are very unlikely to be available). Moreover, clinical experts advised the ERG that patients with DMO considered unsuitable for, or insufficiently responsive to non-corticosteroid treatment, are unlikely to receive an alternative active therapy following discontinuation of dexaethasone in routine clinical practice since treatment options have been exhausted.

Clinical expert opinion validated the assumption that both eyes of patients with bilateral DMO at baseline receive the same treatment and have similar symmetrical response. Furthermore, clinical experts expressed the view that, although an eye may actually change from BSE to WSE and vice versa during progression of DMO, this does not happen in the majority of patients, so fixing each eye as BSE or WSE from baseline and throughout the time horizon of the model was a reasonable assumption, and was unlikely to have introduced bias in the analysis. Clinical experts also found acceptable the simplifying assumption that in patients with bilateral DMO both eyes are either phakic

or pseudophakic, as, based on their experience, in routine clinical practice roughly 65% of patients receive bilateral cataract surgery and thus become pseudophakic in both eyes and this includes patients with DMO; so this assumption accounts for the majority (even though not a large one) of DMO patients.

In contrast, clinical expert advice was that the assumption that FEI may occur only at the end of Year 1 or Year 2 is too simplistic and actually FEI may occur after 2 years and during the 15-year time horizon of the analysis in a substantial proportion of patients. The company's argument that the majority of FEI occurred within the first 2 years in the MEAD trials is not robust, as the duration of MEAD trials was only 3 years, so long-term data on FEI that could establish a decline in the risk of FEI over the time horizon of the model (15 years) were not available from these trials. On the other hand, the ERG agrees with the company that modelling of FEI over a period beyond the end of Year 2 of the model would introduce complexity into the model structure; for this reason, a scenario analysis was undertaken by ERG, which assumed an increased probability of FEI at 80% for the first 2 years, to account for the additional risk for FEI over the 15-year time horizon of the model. This analysis overestimates any impact of FEI on the results, as it brings forward, i.e. earlier in time, the additional costs and outcomes associated with the risk of FEI over the 15 years of the model (which, were a model assuming an annual risk of FEI over 15 years implemented, would be discounted). Nevertheless, it allows exploration of the impact of an increased risk of FEI on the cost effectiveness results and shows that an increased risk of FEI increases the cost-savings associated with dexamethasone relative to watch and wait; the impact of changes on risk of FEI is not substantial, given that a significant proportion of patients ([redacted] in the DMO population; [redacted] in pseudophakic patients with DMO as shown in Section 5.4.3.2) is already treated for bilateral DMO at baseline. A description of the analysis carried out by the ERG is presented in Section 5.5.2.2, with results provided in Section 6.1.2.2 (**analysis C1**). This scenario had no significant impact on the base case results of the economic analysis.

The ERG also considers that the assumption that eyes without DMO retain constant vision is acceptable as a simplification, due to the amount of data and the model complexity that would be required in order to accurately represent vision changes due to other ocular comorbidities of DM in eyes not affected by DMO. Nevertheless, the ERG notes that, in reality, the impact of non-DMO eye vision on overall HRQL depends on the level of vision in the DMO-affected eye: if vision acuity is severely deteriorated in the DMO-affected eye (for example, as a result of no treatment or less effective treatment), then the impact of the non-DMO vision on overall visual acuity and HRQL becomes more prominent.

5.4.3 Population

5.4.3.1 Population considered in the economic analysis versus the NICE final scope

The population considered by the company for this STA comprised adult patients with DMO and resulting visual impairment who are either:

- considered unsuitable for non-corticosteroid therapy;
- considered insufficiently responsive to non-corticosteroid therapy;
- pseudophakic,

The company presented results for each of these populations separately. The justification for the selection of these three sub-populations of patients with DMO for consideration in the economic analysis was the marketing authorisation for dexamethasone, which states that dexamethasone is indicated "for the treatment of adult patients with vision impairment due to diabetic macular oedema (DMO) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy".[105]

DMO patients considered unsuitable for non-corticosteroid therapy

The company's economic analysis for patients with DMO who are considered unsuitable for non-corticosteroid therapy utilised data for the whole DMO population in the pooled MEAD studies as a proxy. The population of patients with DMO who are considered unsuitable for non-corticosteroid therapy is a subset of the whole DMO population that is extremely difficult to quantify, according to the company; therefore, no efficacy data specific to this sub-population were possible to obtain in order to inform the economic model. The company's analysis thus made the assumption that there is no differential efficacy of dexamethasone (and sham treatment) in the population of DMO patients who are considered unsuitable for non-corticosteroid therapy compared with the whole DMO population.

DMO patients considered insufficiently responsive to non-corticosteroid therapy

The company's economic analysis for patients with DMO who are considered insufficiently responsive to non-corticosteroid therapy utilised data for the whole DMO population in the pooled MEAD studies as a proxy. This was justified as very limited efficacy data relevant to this sub-population were available and the existing evidence did not, according to the company's view, suggest a differential efficacy of dexamethasone in DMO patients who are considered insufficiently responsive to non-corticosteroid therapy compared with the whole population:

- the majority of patients enrolled in the MEAD trials were pharmacological treatment naïve, as at the start of the study enrolment period (February 2005 to June 2009) no pharmacological treatment was licensed for the treatment of DMO;

- the company reported that the modified intention-to-treat (mITT) population in the MEAD trials, which was used in the economic analysis, included only a very small proportion of dexamethasone patients who had received previous anti-VEGF therapy ([redacted]) from which it would be difficult to draw any meaningful conclusions;
- [redacted] of dexamethasone patients in the mITT population of the MEAD studies had already been exposed to laser treatment, and in these patients there was no significant difference in outcomes compared with the total dexamethasone mITT population.

The company's analysis thus made the assumption that there is no differential efficacy of dexamsethasone (and sham treatment) in the population of DMO patients who are considered insufficiently responsive to non-corticosteroid therapy compared with the whole DMO population.

DMO patients who are pseudophakic

The company's economic analysis for patients with DMO who are pseudophakic utilised dexamsethasone data from the subgroup of pseudophakic patients in the pooled MEAD clinical studies. For the comparators, where possible, efficacy data from a pseudophakic population with DMO were used. However, not all study publications reported the necessary data for pseudophakic patients. Therefore, to ensure a comparison against all treatments of interest was possible, the NMA that informed the economic model utilised efficacy data for the whole DMO population in the absence of data for the pseudophakic sub-population with DMO.

The studies that did not report pseudophakic data included anti-VEGF or laser treatments. The company claimed that, since these treatments are not known to have an increased risk of cataract (as observed with corticosteroid therapies), it is reasonable to assume that they do not have a subgroup effect for pseudophakic patients; consequently it is acceptable to use data for the whole DMO population from these studies as a proxy for the pseudophakic population with DMO, to enable a comparison between these treatments and dexamsethasone in this population.

Nevertheless, the company acknowledged that including evidence for the whole DMO population for some treatments and data for the pseudophakic population for other treatments is a limitation of the analysis, as the whole population will include a mixture of both phakic and pseudophakic patients who, in general, may have different characteristics (for example, DMO patients presenting with a pseudophakic lens may on average be older than those presenting with a phakic lens). However, using mixed data on pseudophakic patients with DMO and on the whole population with DMO was deemed to be necessary by the company to enable comparison of dexamsethasone with other relevant comparators in patients with DMO who are pseudophakic. The trials used in the NMA on pseudophakic patients with DMO, that evaluated treatments considered in the respective economic analysis and the population that provided the efficacy data in each are shown in Table 47.

Table 47. Trials included in the network meta-analysis of treatments for DMO in pseudophakic patients that assessed treatments considered in the respective economic analysis, by population analysed according to phakic status

Trial	Treatments assessed	DMO population analysed by phakic status
MEAD-010	DEX700 PRN Sham/No treatment	Pseudophakic
MEAD-010	DEX700 PRN Sham/No treatment	Pseudophakic
BOLT	Bevacizumab 1.25mg PRN Laser PRN	Mixed
ETDRS	Laser PRN Sham/No treatment	Mixed
Olk	Laser PRN Sham/No treatment	Mixed
PROTOCOL I	Ranibizumab 0.5mg PRN Ranibizumab 0.5mg + laser PRN Laser PRN	Pseudophakic
RESTORE	Ranibizumab 0.5mg PRN Ranibizumab 0.5mg + laser PRN Laser PRN	Mixed
REVEAL	Ranibizumab 0.5mg PRN Ranibizumab 0.5mg + laser PRN Laser PRN	Mixed
Abbreviations used in table: DEX700 PRN, dexamethasone 700µg *pro re nata;* DMO, diabetic macular oedema; PRN, pro *re nata*		

ERG comment

The NICE final scope for this STA specifies the population of the analysis as "people with diabetic macular oedema (DMO)".[53] Nevertheless, given the marketing authorisation of dexamsethasone for patients with DMO, the ERG considers reasonable the company's decision to conduct separate analyses for the sub-populations described under the licensed indication.

Clinical expert advice indicated that the participants in the MEAD trials are not representative of patients with DMO who are considered unsuitable for or non-responsive to non-corticosteroids, and most of them might, in fact, be eligible to be treated with an anti-VEGF, as the large majority had received no previous treatment with an anti-VEGF (see Table 48 in next section). In addition, the ERG notes that a patient who has not previously responded to anti-VEGF or laser treatment, may be overall treatment-resistant and less likely to respond to other treatments as well; this means that consideration of the MEAD population as a proxy for patients with DMO who are insufficiently responsive to non-corticosteroid therapy has likely overestimated the treatment effect in favour of dexamsethasone. In the absence of more appropriate data, the ERG accepts the company's approach to use the whole patient population in the MEAD trials as a proxy for these sub-populations.

However, it is noted that the use of the MEAD population as a proxy for patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy has raised concerns among the clinical experts advising the ERG, is an important limitation of the economic analysis and should be taken into account when interpreting the findings of the analysis.

Regarding the use of efficacy data for anti-VEGF and laser treatments from the whole DMO population as a proxy for the pseudophakic sub-population with DMO in the absence of relevant data, clinical experts commented that both treatments do not increase the risk of cataract, which is the main side effect from DMO treatment affecting BCVA (i.e. the outcome measure of the economic analysis); this means that their effect on BCVA should not be considerably different between the 2 populations (whole DMO and pseudophakic). One the other hand, it was suggested that pseudophakic patients with DMO may have a slightly higher BCVA compared with the whole DMO population, which may enhance the relative effects of treatment.

Moreover, phakic patients with DMO are subject to cataract formation, at a risk that is higher than that observed in the general population (as patients with DM are at higher risk for developing cataract).[106-111] The ERG highlights that formation of cataract in the phakic sub-group reduces the mean visual acuity in the whole DMO population, which is one of the main outcomes of interest in the clinical and economic analysis of this STA. Pseudophakic patients, on the other hand, are at no risk for cataract formation. So the use of the whole DMO population as a proxy for the pseudophakic population with DMO is likely to have underestimated the effect of anti-VEGF and laser treatments on pseudophakic DMO patients.

Another issue that was raised by clinical experts was that some patients who are pseudophakic may develop ‘posterior capsule opacification’ which degrades the retinal image quality. These patients can have a type of laser treatment called Yttrium Aluminum Garnet (YAG) capsulotomy, which breaks open the opacified posterior capsule and improves their vision. This treatment may temporarily affect the degree of DMO and provides a path for anti-VEGF agents to leave the eye via the anterior segment, so pseudophakic patients who have had YAG capsulotomy are a separate subgroup of the pseudophakic group, and should be potentially examined separately, particularly when anit-VEGF agents are used.

Also, clinical expert opinion was that laser treatment is easier to perform in patients who are pseudophakic (because light penetrates the eye better) and thus it is possible that pseudophakic patients with DMO may respond (anatomically) better to laser compared with the whole DMO population.

The ERG concludes that use of the whole DMO population as a proxy for pseudophakic DMO patients for anti-VEGF and laser treatments is not ideal and should be avoided, but in the absence of clinical data that are specific to pseudophakic patients with DMO, use of the whole DMO population as a proxy is acceptable for the purposes of this STA. However, the ERG recommends that results referring to the pseudophakic DMO population, in comparisons where the whole DMO population has been used as a proxy, be interpreted with caution.

Given the marketing authorisation of dexamsethasone, the availability of clinical data, and clinical expert advice, the ERG finds reasonable the company's approach regarding the sub-populations considered in the company's economic analysis but has concerns about the assumptions made in order to populate the model with relevant data for each sub-population, especially with regard to DMO patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy. Therefore, the ERG wishes to emphasise that the results of these analyses should be interpreted with caution.

5.4.3.2 Baseline characteristics of modelled population

The baseline characteristics of the modelled population were based on data obtained from the population of the pooled dexamsethasone 700µg arms in the MEAD trials, as the company claimed that there were no differences in baseline demographic or study eye characteristics between the dexamsethasone 700µg and sham treatment groups in the MEAD studies The economic analysis utilised data obtained from a modified intention to treat (mITT) population, which included only patients who had at least one follow-up visit. Data from 2 patient populations (i.e. all DMO and pseudophakic) were utilised, in accordance with the 3 analyses undertaken: data from the mITT whole population with DMO (as a proxy for patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy); and data from the pseudophakic mITT population with DMO. More specifically, the following baseline characteristics and data were utilised from the pooled dexamsethasone arms of the MEAD trials:

- The average age and gender (to calculate age-and gender-related risk of mortality);
- The proportions of patients within the cohort who have unilateral DMO in the BSE or the WSE, or bilateral DMO at baseline;
- The proportion of patients within the cohort who develop FEI;
- The baseline distribution of vision across BCVA states for BSE and WSE of every patient.

Table 48 shows a number of baseline characteristics of the whole DMO population and of pseudophakic patients with DMO for both the ITT and mITT dexamsethasone and sham treatment arms from the pooled MEAD trials.

Table 48. Baseline characteristics of all patients with DMO and of pseudophakic patients with DMO in the pooled MEAD trials

Characteristic	**ITT population (CS Table 15)**		**Modified ITT population (mITT)[112]**	
	All DMO patients			
	DEX700 (n=351)	**Sham (n=350)**	**DEX700 (n=[redacted])**	**Sham (n=[redacted])**
Mean age (SD)	62.5 (8.3)	62.5 (9.5)	[redacted]	[redacted]
Male, n (%)	213 (60.7)	217 (62.0)	[redacted]	[redacted]
Previous treatment for DMO in study eye, n (%)				
Focal/grid laser	231 (65.8)	243 (69.4)	[redacted]	[redacted]
Anti-VEGF	25 (7.1)	26 (7.4)	[redacted]	[redacted]
None	104 (29.6)	89 (25.4)	[redacted]	[redacted]
Characteristic	**ITT population (estimated from data reported in CS Appendix 21)**		**Modified ITT population (mITT)[112]**	
	Pseudophakic patients with DMO			
	DEX700 (n=[redacted])	**Sham (n=[redacted])**	**DEX700 (n=[redacted])**	**Sham (n=[redacted])**
Mean age (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Previous treatment for DMO in study eye, n (%)				
Focal/grid laser	[redacted]	[redacted]	[redacted]	[redacted]
Anti-VEGF	[redacted]	[redacted]	[redacted]	[redacted]
None	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; mITT, modified intension-to-treat; NE, non-estimable; ITT, intension-to-treat; SD, standard deviation.				

Table 49 provides the baseline distributions of the whole DMO population and the pseudophakic patients with DMO by DMO status, as observed in the pooled dexamsethasone arms of the MEAD trials, which were utilised in the economic model.

Table 49. Baseline distributions by DMO status in the whole DMO population and the pseudophakic patients with DMO in the pooled dexamsethasone arms of MEAD trials that were utilised in the economic model

Characteristic	**Whole DMO population**	**Pseudophakic patients with DMO**
Proportion of patients with • Unilateral DMO in the WSE • Unilateral DMO in the BSE • Bilateral DMO	[redacted]	[redacted]
Abbreviations used in table: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.		

The proportion of fellow eyes that developed DMO over Years 1 and 2 in the model was assumed to be [redacted], which was the incidence of FEI in the pooled MEAD dexamsethasone arms over the 3-year study duration. This was 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" as recorded in the MEAD trials. This proportion was converted by the company into an annual rate of [redacted], using the exponential cumulative distribution function and assuming that the risk is constant over time. A scenario analysis was undertaken whereby the rate of FEI was based on the specific fellow-eye occurrence of "diabetic macular (o)edema" recorded in the non-study eye during the MEAD study. This resulted in a lower rate of FEI over the 3-year duration of the MEAD study of [redacted]% of dexamethasone patients, which was converted into an annual rate of [redacted] over Years 1 and 2 of the model using the exponential cumulative distribution function, assuming that the risk is constant over time. Moreover, a scenario assuming no FEI was considered by the company.

The baseline distribution of vision assumed for patients within the cohort with unilateral DMO in the BSE or WSE or with bilateral DMO is shown in Table 50. The distribution for a BSE or WSE affected with DMO was taken from the study eye data; for a BSE or WSE without DMO this was taken from the non-study eye data in the MEAD trials.

Table 50. Baseline distribution of vision by DMO status in the whole DMO population and the pseudophakic patients with DMO in the pooled dexamsethasone arms of MEAD trials that were utilised in the economic model (adapted from CS Tables 71 and 72)

DMO status	Eye	Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
All DMO patients							
Unilateral DMO in BSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in WSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pseudophakic patients with DMO							
Unilateral DMO in BSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in WSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in table: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.							

ERG comment

The ERG asked the company to clarify why mITT data were used instead of ITT data. The company's response is presented in Box 14.

Box 14. Company's response regarding use of baseline characteristics from the modified intension-to-treat population in the economic model (Company's response to clarification, pg 43)

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).
Abbreviations used in box: DEX700 PRN, dexamethasone 700µg *pro re nata*; LOCF, last observation carried forward; mITT, modified intention-to-treat.

The ERG is satisfied that there are no important differences between mITT and ITT datasets, as very few participants ([redacted] out of 351 patients ([redacted]) in the whole DMO population and [redacted] out of [redacted] patients ([redacted]) in the pseudophakic population), were excluded from analysis.

The ERG also asked the company to clarify why the following data were taken selectively from the dexamethasone arm of the pooled MEAD trials, and not from the pooled population of both dexamethasone and sham treatment arms of the pooled MEAD trials:

- The proportions of patients within the cohort who have unilateral DMO in the BSE or the WSE, or bilateral DMO at baseline;
- The proportion of patients within the cohort who develop FEI.

The company's response was that "baseline data was taken from the dexamethasone treatment arm in order to reflect the characteristics of patients who were actually treated with dexamethasone 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 dexamethasone patients are representative of a general DMO population". The company subsequently presented data on 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 the pooled MEAD trials (Table 51). These data, as stated by the company and agreed by the ERG, demonstrate that there is very little difference between the

proportions observed in each of the dexamethasone, sham and pooled populations and therefore the choice to use the dexamethasone data is unlikely to have affected the results of the analysis.

Table 51. Baseline distributions by DMO status in the whole DMO population and the pseudophakic patients with DMO in the pooled MEAD trials, by treatment arm (Company's response to clarification, Table 39)

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%

Abbreviations used in table: BSE, better-seeing eye; DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; WSE, worse-seeing eye.

The company also presented data on the proportion of patients within the cohort who develop FEI, by treatment arm in the pooled MEAD trials (Table 52). The company acknowledged that there was some difference in the rate observed across the treatment arms and the pooled dataset; however, it was noted that the rate was highest in the dexamethasone treatment arm (broad definition used in base case). Scenario analyses were presented within the submission using the lower rate (strict definition) and also including no FEI. The company claimed that the rate of FEI 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 FEI was assumed. The ERG can confirm that the rate of FEI has no substantial impact on the results of the analysis.

Table 52. Proportion of patients with unilateral DMO at baseline who developed DMO in their fellow eye during the MEAD trials, by treatment arm (Company's response to clarification, Table 40)

Population	Proportion of patients with unilateral DMO at baseline who developed FEI 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%

Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; FEI, fellow eye involvement.

Overall, the ERG believes that, although ideally the economic model should be informed by baseline data from both arms (dexamethasone and sham) of the pooled MEAD trials, the use of baseline data exclusively from the pooled dexamethasone arms has low risk of bias and is unliekely to have had any substantial impact on the results of the economic analysis.

The ERG consulted with clinical experts around the generalisability of the baseline characteristics of participants in the pooled MEAD trials. In general, the trials were considered to be representative of the patient population in UK clinical practice. The ERG notes that the mean age of the pooled mITT dexamethasone patients at baseline is [redacted] years for the whole DMO population and [redacted] years for the pseudophakic population with DMO. This is very similar to the respective figures reported for the pooled mITT sham treatment arm. According to clinical expert advice, these figures are reflective of patients with DMO in routine clinical practice; moreover, clinical experts confirmed that pseudophakic patients with DMO are expected to be older that the general population of patients with DMO.

The proportions of patients within the cohort who have unilateral DMO in the BSE or the WSE, or bilateral DMO at baseline were based on the dexamethasone pooled arms in MEAD trials. The ERG notes that the baseline distribution of BSE and WSE 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 company was subsequently asked to provide an explanation for their choice during clarification. The company's response is provided in Box 15.

Box 15. Company's response regarding the estimation of the baseline distribution of BSE and WSE in bilateral DMO (Company's response to clarification, pg 35)

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.
Abbreviations used in the box: BCVA, best corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.

Furthermore, the company estimated baseline BCVA state distributions for unilateral DMO in BSE and WSE and bilateral DMO, using the actual data directly from dexamethasone patients with unilateral and bilateral DMO in the pooled MEAD studies. Results of this distribution are provided in Table 53 (all DMO patients) and Table 54 (pseudophakic DMO patients). Data estimated using the

pooled dexamethasone and sham population from the MEAD studies were also presented by the company for comparison.

Table 53. Baseline distribution of vision by DMO status in the whole DMO population in the pooled MEAD trials, after taking account of the unilateral/bilateral DMO status of patients in the trials (Company's response to clarification, Tables 29 and 30)

DMO status	Eye	Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
All DMO patients – pooled DEX700 arms							
Unilateral DMO in BSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in WSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All DMO patients – pooled DEX700 + sham arms							
Unilateral DMO in BSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in WSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in table: BSE, better-seeing eye; DEX700, dexamethasone 700µ; DMO, diabetic macular oedema; WSE, worse-seeing eye.

Table 54. Baseline distribution of vision by DMO status in the pseudophakic DMO population in the pooled arms of MEAD trials, after taking account of the unilateral/bilateral DMO status of patients in the trials (Company's response to clarification, Tables 33 and 34, pgs 39-40)

DMO status	Eye	Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
Pseudophakic DMO patients – pooled DEX700 arms							
Unilateral DMO in BSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in WSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pseudophakic DMO patients – pooled DEX700+ sham arms							
Unilateral DMO in BSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in WSE	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in table: BSE, better-seeing eye; DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; WSE, worse-seeing eye.

The company noted that by determining the baseline BCVA distribution in the BSE and WSE for unilateral and bilateral patients separately, the baseline distribution of vision was different from the baseline distribution assumed in the submitted economic model for the whole DMO population. For this purpose the company submitted a revised economic analysis, using the above data from the pooled dexamethasone arms. Use of these data appeared to favour the less effective interventions (i.e. watch and wait in the whole DMO population and dexamethasone in the pseudophakic DMO population); nevertheless, overall conclusions on cost effectiveness were not affected. This analysis is described in Section 5.5.1 with results being provided in Section 6.1.1 (**Analysis A1**).

The proportion of patients within the cohort who developed FEI over Years 1 and 2 in the model was assumed to be [redacted]. This figure needs to be slightly amended to [redacted].[[redacted]][112] This proportion was converted by the company into an annual rate of [redacted], using the exponential cumulative distribution function and assuming that the risk is constant over time. However, the figure of [redacted] expresses instantaneous risk should be converted into an annual probability of [redacted] before it was applied into the model, as shown in the equations below.

Instantaneous rate r = - [ln (1-P)]/t = - [ln (1- [redacted])]/2 = [redacted]

Annual probability p = 1 – exp (-r*t) = 1 – exp (-[redacted]*1) = [redacted]

Similarly, the annual rate of FEI of [redacted] that was utilised over Years 1 and 2 in a scenario analysis expresses instantaneous risk that should be first converted into an annual probability of [redacted] in order to be applied into the model. However, the impact of these changes on the ICER was negligible. An analysis undertaken by the ERG that uses the amended figure of [redacted] is described in Section 5.5.2.1, with results provided in Section 6.1.2.1 (**analysis B1**). The impact of the correction on the base case results was negligible.

Regarding the baseline distribution of vision across BCVA states for the BSE and the WSE, the ERG was not clear how the baseline BCVA state was determined for the BSE and WSE of every patient in the model and whether there was any correlation assumed between the BCVA of the eyes of each patient. The company's response to the ERG's' clarification question is presented in Box 16.

Box 16. Company's response regarding the approach for determining the baseline distribution of vision for the BSE and the WSE of each patient (Company's response to clarification, pgs 34-35)

"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 [of the CS], 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). […] This assumes that the overall vision 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."
Abbrevations used in the box: BSE, better-seeing eye; CS, company submission; WSE, worse-seeing eye.

The ERG believes that to assume that the distributions of vision in BSE and WSE are independent reduces the face validity of the model, as it does not restrict the possibility that the WSE enters the economic model having substantially better vision than the BSE. For example, in a person with unilateral DMO in the BSE and with BSE vision at baseline in BCVA state 1, the WSE has [redacted] probability to be in BCVA state 1 and [redacted] probability to be in BCVA state 5, which is unrealistic. Given time constrains, the ERG was unable to resolve this problem, however it is noted that this assumption of independence between the baseline BCVA of the two eyes reduces the validity of the model and may have introduced bias in the estimation of QALYs, as the baseline distribution of eyes and the 'fixing' of BSE and WSE throughout the model are central assumptions affecting estimation of QALYs.

5.4.4 Interventions and comparators

5.4.4.1 Comparison with the NICE scope

The NICE final scope for this STA[53] describes the technology as dexamethasone intravitreal implant, alone or in combination with laser photocoagulation; the following comparators are specified in the scope:

- laser photocoagulation alone;
- ranibizumab, alone or in combination with laser photocoagulation;
- fluocinolone acetonide intravitreal implant releasing 0.2 μg fluocinolone acetonide per day, alone or in combination with laser photocoagulation;
- bevacizumab, alone or in combination with laser photocoagulation, for people in whom ranibizumab and fluocinolone acetonide intravitreal implants are unsuitable.

The company submission notes that the marketing authorisation for dexamethasone in patients with DMO is based on monotherapy given as needed with minimum interval between-injections of approximately 6 months. This dosing regimen is in line with that used in the MEAD clinical trials, and hence dexamethasone monotherapy has been considered in the company's economic analysis, based on dosing and efficacy as observed in the MEAD clinical trials.

In terms of comparators:

- for patients with DMO who are considered unsuitable for non-corticosteroid therapy (i.e. anti-VEGF and laser therapy), the company's economic model used watch and wait as the comparator, as according to the company there are currently no alternative first-line treatment options available for this patient population.

- for patients with DMO who are considered insufficiently responsive to non-corticosteroid therapy (i.e. anti-VEGF and laser therapy), the company's economic model used watch and wait as the comparator in the base case analysis, as according to the company there is an unmet need for a treatment option in this patient population. A sensitivity analysis that incorporated fluocinolone acetonide as a comparator for this patient population was undertaken. The company excluded fluocinolone acetonide from the base case analysis as it was claimed that market share data indicated minimal use of fluocinolone acetonide in clinical practice, which the company attributed to the restrictions placed on its use in clinical practice both by its marketing authorisation (treatment of vision impairment associated with chronic DMO that is considered insufficiently responsive to available therapies)[113] and by further NICE guidance (fluocinolone acetonide is only to be used in an eye with a pseudophakic lens);[46] morover, there were important limitations characterising the efficacy data available on fluocinolone acetonide that are discussed in Section 5.4.6.2). Nevertheless, fluocinolone acetonide was included as a comparator in a sensitivity analysis

- for patients with DMO who are pseudophakic, the company's economic model used ranibizumab in the base case analysis. The company claimed that ranibizumab is the most common first-line treatment for DMO used in clinical practice, and this was supported by presentation of market share data. Bevacizumab, laser and watch and wait were incorporated as comparators in a scenario analysis. Bevacizumab and laser were considered in the scenario analysis because they were both included in the scope for this STA. However, the company claimed that, according to clinical expert opinion, bevacizumab is not established NHS practice for the treatment of DMO in England and Wales and has currently very limited use for this condition; moreover, it is not formulated for intraocular use and therefore there are risks of adverse events associated with pharmacy-compounded formulations of bevacizumab.

It was also argued that laser is rarely appropriate or beneficial and is no longer routinely used as a monotherapy in the UK. Watch and wait was also included in this scenario analysis for completeness.

The NICE scope included ranibizumab, bevacizumab and fluocinolone acetonide as either monotherapy or in combination with laser. The company claimed that no evidence was identified for bevacizumab + laser or fluocinolone acetonide + laser and that ranibizumab + laser was not considered in the submitted economic analysis because in the technology appraisal of ranibizumab for the treatment of DMO, ranibizumab + laser was dominated by ranibizumab monotherapy.[114] Furthermore, based on clinician advice, the company claimed that laser is more likely to be used in combination with anti-VEGF or fluocinolone acetonide on an *ad-hoc* basis (reflected by the use of "rescue" laser therapy in clinical trials) rather as a true combination therapy regimen. Therefore ranibizumab, bevacizumab and fluocinolone acetonide were included in the company models as monotherapies only.

ERG comment

Following consultation with clinical experts, the ERG finds appropriate the consideration of DEX700 PRN (dexamethasone 700µg pro *re nata*) and the exclusion of other dosing regimens that were considered in the clinical analysis (such as DEX700 CNT, DEX700 PRN ≥ 4 months and DEX700 PRN combined with laser) from the economic analysis, as the latter constitute distinct interventions that are not compliant with the marketing authorisation of dexamethasone for patients with DMO. From this point onwards, the use of 'dexamethasone' in the report will refer to dexamethasone 700µg pro *re nata* unless otherwise specified.

The ERG believes that the selection of comparators in the three analyses is overall appropriate. Clinical experts understood the rationale for selecting watch and wait as a comparator for patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, despite of the fact that it was not specified as a comparator in the NICE scope for this STA. On the other hand, the ERG notes that clinical experts did not agree with the company's rationale for excluding fluocinolone acetonide from the base case analysis for DMO patients who are considered insufficiently responsive to non-corticosteroid treatment.

Clinical experts agreed with the selection of ranibizumab as a comparator in the analysis on pseudophakic patients and confirmed that, following introduction of other pharmacological agents in routine clinical practice for the treatment of DMO, bevacizumab does not currently represent routine clinical practice for this condition. Clinical experts disagreed with the company's assertion that laser is rarely appropriate or beneficial and is no longer routinely used as a monotherapy in the UK, and noted that laser is routinely used for the treatment of DMO with central retinal thickness < 400

microns, where ranibizumab is not an option, according to NICE guidance.[115] Therefore, clinical experts advised that ERG that laser treatment is a relevant comparator in pseudophakic if the oedema is associated with central retinal thickness below 400 microns. In any case, both bevacizumab and laser treatment have been considered by the company in a scenario analysis. In addition, fluocinolone acetonide was considered by clinical experts to be an appropriate comparator for people with DMO who are pseudophakic, and therefore the ERG asked the company to provide a rationale for the omission of fluocinolone acetonide from the respective analysis. The company's response is provided in Box 17.

Box 17. Company's response regarding no consideration of fluocinolone acetonide as a relevant comparator for the economic analysis on pseudophakic patients with DMO (Company's response to clarification, pgs 43 to 44)

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.

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). 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:

- 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 o 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.
Abbreviations used in box: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; IMS, Index of Medical Specialties; NICE, National Institute for Health and Care Excellence.

The ERG also notes that omission of fluocinolone acetonide from the analysis on pseudophakic patients could be justified if efficacy data for fluocinolone acetonide on pseudophakic sub-populations are not publicly available, as use of efficacy data derived from the whole DMO population for fluocinolone acetonide would most likely underestimate its efficacy relative to dexamethasone (for which data on pseudophakic patients are available and have been used in the analysis), given the increased risk of cataract associated with corticosteroid ocular use.

The ERG notes the use of sham treatment efficacy data from the pooled MEAD trials as a proxy for watch and wait. Clinical expert opinion indicated that this is a reasonable assumption in the absence of more appropriate data, although it was acknowledged that participants in the sham treatment arms of the MEAD trials are expected to have a better natural history due to the MEAD trial protocol, according to which patients who received non-study treatment (such as laser 'rescue' treatment) due to lack, or loss, of efficacy, were censored from analysis. This means that the use of MEAD sham treatment data as a proxy for watch and wait may have overestimated the treatment effect of watch and wait and subsequently may have biased the clinical efficacy results against dexamethasone.

On the other hand, an exploratory analysis undertaken by the ERG (**Analysis C3**) in patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroids, which set discontinuation rates of both dexamethasone and watch and wait at zero, showed that the number of QALYs for both interventions was reduced, while the total costs for both interventions increased compared with the base case analysis. The impact of this scenario was more significant for watch and wait than for dexamethasone. This finding implied that patients who discontinued treatment (either dexamethasone or watch and wait) in the model had higher benefits and incurred lower costs compared with those who continued treatment, in particular those receiving watch and wait. The results of this analysis, which is presented and discussed further in Section 5.5.2.2, suggest that the patient group in the MEAD trials receiving sham (which was used as a proxy for watch and wait in the model) did not have better natural history than expected; therefore, the effect of sham (and, consequently, watch and wait) may not have been overestimated in the economic analysis.

5.4.4.2 Treatment duration, retreatment and rescue therapy

Treatment characteristics, including duration, retreatment and use of rescue therapy, were based on key clinical trials that provided clinical and resource use input parameters for the economic analysis; these trials were selected from trials included in the NMA, and are presented in more detail in Section 5.4.6.2.

The company's model assumed a maximum duration of treatment of 3 years in the base case analysis, as this was consistent with the maximum duration of the key clinical trials. Extension of treatment duration to a maximum of 5 years was tested in scenario analyses.

Re-treatment of dexamethasone in the model was provided according to the marketing authorisation for dexamethasone in patients with DMO, that is, as needed, with minimum interval between-injections of approximately 6 months. This is in line with the MEAD trial protocols and therefore in the company's analysis patients were assumed to be re-treated with dexamethasone at the rates observed at the pooled MEAD clinical trials. In addition, all comparators in the model were assumed to be given on an as needed basis; re-treatment rates for all comparators were derived from the key clinical trials identified for each comparator. The average number of treatments per patient who remained on treatment was calculated using monthly trial data for the average number of treatments received and the proportion of patients receiving treatment from the last to current observation. The company argued that using monthly inputs allowed accurate entry of data into the model, despite different visit and dosing schedules reported across trials. Where data were not available for the full 3-year treatment duration, treatment rates with intravitreal injections were extrapolated in line with expected use in clinical practice, and treatment rates with laser were extrapolated based on last observation carried forward. Table 55 summarises the average numbers of treatment assumed in the model for Years 1-3, that is, over the total duration of DMO treatment, for all interventions considered in the company's base case and sensitivity/scenario economic analyses.

Table 55. Average number of treatments per year, utilised in the economic model (adapted from CS, Tables 65, 67 and 68)

Treatment	Average number of treatments			Source of data & notes
	Year 1	Year 2	Year 3	
All DMO patients [unsuitable for, and/or insufficiently responsive to non-corticosteroid therapy]				
DEX700	[redacted]	[redacted]	[redacted]	MEAD[112]
Watch and wait	0.00	0.00	0.00	Non-applicable
Fluocinolone acetonide	1.00	0.26	0.26	FAME[90,116]
DMO patients who are pseudophakic				

DEX700	[redacted]	[redacted]	[redacted]	MEAD[112]
Ranibizumab	7.00	3.90	2.90	RESTORE [94,117,118]; data for all DMO patients (no available data for pseudophakic patients)
Bevacizumab	9.00	4.00	2.90	BOLT[92,119] to Year 2 then assumed equal to ranibizumab based on clinical expert opinion; data for all DMO patients (no available data for pseudophakic patients)
Laser	[redacted]	[redacted]	[redacted]	Allergan analysis of PROTOCOL I [120] to Year 2, then LOCF, as in Year 3 of sham + laser patients were allowed to receive ranibizumab, hence data for Year 3 were not applied
Watch and wait	0.00	0.00	0.00	Non-applicable
Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; LOCF, last observation carried forward.				

Further to re-treatment, the model allowed the use of 'rescue' laser therapy for specific interventions, if this was allowed as part of the intervention's key clinical trial protocols. This was justified as rescue therapy, where available, has an additional effect that is not possible to disaggregate from the reported overall efficacy of the examined intervention in the trials. Since the overall efficacy of interventions has been utilised in the NMA that informed the economic model, the company's model incorporated, where relevant, rescue therapy and the associated cost as part of some interventions. Modelled rates of rescue laser therapy corresponded to respective rates observed in relevant key clinical trials. Patients within the MEAD trials who received rescue laser therapy were censored and hence efficacy estimates from the MEAD trials do not include the effect of rescue laser therapy; consequently no rescue therapy was assumed for dexamethasone or watch and wait (reflecting sham treatment) in the economic model. The company reported that according to clinical expert opinion use of laser treatment as rescue therapy is consistent with clinical practice. The company suggested that the efficacy of treatment regimens where rescue laser therapy was allowed may have been inflated, resulting in an underestimation of the relative efficacy of dexamethasone. Table 56 summarises the average numbers of rescue laser therapy assumed in the model for Years 1-3, that is, over the total duration of DMO treatment, for all interventions considered in the company's base case and sensitivity/scenario economic analyses.

Table 56. Average number of rescue laser treatments per year, utilised in the economic model (adapted from CS, Tables 66 and 68)

Treatment	**Average number of treatments**			**Source of data & notes**
	Year 1	**Year 2**	**Year 3**	
All DMO patients [unsuitable for, and/or insufficiently responsive to non-corticosteroid therapy]				

DEX700	0.00	0.00	0.00	No rescue therapy allowed in MEAD
Watch and wait	0.00	0.00	0.00	No rescue therapy allowed in MEAD
Fluocinolone acetonide	0.00	0.00	0.80	FAME;[90,116] average number of laser treatments reported over 3 years, no data reported for Year 1-2
DMO patients who are pseudophakic				
DEX700	0.00	0.00	0.00	No rescue therapy allowed in MEAD
Ranibizumab	0.00	0.20	0.40	RESTORE;[94,117,118] laser therapy allowed in Year 2+; data for all DMO patients (no available data for pseudophakic patients)
Bevacizumab	0.00	0.00	0.00	no rescue therapy allowed in BOLT[92,119]
Laser	0.00	0.00	0.00	Rescue therapy non-applicable
Watch and wait	0.00	0.00	0.00	No rescue therapy allowed in MEAD
Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema.				

ERG comment

The ERG consulted with clinical experts regarding the optimal duration of treatment of DMO. Clinical expert opinion indicated that re-treatment with a specific treatment regimen may continue as long as there is clinical improvement and may well last beyond 3 years, possibly in a small proportion of patients who respond to the specific treatment regimen and have recurrence of DMO. It was advised that treatment would be stopped only if the patient becomes unresponsive and no significant visual improvement can be gained, or if visual acuity has returned to normal levels. However, in the longer term, DMO may progress into proliferative diabetic retinopathy, which will have an impact on the treatment effect and needs to be taken into account if extrapolation of treatment (and its effect) is modelled beyond 3 years. On balance, the ERG considers reasonable the decision of the company not to extrapolate treatment duration (and treatment effect) beyond 3 years as there are no sufficient data to allow accurate prediction of the treatment effects beyond this period.

Regarding re-treatment, the ERG is aware that patients with DMO in clinical practice may experience more advanced visual impairment than those in clinical trials; hence they may require more frequent treatment and monitoring than what has been assumed in the company's model. However, clinical experts have advised the ERG that the baseline characteristic of the patients in MEAD were generally representative of the UK population with DMO and therefore the ERG accepts the resource use estimates derived from the MEAD trials. Due to time constraints, the ERG has not explored in depth the characteristics of patients in the other key trials that provided resource use data, and therefore cannot comment on reported resource use.

The ERG checked the average number of treatments per year for each intervention and noted that the number of fluocinolone acetonide treatments received per patient has been overestimated in year 3, according to data reported in the FAME trials.[90,116] The ERG was able to verify that 0.26 additional

fluocinolone acetonide treatments were received by patients at the end of Year 2;[90] however, cumulative data on Year 3 suggested that 0.296 additional treatments were received by the end of Year 3.[116] This means that the number of treatments in Year 3 for fluocinolone acetonide should be corrected to 0.036 (instead of 0.26, which was the value used in the company model, based on LOCF). The ERG ran an additional economic analysis following this correction (**analysis B2**). This is described in 5.5.2.1 with results being presented in 6.1.2.1. The impact of this correction on the results of the scenario analysis that included fluocinolone acetonide was significant, as fluocinolone acetonide became more cost-effective than dexamethosne even at list price.

In addition, clinical expert advice indicated that the frequency of laser treatment is generally lower in routine practice compared with relevant data presented in Table 55. Diffuse laser treatment is typically applied once; if there is improvement of DMO following treatment and recurrence of DMO later in time, diffuse laser treatment may be occasionally repeated. More localised laser treatment may be performed multiple times, with at least 6-month intervals before considering re-treatment. Nevertheless, using a lower frequency for laser treatment in patients with DMO who are pseudophakic would only further favour laser treatment in its comparison with dexamethasone (laser treatment dominates dexamethasone according to company's scenario analysis 2 in this population), as it would reduce its total intervention cost. Therefore, no additional analysis was carried out by the ERG regarding this aspect of the model.

Finally, in terms of consideration of rescue laser therapy for some therapies but not for dexamethasone in the model, the ERG was advised by clinical experts that laser therapy can be used as a rescue therapy in patients treated with dexamethasone who are not responsive. However, the ERG found reasonable the exclusion of rescue laser treatment from the cohorts treated with dexamethasone, as this was not allowed in the MEAD trials that provided the efficacy data for dexamethasone.

5.4.5 Perspective, time horizon and discounting

5.4.5.1 Perspective and discounting

The company adopted an NHS and personal social services (PSS) perspective for the analysis, and applied a discount rate of 3.5% for costs and QALYs beyond the first year of the model. Discounting was applied on a 3-monthly basis. The company submission includes a description of an approach to discounting using an area under the curve (CS, Appendix 19, pg 678). This formula was not applied in the model and this was confirmed by the company following a clarification question.

ERG comment

The ERG considers the perspective and discounting to be appropriate and in line with the NICE reference case; applying discounting on an annual basis did not have any impact on the results.

5.4.5.2 Time horizon

The time horizon for the analysis was set to 15 years. The justification provided for a 15-year time horizon was as follows: "The baseline age of patients entering the model is [redacted] years (mITT) and [redacted] years (pseudophakic). Therefore 15 years is considered sufficiently long to capture all important differences in costs and outcomes, specifically in terms of reaching (or avoiding) the impact of severe visual impairment." (CS; Table 63, pg324). The company also presented results of scenario analyses in which the time horizon was set to 1, 5, 10 and 20 years to determine the impact of varying the time horizon on the results. The results of these scenario analyses are described in Section 5.4.13.1.

ERG comment

The ERG notes that ISPOR modelling good practice guidelines present two common approaches to setting a sufficiently long time horizon: modelling to an average cohort age of 120 years, and tracking the modelled cohort until more than 99.9% of the individuals are dead.[121] Following consultation with clinical experts, the ERG considers that 15 years is a reasonable base case time-frame in which to capture the key costs and consequences of DMO and its treatment, without the need to introduce extra assumptions in the model regarding development of other ocular comorbidities of DM, which would be required were a longer time horizon be used. Previous economic models undertaken for TAs 237/274 & 271/301 also considered 15-year time horizons. A reduced 10-year time horizon was adopted for TA237/274 in the revised patient access scheme submission.

5.4.6 Treatment effectiveness

5.4.6.1 Choice of baseline treatment

The baseline treatment in the model, upon which treatment effects are applied, was dexamethasone. The company chose to use dexamethasone as the baseline treatment, and not watch and wait, which would be expected to comprise the baseline 'standard care' treatment. The company's justification for the choice of baseline is provided in Box 18.

Box 18. Company's justification for the choice of baseline treatment in the economic model (CS, pg 332)

"Watch and wait has been assumed to be represented by the 'sham injections or no treatment' node in the NMA that provided the efficacy data for the economic model. If watch and wait was used as baseline, then the baseline data should be taken from the pooled MEAD sham treatment arms However, the company argued that the "MEAD sham treatment arm is likely to overestimate the true [absolute] efficacy of a watch and wait strategy due to the unexpectedly positive efficacy observed in the sham arm. This is partly explained by the protocol governing continuation in this arm of the study. Patients who lost ≥15 letters from baseline were exited from the MEAD trial programme at the investigator's discretion and classed as a treatment failure and patients who required rescue therapy and were not exited were censored; hence the true deterioration of their BCVA was not captured. By

the end of the study [redacted] sham patients had discontinued from the study due to lack or loss of efficacy and [redacted] sham patients had been censored due to receipt of escape therapy, therefore towards the end of the study period, sham treatment arms in both MEAD studies consisted of what may be classed as 'super-responders'. BCVA outcomes in this population were closer to those observed in trials that allowed rescue therapy to be administered to 'sham treated' patients rather than what we would expect to observe with no active treatment in clinical practice."
Abbreviations used in the box: BCVA, best corrected visual acuity; NMA, network meta-analysis.

To strengthen this argument, the company compared the response to sham treatment in the MEAD trials with 4-year outcomes from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[31] and noted that, although the proportion of patients who gained at least 10 letters from baseline to study end in the MEAD sham arms was in line with observed natural history data from WESDR, a much higher proportion of patients in the WESDR study lost at least 10 letters from baseline to study end compared with the MEAD sham arms, as illustrated in Table 57. The data indicated, according to the company, that sham arms of the MEAD studies had a much lower rate of visual decline compared with natural history of DM, and therefore were not representative of a true "watch and wait" treatment arm.

Table 57. Comparison of sham result in MEAD with natural history data (adapted from CS, Table 70)

Type of outcome	Sham			Natural history
	MEAD-010	MEAD-011	MEAD - pooled	WESDR
Proportion gaining ≥ 10 letters from baseline	[redacted]	[redacted]	[redacted]	25%
Proportion losing ≥ 10 letters from baseline	[redacted]	[redacted]	[redacted]	36%
Abbreviations used in the table: WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.				

Based on the above evidence, the company argued that the sham treatment arm of the MEAD studies is not an ideal proxy for "watch and wait" as it is likely to over-estimate the true absolute efficacy of watch and wait in patients with DMO. Moreover, the company argued that the better (than would normally expected) outcome for sham treatment in MEAD resulted in an underestimation of the true relative efficacy of dexamethasone versus sham.

Furthermore, the company claimed that the relative effects obtained from the NMA for dexamethasone came exclusively from the MEAD studies, as these were the only studies for dexamethasone in the network. However, the relative efficacy for all treatments in the network versus sham/no treatment was based on evidence for sham/no treatment for 4 studies in the network (2

MEAD trials, ETDRS/Hornberger subgroup[67]and Olk[91] (CS, page 333). Therefore the company argued that to use sham/no treatment as the reference for efficacy, with transition probabilities based only on the MEAD studies, would result in a 'disconnect' between the baseline transition probabilities (based on MEAD studies only) and the estimates of relative effectiveness (based on the four studies for sham/no treatment).

Consequently, the company chose dexamethasone as the reference treatment for efficacy, with dexamethasone transition probability matrices taken from the pooled MEAD studies.

ERG comment

The ERG agrees, to some extent, with the company's assertion that use of the sham treatment arm as a proxy for watch and wait may have overestimated the effect of watch and wait and may have therefore underestimated the relative efficacy of dexamethasone versus watch and wait. Clinical expert opinion was that the results for the sham treatment arm in the pooled MEAD trials should not be, in principle, more favourable for sham treatment than those expected for a no treatment arm. Nevertheless, the ERG accepts the argument that the pooled MEAD sham treatment arms were characterised by particularly high discontinuation rates and that the protocol design allowed for 'super-responders' to remain in the trial and potentially overestimate the effect of sham treatment, but notes that the pooled dexamethasone arms were also subject to high discontinuation rates and continuers of dexamethasone potentially comprised 'super-responders' due to the protocol design as well. The ERG acknowledges though that this effect was likely stronger in the pooled MEAD sham treatment arms, meaning that the relative effect of dexamethasone versus sham (watch and wait) has been underestimated to a certain degree in the MEAD trials, but potentially not as much as claimed by the company. This limitation (underestimation of the relative treatment effect of dexamethasone), if true, is inherent to the MEAD trial design, and is not possible to remove from any analysis incorporating the MEAD data, including the NMA.

On the other hand, an exploratory analysis undertaken by the ERG (**Analysis C3**) in patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroids, which set discontinuation rates of both dexamethasone and watch and wait at zero, showed that the number of QALYs for both interventions was reduced, while the total costs for both interventions increased compared with the base case analysis. The impact of this scenario was more significant for watch and wait than for dexamethasone. This finding implied that patients who discontinued treatment (either dexamethasone or watch and wait) in the model had higher benefits and incurred lower costs compared with those who continued treatment, in particular those receiving watch and wait. The results of this analysis, which is presented and discussed further in Section 5.5.2.2, suggest that the patient group in the MEAD trials receiving sham (which was used as a proxy for watch and wait in

the model) did not have better natural history than expected; therefore, the effect of sham (and, consequently, watch and wait) may not have been overestimated in the economic analysis.

In the NMA, the relative treatment effect of dexamethasone versus sham/no treatment has been exclusively informed by the MEAD trials: these were the only trials connecting the two treatment options, and no indirect comparison was available between them in the network. This means that the relative effect of dexamethasone versus sham/no treatment as estimated in the NMA should be equal to that observed from their head-to-head comparison in the MEAD trials (and be underestimated to exactly the same degree). Therefore, use of the pooled MEAD sham arm transition probabilities (as a proxy for watch and wait) as baseline in the base case economic analysis for people unsuitable for, or insufficiently responsive to non-corticosteroid therapy should not affect the results of that economic analysis in any way; this is because the application of the NMA relative effects of dexamethasone versus sham/no treatment should, in theory, only reproduce the pooled MEAD absolute effects of dexamethasone in the economic analysis. Conversely, using the pooled MEAD dexamethasone transition probabilities as baseline and applying the relative effects of sham/no treatment versus dexamethasone from the NMA (which is what the company chose to do), should only have replicated the absolute effect of sham as observed in the pooled MEAD trials, in the economic model. Therefore, the ERG argues that, for the comparison between dexamethasone and watch and wait, the selection of baseline treatment for the estimation of baseline transition probabilities (taken from the pooled MEAD trials) should not have any differential impact on the results of the economic analysis. This also means that the relative effect of dexamethasone is going to be underestimated by the same degree whether dexamethasone or sham (used as a proxy for watch and wait) is selected as baseline treatment in the economic model.

The ERG does not agree with the company's assertion that the relative efficacy for all treatments in the network versus sham/no treatment was based on evidence for sham/no treatment for 4 studies in the network (i.e. the 2 MEAD trials, ETDRS/Hornberger subgroup[67] and Olk.[91] The relative treatment effect of laser versus sham/no treatment in the NMA has been determined by the relative effect of laser versus no treatment + deferred laser as reported in ETDRS[67] and of laser versus no treatment as reported in Olk[91] The relative treatment effect of laser (and, indirectly, of the other interventions that are connected to laser) versus sham/no treatment has not been affected in any way by the MEAD sham arm, in the same way that the relative treatment effect of dexamethasone versus sham/no treatment has not been affected by the 'no treatment' arms in the ETDRS and Olk trials. The ERG would like to emphasise the fact that the estimated relative treatment effects for any pair of treatments included in a network are exclusively determined by the estimated relative effects reported in each of the trials that link, directly or indirectly, these treatments in the network, and are not

influenced in any way by the absolute effects of these treatments within the network, as estimated by cumulating the absolute effects of the treatments that are observed in each of the individual trials.

However, the ERG acknowledges the possibility that the relative effect of dexamethasone versus all other treatments included in the network (laser, ranibizumab, bevacizumab and fluocinolone acetonide in the scenario analysis) may have been underestimated, if the dexamethasone relative effect in the MEAD trials, which have informed the network, has been underestimated. The ERG notes that, on the other hand, the possibility of underestimation (or overestimation) of the laser relative treatment effect in the ETDRS/Olk trials has not been explored, so the degree of underestimation of the relative effect of dexamethasone versus laser (and versus the other treatments in the network) is unknown.

The ERG accepts the company's assertion that use of the pooled MEAD sham treatment transition probabilities may not be appropriate for the estimation of the baseline effect, due to its likely overestimated absolute effect compared with watch and wait. Using the no treatment arm in ETDRS/Olk trials as baseline would be likely more appropriate as it most closely reflects watch and wait. However, detailed 3-monthly transition probabilities for no treatment, which would be required to populate the economic model as discussed in 5.4.6.2, were not available. Therefore, the ERG accepts the use of dexamethasone as the baseline treatment across all populations and analyses considered by the company. However, the ERG wishes to highlight once again, that, as argued above, the selection of pooled MEAD sham treatment as baseline comparator (instead of dexamethasone) in the comparison between dexamethasone and sham should not have any impact on the results of the economic analysis.

5.4.6.2 Efficacy data utilised in the model

Overview of efficacy outcomes

The main outcome measure that was utilised in the model and was subsequently used to estimate QALYs was the changes in BCVA over time following treatment. Clinical efficacy over the 3 years of treatment duration was modelled using the following evidence:

- Baseline effect: 3-month transition probabilities between BCVA states for dexamethasone; these were generated using data from the dexamethasone arm of the pooled MEAD studies that were collected at 3-month intervals over the 3 years of the trial's duration;
- Relative effects: the relative risks of
    - improving vision (moving up one 10-letter state);
    - worsening vision (moving down one 10-letter state) or
    - maintaining stable vision (remaining in the same 10-letter state)

for each intervention versus dexamethasone were obtained directly from the NMA of relevant clinical trials that was undertaken as part of the company submission and is described in Section 4.6. The relative risks obtained from the NMA were estimated using exclusively 12-month efficacy data across the trials included in the network. These relative risks were applied onto the 3-month transition probabilities for dexamethasone (baseline treatment), to obtain BCVA transition probabilities for each of the other interventions considered in the analysis.

Estimation of 3-month baseline transition probabilities between BCVA health states for dexamethasone

The 3-month transition probabilities between BCVA states for dexamethasone were generated from the pooled MEAD data over the whole 3-year duration of the trial. These transition probabilities were based on the observed movements between BCVA states in the study eye during each 3-month cycle, as recorded for the mITT population, which, as described in Section 5.4.3.2, included only patients who had at least one follow-up visit. These baseline transition probabilities were utilised only over the 3 years of dexamethasone treatment, and only in those patients continuing treatment (i.e. they were not applied following discontinuation of dexamethasone).

The transition probabilities were allowed to vary in every 3-month cycle over the 3-year treatment period, and were restricted by movement by one state up or down in each cycle. Transition probabilities for each 3-month cycle were recorded in transition probability matrices; these present the probabilities of moving from a particular BCVA health state to all other BCVA states during that cycle. The sum of probabilities in each row of the matrix should equal 1 to ensure that all patients who began the cycle in each state were accounted for by the movements described by the probabilities in the corresponding row. All baseline transition probability matrices for dexamethasone were provided in Appendix 15 of the company submission.

The company presented an example of how transition probabilities were derived using data from baseline to Month 3 for the all DMO patients (mITT population), which are provided in Table 58. This table shows that of the [redacted] patients whose study eye was in Health State 3 at baseline, the number of patients whose study eye moved from Health State 3 to Health State 4 from baseline to Month 3 was [redacted]. Therefore the probability of moving from Health State 3 to Health State 4 from baseline to Month 3 is calculated as [redacted] (it should be noted that Table 58 presents 3-month transitions for dexamethasone patients after applying a restriction of transitions by one -adjacent- health state up or down, as confirmed by the company during clarification). Table 59 shows all the transition probabilities that have been estimated from baseline to Month 3 for all DMO patients, using the method described in the example.

Table 58. Patient-level study eye movements between visual acuity states: Baseline to Month 3 for dexamethasone patients; all DMO patients (taken from CS, Table 74)

		To						Total
		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6	
From	Health State 1	[redacted]	[redacted]	0	0	0	0	[redacted]
	Health State 2	[redacted]	[redacted]	[redacted]	0	0	0	[redacted]
	Health State 3	0	[redacted]	[redacted]	[redacted]	0	0	[redacted]
	Health State 4	0	0	[redacted]	[redacted]	[redacted]	0	[redacted]
	Health State 5	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 6	0	0	0	0	[redacted]	[redacted]	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema.

Table 59. Transition probability matrix from baseline to Month 3 for dexamethasone patients; all DMO patients (taken from CS, Table 75)

		To						Total
		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6	
From	Health State 1	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00	[redacted]
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00	[redacted]
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00	[redacted]
	Health State 5	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema.

ERG comment

The derivation of transition probabilities for baseline treatment (dexamethasone) from the pooled MEAD dexamethasone arms is reasonable, although it is noted that clinical experts have expressed their concern that the populations included in the MEAD trials are not directly relevant to the study population determined in the decision problem. The use of actual data recorded in each of the 3-month intervals is a strength of the analysis, as it is likely that baseline transition probabilities may change over time for dexamethasone, given the fluctuation in the clinical outcomes expected for dexamethasone, due to its administration schedule. According to clinical expert advice, improvement in visual acuity is likely to be observed about one month after dexamethasone injection, with the

greatest improvement around 2 to 3 months after injection. Fluctuations in clinical outcome are likely to be observed over the 6 months after injection (which is the recommended duration of implant use before the steroid effect is expected to wear off and replacement is considered), although the expectation is that overall clinical improvement will be more significant than the fluctuations in those patients who respond to treatment.

Relative risks obtained from the network meta-analysis

Treatment in the model was assumed to be administered for up to 3 years; patients were assigned the efficacy associated with treatment for as long as they remained on treatment. Transition probabilities for all treatments other than dexamethasone were estimated by applying the relative risks obtained from the NMA for each treatment versus dexamethasone onto the baseline transition probabilities for dexamethasone that were observed in the pooled MEAD clinical studies. One NMA model was used to estimate all three outcomes described earlier to ensure that correlation between the three outcomes would be accounted for. The NMA used exclusively Month 12 data. The company justified the selection of data from Month 12 because this was the most commonly reported time-point in relevant clinical trials (more than any other point) and therefore enabled collection of the maximum possible information on efficacy from treatments of interest; analysis of further time-points was not be possible for all treatments within the network. During clarification, the company argued that 12 months was the primary efficacy analysis time point in five of the seven comparator trials used in the NMA.

The main NMA was performed using data for all DMO patients; this analysis excluded the FAME study, which was the key trial on flucinolone.[90] Sensitivity analyses were performed for all DMO patients including those in the FAME study and for pseudophakic DMO patients. Inclusion of the FAME trial in the main NMA was excluded from the main analysis due to the following limitations, as listed by the company:

- The network of evidence was based around 12-month data for all treatments; the FAME study only reported 24-month outcomes, therefore this was used in the absence of 12-month data;
- The network of evidence was based around “all DMO patients”, and for the majority of studies this included some patients who were prior treated and some who were not; the FAME study included a patient population which was 100% prior treated;
- The network of evidence considered (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 reported data for the proportion of patients who gained at least 15 letters. This was a limitation for two reasons:
    i. The study only reported the probability of gaining at least 15 letters, meaning that the probability of gaining at least 10 letters needed to be imputed in the model, as discussed in Section 4.6.

ii. The study only reported one of the three outcomes of interest (gaining letters), meaning that the remaining two outcomes needed to be imputed.

Given these limitations, the company claimed that it was difficult to draw any meaningful conclusion from an analysis including fluocinolone acetonide. Therefore this comparison was provided as a sensitivity analysis, only because this treatment was included as a relevant comparator in the final scope for the appraisal.

Of the key trials that were included in the NMA, those that provided clinical and resource use data for the economic model are shown in Table 60. The NMA outputs that were utilised in the economic model are shown in Table 61.

Table 60. Key clinical trials providing clinical and resource use inputs to the economic model (adapted from CS, Table 91)

Treatment	Key publication	Trial duration	Company access to data
DEX	MEAD	3 years	Patient-level
Watch and wait ("sham")	MEAD	3 years	Patient-level
Ranibizumab	RESTORE	3 years	Study publication
Bevacizumab	BOLT	2 years	Study publication
Laser ("sham + laser")	DRCR.net PROTOCOL I	2 Years	Patient-level
Fluocinolone acetonide	FAME	3 years	Study publication
Abbreviations used in table: DEX, dexamethasone **Note:** In Year 3 of PROTOCOL I sham + laser patients were allowed to receive ranibizumab, hence data for Years 1 and 2 only have been applied.			

Table 61. Relative risks of all treatments versus dexamethasone derived from the NMA and utilised in the economic model

Treatment	RR (95% CrI)		
	Improving vision	Stable vision	Worsening vision
All DMO patients: DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy (base case analysis)			
Watch and wait	[redacted]	[redacted]	[redacted]
All DMO patients: DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy (scenario analysis)			
Watch and wait	[redacted]	[redacted]	[redacted]
Fluocinolone acetonide	[redacted]	[redacted]	[redacted]
DMO patients who are pseudophakic			
Ranibizumab	[redacted]	[redacted]	[redacted]
Watch and wait	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
Laser	[redacted]	[redacted]	[redacted]
Abbreviations used in table: CrI, credible interval; DMO, diabetic macular oedema; NMA, network meta-analysis; RR, relative risk.			

In order to fit RRs from the NMA to modelled efficacy outcomes, the following assumptions were made:

- The relative risk of gaining ≥ 10 letters from baseline was assumed to be equivalent to the relative risk of moving up one 10-letter health state (improving vision);
- The relative risk of losing ≥ 10 letters from baseline was assumed to be equivalent to the relative risk of moving down one 10-letter health state (worsening vision);
- The relative risk of gaining or losing <10 letters is assumed to be equivalent to remaining in the same 10-letter health state (stable vision).

These key assumptions were necessary to allow the NMA output to inform the Markov model structure, and built upon previous modelling in the TA of aflibercept for central retinal vein occlusion.[104] The model on aflibercept used NMA to estimate the relative risk of improving vision only, assuming that the probability of worsening vision was equal across treatment arms. The exclusion of modelling for relative risk of worsening vision was, as reported by the company, criticised by both the ERG and the Appraisal Committee of that TA.

The relative risks were applied to the 3-monthly transition probabilities for dexamethasone to obtain transition probabilities for each treatment, in each population, as follows:

- The relative risk of improving vision was applied to all dexamethasone transition probabilities demonstrating an improvement of vision (i.e. all probabilities of moving up one BCVA state), regardless of the starting state.
- The relative risk of worsening vision was applied to all dexamethasone transition probabilities demonstrating a worsening of vision (i.e. all probabilities of moving down one BCVA state), regardless of the starting state.
- The relative risk of vision remaining stable was applied to all dexamethasone transition probabilities where vision remained stable (i.e. all probabilities of remaining in the same BCVA state).

The relative treatment effects (relative risks) were applied across all BCVA states and all time points. This means that, for example, the relative risk of moving from state 1 into state 2 at 3 months was the same as the relative risk of moving from state 5 to state 6 at 27 months. Similarly, the relative risk of moving from state 5 into state 4 at 9 months was the same as the relative risk of moving from state 3 to state 2 at 24 months, and so on. This means that relative treatment effects of each treatment versus dexamethasone were assumed to be constant over time and across all BCVA states (i.e. regardless of the baseline level of vision). This was acknowledged by the company as a limitation of the analysis, however, it was claimed to be a necessary assumption as it allowed a single NMA to be performed for each population of interest, using all available data for the 3 outcomes at the most commonly reported time-point (12 months) in relevant clinical trials, in order to provide estimates of relative effectiveness for all outcomes of interest. The company argued that estimation of relative effects of treatments

dependent on starting health state would need to be based on smaller sample sizes and hence would produce less robust analyses; moreover, such level of detail in data was unlikely to be available from key study publications for comparators where only aggregate data were available.

Applying the relative risks obtained from the NMA to the baseline transition probabilities for dexamethasone would not necessarily result in transition probabilities in each row of the matrix summing to 1. For this reason, the company reported that the resulting transition probabilities were 'normalised' to ensure that the probabilities in each row of the resulting matrix would sum to 1.

To illustrate this, the company applied the relative risks for watch and wait for all DMO patients to the baseline transition probabilities for dexamethasone from baseline to month 3. Simply applying the relative risks to the baseline transition probabilities resulted in the probabilities shown in Table 62, which do not sum to 1 across rows as required.

Table 62. Transition probability matrix for watch and wait: baseline to Month 3; all DMO patients (taken from CS, Table 79)

		To						Total
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**	
From	**Health State 1**	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00	[redacted]
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00	[redacted]
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00	[redacted]
	Health State 5	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema.

Therefore normalised transition probabilities were calculated, where for each row of Table 62, the probability of each movement was divided by the sum of all movements from that health state (i.e. the value in the 'Total' column), ensuring that the sum of probabilities in each row of the matrix was equal to 1 (Table 63). For example, applying the relative risks to baseline transition probabilities gave transition probabilities of movements for watch and wait from health state 1 to state 1 of [redacted] and state 2 of [redacted] (Table 62). The sum of these probabilities was [redacted] The normalised probability of moving from state 1 to state 1 was calculated as ([redacted]) and the probability of moving

from state 1 to state 2 was calculated as [redacted] as shown in Table 63, giving a total probability of moving from state 1 to any state of 1.00.

Table 63. Normalised transition probability matrix for watch and wait: baseline to Month 3; all DMO patients (taken from CS, Table 80)

		To						Total
		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6	
From	Health State 1	[redacted]	[redacted]	0.00	0.00	0.00	0.00	[redacted]
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00	[redacted]
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00	[redacted]
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00	[redacted]
	Health State 5	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema.

The company claimed that clinical data, including treatment efficacy, were not extrapolated beyond the trial results, given that the duration of all trials was 2-3 years, and the duration of treatment in the model was 3 years. Treatment efficacy was modelled using 3-year data from the dexamethasone treatment arm of the pooled MEAD studies, with constant relative treatment effects assumed.

ERG comment

Consideration of 3 distinct and mutually exclusive outcomes (i.e. improving vision by at least 10 letters, worsening vision by at least 10 letters and maintaining vision within a 10-letter change) increases the face validity of the model structure, as this reflects all potential patient outcomes following DMO treatment in clinical practice. In principle, the ERG considers appropriate the estimation of relative effects of all DMO treatments versus dexamethasone for each of these outcomes from a NMA, as this enables appropriate synthesis of data without breaking randomisation, allows comparisons across treatments that have not been evaluated in head-to-head comparisons and also permits consideration of more than two treatment options in incremental analysis.

The NMA model which informed the economic analysis also appears to be appropriate: concurrent analysis of the 3 clinical outcomes (improving vision, worsening vision and maintaining vision) in a single NMA has, in principle, retained the underlying correlation across the 3 mutually exclusive outcomes; the aim of such multinomial models is to ensure that the sum of the probabilities of one person experiencing each of the mutually exclusive outcomes always equals 1 – this is essential when

modelling patients' transitions through the economic model. The ERG considers the trial sources included in the NMA that informed the economic analysis to be appropriate and comprehensive, although it notes that the network could possibly by formed by a higher number of trials, which might improve coherence. These issues have been discussed in Section 4 of the report.

The ERG acknowledges the limitations arising from consideration of fluocinolone acetonide data in the NMA and, subsequently, in the economic analysis, and agrees with the company claim that results from comparisons between dexamethasone and fluocinolone acetonide in DMO patients who are infsufficiently responsive to non-corticosteroid therapy should be interpreted with caution.

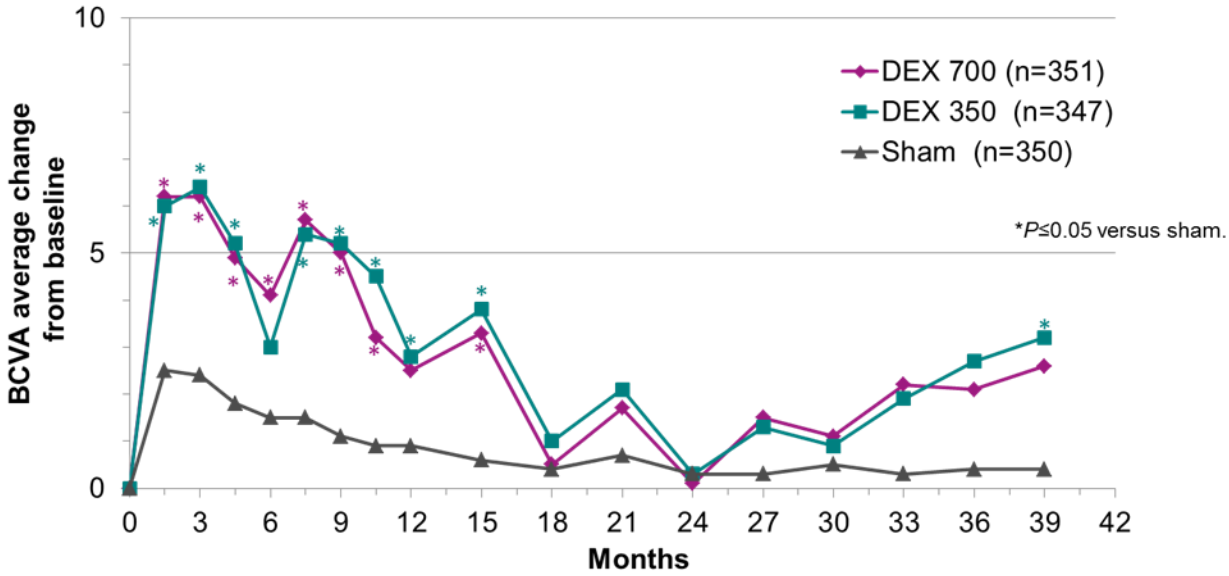
The ERG had major concerns with the implicit assumption that relative treatment effects (in terms of gain in vision, loss in vision, and no change in vision) of each treatment versus dexamethasone were constant over time (from 3 to 36 months) and independent of the baseline level of vision. Clinical experts found reasonable the assumption of relative effects being independent of the baseline level of vision, as there was no evidence to support a different assumption, although the expectation would be for more severe health states to show greater improvements with treatment. Clinical experts found more concerning that relative effects were assumed to be constant over time, as most treatments are associated with fluctuations in their effects depending also on their administration schedule. Moreover, the treatments considered in the economic analysis show their peak effect at different time points; for example, laser tends to show slower (although more persistent) effects compared with dexamethasone and anti-VEGFs. Nevertheless, clinical experts accepted this assumption as a necessary compromise, to enable the economic model to be informed by the results of the NMA.

On the other hand, the ERG notes that such an assumption is highly unlikely to hold for the relative effect of sham (watch and wait) versus dexamethasone, and in fact this relative effect has probably been underestimated in the economic analysis:

Figure 30 (reproduced from Figure 16 of the company submission) shows the mean BCVA changes from baseline for dexamethasone 700µg, dexamethasone 350µg and sham at each study visit in the pooled MEAD trials. Dexamethasone 700µg shows greater BCVA improvement compared with sham over the first 15 months. However, between 18 and 30 months the mean BCVA change from baseline in dexamethasone 700µg and sham arms is similar, with the effect for dexamethasone 700µg increasing again after 30 months and up to the end of the trial. According to the key MEAD study publication, this substantial reduction in the effect of dexamethasone 700µg relative to sham occurs at the same time with an increase in cataract formation as an adverse event of dexamethasone 700µg, which is responsible for the reduced effect of dexamethasone treatment.[51] This reduction in the effect of dexamethasone 700µg is not observed in the subgroup of pseudophakic DMO patients, for whom formation of primary cataract is not a possibility, in the pooled MEAD trials, as shown in Figure 31.

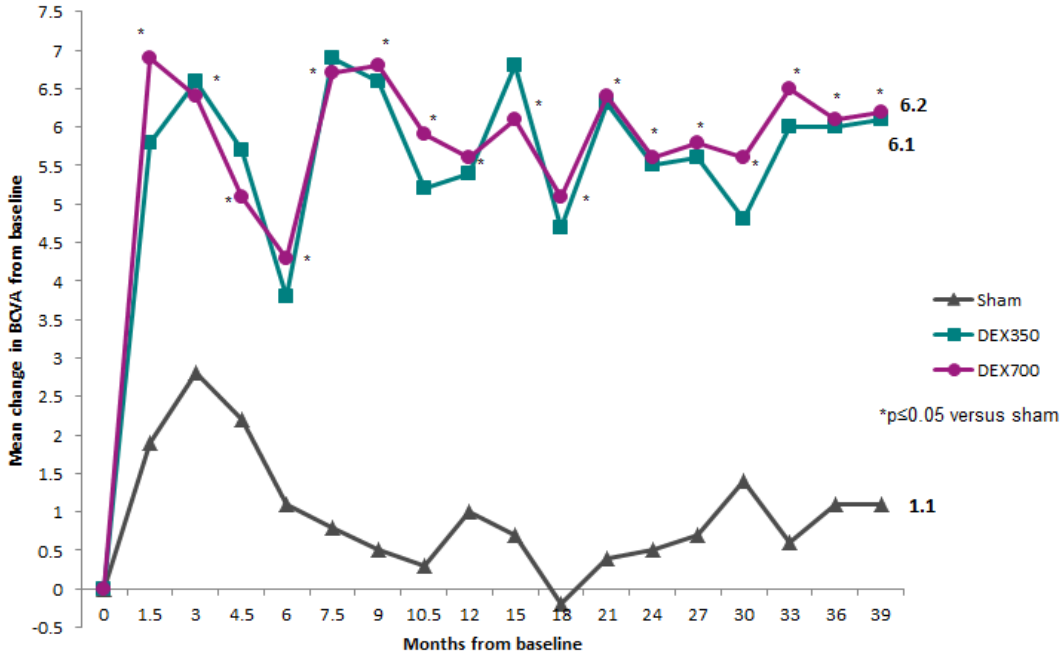
Nevertheless, the figures demonstrate that, at least in the whole DMO population, the assumption that the relative effect of watch and wait versus dexamethasone 700µg is stable over time, is not valid.

Figure 30: Mean BCVA change from baseline in the MEAD trial programme, ETDRS letters – pooled analysis, all DMO patients (reproduced from CS, Figure 16 pg 157)



Abbreviations used in figure: BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study.

Figure 31: Mean BCVA change from baseline in the MEAD trial programme, ETDRS letters – pooled analysis, pseudophakic patients with DMO (reproduced from CS, Figure 17 pg 159)



Abbreviations used in figure: BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study.

It is noted that Figure 31 suggests that the the relative effect of watch and wait versus dexamethasone 700µg in the pseudophakic population with DMO has fewer fluctuations over time, and therefore it could be argued that the company's assumption regarding the stability of relative effects over time may be acceptable in this population. However, the graph shows the fluctuations in the effects of dexamethasone and watch and wait; fluctuations in effects of other treatments considered for this population are not known, and therefore the ERG is unable to confirm whether the assumption of stable relative effects over 3 years across all treatments considered is reasonable in DMO patients who are pseudophakic. Although the risk of cataract formation which could affect the BCVA outcomes is not relevant in this population, there might be other factors relating to specific treatments that might impact on the relative effects over time.

The ERG notes that, to resolve this problem, the company would ideally need to run multiple NMAs with data collected at different time points corresponding to the cycles of the economic model, i.e. at 3, 6, 9 months, etc. This would provide more accurate data to the economic model, as it would take into account fluctuations in the effect of treatments over time, and thus changes in relative treatment effects. However, the ERG acknowledges that this would be a time-consuming process; moreover, it is likely that the data required for such a task are missing for a great part of the relevant comparators of dexamethasone that were considered in the economic analysis.

The ERG also felt that, given that the company has assumed that relative effects are constant over time, regardless of time point, it might be more appropriate for the NMA to be run with endpoint data for each trial participating in the network, rather than to collect data from 12-month time points only. This would be appropriate given that the company implicitly assumed that 12-month relative effects were equal to 3-month, 6-month, 24-month, and so on, relative effects, up to 36 months (which was the duration of treatments in the model). Use of endpoint data would enable inclusion in the network of studies that had been excluded from the company's submitted NMA because they did not report 12-month data, such as the NCT0003590, which had a 6-month duration and was thus excluded from the NMA. Such an analysis would also demonstrate whether consideration of 12-month efficacy data in the NMA and economic analysis produced different results from consideration of 36-month data. If results between the 2 analyses were broadly similar, then this would be an indication that the company's assumption about the stability of relative effects of treatments over time might potentially hold. If results were substantially different between the original (i.e. using 12-month data) and the updated (i.e. using endpoint data) NMA and economic analysis, then the company's assumption should be rejected and an alternative method of data synthesis and application in the economic model should be sought.

Consequently, the ERG requested from the company an updated NMA (and subsequently an updated economic analysis) using endpoint data from all trials and thus including NCT00035906. In response, the company updated the NMA using endpoint (6-month) data for NCT00035906, but without updating the data derived from the existing trials in the network (so that in the updated analysis 12-month data were still used). Inclusion of NCT00035906 in the NMA did not have any substantial effect in the clinical results (as shown in Section 4) or the results of the economic analysis. The updated economic analysis utilising the outputs of the updated NMA following inclusion of NCT00035906 (**Analysis A2**) is discussed in Section 5.5.1 with results being provided in Section 6.1.1.

Another point to raise in relation to the use of 12-month data in the economic model, is the company's assertion that, as duration of treatment in the economic model was 3 years, and most trials included in the NMA had a duration of 2-3 years, the amount of data extrapolation required was limited (CS, page 335). However, in reality, the economic model utilised 12-month relative efficacy data, which were applied onto 3-month baseline data and used over the 3-year treatment period; any efficacy data collected after 12 months for any treatment other than dexamethasone were ignored. It could be argued that, if the relative effects are constant over time, then use of 12-month efficacy data should be equivalent to use of any intermediate efficacy data up to endpoint efficacy data. However, as described above, the ERG is not convinced with the assumption of relative effects being constant over time, and considers the application of 12-month relative effect data onto 3-month baseline transition

probabilities over the whole 3-year duration of treatment in the model as a significant data extrapolation.

The NMA that informed the economic model synthesised data on three mutually exclusive outcomes of gaining vision, losing vision or maintaining stable vision. The company used one multinomial likelihood model "to estimate all three outcomes to ensure that correlation between the three outcomes would be accounted for" (company submission, pg334). The NMA outputs used in the economic analysis were the relative risks of each treatment versus dexamethasone (baseline) for each outcome. However, the ERG notes that correlations across mutually exclusive outcomes are "essentially within-trial, negative correlations between outcomes, applying in each arm of each trial. They arise because the occurrence of outcome events is a stochastic process, and if more patients should by chance reach one outcome, then fewer must reach the others" (NICE TSU document 2, page 23).[89] So the correlations characterise mutually exclusive outcomes (absolute effects) of every treatment, and not multiple relative outcomes between treatments. Therefore, by applying relative risks for each of the mutually exclusive outcomes in the economic model, the correlation between absolute outcomes was not maintained.

However, retaining the underlying correlations across the absolute outcomes was essential in the economic model in order to keep the sum of the probabilities of each of the mutually exclusive outcomes equal to 1. To force the sum of outcome probabilities to equal 1, the company described a method of 'normalisation' at the application of each of the 3 relative risks of every treatment versus dexamethasone associated with each of the 3 mutually exclusive outcomes, respectively, as described earlier. The ERG used the baseline transition probabilities for dexamethasone from baseline to month 3 (Table 59) and the non-normalised and normalised transition probability matrices for watch and wait from baseline to month 3 (shown in Table 62 and Table 63, respectively) for all DMO patients, to calculate the relative risks of watch and wait versus dexamethasone before and after normalisation, in order to explore the impact of normalisation on resulting relative risks. The ERG calculations are shown on Table 64 and

Table 65, respectively. The formula used to estimate relative risks (RRs) for every outcome in every cell of the transition matrix is:

$$RR = probWW / probDEX700$$

where probWW is the transition probability of watch and wait in every cell in the matrix and probDEX700 is the baseline probability of dexamethasone in every cell in the matrix.

The relative risks of watch and wait versus dexamethasone that were calculated by the ERG before normalisation took place (Table 64), should replicate the relative risks derived from the NMA that are

presented in Table 61. This is true for the relative risks for improving vision and retaining stable vision, which approximate [redacted] and [redacted], respectively, across all BCVA states (minor discrepancies due to figures having been rounded can be observed, as expected). However, for worsening vision, the relative risk of watch and wait versus dexamethasone shows a moderate discrepancy between milder and more severe BCVA state: in states 4 and 5 it approximates the figure estimated in the NMA ([redacted]), but in states 2 and 3 it is quite lower ([redacted] and [redacted], respectively). The ERG cannot explain the discrepancy across figures for the relative risk of watch and wait versus dexamethasone for worsening vision, but can confirm that the probability matrices which were used for the calculations and were presented in the CS are identical to those included in the Excel file DMO_NICE_Oct2014_All DMO. The ERG speculates that there may be an error in the estimated transition matrix for watch and wait prior to normalisation.

Table 64. Relative risks of watch and wait versus dexamethasone: baseline to Month 3; all DMO patients, derived from the NMA (calculated by ERG, using dexamethasone baseline transition probabilities from Table 59 and watch and wait transition probabilities, as estimated by the company, from Table 62)

		To					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
From	**Health State 1**	[redacted]	[redacted]	0.00	0.00	0.00	0.00
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00
	Health State 5	0.00	0.00	0..00	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	0.00	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema; ERG, evidence review group; NMA, network meta-analysis.

The relative risks calculated after normalisation are effectively the relative risks that were (implicitly) utilised in the model. The ERG notes that the relative risks estimated following normalisation, although of the same direction, are quite different in magnitude from those estimated from the NMA. Relative risks for all 3 outcomes are higher than the figures derived from the NMA, and overall increase as health states become milder (the exception is the relative risk of worsening vision, which is not constantly increasing with milder health states, but this is probably due to the speculated error in the transition matrix for watch and wait prior to normalisation). The relative risk for improving vision after normalisation ranges from [redacted] to [redacted] (the respective figure derived from the NMA was

[redacted]). The relative risk for retaining stable vision after normalisation ranges from [redacted] to [redacted] (the respective figure derived from the NMA was [redacted]). The relative risk for worsening vision after normalisation ranges from [redacted] to [redacted] (the respective figure derived from the NMA was [redacted]).

Table 65. Relative risks of watch and wait versus dexamethasone, following normalisation: baseline to Month 3; all DMO patients (calculated by ERG, using dexamethasone baseline transition probabilities from Table 59 and normalised watch and wait transition probabilities, as estimated from the company, from Table 63)

		To					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
From	**Health State 1**	[redacted]	[redacted]	0.00	0.00	0.00	0.00
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00
	Health State 5	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	0.00	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema; ERG, evidence review group.

By looking at the relative risks estimated by the ERG after normalisation took place, one might think that normalisation resulted in higher relative risks, which overestimated all vision-related relative effects (improving, worsening, or maintaining stable vision), especially at milder health states. In order to investigate whether this is true, the ERG used data from the Excel file DMO_NICE_Oct2014_All DMO and calculated the relative risks for watch and wait versus dexamethasone following normalisation from two more cycles: from 21 to 24 months, and from 33 to 36 months. The findings of these calculations, shown in Table 66 and Table 67, indicate that there is no clear pattern in the change of magnitude of the relative risks that were effectively utilised in the model following normalisation. Nevertheless, these findings demonstrate that normalisation has affected, to some degree, all relative efficacy outcomes of the economic analysis (improving, worsening and retaining stable vision), and therefore is very likely to have affected the results of the economic analysis. To what direction and at what degree cannot be determined by simply looking at the ERG calculations.

Table 66. Relative risks of watch and wait versus dexamethasone, following normalisation: Month 21 to Month 24; all DMO patients (calculated by ERG, using dexamethasone baseline transition probabilities and normalised watch and wait transition probabilities from the Excel file DMO_NICE_Oct2014_All DMO)

		To					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
From	**Health State 1**	[redacted]	[redacted]	0.00	0.00	0.00	0.00
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00
	Health State 5	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	0.00	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema; ERG, evidence review group.

Table 67. Relative risks of watch and wait versus dexamethasone, following normalisation: Month 33 to Month 36; all DMO patients (calculated by ERG, using dexamethasone baseline transition probabilities and normalised watch and wait transition probabilities from the Excel file DMO_NICE_Oct2014_All DMO)

		To					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
From	**Health State 1**	[redacted]	[redacted]	0.00	0.00	0.00	0.00
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00
	Health State 5	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	0.00	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema; ERG, evidence review group.

Given the limitation of the assumption that relative effects remain stable over time and the impact of normalisation on relative risks across all 3 outcomes of the analysis, the ERG requested that the company run the base case economic analysis for people that are unsuitable for, or insufficiently responsive to non-corticosteroids using the actual data for dexamethasone (as in the economic model submitted by the company) but also for watch and wait from the pooled MEAD trials. This analysis would effectively use the actual relative effects between dexamethasone and sham as observed over

time, without the need to assume that relative effects are constant over time, and without the need for normalisation, thus removing two of the biggest potential flaws of the economic model. To explore the impact of the assumption that imposed restriction of movements to adjacent health states (once BCVA state up or down at maximum) on the results of the economic analysis, the ERG requested that the company provide two separate analyses using the actual data: one analysis that restricts eye movements to adjacent health states (**Analysis A3**), and one analysis that does not make use of this assumption, and therefore transitions may happen between any two health states, as observed in the MEAD trials (**Analysis A4**).

Results of these analyses were utterly different from the base case analysis provided by the company: in **Analysis A3**, watch and wait dominated dexamethasone; in **Analysis A4**, dexamethasone was slightly more effective than watch and wait, at an additional cost of £1,411,676 per QALY. These findings indicate that a. the assumption of a stable relative effect over time does not hold, at least between dexamethasone and watch and wait, as the QALY difference between the two treatments estimated using the actual MEAD efficacy data and without imposing any restriction on transitions (**Analysis A4**) is much smaller than the QALY difference estimated using the NMA relative effects b. the assumption of movements occurring only between adjacent health states had a great impact on the results, as when actual data and the assumption of restriction were applied into the model, watch and wait became more effective than dexamethasone, while when actual data without the assumption of restriction were applied, dexamethasone was more effective than watch and wait. A possible explanation of these results is that either dexamethasone tends to result in improvements in vision of more than one BCVA state up, or that watch and wait tends to cause deterioration of more than one BCVA state down. These analyses are discussed in Section 5.5.1, with results being presented in Section 6.1.1, along with company's and ERG's comments.

Transition probabilities following end of treatment or discontinuation

Following the 3-year treatment period or discontinuation within the 3-year treatment period, the model assumed that patients received no further treatment and as a result the vision in their DMO-affected eye(s) transitioned through the BCVA states at a rate consistent with the natural history of vision in patients with DMO, taken from Mitchell *et al.* (2012).[31] This study used data from the WESDR adjusted to account for the improvement in DM management since WESDR was undertaken, and calculated a 3-month probability of gaining or losing at least 10 letters of BCVA (i.e. moving up or down one health state) of 3.5% and 4.5%, respectively (with 96.5% of patients remaining stable). These transition probabilities were applied in the company's model to all eyes with DMO from Year 4 onwards (or year 5/6 in the case of FEI), for the remainder of the model time horizon.

The same natural history of vision was assumed for all eyes with DMO following end of treatment or discontinuation; natural progression of vision in eyes with DMO was assumed to be constant over

time. Both assumptions were made, according to the company, due to lack of evidence to inform an alternative assumption.

ERG comment

The ERG finds reasonable the application of natural progression data onto eyes with DMO following end of the 3-year treatment or discontinuation because of lack of more suitable data. The study by Mitchell *et al*. (2012)[31] that is cited by the company as the source of the natural history data on DMO is an economic evaluation of ranibizumab for DMO, based on decision-analytic economic modelling and using the clinical findings reported in the RESTORE trial.[94] The method of identification and selection of this study as the data source for the natural progression of vision loss due to DMO was not reported in the CS, therefore the ERG asked the company to clarify this issue; the company's response was that the study was identified as a source of this information in previous economic evaluations for DMO within the literature review conducted to identify published economic evaluations of treatments for DMO.

Mitchell *et al*. (2012)[31] estimated the long-term natural progression of DMO in order to inform their economic model using mainly two sources of information (in combination with model calibration):

- Data from the DRCR.net protocol I study,[93] which showed that the improvement achieved after 12 months with ranibizumab plus laser therapy) and with laser monotherapy was maintained after 24 months. This was taken by the authors as an indication that the mean visual acuity is stable in year 2.
- Observational data from the WESDR,[122] which showed that the proportion of diabetic patients with a decrease in visual acuity exceeded the proportion with an improvement 4 years after onset. This was taken by the authors as an indication that visual acuity tends to decrease.

It was acknowledged that the 4-year incidence of vision loss in patients with DM in the WESDR might overstate the proportion of patients with a worsened BCVA, because the WESDR population received less intensive systemic DM than currently practiced in clinical routine. The 4-year incidence was therefore adjusted to reflect current practice. Adjustments were guided by data derived from two long-term studies investigating the relationship between level of glycaemic control and the risk of developing microvascular complications such as diabetic retinopathy: the Diabetes Control and Complications Trial[123] and the UK Prospective Diabetes Study.[124] Following adjustments of WESDR data and model calibration based on the RESTORE data, the 3-month probability of gaining or losing at least 10 letters of BCVA (i.e. moving up or down one health state) was estimated at 3.5% and 4.5%, respectively.

The ERG reviewed other TAs of treatments for DMO, to investigate whether the values used by the company were consistent with those used in other reports. The company submission for NICE TA271 on fluocinolone acetonide for DMO[125] assumed that, beyond 36 months and in every 3-month cycle

of the submitted model, in those discontinuing fluocinolone acetonide a proportion of patients (figure not reported due to confidentiality issues) in each health state would worsen by 5 letters; in those in the sham arm, the proportion of patients that would worsen by 5 letters was 3%. The company submission for NICE TA237 on ranibizumab[114] utilised a 3-month probability of improving or worsening vision of 2.5% and 3.5%, respectively, to account for long-term progression of DMO in the model; figures were based on WESDR/ETDRS, but it was unclear to the ERG of TA237 how these 3-month figures were estimated.

The ERG consulted with clinical experts who expressed the view that the reason for discontinuation is important and affects natural progression of DMO. If patients discontinue due to lack of efficacy, then natural progression is expected to be different from the natural progression of a patient discontinuing treatment due to an adverse event, and in this case progression would also depend on the type of the adverse event that led to discontinuation. A 4.5% 3-month probability of deterioration due to a lack (or loss) of efficacy might be a reasonable estimate, according to clinical expert advice, but might be potentially higher if this was due to an adverse event. A small proportion of patients might experience improvement in their DMO following treatment discontinuation, especially those with relatively recent DMO. The ERG was not able to identify alternative data that would indicate the natural progression of DMO in people discontinuing due to adverse events as opposed to people discontinuing due to lack (or loss) of efficacy that would be suitable to use in the economic model.

Moreover, as shown in Section 5.4.7, the proportions of people discontinuing due to lack (or loss) of efficacy and due to adverse events were available only for dexamethasone, watch and wait and laser treatment in the economic model, as, with the exception of MEAD and DRCR.net PROTOCOL I, the reason for discontinuation was not reported in the other key trials that informed the economic model. Discontinuations due to side effects were assumed to be zero for watch and wait in the base case analysis. Therefore, natural progression data that were specific to the reason for discontinuation would only affect dexamethasone and laser. The ERG attempted an additional analysis to explore the impact of a higher degree of vision deterioration following discontinuation or end of treatment; in this analysis, the 3-month probability of gaining at least 10 letters of BCVA was retained at 3.5%, but the respective probability of losing at least 10 letters of BCVA was increased at 5.5%, with the probability of remaining in the same BCVA state being, consequently, reduced at 91% (**Analysis C2**). This analysis is reported in Section 5.5.2.2 with results presented in Section 6.1.2.2. This scenario had no significant impact on the base case results.

Effect on patient's vision due to the development of DMO in the fellow eye

The model assumed that there was no effect on a patient's vision due to the development of DMO in the fellow eye. The company considered this assumption justifiable, as it was based on the assumption that development of DMO in the fellow eye would be caught early due to the regular monitoring that

is already in place as a result of the initial eye being affected with DMO. A sensitivity analysis was performed by the company whereby a decrement equal to one cycle of natural history of vision in an eye with DMO was applied on development of fellow eye involvement.

ERG comment

Following clinical expert advice, the ERG finds the model assumption that a patient's vision is not affected following development of DMO in the fellow eye reasonable. Clinical experts confirmed that patients with DMO are regularly monitored in both eyes, and therefore development of DMO in the fellow eye would be caught early and prior to any substantial deterioration in the fellow eye's visual acuity.

Transition probabilities in eyes without DMO

Eyes without DMO were assumed to maintain constant vision and thus remain in the same BCVA state in each 3-month cycle of the model time horizon (unless they developed FEI).

ERG comment

As already discussed in Section 5.4.2, the ERG finds acceptable the assumption that eyes without DMO retain constant vision, which was made for simplification purposes due to the amount of data and the model complexity that would be required in order to accurately represent vision changes due to other ocular comorbidities of DM in eyes not affected by DMO. Nevertheless, the ERG notes that, in reality, the company's assumption that 'any vision loss resulting from ocular comorbidities other than DMO would affect all cohorts equally' is not necessarily true. In reality, the impact of non-DMO eye vision on overall HRQL depends on the level of vision in the DMO-affected eye: if vision acuity is severely deteriorated in the DMO-affected eye (for example, as a result of no treatment or less effective treatment), then the impact of the non-DMO vision on overall visual acuity and HRQL becomes more prominent.

5.4.7 Treatment discontinuation

As described in Section 5.4.2, at any time during the 3-year treatment patients in the model may discontinue their initiated treatment (and move to no treatment) either due to lack (or loss) of efficacy of treatment or due to adverse events and other non-efficacy related reasons (for example, withdrawal of consent, lost to follow-up, protocol violation, personal reasons,) . The company stated that these two reasons were modelled as independent, to allow disaggregation of outcomes attributable to each reason. However, visual acuity outcomes were not affected by the reason for discontinuation; visual acuity following discontinuation was assumed to follow the natural history of vision in eyes with DMO, as described in Section 5.4.6.2.

The proportion of patients discontinuing each treatment was estimated from the patient-level data (where available) or from key study publications and were entered into the model as a proportion per

month. The company argued that monthly inputs allowed data to be entered accurately despite different clinical trials having different time periods between visits, and also despite the varied time-points reported in study publications (where patient-level data were not available). Where patient-level data were available these data were input at the month of the observation. Where patient-level data were not available, the rate reported in the study publications was applied at the end of the time-point at which the data were reported. Beyond the study duration, discontinuation rates were extrapolated using the average rate over the study duration applied in line with the relevant study cycle length. The company chose this method chosen in preference to other methods (such as LOCF) as there was no clear pattern to the discontinuation rates over time. The majority of study publications did not specify all reasons for discontinuation within the study; in such cases, all discontinuations were assumed to be due to adverse events and other non-efficacy related reasons. This assumption did not affect the outcomes of the analysis as all patients had the same outcome following discontinuation for either reason.

Patients in the sham treatment arms of MEAD models discontinued due to lack or loss of efficacy, adverse events from sham injection, or were censored due to receipt of escape therapy; outcomes for these patients were therefore not available. The company argued that to assume no discontinuation from watch and wait (which is clinically plausible) would over-estimate the true efficacy of watch and wait. Therefore, discontinuation from watch and wait due to lack or loss of efficacy was included within the model, with patients discontinuing assumed to follow the natural history of vision in eyes with DMO. The base case analysis assumed that there is no discontinuation from watch and wait due to adverse events and other non-efficacy related reasons; however, discontinuation from watch and wait due to adverse events and other non-efficacy related reasons was considered in a scenario analysis in the populations of patients who are unsuitable for or insufficiently responsive to non-corticosteroid therapy, using relevant discontinuation data from the sham arm of the MEAD studies.

Table 68 provides the rates of discontinuation for each treatment over the 3 Years of treatment, disaggregated by reason for discontinuation.

Table 68. Proportion of patients discontinuing treatment during each year, by reason for discontinuation (adapted from CS, Appendix 16)

	Reason for discontinuation					
Treatment	**Adverse events and other non-efficacy related reasons**			**Lack (or loss) of efficacy**		
	Year 1	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
All DMO patients (DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy)						

DEX	5.19%	9.56%	6.15%	3.46%	5.79%	4.98%
Watch and wait	10.86%*	8.33%*	3.50%*	15.85%	19.12%	7.85%
Fluocinolone acetonide	0.00%	20.00%	7.20%	0.00%**	0.00%**	0.00%**
DMO patients who are pseudophakic						
DEX	5.88%	11.76%	5.93%	4.71%	9.41%	5.88%
Watch and wait	0.00%	0.00%	0.00%	13.60%	15.22%	2.77%
Ranibizumab	9.48%	5.40%	3.24%	0.86%**	0.00%**	0.00%**
Bevacizumab	0.00%	14.29%	6.12%	0.00%**	0.00%**	0.00%**
Laser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in table: DEX, dexamethasone; DMO, diabetic macular oedema; PRN, pro re nata.

*only in scenario analysis, as base case analysis assumed no discontinuation due to adverse events and other non-efficacy related issues

**all discontinuations assumed to be due to adverse events and other non-efficacy related reasons, as reasons for discontinuations not reported in the key published studies

ERG comment

The ERG notes that, depending on each trial design, the reasons for discontinuation are likely to differ across trials. For example, patients in the MEAD trials who lost ≥15 letters from baseline were discontinued from treatment at the investigator's discretion; this resulted in high discontinuation rates in both MEAD arms. On the other hand, this criterion of discontinuation was not applied in other key trials of comparators considered in the economic analysis. This has presumably resulted in an overestimation of the risk of discontinuation for dexamethasone relative to other treatments in the analysis.

It is also noted that the economic model has been informed by discontinuation rates taken directly from clinical trial data without any adjustment between comparisons. However, adjustment of data is required, as discontinuation is a parameter that may be greatly influenced by trial protocols, as discussed in the previous paragraph. This naïve addition of trial data from different trials, without appropriate synthesis, is likely to have introduced bias in the economic analysis.[126] Ideally, a NMA of discontinuation data should have been undertaken, to adjust for any baseline differences across the studies. However, this flaw (naïve addition of trial data) does not apply in the comparison between dexamethasone and watch and wait (sham), because in this case head-to-head data from the pooled MEAD trials have been used and thus randomisation has not been broken.

The company assumed in the base case analysis that there was no discontinuation from watch and wait due to adverse events and other non-efficacy related reasons, so all related discontinuations in the pooled MEAD sham treatment arms were ignored and patients discontinuing for those reasons were counted as continuers and applied the efficacy estimated for sham/no treatment (which was used as a proxy for watch and wait). The ERG notes that this assumption has potentially over-estimated the risk of discontinuation for dexamethasone relative to watch and wait.

Another point for concern is the fact that efficacy outcomes for people who discontinued in the MEAD trials (and potentially in other trials) appear to have been considered in the efficacy analysis that informed the NMA, which, in turn, informed the economic model: according to the company, the MEAD trial efficacy analyses were based on the ITT approach, with discontinuations being accounted for using the LOCF method (CS, page 158). At the same time, discontinuers in the economic model were counted separately and were assumed to follow the natural progression of DMO. If the efficacy outcomes from MEAD have been considered in the NMA using the ITT approach (there is no indication in the company submission that an alternative approach was adopted), then both dexamethasone and watch and wait discontinuers (and likely discontinuers in other key trials, too, if efficacy analysis was based on the ITT approach) have been double-counted in the model. This may have potentially underestimated the effect of each treatment in the economic model for which ITT efficacy analysis has been utilised in the NMA. However, it is difficult to estimate to which direction the relative effect between 2 treatments has been affected from this flaw in the economic analysis, as the direction and the degree of the discrepancy between the actual relative effect and the relative effect estimated from the economic analysis depends on the relative risk of discontinuation between treatments (which, as argued above, cannot be accurately estimated using the trial discontinuation data without any synthesis) and the relative efficacy between treatments.

Due to time restrictions, it was not possible for the ERG to explore the impact of discontinuation further, and synthesise the discontinuation data coming from different trials in an appropriate way. Nevertheless, the ERG carried out a scenario analysis in which the rates of discontinuation for all treatment options were set at zero (**Analysis C3**). This scenario does not reflect a realistic situation, but aimed to reveal the impact of discontinuation on the relative cost effectiveness between treatments assessed in the economic models. This scenario, which had no impact on the base case results, is discussed in Section 5.5.2.2, with results presented in Section 6.1.2.2.

5.4.8 Adverse events

The economic analysis considered explicitly 5 key adverse events associated with DMO treatment that may require medical or surgical intervention. These included cataracts, raised IOP, retinal detachment, endophthalmitis and vitreous haemorrhage. These adverse events were selected by the company to retain consistency with those included in previous economic models for DMO. The proportions of patients experiencing these adverse events during each year of the 3-year treatment period were taken primarily from the key clinical trials for each intervention, as shown in Table 69. The risks of adverse events for pseudophakic patients with DMO were assumed to be the same as those for the whole DMO population, with the exception of the risk of cataract, which was estimated to be zero in the pseudophakic population as these patients had already an artificial lens in their eyes.

Clinical inputs for adverse events of treatment were applied only during the 3-year treatment period, with the exception of cataract, as discussed below, as DMO patients are at higher risk of requiring cataract extraction compared with the whole population, and therefore DMO patients in the model may still require a cataract extraction after end of treatment. For treatments with 3-year trial follow-up no extrapolation was required. For treatments with less than 3 years of follow-up laser (PROTOCOL I) and bevacizumab (BOLT) data were extrapolated beyond the trial follow-up using LOCF.

Table 69. Data sources and assumptions used for the estimation of proportions of patients experiencing adverse events requiring treatment within each year of DMO treatment

Intervention	Data source	Further assumptions made by the company
DEX	MEAD[112]	
Watch & wait	Blue Mountains study[111]	Natural history assumed for cataract development; the proportion of patients experiencing other adverse events requiring treatment was assumed to equal 0.00%
Ranibizumab	RESTORE[94,117,118]	
Bevacizumab	BOLT[92,119]	
Laser	PROTOCOL I[120] to Year 2 then LOCF	In Year 3 of PROTOCOL I sham + laser patients were allowed to receive ranibizumab, hence only data for Years 1 and 2 have been applied in the model; data for Year 3 were extrapolated using LOCF.
Fluocinolone acetonide	FAME[90,116,127]	FAME reported data only for Years 2 and 3, hence it was assumed that no patients receiving fluocinolone acetonide experience adverse events in Year 1 (probability 0.00%)
Abbreviations used in table: CSR, clinical study report; DEX, dexamethasone; DMO, diabetic macular oedema; LOCF, last observation carried forward.		

Table 70 summarises the probabilities of adverse events requiring medical or surgical intervention that were utilised over the 3 years of DMO treatment in the economic model.

Table 70. Proportions of patients experiencing each of the 5 adverse events considered in the economic model, within each year over the 3-year duration of DMO treatment

Adverse event	Year	DEX700	Watch & wait	Ranibizumab	Bevacizumab	Laser	Fluocinolone acetonide
Cataract requiring extraction in phakic patients	1	8.40% (11.83%)	2.34%	NA	NA	NA	0.00%
	2	19.17% (37.66%)	2.34%	NA	NA	NA	65.53%
	3	2.94% (26.39%)	2.34%	NA	NA	NA	41.98%
Raised IOP treated with medication or surgery	1	12.10%	0.00%	0.86%	9.52%	[redacted])	0.00%
	2	4.61%	0.00%	0.00%	0.00%	[redacted]	4.80%
	3	1.15%	0.00%	0.00%	0.00%	[redacted]	32.30%

Retinal detachment	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
	2	0.29%	0.00%	0.00%	0.00%	[redacted]	0.00%
	3	0.29%	0.00%	0.00%	0.00%	[redacted]	0.00%
Endophthalmitis	1	0.29%	0.00%	0.00%	0.00%	[redacted]	0.00%
	2	0.29%	0.00%	0.00%	0.00%	[redacted]	0.00%
	3	0.00%	0.00%	0.00%	0.00%	[redacted]	0.00%
Vitreous haemorrhage	1	4.03%	0.00%	0.00%	0.00%	[redacted]	0.00%
	2	1.15%	0.00%	0.00%	0.00%	[redacted]	0.00%
	3	1.73%	0.00%	0.00%	0.00%	[redacted])	0.00%

Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; IOP, intraocular pressure; NA, non-applicable.

Note: Corrected proportions for cataract requiring extraction in phakic patients for DEX700 (all years), raised IOP for laser (Year 1) and vireous haemorrhage for laser (Year 3) are presented in brackets following clarification from the company; with the exception of cataract proportions, all other figures reported in this table are those that have been used in the original economic models submitted by the company.

Cataract surgery is not applicable to pseudophakic patients, hence not applicable to ranibizumab, bevacizumab or laser therapy as these were included only in the analysis on pseudophakic patients with DMO.

Further details on the company's estimation of proportions of patients experiencing cataract and increased intraocular pressure and types of treatment for the latter are described below.

5.4.8.1 Cataract

Cataract has been considered only in the analyses on patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, and, within this patient group, only in those who were phakic. The proportion of patients with DMO who were phakic at initiation of treatment was 75.50% in the pooled MEAD dexamethasone arms (as well as in the pooled MEAD sham treatment arms), and this proportion was applied at baseline across all relevant treatment options (i.e. dexamethasone, watch and wait, and fluocinolone acetonide in scenario analysis); each year, this proportion was reduced by the proportion of patients who had developed cataract within the previous year.

Data on the proportion of phakic patients developing cataract were taken from the key trials for dexamethasone and for fluocinolone acetonide; phakic patients in the watch and wait arm of the model were assumed to follow the natural history of cataract in people with DM. The Blue Mountains Study, a population-based cohort study of vision, common eye diseases and other health outcomes in an urban older Australian population, demonstrated a cumulative incidence of cataract surgery in a population of patients with DM of 20.9% over 10 years.[111] Assuming that the risk of cataract is constant over time and using the exponential cumulative distribution function, the company estimated an annual risk of cataract of 2.34%, which was applied to phakic eyes in the watch and wait arm of the model. This annual risk of 2.34% was also applied to all phakic patients with DMO after the 3

years of treatment and up to the 15 years of the model duration, as well as to phakic patients that discontinued treatment, to reflect the increased risk of cataract characterising patients with DMO compared with the general population.

5.4.8.2 Raised intraocular pressure

The proportions of patients with raised IOP requiring medical or surgical intervention were estimated using two types of data, depending on the level of information reported in the key trials:

- the rate of raised IOP reported as an adverse event of treatment; or
- the incidence of IOP ≥30mmHg, which was indicated by clinical experts to result in initiation of treatment.

The proportion of cases of raised IOP that were treated with medication and with surgery were estimated using data reported in the key trials and further assumptions based on clinical expert opinion. Based on this input, it was indicated that patients with IOP ≥30mmHg would require treatment with medication, and patients with IOP ≥40mmHg would require surgical intervention. The proportions of patients with raised IOP that were treated with medical or surgical intervention in the economic model are shown in Table 71.

Table 71. Proportions of patients with raised IOP that were treated with medical or surgical intervention (adapted from CS, Table 87)

Intervention	Proportion of patients with raised IOP that is treated with	
	Medication	Surgery
DEX700	72.58%	27.42%
Watch & wait	0.00%	0.00%
Ranibizumab	100.00%	0.00%
Bevacizumab	100.00%	0.00%
Laser	[redacted]	[redacted]
Fluocinolone acetonide	11.11%	88.89%
Abbreviations used in table: DEX700, dexamethasone 700µg; IOP, intraocular pressure		

ERG comment

Following consultation with clinical experts, the ERG agrees that the 5 side effects modelled are the most important ones in terms of their frequency following DMO treatment and their impact on HRQL and costs incurred by their management. The ERG finds reasonable the fact that all side effects except cataract were considered only over the 3 years of treatment. The ERG also agrees with the assumption that, with the exception of cataract, the risk of all other adverse events in pseudophakic patients with DMO was equal to the respective risk in the whole DMO population. Clinical experts consulting the ERG suggested that pseudophakic DMO patients may have a slightly higher risk for retinal detachment compared with the whole DMO population, but this additional risk could be ignored and

should not raise concerns regarding the validity of the assumption. Clinical experts also confirmed that the risk of cataract is constant over time in DMO patients, and higher in patients receiving corticosteroid DMO therapy.

The ERG notes that adverse event risks have been derived from trial arms without any data synthesis. Although ideally adverse event data should have been taken from observational studies, the ERG accepts that such observational data may not be available across all treatments included in the analysis; moreover, the ERG's opinion is that lack of synthesis of side effect data is unlikely to have introduced strong bias in the analysis, as the rates of most adverse events associated with DMO appear to be very small, and therefore their impact on costs is expected to be trivial (as discussed later, the company's analysis assumed that adverse events have no impact on HRQL). ERG's clinical experts confirmed that the rates of adverse events recorded in trials broadly reflected adverse event rates observed in clinical practice.

Data for cataract in dexamethasone have been amended by the ERG, following a clarification query to the company, regarding relevant data reported in the company clinical study reports for the MEAD studies [Tables 12-21].[54,55] The company confirmed that "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". However, in the submission the company had treated the data as cumulative when estimating the frequency of cataract in each year for dexamethasone in the economic model. The actual data provided by the company and updated risks of cataract for dexamethasone, as estimated by the ERG, are shown in Table 72.

Table 72. Proportions of phakic patients experiencing cataract within each year over the 3-year duration of the MEAD trials (ERG calculations on data provided by the company)

Study visit	**MEAD-10[54]** **N = [redacted]**	**MEAD-11[55]** **N = [redacted]**	**Risk of cataract for dexamethasone in each year of treatment**	
			ERG calculation	**ERG estimate**
Month 6	[redacted]	[redacted]		
Month 12			=([redacted]+[redacted]+[redacted]+[redacted])/([redacted]+[redacted]) = [redacted]/[redacted]	Year 1: [redacted]
Month 18				
Month 24			=([redacted]+[redacted]+[redacted]+[redacted])/([redacted]-[redacted]) = [redacted]/[redacted]	Year 2: [redacted]
Month 30				
Month 36			=([redacted]+[redacted]+[redacted]+[redacted])/([redacted]-[redacted]) = [redacted]/[redacted]	Year 3: [redacted]
Abbreviations used in the table: ERG, evidence review group.				

Regarding the incidence of cataract in patients with DM, the ERG reviewed 2 relevant publications considered in the NICE STA of fluocinolone acetonide for DMO:[45]

- the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) recruited 2,366 people receiving care for DM for a prevalence study of diabetic retinopathy and followed them for 10 years. The study found that in the younger-onset group there was an 8.3% cumulative incidence, and in the older-onset group there was a 24.9% cumulative incidence of cataract surgery over the 10-year period;[128]
- a Danish study that followed a population-based cohort of 727 patients with type 1 diabetes reported a 25-year crude cumulative incidence of cataract surgery of 20.8%, corresponding to a mortality-adjusted incidence of 29.4% by 25 years after onset.[129] The latter corresponds to an incidence of 13.0% by 10 years, assuming the risk is constant over time and using the exponential cumulative distribution function.

The ERG accepts the use of the 20.9% figure for the 10-year probability of cataract in people with DM for the watch and wait arm and for all patients with DMO after discontinuation or after receiving 3 years of treatment. The ERG identified a minor error in the estimation of the annual probability derived from this 10-year probability, as the 2.34% figure is the instantaneous rate of cataract, not the annual probability. The annual probability is 2.32%:

$$\text{Instantaneous rate } r = -[\ln(1-P)]/t = -[\ln(1-0.209)]/10 = 0.0234$$

$$\text{Annual probability } p = 1 - \exp(-r \times t) = 1 - \exp(-0.0234 \times 1) = 0.0232$$

One point to highlight following comparison of the incidence of cataract in DMO patients treated with dexamethasone and the epidemiological data on the incidence of cataract in patients with DM is the company's assertion that "DEX700 would be viewed to accelerate rather than cause primary cataract formation in elderly patients" (CS, page 274). The company made this claim after considering that "in the majority of DMO patients that are over the age of 60, cataract would be anticipated as a result of their underlying DM in the near future with a cumulative incidence of cataract surgery in DM patients of 20.9% over 10 years". However, the amended data on cataract incidence in DMO patients treated with dexamethasone suggest a 3-year probability of cataract with dexamethasone of [redacted] in phakic patients. If we accept the 10-year cumulative incidence of 20.9% in patients with DM as reported for the Blue Mountains Study,[111] (which was the cataract incidence used by the company for watch and wait in the economic model), assume a constant risk of cataract over time, and use the exponential cumulative distribution function, then it is estimated that it will take [redacted] years before [redacted] of patients with DM develop cataract. This number of years is far beyond the mean life expectancy of the cohort of DMO patients treated with dexamethasone given that their starting age is [redacted] years, meaning that the probability of cataract of [redacted] would never be reached in reality by patients with DMO without their being treated with dexamethasone. These estimations indicate that dexamethasone does not just accelerate the formation of cataract, but in many patients it may cause it.

Related to the above, the ERG wishes to note that the European Medicines Agency (EMA) assesment report on dexamethasone for the treatment of DMO states that "the total incidence of cataract adverse events was 67.9%, 64.1%, and 20.4% in the DEX 700, DEX 350, and Sham groups, respectively" (page 46).[105] The total incidence of cataract of 67.9% in the dexamethasone group over three years is even higher than the incidence estimated by the ERG (▇▇▇▇▇) using the data provided by the company. The ERG is unclear as to why there is this discrepancy between the two figures, but the figure in the EMA report confirms that the incidence of cataract is probably higher that what would be expected if cataract was developed only as a result of underlying DM.

Another issue to consider is that the economic model has assumed that eyes are either phakic or pseudophakic in all patients. Therefore, the model appears to assume that once cataract has been removed, there is no additional risk for cataract in the other eye. This assumption seems to be reasonable for patients with unilateral DMO, as the non-affected eyes can be assumed to have the same risk for cataract across cohorts, which is independent of treatment received, and therefore the assumption does not have any substantial impact on the results of economic analysis. However, in patients with bilateral DMO at baseline or following FEI, this assumption results in the risk for cataract in the second DMO eye becoming zero, once cataract formation and extraction has occurred in the first eye. Due to time constraints, the ERG did not have the opportunity to check whether this assumption holds in the economic model, but if it does, it considerably reduces the actual risk of cataract formation and extraction (and associated costs) in patients with bilateral DMO, and has therefore underestimated the costs of dexamethasone and fluocinolone acetonide relative to watch and wait, as both treatments, as corticosteroids, are characterised by high risk of cataract.

Regarding the proportions of patients with raised IOP that were treated with medical or surgical intervention in the economic model, clinical experts confirmed that the proportion of medical versus surgical treatment is affected by type of treatment. It was agreed that increased IOP caused by corticosteroids has a higher probability of being treated surgically, although the large discrepancy in the respective figures (27.42% for dexamethasone versus 88.89% for fluocinolone acetonide was questioned by one of the ERG's clinical experts (but was considered reasonable by two other clinical experts, due to the higher risk of raised IOP with fluocinolone acetonide).

For non-corticosteroids, the ERG was informed that between 0 and 10% of patients with raised IOP would require surgical treatment; this suggests that the ▇▇ figure for patients with laser requiring surgery is probably high; nevertheless, given the low risk of raised IOP with laser (less than ▇ in any year), the ▇▇ figure is unlikely to have affected the results of the economic analysis.

In conclusion, the adverse event data used in the economic analysis appear to be overall reasonable. The ERG ran an additional economic analysis following the corrections in the cataract data for

dexamethasone, and the minor correction in the annual probability of cataract in patients receiving no treatment or watch and wait (**analysis B3**) and found the corrections to have no impact on the conclusions of the base case analysis. This analysis is described in Section 5.5.2.1 with results being presented in Section 6.1.2.1.

5.4.9 Mortality

All patients were at risk of death throughout the model. The risk of all-cause mortality was applied to all patients, adjusted for the additional mortality due to DM (relative to the general population) and due to DMO (relative to the population with DM) and assuming that mortality occurred equally across all BCVA states in the base case. A scenario analysis considered additional mortality for patients who experienced clinical blindness (severe vision loss), i.e. those whose BSE had BCVA ≤ 35 letters, as there is evidence of increased mortality in blind patients.[130] This additional mortality was assumed only in a scenario analysis to avoid double-counting of the mortality risk for patients with severe vision loss in the base case analysis, as the hazard ratio for DMO is likely to include some patients who are clinically blind. The company claimed that omission of additional mortality due to severe vision loss from the base case analysis was also in line with previous economic evaluations in DMO.

All-cause mortality was taken from interim life tables for England[131] and was based on the cohort's mean age (reported in Section 5.4.3.2). The hazard ratio for the additional mortality due to DM relative to the general population was 1.93 (Mulnier *et al.*)[132] and the hazard ratio for the additional mortality due to DMO relative to the DM population without DMO was 1.27 (Hirai *et al.*).[34] These two hazard ratios were multiplied together to give a hazard ratio for the additional mortality relative to DM and DMO of 2.45.

The company acknowledged that there might be some double-counting in the application of these two hazard ratios, as it is possible that the DM population from which the hazard ratio for the additional mortality due to DM was derived included some patients with DMO. However it would not be possible to disaggregate the impact of this scenario if this was the case, therefore in the base case these hazard ratios were applied together, in accordance with previous technology appraisals for DMO.[114,125] As this combination of hazard ratios was possible to have over-estimated the additional mortality due to DM and DMO, scenario analyses were performed applying each hazard ratio in isolation, to determine the impact on the results of lowering the risk of mortality for the DMO population.

All-cause mortality was available for males and females. The proportion of males at baseline in all DMO patients and pseudophakic DMO patients was taken from the mITT population in the pooled MEAD dexamethasone arms, as described in Section 5.4.3.2. The proportion of male and female patients who remained alive was expected to change over time, due to the differential mortality

experienced by each gender. Therefore the model used the annual risk of mortality for males and females, adjusted for DM and DMO to calculate the proportion of patients who remained alive and who were male and female in each year from the baseline age in the model. This, according to the company, increased the accuracy of the general mortality applied within the model.

Age-specific all-cause mortality was obtained from interim life tables for England[131] and was applied as the underlying risk of death to all patients, which varied over time according to patient age. The adjustments to mortality due to DM relative to the general population[132] and due to DMO relative to the DM population[34] were assumed to remain constant over time, given that the background mortality was already age-dependent, to avoid double counting.

Regarding the scenario analysis that assumed increased mortality for patients whose BSE fell into BCVA state 1 (severe vision loss considered clinical blindness, BCVA ≤ 35 letters), an increased mortality rate was applied to BCVA state 1 in the BSE of 1.54 times that of the general population.[130] To ensure that the total mortality experienced by the patient was equal across both eyes (so that both eyes carried equal weight and mortality was applied equally across the BSE and the WSE), an adjustment was applied to the mortality for the proportion of patients whose WSE fell into the Health State 1, using the following formula:

(general mortality × sum of probability that the BSE is in health states 2 to 6 + severe vision loss mortality × probability that BSE is in Health State 1 - general mortality × sum of probability that the WSE is in health states 2 to 6) / (probability that WSE is in Health State 1)

A separate adjustment was therefore calculated for each type of patient (on initial treatment versus discontinued from initial treatment and unilateral versus bilateral DMO).

ERG comment

The ERG was unclear how the studies reporting mortality rates for patients with DM or DMO were identified by the company. Following a clarification question, the company stated that Mullnier *et al*.,[132] Hirai *et al*.[34] and Christ *et al*.[130] were identified as references that had been used in previous economic evaluations of treatments for DMO.

The company estimations and the application of hazard ratios in the electronic copy of the model appear to be correct.

The ERG for the TA271 and TA274 (the same ERG worked on both TAs) conducted a review of studies on mortality in people with DM with and without retinopathy and concluded that

- mortality is higher in people with DM, compared to the general population;

- in those with DM, mortality is much higher in those with advanced retinopathy, with relative risks in the range 3 to 4.

Based on their review, the ERG for TA271/TA274 decided to do a sensitivity analysis using a mortality relative risk of 3.5.

Following the review of previous STAs, the ERG decided to also undertake a scenario analysis in which an increased mortality hazard ratio of 3.5 was applied. The use of a higher risk of mortality reduced the cost effectiveness of ranibizumab relative to dexamethasone in pseudophakic patients with DMO, but did not affect overall conclusions of base case analyses. This analysis (**analysis C4**) is reported in Section 5.5.2.2 with results provided in Section 6.1.2.2.

The study by Christ[130] that was used to inform a scenario analysis that considered an increased risk for mortality in people with severe vision loss appears to be of good quality. The formula used by the company to account for increased mortality for patients whose BSE fell into BCVA state 1 appears to have considered the BCVA state of both the BSE and the WSE; this is because BSE and WSE were fixed at baseline (structural assumption of the model), so in the model it was not possible to determine if a person was blind by looking at the BCVA of BSE only. Due to time constraints, the ERG did not make any further assessment or potentially needed adjustments to the formula used to estimate the extra risk for mortality in people with severe vision loss; nevertheless, this formula was used only in a scenario analysis in the company's model.

5.4.10 Health related quality of life

In the economic analysis, patient health related quality of life (HRQL) was assumed to depend on patients' visual acuity, as expressed by the BCVA states of each of their eyes. This was supported by evidence suggesting that adults experiencing sight loss incur an associated loss in their HRQL.[133] The company argued that visual impairment can have a negative impact on both the physical and emotional functioning of the DM patient; DMO can have a damaging effect on vision which, in turn, can limit the patients' ability to perform everyday activities.

This section describes the company's systematic review of the HRQL literature on utility data associated with changes in visual acuity, followed by a description and critique of the methods used in order to attach utility values onto the BCVA health states within the company's model.

5.4.10.1 Company's systematic review of utility values associated with DMO

The company conducted a systematic review to identify published HRQL data for patients with DMO, including the effect of adverse events of treatments for DMO on HRQL. The search was carried out in February 2014 and updated in July 2014.

Searches were performed in Medline and Medline In-Process and other non-indexed citations, Embase, Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Review and Effects (DARE), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and EconLit. Search terms captured the condition of interest (DMO); filters for quality of life were used, based on SIGN recommendations.[134] No date or language limits were applied. Further details of the search strategy are provided in the company submission (CS, Appendix 12; pgs 624-638). All search strategies developed by the company for identification of relevant economic evidence, data on health related quality of life (HRQL) and resource use and costs are presented in Appendix 9.9.

Studies were included in the review if they reported utility or HRQL data related to either changes in BCVA or absolute BCVA in patients with DMO: or they reported utility or HRQL data related to adverse events resulting from the treatment of DMO. Studies were excluded if they reported utility or HRQL data that were not related to DMO or adverse events not resulting from DMO treatment.

The company identified no relevant studies through database searching in the initial review or update. Subsequently, the company reviewed relevant NICE guidance to identify HRQL data that were used in previous NICE TAs for DMO treatments (TA237/274 on ranibizumab for DMO, and TA271/301 on fluocinolone for DMO). Subsequently, the company provided a description of the HRQL data used in these TAs.

For TA237/TA274, the submitted model used EQ-5D utility data collected from the RESTORE trial[94] that were related to BCVA health states using linear regression; analysis was based on the treated eye. No utility decrements were applied for adverse events associated with treatment of DMO. An extended regression analysis that was performed to address the Committee's concerns identified BCVA and sex as the only significant predictors of utility. In addition to this, scenario analyses were included that used utility values from published sources: Lloyd *et al*.,[135] Sharma *et al*.,[136] and Czoski-Murray *et al*. (2009)[99] The latter was preferred by the Appraisal Committee.

Sharma *et al.*[136] reported time-trade-off (TTO) utility values associated with visual loss secondary to diabetic retinopathy in the BSE in a sample of Canadian patients. Lloyd *et al*.[135] reported standard gamble, EQ-5D and HUI-3 utilities, and the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) score for patients with diabetic retinopathy, based on their BSE. Czoski-Murray *et al*.[99] reported TTO utility values for members of the general population wearing lenses to simulate bilateral visual impairment resulting from age-related macular degeneration.

The ERG for TA274 explored the impact of vision in the WSE on HRQL through scenario analyses in which the impact of treating the WSE was varied, using the Czoski-Murray et al. utilities. The

committee preferred the analysis in which treating the WSE had 30% of the HRQL impact for the same change in vision from treating the BSE.

For TA301 the submitted model used TTO data from Brown *et al*. (2000)[96], a US study that measured utility in five visual acuity groups defined by the BSE in patients with age-related macular degeneration. The model did not consider utility decrements due to adverse events of treatment. A revised analysis was used applying utility data from Heintz *et al*.,(2012)[97] which estimated TTO, visual analogue scale, EQ-5D and HUI-3 utilities for Swedish diabetic retinopathy patients based on visual impairment in their BSE. This approach was not preferred by the committee as the "very slight differences" between vision loss in the BSE and WSE were deemed to lack face validity.

The ERG for TA301 conducted a further sensitivity analysis using BSE utilities from Brown *et al*. (1999)[98], a US study that measured utilities according to BSE visual acuity in a population of patients with impaired vision in at least one eye (for a variety of reasons). The ERG also explored the impact of vision in the WSE on HRQL through scenario analyses in which the impact of treating the WSE was varied, using BSE utilities from Brown *et al*. (2000)[96], Brown *et al*. (1999)[98], and Czoski-Murray *et al*. (2009).[99] The Committee expressed a preference for the analyses in which treating the WSE had 30% of the HRQL impact for the same change in vision from treating the BSE.

The company concluded that the published utility values used within TA274 and TA301 were subject to a large number of limitations. Firstly the published utility values corresponded to visual impairment resulting from causes other than DMO, and therefore they might not be directly representative of the utility experienced by patients with DMO. Secondly the majority of utility values were based on vision in the BSE only, requiring assumptions for the impact of vision resulting from treatment of the WSE or bilateral treatment. Thirdly the health states for which utility values were available did not match the health states in the company's model, thus requiring adjustments or assumptions to make the published utility data 'fit' within model structures.

Consequently, the company conducted their analyses using the Visual Function Questionnaire – utility index (VFQ-UI) data obtained from the MEAD clinical trials which related specifically to the DMO population and included vision in the BSE and vision in the WSE separately as explanatory variables in the utility equation used in the economic model. EQ-5D values obtained from the MEAD clinical trials were used in sensitivity analysis.

ERG comment

The ERG considers the search terms and inclusion criteria used by the company to identify relevant utility data to be too restrictive. The ERG noted that the company was unable to access six full texts of references that were identified through the search; full references of these studies were requested

by the company during clarification period. The ERG believes that it is unlikely that these studies would contain sufficient information for use within the economic model.

During the clarification period, the company was also asked to provide a rationale for the strict inclusion criteria used for the identification of HRQL studies (i.e. HRQL data relating to BCVA or adverse events exclusively in patients with DMO). The company's response (Company's clarification response, page 55) is shown in Box 19.

Box 19. Company's justification of the strict inclusion criteria set for the systematic review of HRQL and utility data for patients with DMO (Company's response to clarification, C11; pg 55)

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.
Abbreviations used in the box: DM, diabetes mellitus; DMO, diabetic macular oedema; HRQL, health-related quality of life.

The ERG was sceptical about the restriction of inclusion criteria and the justification provided by the company during clarification. The ERG notes that the company has argued that HRQL in people with DMO depends exclusively on the levels of visual acuity. The VFQ-UI, which is the measure used in the company's economic analysis for the estimation of QALYs, is a condition-specific preference-based measure (PBM) focusing on visual functioning, and is not designed to capture the impact of DM on patients' HRQL either. On the other hand, the ERG accepts that use of HRQL data derived from the population of interest (patients with DMO in the MEAD trials), is probably more directly relevant to the decision problem compared with use of published utilities elicited from other populations with visual problems. Since DMO-specific data were available from the MEAD trials, the ERG finds reasonable the restriction of the systematic review to HRQL data on patients with DMO.

5.4.10.2 Utility values applied within the company's economic model

Preference-based measures used to collect information on HRQL – comparison with NICE reference case

Patients' HRQL in the MEAD trials was measured at baseline in each study arm using 2 generic PBMs: the short form 36 question health survey version 1 (SF-36v1) and the EQ-5D; and one condition-specific measure: the VFQ-25.

The company stated that SF 36 and EQ-5D were not administered during follow up of the MEAD studies, because they do not contain vision-specific items, and were therefore judged to be less appropriate for measuring DMO treatment-related benefit compared with the VFQ-25. Although EQ-5D is consistent with the NICE reference case, the company provided evidence that EQ-5D is relatively insensitive to changes in visual functioning and cannot accurately capture the true impact of such changes on the HRQL of patients with DMO; it was therefore argued that EQ-5D is not appropriate for the estimation of QALYs in patients with DMO. The following evidence was presented in support of this argument:

- A cross-sectional study that assessed the performance of EQ-5D in a population with age-related macular degeneration suggested that EQ-5D was not able to capture the impact of loss of visual function on patients' health status.[137] The company argued that the impact of vision loss is likely to be worse in patients with DMO compared with those with age-related macular degeneration, as vision loss in patients with DMO is likely to reduce their ability to manage their own DM in addition to performing other everyday activities. Therefore, it was suggested that the EQ-5D is likely to fail to capture the true impact of vision loss caused by DMO, too.
- A review by Tosh *et al*. examining the performance of generic PBMs in patients with visual disorders showed that EQ-5D was not sensitive to changes in vision and hence was not able to accurately capture the effect of changes in vision on HRQL.[138]
- Kay & Ferreira[139] mapped VFQ-25 scores on to EQ-5D scores using paired data from 344 DMO patients in the RESTORE clinical trial. They found that EQ-5D values within the RESTORE trial demonstrated a clear ceiling effect, with approximately 37% of observations having EQ-5D score of 1, which represents "perfect health". Scatter plots of VFQ-25 composite and subscale scores against EQ-5D utility scores confirmed this celling effect and did not demonstrate strong correlation between the two measures.
- The mapping algorithm generated by Kay & Ferreira[139] consistently predicted EQ-5D utility scores which were above the population average given the age of the population. Scatter plots showing observed versus predicted EQ-5D scores also demonstrated weak correlation. The predictive power of the preferred mapping equation was moderate (squared Spearman correlation coefficient 0.34).
- The lack of correlation between VFQ-25 and EQ-5D scores (based on EQ-5D visual analogue scale scores) was also demonstrated by Lloyd *et al*.,[135] who found only low to moderate correlation between the two measures in patients with DMO.

- Fenwick *et al*.[140] additionally demonstrated that the presence or severity of DMO and its associated vision loss are not associated with the EQ-5D score. They concluded that EQ-5D is not sensitive to the impact of severity of DMO.
- The Appraisal Committee for TA237[48] and TA274[115] considered the originally submitted analysis of EQ-5D from the RESTORE trial alongside scenario analyses which used published utility values and ultimately preferred values provided by a study by Czoski-Murray *et al*., [99] which was a study that elicited TTO utility values from members of the general population wearing lenses to simulate bilateral visual impairment resulting from age-related macular degeneration.
- The Appraisal Committee for TA271[141]] and TA301[142] considered a range of utility sources, none of which were based on EQ-5D utility values.

In addition to these arguments, the company assessed the validity of EQ-5D utility data obtained from DMO patients enrolled in the MEAD studies. In the pooled MEAD studies, 946 patients receiving dexamethasone 700µg, dexamethasone 350µg or sham had EQ-5D recorded at baseline (204 of these were treated in their BSE and 742 were treated in their WSE). The overall mean score was 0.76 for patients treated in their BSE and 0.78 for patients treated in their WSE. These figures are similar to the UK population means for patients of the same age reported by Sullivan *et al*., who reported the mean EQ-5D score for adults in the UK aged 60-69 to be 0.774.[143] However, these are at odds with the mean EQ-5D score for patients with DM reported by Sullivan *et al*. of 0.644 without complications and 0.570 with complications.[143] According to the company, these findings suggested that the EQ-5D may not be accurately capturing the impact of DM or DMO in the MEAD study population and ultimately demonstrated the inappropriateness of the EQ-5D for differentiating between changes in HRQL resulting from changes in vision.

The VFQ-25 is a vision-specific quality of life measure that has been validated in a DMO population.[144] It is non-preference based and thus does not allow the direct estimation of utility weights.

Kowalski *et al*.[145] used a subset of six items from the VFQ-25, which describe the impact of central and peripheral vision loss on daily functioning and well-being to produce a health-state classification system, the VFQ-UI. Preference scores for the VFQ-UI were elicited from 607 members of the general population in the UK, Canada, Australia and the USA using TTO.[101] An algorithm (the VFQ-UI algorithm) was subsequently produced using econometric modelling to allow the estimation of preference-based utility values from the VFQ-UI, using scores from the VFQ-25. This research was conducted by an independent academic group including Professor John Brazier (University of Sheffield, UK) on behalf of Allergan.

The company reported that use of the VFQ-UI algorithm for generating utilities was evaluated and accepted by NICE in the submission for dexamethasone in retinal vein occlusion, which received a positive recommendation[146].

ERG comment

The ERG agrees with the company that the evidence presented suggests that EQ-5D may not be appropriate for the measurement of HRQL in people with DMO. In such circumstances, NICE accepts that "alternative health-related quality of life measures may be used and must be accompanied by a carefully detailed account of the methods used to generate the data, their validity, and how these methods affect the utility values".[147] Moreover, NICE states that "the valuation of health-related quality of life measured in patients (or by their carers) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method".[147]

The VFQ-UI, which is the mesure used by the company for the estimation of QALYs in the economic analysis, is a vision-specific PBM that has been derived from the VFQ-25 using Rasch analysis. It consists of 6 items, that express near vision activities, distance vision activities, vision-specific social functioning, role difficulties, vision dependency, and mental health.[145] The methods used for the derivation of VFQ-UI from VFQ-25 appear to be appropriate. The VFQ-UI can describe 15,625 possible health states, of which 8 were selected for valuation, using 'full health' and 'death' as anchor states; valuation of VFQ-UI was based on the preferences of 607 members of the public from 4 countries (UK, Canada, Australia and the US) using TTO, which is a choice-based method. The protocol used at valuation was based on the protocol used at the valuation of EQ-5D.[101]

The ERG considers the methods used at valuation to be appropriate and in accordance with relevant NICE guidance. However, of the 607 valuation survey participants, only 152 were members of the UK public. The ERG notes that the publication describing the valuation of VFQ-UI reported significant country-specific differences for 2 of the 8 health states valued.[101] Table 73 presents the utility valuations for the 8 health states obtained from all 607 participants in the survey, and those derived from the 152 UK members of the public. It can be seen that UK utility values are consistently lower than the mean utility values obtained from survey participants across the 4 countries, with standard deviations being generally wider. The difference in mean utility between the best and worst health state is somewhat wider in the UK sample (0.652) compared with the total sample (0.613). This means that use of the overall utility values in the economic analysis may have potentially resulted in somewhat more conservative utility gains than those that would have been estimated if the preferences of the UK population had been exclusively considered.

Table 73. Utility values obtained in the valuation survey of VFQ-UI: overall valuations across 4 countries and valuations of the UK members of the public (adapted from Rentz *et al*)[101]

Health State	Total number of participants (4 countries)	Mean utility values (SD)	
		Overall (4 countries)	UK
1 (best state)	606	0.956 (0.124)	0.916 (0.168)
2	607	0.906 (0.147)	0.851 (0.189)
3	604	0.828 (0.173)	0.795 (0.185)
4	607	0.750 (0.212)	0.717 (0.231)
5	606	0.717 (0.215)	0.687 (0.220)
6	606	0.550 (0.283)	0.534 (0.302)
7	607	0.402 (0.312)	0.378 (0.335)
8 (worst state)	607	0.343 (0.395)	0.264 (0.401)

Abbreviations used in table: SD, standard deviation; VFQ-UI, Visual Functioning Questionnaire Utility Index.
Note: states have been ranked from best to worst; description of the health states is provided in Rentz *et al*.[101]

During clarification, the ERG requested that the company 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. The company's clarification response, shown in Box 20, provides an overview of the methods used for the development of NFQ-UI and the arguments supporting its use in the submitted economic model for this STA.

Box 20. Company's response regarding the methods used at the development of NFQ-UI and its appropriateness in being used as a preference-based measure in the economic analysis of dexamethasone in people with DMO (Company's response to clarification, B9b; pgs 44-46)

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*.[145] 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.[101] 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.[148]

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. 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
- 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.

Abbreviations used in the box: BSE, best-seeing eye; DMO, diabetic macular oedema; HRQL, health-related quality of life; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; NICE, National Institute for Health and Care Excellence; QALYs, quality-adjusted life years; TTO, time trade-off; VFQ-UI, visual function questionnaire utility index; WSE, worst-seeing eye.

Abbreviations used in the box: BSE, better-seeing eye; DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; HRQL, health-related quality of life; NICE, National Institute for Health and Care Excellence; QALYs, quality-adjusted life years; TTO, time trade-off; VFQ-UI, visual functioning questionnaire utility index; WSE, worse-seeing eye.

The ERG notes that VFQ-UI has not been validated in patients with DMO. Nevertheless, the ERG acknowledges that none of the other available utility data relating to visual functioning have been validated in patients with DMO either. Overall, after considering the evidence presented by the

company, the ERG is satisfied that the methods used at the development and valuation of the VFQ-UI meet NICE criteria and considers the use of VFQ-UI for the estimation of QALYs in the economic analysis to be justifiable and, in principle, appropriate.

EQ-5D and VFQ-UI data collected in the MEAD trials

EQ-5D and VFQ-UI were collected from patients receiving either dexamethasone 700µg, dexamethasone 350µg or sham in the MEAD trials. EQ-5D data were collected from participants only at baseline, whereas VFQ-UI data were collected at baseline and at every 3-month interval over the 3-year duration of the study. The company submission did not provide baseline SF-36 data, although it was stated that such data had been collected in the MEAD trials.

The EQ-5D data collected from participants in MEAD trials at baseline are shown in Table 74; data are presented separately for patients with DMO treated in their BSE and those treated in their WSE, as determined at the baseline visit. The table shows the distribution of EQ-5D data across BCVA health states. The company noted that, although utility would be expected to increase as vision improves and decrease as vision deteriorates, this was not demonstrated by inspection of the EQ-5D data. Further, each health state had a large amount of variability indicated by large standard deviations around the mean values and the wide variation between the minimum and maximum observations, which spanned between negative utility and perfect health in the majority of visual acuity states.

Table 74. Distribution of EQ-5D scores across BCVA health states at baseline, in MEAD trials (pooled DEX700, DEX350 and sham patients) (taken from CS, Table 93)

	Patients treated in baseline-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]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Patients treated in baseline-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]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in Table: BCVA, best corrected visual acuity; BSE, better-seeing eye; DEX700, dexamethasone 700µg; DEX350, dexamethasone 350µg; SD, standard deviation; WSE, worse-seeing eye.

Figure 32 shows the scatterplots of baseline EQ-5D scores against BCVA in the BSE and the WSE. This illustrates the wide variability in the EQ-5D scores at each level of visual acuity as well as a clear ceiling effect, with a large number of observed EQ-5D values of 1.

Figure 32. Scatterplots of baseline EQ-5D score versus BCVA in the BSE and WSE (reproduced from CS, Appendix 18, Figures 96 and 97)

These figures have been redacted

Abbreviations used in figure: BCVA, best-corrected visual acuity; BSE, better-seeing eye; WSE, worse-seeing eye

The VFQ-UI data collected from MEAD participants at baseline are shown in Table 75; data are presented separately for patients with DMO treated in their BSE and those treated in their WSE, as determined at the baseline visit.

Table 75. Distribution of VFQ-UI scores across BCVA health states at baseline, in MEAD trials (pooled DEX700, DEX350 and sham patients) (taken from CS, Table 94)

	Patients treated in baseline-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]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Patients treated in baseline-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]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in Table: BCVA, best corrected visual acuity; BSE, better-seeing eye; DEX700, dexamethasone 700µg; DEX350, dexamethasone 350µg; SD, standard deviation; WSE, worse-seeing eye.

Figure 33 shows the scatterplots of baseline VFQ-UI scores against BCVA in the BSE and WSE.

Figure 33. Scatterplots of baseline VFQ-UI score versus BCVA in the BSE and WSE (reproduced from CS, Appendix 18, Figures 92 and 93)[redacted]

These figures have been redacted

Abbreviations used in figure: BCVA, best-corrected visual acuity; BSE, better-seeing eye; VFQ-UI, visual functioning questionnaire utility index; WSE, worse-seeing eye.

In a pooled sample across all time-points at which NEI VFQ-25 was measured, there were 9,033 observations of NEI VFQ-25 that were converted to VFQ-UI scores. The pooled VFQ-UI data collected from MEAD participants across all time points are shown in

Table 76; data are presented separately for patients with DMO treated in their BSE and those treated in their WSE. Classification of the eye as BSE or WSE was defined at each visit, to enable accurate classification of patients for utility calculations.

Table 76. Distribution of VFQ-UI scores across BCVA health states, across pooled visits in MEAD trials (pooled DEX700, DEX350 and sham patients) (taken from CS, Table 95)

	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]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max	[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]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in Table: BCVA, best-corrected visual acuity; BSE, better-seeing eye; DEX700, dexamethasone 700µg; DEX350, dexamethasone 350µg; SD, standard deviation; VFQ-UI, visual functioning questionnaire utility index; WSE, worse-seeing eye.

Note: the overall number of observations has been amended by the ERG to 9028, which is the sum of observations across health states 1 to 6 for patients treated in visit-defined BSE and for those treated in visit-defined WSE (the figure originally reported by the company was 9033)

Data in both tables illustrate wide variability in the VFQ-UI scores at each level of visual acuity, as indicated by the wide ranges and large standard deviation around the mean VFQ-UI values in each visual acuity state. However, the company noted that mean utility scores in each BCVA state appeared to be reasonable and behaved as expected, with utility values increasing as visual acuity improved. The data also suggest that changes in vision in the BSE have a larger impact on utility compared with the same change in the WSE, with the difference between worst and best health state being larger for patients treated in the BSE than the WSE.

The scatterplots of VFQ-UI scores pooled across visits against BCVA are shown in Figure 34. As the company noted, the associations between VFQ-UI scores and BCVA in both BSE and WSE were

positive and statistically significant; however there was a large amount of variation in the estimates and a clear ceiling and floor effect, shown in both Figure 33 and Figure 34.

Figure 34. Scatterplot of VFQ-UI score versus BCVA in the BSE and WSE in pooled visits (reproduced from CS, Appendix 18, Figures 94 and 95)

These figures have been redacted

Abbreviations used in figure: BCVA, best-corrected visual acuity; BSE, better-seeing eye; VFQ-UI, visual functioning questionnaire utility index; WSE, worse-seeing eye.

ERG comment

The ERG notes that both EQ-5D and VFQ-UI were characterised by wide variability in utility scores across BCVA health states and scores. Both measures demonstrated significant ceiling effects; in addition, VFQ-UI demonstrated floor effects. EQ-5D appeared to lack construct validity, as EQ-5D values decreased with increasing levels of visual acuity (and therefore with increasing levels of HRQL). On the other hand, VFQ-UI behaved as expected, with utility values overall increasing with increasing levels of visual acuity. The ERG is concerned, however, with the substantial variability of VFQ-UI values at each BCVA health state, which indicates a rather weak correlation of VFQ-UI with BCVA, and with the ceiling and floor effects, which indicate that the measure may not be well targeted to the study population (patients with DMO), in the sense that it cannot measure the whole

range of HRQL experienced by these patients. Consequently, VFQ-UI may be potentially unable to capture significant improvement or deterioration in HRQL if the initial or final point of change lies beyond the range of HRQL that the VFQ-UI is able to capture.

The ERG also notes that Table 74and Table 75, which show the distributions of EQ-5D and VFQ-UI scores, respectively, across BCVA health states, in pooled MEAD arms at baseline, present results separately for patients treated in their BSE and patients treated in their WSE at baseline. In contrast, Table 76, which shows the distributions of VFQ-UI scores across BCVA health states after pooling relevant data from all visits over the duration of the MEAD trials, presents the overall utility across all [redacted] observations, first categorised by the BCVA health state of *every* BSE determined at visit (whether this was treated or not) and then categorised by the BCVA health state of *every* WSE determined at visit (whether this was treated or not), and not by whether the patients were treated in their visit-defined BSE or WSE, as stated in the Table. Although taking account of the BCVA in both eyes (BSE and WSE), regardless if whether these were treated or not, when estimating utility is methodologically correct, the ERG feels that the presentation of these data is potentially misleading and is not comparable with data presented in Table 74 and Table 75.

To support the argument that EQ-5D is not appropriate for use in patients with DMO, the company highlighted the fact that in 946 patients who had EQ-5D recorded at baseline in MEAD, the overall mean score was 0.76 for patients treated in their BSE and 0.78 for patients treated in their WSE. The company noted that these figures were at odds with the mean EQ-5D score for patients with DM reported by Sullivan *et al*. of 0.644 without complications and 0.570 with complications[143] and argued that EQ-5D may not be accurately capturing the impact of DM or DMO in the MEAD study population.

On the other hand, the ERG notes that in 932 patients who had VFQ-UI recorded at baseline in MEAD, the overall mean score was [redacted] for patients treated in their BSE and [redacted] for patients treated in their WSE. Across all time points and 9,033 observations, the pooled mean utility value was reported to be [redacted]. Although these figures are lower than those obtained using EQ-5D, they are still higher than the EQ-5D scores reported by Sullivan et al. for patients with DM. The ERG acknowledges that EQ-5D utility scores and VFQ-UI values are not necessarily comparable; nevertheless, it is noted that using VFQ-UI scores to express the HRQL of patients with DMO results in higher utility values compared with EQ-5D utility values in patients with DM with (0.57) or without (0.64) complications.

Regression analysis using BCVA states in BSE and WSE as explanatory variables

Linear regression analyses were performed using the VFQ-UI and EQ-5D pooled data across MEAD treatments (dexamethasone 700µg, dexamethasone 350µg and sham). The VFQ-UI analysis utilised

pooled data across all time-points at which NEI VFQ-25 was collected, whereas the EQ-5D utilised baseline measurements only (since EQ-5D was collected only at baseline). The following algorithm was used for the estimation of whole person utility from the BCVA in both the BSE and the WSE:

$$\text{Utility} = \text{constant} + \text{coefficient}_{BSE} \times \text{BCVA}_{BSE} + \text{coefficient}_{WSE} \times \text{BCVA}_{WSE}$$

The values for the regression parameters for the VFQ-UI and EQ-5D analyses are shown in Table 77 and Table 78, respectively.

Table 77. Regression analysis parameters – VFQ-UI (base case analysis) (reproduced from CS, Table 96)

Parameter	Number of observations	Mean	Standard error	P value
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Coefficient_{BSE}		[redacted]	[redacted]	[redacted]
Coefficient_{WSE}		[redacted]	[redacted]	[redacted]
Abbreviations used in table: BSE, better-seeing eye;; VFQ-UI, Visual Functioning Questionnaire Utility Index; WSE, worse-seeing eye. **Note:** analysis is based on observed data without imputation for missing values. Patients, treatment arm, and study (010 vs 011) were treated as random effects				

Table 78. Regression analysis parameters – EQ-5D (scenario analysis) (reproduced from CS, Table 97)

Parameter	Number of observations	Mean	Standard error	P value
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Coefficient_{BSE}		[redacted]	[redacted]	[redacted]
Coefficient_{WSE}		[redacted]	[redacted]	[redacted]
Abbreviations used in table: BSE, better-seeing eye; NS, non-significant; WSE, worse-seeing eye				

The company noted that regression analysis on VFQ-UI data demonstrated that changes in vision in the BSE has a larger impact on utility than the same change in the WSE, although changes in both eyes affect visual functioning. This is consistent with the findings of Bressler *et al*.[149]

In contrast, the EQ-5D regression equation implied that changes to the level of vision in the WSE did not impact utility (as the respective co-efficient was not statistically significant), which is counter-intuitive and not consistent with published literature.

The company acknowledged that the linear regression was performed assuming normality, although the relationship between BCVA and utility estimated using VFQ-UI was unlikely to be normal, as illustrated by the clear ceiling and floor effects in Table 76 and Figure 34. The company argued that

the mean utility in each health state appeared to follow an approximately linear pattern, which supported the use of linear regression to approximate utility from BCVA in the BSE and the WSE. The company expressed the view that the regression equation captured the linearity and variability characterising the data in an appropriate way, while providing the best and a novel solution to modelling changes in utility resulting from changes in BCVA in both eyes.

ERG comment

The results of the regression analysis on VFQ-UI data appear to be robust and reflective of the anticipated impact of visual acuity on HRQL, with coefficients for BCVA in both BSE and WSE being statistically significant. Both coefficients were positive, as expected, meaning that higher BCVA in any of the two eyes resulted in higher HRQL/utility. The coefficient for the BSE was higher than the coefficient for the WSE, indicating that the impact of the visual acuity in the BSE on HRQL is stronger than that of the visual acuity in the WSE; the ERG notes that this finding appears reasonable, is in agreement with published literature,[149] and is consistent with assumptions supported by the Appraisal Committee in previous NICE TAs of treatments of DMO (TA274[115]/TA301[142]).

During clarification and following request by the ERG for more details on the methods of the regression analysis (discussed later in this section), the company argued that "as a significant proportion of DMO patients have bilateral disease, [the company's] 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" (Company's response to clarification question B2, page 17).

The ERG agrees with the company that the regression model proposed by the company which allows modelling changes in utility resulting from changes in BCVA in both eyes, whether the patient has unilateral or bilateral disease, is an improvement over previous approaches that required focus on either the BSE or WSE and further assumptions regarding the impact of each on HRQL.

The ERG also agrees with the company that the regression model based on EQ-5D has flaws and is therefore less appropriate for the estimation of QALYs.

Nevertheless, the ERG felt that the company had not provided detailed information regarding the rationale for the selection of explanatory variables, any alternative models tested and the method for identifying the preferred final model, the handling of missing data (if any), and, importantly, goodness-of-fit measures used to assess the selected regression model. This information was requested by the ERG during clarification.

In response, the company clarified that exploration of potential utility specifications proceeded in discrete steps, primarily correlating VFQ-UI outcomes with vision in the pooled sample of dexamethasone 700µg, dexamethasone 350µg and Sham patients with and without covariate-adjustment for relevant patient characteristics (Company's response to clarification question B2, pgs 16-26). The company stated that 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 were tested, with patient, treatment arm, and study (MEAD-010 vs MEAD-011) included as random effects. Analyses had been conducted in a step-wise fashion, controlling for:

a. BCVA only:
    iii. BCVA in the BSE only;
    iv. BCVA in the WSE only;
    v. 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 were based on vision only and did not account for changes in patients' general health);
c. Additional interaction term between BCVA in the BSE and BCVA in the WSE.

The company provided the results of all these analyses, which are shown in Appendix 9.10 of this report. This Appendix also includes company's commentaries on the findings of each of the regression analyses.

For linear regression analyses of baseline visit data, the company reported model coefficients, standard-errors and p-values; goodness of fit was assessed by the R-squared. For the linear mixed-effects analyses on pooled visit data, the company provided model coefficients, standard-errors and p-values; goodness of fit was assessed using the Akaike information criterion (AIC), Bayesian information criterion (BIC) and AICC (AIC with correction for finite sample size). The company stated that all analyses had been conducted in SAS Version 9.3.

The company reported that 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. The company 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.

The ERG is overall satisfied with the details on analyses provided by the company and finds the series of the undertaken analyses comprehensive and justified.

Regression analysis including adverse events as explanatory variables

According to the company submission, adverse events associated with treatment for DMO were expected to have little effect on HRQL due to their nature. The main adverse events associated with dexamethasone treatment in the MEAD trials were increases in IOP and a higher incidence of cataracts. The company stated that increases in IOP were predictable, transient and mainly required no treatment or were managed successfully with standard topical pressure-lowering medications. Cataracts were likely to have a detrimental effect on HRQL due to the effect on visual acuity; however, this effect would be expected to be captured implicitly within the BCVA outcomes of the clinical trials. The company argued that any disutility associated with the cataract extraction procedure would be experienced for a very short period of time and was therefore not considered.

In any case, the company conducted regression analyses to determine the effect of IOP elevation and cataract on VFQ-UI score. Regressions for IOP estimated coefficients for a change ≥10mmHg or receipt of IOP-medication and for IOP ≥30mmHg or receipt of IOP-medication. Regressions for cataract estimated coefficients for cataract in the BSE, cataract in the WSE and cataract surgery. Each adverse event indicator was recorded at each visit. The results of these regressions are shown in Table 79. The estimated coefficients for adverse events of treatment were very small (<0.01) and statistically non-significant at the 5% significance level. Since the adverse events of raised IOP and cataract were not found to be statistically significant predictors of the VFQ-UI score, the impact of adverse events on utility was not modelled.

Table 79. Utility regression equations: Impact of adverse events on VFQ-UI score (reproduced from CS Appendix 18, Table 262)

Parameter	Mean	SE	P=value
Impact of IOP Change ≥10mmHg or IOP-Medication			
Constant	[redacted]	[redacted]	[redacted]
$Coefficient_{BSE}$	[redacted]	[redacted]	[redacted]
$Coefficient_{WSE}$	[redacted]	[redacted]	[redacted]
$Coefficient_{IOP}$ (IOP Change ≥10mmHg or IOP-Medication; yes vs no)	[redacted]	[redacted]	[redacted]
Impact of IOP ≥30mmHg or IOP-Medication			
Constant	[redacted]	[redacted]	[redacted]
$Coefficient_{BSE}$	[redacted]	[redacted]	[redacted]
$Coefficient_{WSE}$	[redacted]	[redacted]	[redacted]
$Coefficient_{IOP}$ (IOP ≥30mmHg or IOP-Medication; yes vs no)	[redacted]	[redacted]	[redacted]
Impact of cataract in either the BSE or WSE			
Constant	[redacted]	[redacted]	[redacted]
$Coefficient_{BSE}$	[redacted]	[redacted]	[redacted]
$Coefficient_{WSE}$	[redacted]	[redacted]	[redacted]
$Coefficient_{BSE\ cataract}$	[redacted]	[redacted]	[redacted]
$Coefficient_{WSE\ cataract}$	[redacted]	[redacted]	[redacted]
Impact of cataract surgery			
Constant	[redacted]	[redacted]	[redacted]
$Coefficient_{BSE}$	[redacted]	[redacted]	[redacted]
$Coefficient_{WSE}$	[redacted]	[redacted]	[redacted]
$Coefficient_{cataract\ surgery}$	[redacted]	[redacted]	[redacted]
Abbreviations used in table: BSE, better-seeing eye; IOP, intraocular pressure; mmHg, millimetres of mercury; SE, standard error; VFQ-UI, visual functioning questionnaire utility index; WSE, worse-seeing eye Note: analyses based on [redacted] observations			

ERG comment

During clarification, the ERG requested more details on all the regression analyses undertaken by the company on the utility data. In response, the company stated that, as the company's submission for TA237 was criticized for not incorporating a disutility for patients suffering an ocular adverse event, the company 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; this 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.

Detailed results of the company's regression analyses that considered adverse events as covariates are also presented in Appendix 9.10 of this report. Results are accompanied by company's commentaries.

The ERG noted that in the regression analysis that considered adverse events, the coefficients of adverse events, although not statistically significant, were in fact larger than the coefficients related to BCVA in BSE and WSE, implying a greater impact on utility, and asked the company to comment on this during clarification. In response, the company reported that it was not possible to consider the regression equations accounting for the impact of adverse events on utility within the economic model, due to re-programming requirements that were impossible to satisfy within the clarification period. Nevertheless, in order to determine the impact of consideration of adverse events on estimated utility and, subsequently, on the results of the analysis, the company presented a side calculation using the coefficients for cataract surgery and for increased intraocular pressure (IOP) ≥30mmHg or initiation of IOP medication, and the proportions of patients who experienced each of these events.

The results of these calculations are shown in Appendix 9.10. The company's calculations on utility decrement due to cataract were amended by the ERG, following a correction in the annual risk of cataract in patients receiving dexamethasone, as discussed in Section 5.4.8 (corrected figures provided in Table 72).

The company's calculations showed that the impact of adverse events on utility was very small, and this finding persisted following ERG corrections. Given these results, the company felt it was reasonable to ignore the impact of adverse events on utility values from the economic model as the impact of including them would be negligible.

The ERG finds the company's extra analyses satisfactory, and agrees that the impact of cataract and raised IOP on HRQL, as measured by VFQ-UI, is negligible, considering also the incidence of these adverse events from treatment in the DMO population.

Regression analysis utilised for the estimation of QALYs in the company's economic analysis

The VFQ-UI regression analysis that used BCVA in BSE and WSE as explanatory variables (Table 77) was used in the base case analysis. The justification for the use of VFQ-UI data was that VFQ-UI is a vision-specific PBM and EQ-5D was not shown to be sensitive to changes in vision. Furthermore, the VFQ-UI was measured throughout the MEAD trials, whereas EQ-5D was only measured at baseline; hence the VFQ-UI analysis included more data points than the EQ-5D analysis.

The EQ-5D regression analysis (Table 78) was included as a sensitivity analysis to show the impact of the choice of utility measure on the results of the economic model; however, according to the company, the results of this analysis should be interpreted with caution, as the EQ-5D regression equation implied that changes to the level of vision in the WSE did not impact utility (as the respective co-efficient was not statistically significant), which is counter-intuitive and not consistent with published literature.

According to the regression equation used (Table 77), the higher the BCVA in each eye, the better visual functioning and HRQL would be, with changes in vision in the BSE having a greater effect on HRQL than the same changes in the WSE, as the coefficient for BCVA in the BSE was higher than the coefficient for BCVA in the WSE.

The impact of adverse events on utility values was found to be non-significant in regression analysis, therefore this was not considered at the estimation of utility values in the economic analysis.

Within the economic model, the changes in vision in BSE and WSE were modelled independently for all patients within the cohort. Utility values for the patients within the cohort in each cycle were calculated directly from the distributions of BCVA in the patient's BSE and WSE. This was achieved by applying the regression equation for VFQ-UI (and EQ-5D in sensitivity analysis) to the expected distribution of vision in the BSE and the WSE across the visual acuity states, assuming that the mean BCVA in each visual acuity state was consistent with the data reported in

Table 80, as estimated from MEAD trial data.

Table 80. Mean BCVA in each visual acuity state (reproduced from CS, Tables 98 and 99)

Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
All DMO patients					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DMO patients who are pseudophakic					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in table: BCVA, Best-corrected visual acuity; DMO, diabetic macular oedema.					

A summary of utility values based on the combinations of health states for the BSE and WSE are provided in Table 81 and Table 82 for the whole population of patients with DMO and patients with DMO who are pseudophakic, respectively, based on the mean BCVA in each health state given in Table 80. Health State 1 represents clinical blindness if the BSE falls into this state.

Table 81. Utility values for BCVA states across two eyes – all DMO patients (DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy) (reproduced from CS, Table 100)

		BSE					
		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
WSE	Health State 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Health	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	State 2						
	Health State 3	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 4	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
	Health State 5	N/A	N/A	N/A	N/A	[redacted]	[redacted]
	Health State 6	N/A	N/A	N/A	N/A	N/A	[redacted]
Abbreviations used in table: BCVA, best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; N/A, not applicable; WSE, worse-seeing eye.							

Table 82. Utility values for BCVA states across two eyes – DMO patients who are pseudophakic (reproduced from CS, Table 101)

		BSE					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
WSE	**Health State 1**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 2	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 3	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 4	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
	Health State 5	N/A	N/A	N/A	N/A	[redacted]	[redacted]
	Health State 6	N/A	N/A	N/A	N/A	N/A	[redacted]
Abbreviations used in table: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; N/A, not applicable; WSE, worse-seeing eye.							

In the base case analysis utilities were not age-adjusted; however, the company undertook a sensitivity analysis whereby utilities were adjusted for age, using a coefficient of -0.00029 per year reported by Sullivan *et al*.[143] This study provided a UK-based catalogue of EQ-5D index scores including a coefficient for age. The mean baseline age in the MEAD trials was 62 years, so the utility values obtained from the MEAD trial data were assumed to be relevant for patients of this age. The coefficient was therefore added to the calculated utility value for every year above the baseline age in the MEAD trials, and subtracted from the calculated utility value for every year below the baseline age in the MEAD trials, to give age-adjusted utility values.

ERG comment

The ERG agrees with the company's selected regression model for the estimation of QALYs that was based on VFQ-UI scores. The assumptions underlying the regression equation appear to be reasonable

and consistent with the perception that the impact of BSE on HRQL is higher than the impact of WSE. The ERG's view is that the model has, in principle, reasonable face validity.

On the other hand, the ERG noted that the range of utility values between the worst BCVA health state that can be experienced by a patient (i.e. when both eyes are in the worst BCVA state and the patient suffers from severe vision loss) and the best BCVA health state that can be experienced by a patient (i.e. when both eyes are in the best BCVA state), as estimated using the selected regression model, is rather narrow: [redacted] to [redacted] in the whole DMO population, as seen in

Table 81. This was expected to some degree, as the selected regression model had a rather high constant ([redacted]). Nevertheless, the ERG is concerned about the face validity of the range of utility values experienced by patients with DMO, as estimated by the selected VFQ-UI regression model, and asked the company to comment on this issue at clarification. The company's response is presented in Box 21.

Box 21. Company's response regarding the validity of the utility range experienced by patients with DMO, estimated using the company's selected VFQ-UI regression model (Company's response to clarification, B3; pgs 27-29)

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 varied 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 […]. 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.[114,125] The committee for the most recently published technology appraisal in DMO (Fluocinolone acetonide, TA301) considered ICERs using three different publications,[46] Brown (1999),[98] Brown et al.,(2000)[96] and Czoski-Murray et al.[99] 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.[43] 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.[43] The range of utilities for this appraisal is smaller than this range and hence is more appropriate.

Brown (1999)[98] 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. (2000)[96] measured utility in five visual acuity groups defined by the BSE in patients with age-related macular degeneration. Czoski-Murray et al.[99] used contact lenses to simulate bilateral visual impairment due to age-related macular degeneration (ARMD) in healthy participants. […]

It is of note that the values [reported in the above studies] 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.

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.(2000)[96] but lower than the utility given by Brown (1999)[98] and Czoski-Murray et al.[99]

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.

Abbreviations used in the box: ARMD, age-realted macular degeneration; BSE, best-seeing eye; DM, diabeties mellitus; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; VFQ-UI, visual functioning questionnaire utility index; WSE, worst-seeing eye.

The values used in previous technology appraisals, as provided by the company, are summarised in Table 83 for comparison. The ERG is unclear as to how the utility values reported by the company for Czoski-Murray *et al*.[99] were estimated or sourced. The uitility values reported for the other two studies are consistent with the values reported in the ERG report for TA301 (Table 3, page 5).[150] The ERG identified a table in the ERG report for TA274, which presents utility values derived from all 3 studies by BCVA in the BSE. These data are presented in Table 84. The ERG notes that the utility values in both tables refer to visual acquity in the BSE.

Table 83. Alternative utility values associated with visual functioning in BSE that have been used in previous NICE TAs of treatments for DMO, as presented by the company (company response to clarification, Tables 16-18, pg 28; slight amendments by ERG to ensure consistency with Table 3 of ERG report for TA301)[150]

Brown et al. (2000)[96]		Czoski-Murray et al.[99]		Brown (1999)[98]		
ETDRS letters	**Utility**	**ETDRS letters**	**Utility (TTO)**	**Snellen**	**Approximate ETDRS****	**Utility**

80-85	0.89	≥ 75	0.86	20/20 to 20/25	80-85	0.89
≥ 60 to < 75	0.81	≥ 65 to < 75	0.813	20/30	75-80	0.84
≥ 50 to < 60	0.57	≥ 55 to < 65	0.802	20/40	70	0.80
≥ 35 to < 50	0.545*	≥ 45 to < 55	0.77	20/50	65	0.77
≥ 20 to < 35	0.52	≥35 to < 45	0.76	20/70	55-60	0.74
<20	0.40	≥25 to < 35	0.681	20/100	50	0.67
		<25	0.547	20/200	35	0.66
				20/300	25-30	0.63
				20/400	20	0.54
Abbreviations used in table: BSE, better-seeing eye; DMO, diabetic macular oedema; ERG, evidence review group; ETDRS, Early Treatment Diabetic Retinopathy Study; TTO, time trade-off. Notes: *Estimated as mid-point between 0.52 and 0.57; **Converted using Gregori *et al*.[102]						

Table 84. Alternative utility values associated with visual functioning in BSE that have been used in previous NICE TAs of treatments for DMO, as presented in the ERG report for TA274[151] (Table 14, pg 18)

		Utility values		
ETDRS	**ETDRS letters**	**Czoski-Murray et al.[99]**	**Brown (1999)[98]**	**Brown et al. (2000)[96]**
86-100	>20/20	0.850	0.920	0.890
76-85	>20/32 to ≤20/20	0.758	0.920	0.890
66-75	>20/50 to ≤20/32	0.685	0.840	0.810
56-65	>20/80 to ≤20/50	0.611	0.770	0.570
46-55	>20/125 to ≤20/80	0.537	0.740	0.570
36-45	>20/200 to ≤20/125	0.464	0.670	0.570
26-35	>20/320 to ≤20/200	0.390	0.660	0.520
0-25	≤20/320	0.353	0.540	0.520
Abbreviations used in table: BSE, better-seeing eye; DMO, diabetic macular oedema; ERG, evidence review group; ETDRS, Early Treatment Diabetic Retinopathy Study.				

Following inspection of alternative published utility values used for the BSE in previous NICE TAs, and taking into account the company's argument that published utilities were not specific to patients with DMO and therefore, in contrast to VFQ-UI they do not capture the underlying impact of the patients' DM, the ERG considers the range of utility values produced using the VFQ-UI regression model that was estimated from MEAD trial data reasonable and appropriate for the study population.

Overall ERG comment on the approach selected for the estimation of QALYs in the company's economic analysis

The ERG's believes that the company's approach for modelling utility values is reasonable and pragmatic. The regression model based on VFQ-UI data reflects the perception that HRQL is affected by both BSE and WSE, with BSE having a greater impact on HRQL, as expected. The model allows estimation of QALYs considering changes in vision in both eyes of a patient, and therefore allows

estimation of QALYs in patients with unilateral as well as bilateral DMO; this approach is therefore an improvement over previous methodologies that linked HRQL to changes in vision of BSE, and then required further assumptions in order to determine the impact of changes in vision resulting from treatment of the WSE or of bilateral treatment on HRQL.

On the other hand, the ERG believes that the estimation of QALYs based on VFQ-UI may have failed to capture the impact of adverse events from treatment, as well as potentially other comorbidities that may be present in patients with DMO. This is because VFQ-UI is derived from the VFQ-25, and is therefore a vision-specific PBM. One of the characteristics of condition-specific PBMs, which are acknowledged to be limiting their comparability to generic ones, is their inability to capture adverse events and comorbidities.[152] The company provided evidence that the adverse events of cataract and raised IOP did not have a significant impact on HRQL/utility. This was not surprising, as VFQ-UI has not been designed to capture the impact of adverse events of treatment. Therefore, the fact that in the regression of utility values the co-efficients of adverse events were non-significant does not necessarily mean that adverse events from dexamethasone did not have an impact on the HRQL of patients with DMO in the MEAD trials; it may mean that the VFQ-UI was not able to capture any such impact. If adverse events do have an impact on the HRQL of patients with DMO, then the utility gains due to treatment may have been overestimated. However, the ERG anticipates that the main two adverse events (cataract and raised IOP) are likely to have only a small impact on HRQL other than that caused by visual impairment (which is already captured by VFQ-UI), and therefore their potential impact on the results of the economic analysis is expected to be small and insignificant. This hypothesis is consistent with previous NICE TAs of DMO treatments, where the impact of adverse events on HRQL was not considered in the economic analysis.

It has to be noted, that although VFQ-UI has not been designed to capture morbidity other than that affecting vision, it may have implicitly captured, up to a degree, comorbidities due to DM affecting patients' activities. This is due to the wording of the 6 items of VFQ-25 that are included in VFQ-UI, as shown in

Box 22. Although the focus of these items is on activities and roles being affected by vision, the wording is such that potentially allows, even though implicitly, the impact of other comorbidities due to DM to be captured by VFQ-UI. Therefore, the company is likely to be correct when arguing that the VFQ-UI scores resulting from regression analysis of MEAD trial VFQ-UI data relate specifically to the DMO population and are thus more appropriate and relevant for use in the company's economic analysis than alternative utility values used in previous TAs, which are specific to visual impairment but have not been derived from DMO populations. However, overall, VFQ-UI is not able to capture comorbidities to the same degree as generic PBMs, and this may potentially be reflected in the higher mean VFQ-UI values in patients with DMO ([redacted] and [redacted] in patients treated in their BSE and WSE,

respectively, at baseline, [redacted] acorss [redacted] observations over the duration of MEAD trials) compared with the EQ-5D values for people with DM with (0.57) and without (0.64) complications.[143]

Box 22. VFQ-UI items (derived from VFQ-25)

Near vision - difficulty doing work or hobbies that require seeing well up close, such as cooking, sewing, fixing things around the house or using hand tools **Social vision** - difficulty seeing how people react to things I say **Distance vision** - difficulty going out to see movies, plays or sports events **Role difficulty** - limited in how long I can work or do other activities **Vision dependency** – having to stay at home **Mental health** – worying about doing things that will embarrass me or others
Abbreviations used in the box: VFQ-25, Visual Functioning Questionnaire; VFQ-UI, Visual Functioning Questionnaire Utility Index.

Another point to consider is that the disutility due to injections has not been captured by the VFQ-UI and hence in the QALYs estimated in the economic analysis. In the company submission, it was stated that "the reduced injection frequency of dexamethasone versus anti-VEGF therapies therefore represents a considerable advantage to patients, carers and the health service. This is unlikely to be captured within the QALY calculation, as the utilities included within the model are not treatment-specific and are based on the less frequent re-treatment injection schedule of DEX700" (CS, pgs 78-79). The ERG agrees with this statement. On the other hand, the disutility due to dexamethasone injections relative to watch and wait and also relative to fluocinolone acetonide has also not been captured in the QALY estimations in the economic model, meaning that the cost effectiveness of dexamethasone relative to these two treatment options may have been overestimated. However, considering that dexamethasone is administered at a minimum interval of 6 months and that the average annual number of dexamethasone treatments over 3 years was [redacted], [redacted] and [redacted] as suggested in Table 55, it is unlikely that the injections associated with dexamethasone administration would have any considerable negative impact on the total QALYs associated with dexamethasone treatment. It should also be noted that treatment with laser may also result in some disutility which has not been captured in the analysis. Overall, disutility due to treatment should be rather limited relative to the treatment benefits, and is expected to have been implicitly reflected in the rates of discontinuation associated with each treatment, which have been considered in the economic analysis.

Overall, the ERG feels that the use of VFQ-UI as a utility measure in the MEAD trials and the application of the VFQ-UI regression model in the economic analysis have appropriately and adequately captured changes in HRQL of patients with DMO following treatment.

Nevertheless, in order to explore the impact of the use of regression analysis on the results, the ERG requested at clarification that the company provide the results of an analysis for the whole population with DMO (dexamethasone versus watch and wait) where QALYs for the first 3 years have been estimated using mean utilities derived directly from patients' responses on VFQ-UI in the MEAD trials, instead of estimating these from the VFQ-UI regression model (**Analysis A5**). In response, the company applied the utility data provided in Table 76 into the model that utilised transition probabilities derived directly from the MEAD trials. Moreover, the company provided an analysis which combined the utility data reported in Table 76 with the outputs of the updated NMA (**Analysis A6**) for DMO patients who are unsuitable for, or insufficiently responsive to non-corticosteroid treatment. However, the company's method for application of utility data into the model was not appropriate and therefore has not been considered further by the ERG. The details of these analyses are described in Section 5.5.1; the results, together with the ERG comments on the inappropriateness of the approach, are provided in Section 6.1.1.

The ERG also explored the impact of using alternative utility data on the results of the model. The utility data from Czoski-Murray et al.[99] were applied in the original analysis submitted by the company using the NMA outputs (**Analysis C13**) and also in the analysis undertaken by the company during clarification, which utilised transition probabilities derived directly from the MEAD trials, assuming unrestricted transitions (**analysis C14**). The analysis was not performed in the population of DMO patients who are pseudophakic, due to the need for model re-programming and time constraints. The utility values used in these analyses, modified to correspond to the model's health states, are shown in Table 84. To apply these data separately to each eye, the ERG assumed that the contribution of WSE and BSE to the overall utility was 3/13 and 10/13, respectively, based on the assumption that the impact of WSE on overall utility equalled 30% of the impact of the BSE. This assumption is broadly in line with the approach preferred by the committees for TA274 and TA301, according to which treating the WSE had 30% of the HRQL impact for the same change in vision from treating the BSE. These analyses are described in Section 5.5.2.2; results are provided in Section 6.1.2.2. Use of the alternatively utility data obtained from Czoski-Murray et al.[99] considerably favoured dexamethasone by increasing the incremental QALYs versus watch and wait. However, the ERG notes that the utility values reported in Czoski-Murray et al.[99] are likely less relevant (and thus less appropriate to use) than those reported by the company based on the VFQ-UI, and obtained directly from patients with DMO.

Table 85. Alternative utility data by Czoski-Murray et al.[99] used in analyses C13 and C14 undertaken by the ERG

ETDRS	ETDRS letters	Utility data in Czoski-Murray et al. according toTable 84	Data used by ERG in the company's model

86-100	>20/20	0.850	0.804*
76-85	>20/32 to ≤20/20	0.758	
66-75	>20/50 to ≤20/32	0.685	0.685
56-65	>20/80 to ≤20/50	0.611	0.611
46-55	>20/125 to ≤20/80	0.537	0.537
36-45	>20/200 to ≤20/125	0.464	0.464
26-35	>20/320 to ≤20/200	0.390	0.3715*
0-25	≤20/320	0.353	
Abbreviations used in table: DMO, diabetic macular oedema; ERG, evidence review group; ETDRS, Early Treatment Diabetic Retinopathy Study. *average between the two values			

5.4.11 Resources and costs

5.4.11.1 Overview of costs and data sources considered in the company's economic model

The company's model included costs associated with the management of DMO from a NHS and PSS perspective. A systematic review of the literature was carried out to identify published sources resource use and cost evidence for patients with DMO. Key trial data were also used to obtain, where possible, resource utilisation associated with the treatments assessed in the economic model. Clinical expert advice was also sought to obtain estimates on the resources required for the treatment of DMO, including the treatment of adverse events, the number of appointments required for bilateral treatment and the expected monitoring schedule for treatments. Full details of clinician input at the advisory board meeting are provided in the submission (CS; Appendix 14, pgs 647-665). Unit costs were taken from national sources (including the monthly Index of Medical Specialities [MIMS],[153] NHS Reference Costs[154] and Curtis.[155] In addition to these sources, the cost of severe vision loss was taken from a study by Colquitt *et al*.[156] The company stated that NHS Reference Costs were preferred to the PbR Tariffs for the costing of procedures and monitoring appointments because the NHS Reference Costs represent the actual observed national average costs incurred as a result of delivering care, taking into account staff time, event-based time and standard equipment time. Thus, NHS Reference Costs reflect opportunity costs, whereas the PbR Tariffs are prospective costs that may not reflect the actual cost to the NHS. The cost year was 2013.

The sections that follow outline the cost and resource use associated with the five key types of cost identified in the company's economic model:

- intervention costs;
- monitoring and test costs;
- health state costs;
- adverse event costs;

- costs following discontinuation.

5.4.11.2 Company's systematic review of resource use and costs associated with DMO

The company conducted a systematic literature review to identify published resource use data for patients with DMO. The search was carried out in February 2014 and updated in July 2014. Searches were performed in Medline and Medline In-Process and other non-indexed citations, Embase, Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Review and Effects (DARE), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and EconLit. Search terms captured the condition of interest (DMO) and used filters for cost and resource based on SIGN recommendations.[134] No date or language limits were applied. Further details of the search strategy are provided in the company submission (Appendix 13, pgs 583-597). All search strategies developed by the company for identification of relevant economic evidence, data on health related quality of life (HRQL) and resource use and costs are presented in Appendix 9.9.

Studies were included in the review if they reported resource data related to the management of DMO in the UK or if they reported such data from outside the UK in a way that could be applied to the UK setting. Studies were excluded if they reported resource data that was not specifically related to the management of DMO (e.g. screening studies) or if they reported resource data related to the management of DMO outside of the UK that could not be applied to the UK setting.

After removing duplicates, the company identified a total of 432 citations in the initial search and 19 citations in the update. Following review of these citations, the company identified one resource study of relevance to this appraisal by Minassian *et al*. (2012).[4] This study was a direct cost of illness study for DMO, from the perspective of the health and social care providers in Wales. The only treatment considered in the study was laser therapy, but costs associated with screening/detection (not relevant for this appraisal), diagnosis and additional social care related to visual impairment from DMO were also included. Most of the resource use and related costing data were taken from government websites. Excess of routine health and social care service usage attributable to sight loss in general was also calculated per partially sighted or blind person, but as these data were relating to the presence or absence of age-related macular disease, they were considered not to be directly applicable to this appraisal. The company concluded that this study confirmed the paucity of literature in this area and the importance of the costs of blindness in the DMO population.

Two relevant NICE TAs were also identified through additional searches and were reviewed to identify any reported resource use data associated with treatment of DMO. A summary of resource use reported in these appraisals is presented in Table 86.

Table 86. Summary of the resource use and costs applied in previous NICE TAs for the treatment of vision impairment due to DMO

Cost element	NICE TA237/ TA274 (ranibizmumab) Cost year: 2009	NICE TA271/301, (fluocinolone acetonide) Cost year: 2011
Treatment	**Resource use** Original submission assumed 7 RAN injections in Year 1 for RAN monotherapy and combination (RAN + laser); 3 and 2 injections in Year 2 for RAN and combination, respectively. Combination and laser monotherapy were assigned two laser treatments in Year 1 and one in Year 2. Revised model assumed 2 RAN injections in Year 3 and one injection in Year 4; laser was administered once in Year 3 and in Year 4. Further revised model assumed 7 RAN injections in Year 1, 4 in Year 2 and 3 in Year 3, based on a 2-year extension of RESTORE. **Unit costs** Cost of RAN was £761.20 per injection (before confidential PAS). Unit cost of treatment visit to an eye clinic was £150, assuming outpatient attendance for both RAN and laser (NHS Reference Cost). Combination therapy was administered at the same visit at a cost of £184.	**Resource use** Original submission assumed one FA implant would be injected every 3 years, with a further implant injected at 36 months in patients who had gained at least 5 letters of visual acuity since baseline (the ERG performed a sensitivity analysis increasing this criteria to at least 10 letters gained). Patients receiving FA or OSC received laser, TA, RAN, BEV and DEX700 in line with the observed rates in the FAME trials. **Unit costs** Cost of FA was £5,500 per injection; £105 for BEV; £742 for RAN; £7 for TA; £870 for DEX700. All treatments were administered in an outpatient procedure costing £150.
Monitoring	**Resource use** Patients received 12 visits in Year 1 and 10 visits in Year 2 (RAN monotherapy); 12 visits in Year 1 and 8 visits in Year 2 (combination / laser monotherapy). All patients received 4 visits per year in Year 3 onwards. For RAN and combination, a treatment visit was assumed to include monitoring. For laser monotherapy, separate visits for treatment and for monitoring were assumed. In revised model, 12 visits were assumed for RAN and combination in Year 1; 8 visits in Year 2; 6 visits in Year 3. For laser, 4 visits were assumed in each of Years 1, 2 and 3. All patients had 2 visits in Year 4 and all treatment visits included monitoring. **Unit costs** The cost of monitoring visits was £126, including a follow-up attendance (£73), OCT (£53) and VA assessment (£0) based on NHS Reference Costs.	**Resource use** Monitoring of the FA implant took place at quarterly DMO monitoring visits that currently occur in routine clinical practice. The small number of OCT in the first 3 year treatment cycle took place within DMO monitoring visits although additional injection related charges were incurred. **Unit costs** Based on NHS Reference Costs, the cost of monitoring visits was £126 for FA which included follow-up attendances (£73), OCT (£53) and VA assessment (£0); for laser the total cost was £458 because of a fluorescein angiography (£332) which applied to laser only.
Adverse events	Costs of treating cataract (£1,045), endophthalmitis (£2,221), retinal detachment (£1,631) and vitreous haemorrhage (£1,485) considered , based on NHS Reference Cost tariffs for procedures and associated follow-	Included the cost of treating cataract (£796), endophthalmitis (£1,783), retinal detachment (£1,339), vitrectomy (£1,339), glaucoma (£1,128) and elevated IOP (£26.28) based on NHS Reference Costs and the BNF

	up attendances	68.[157]
Severe vision loss	Patients whose treated eye had severe vision loss (BCVA < 35 letters) incurred additional costs associated with low-vision aids, rehabilitation, residential care, district nursing, community care and costs of complications such as depression and falls. Costs largely based on a UK study of blindness;[158] estimated cost £6,067 in the first year and £5,936 in subsequent years.	Based on NICE TA237, an annual cost of blindness of £6,298 was applied to patients whose treated eye BCVA fell below 35 letters taken from Meads and Hyde (2003).[158]
Abbreviations used in the table: BEV, bevacizumab; BCVA, best correct visual acuity; BNF, British National Formulary; BSE, better-seeing eye; CRT, central retinal thickness; DEX, dexamethasone; DMO, diabetic macular oedema; FA, fluocinolone acetonide intravitreal implant; IOP, intraocular pressure; NHSRC, National Health Service reference costs; NICE, National Institute for Health and Care Excellence; OCT, optical coherence tomography; OSC, optimised standard of care; PAS, Patient access scheme; RAN, ranibizumab; TA, triamcinolone; VA, visual acuity		

ERG comment

The ERG considers the search terms and inclusion criteria used by the company to identify resource use and cost data to be comprehensive and appropriate. For completeness, the ERG reviewed the two related NICE appraisals (TA271/301 and TA237/274) and found no additional resource use studies included in their submissions. The ERG noted that the company was unable to access three full texts of references that were identified through the search; full references of these studies were requested by the company during clarification period. The ERG believes that it is unlikely that these studies would contain sufficient information for use within the economic model.

5.4.11.3 Intervention costs

The list prices of acquisition of each treatment included in the economic analysis were taken from published sources. Ranibizumab and fluocinolone acetonide have been recommended for the treatment of DMO by NICE subject to restrictions and only if they are provided with the discount agreed in their patient access schemes (PAS). The exact discount provided to the NHS is confidential; therefore the company used list prices for these interventions in all base case analyses and varied the discount in price between 0% discount (list price) and 50% discount in scenario analyses. These analyses are presented in Section 5.4.13.1.

No acquisition cost was assumed for laser, as it was presumed that all services have access to existing equipment to perform laser procedures. The cost of administration of laser was estimated to be £117 (based on NHS reference costs 2012/13 BZ23Z, service code 130 Ophthalmology, minor vitreous retinal procedures; outpatient procedure)[154]. All intravitreal injections were assumed to be performed in the outpatient setting at the same cost of £117 (NHS reference costs 2012/13, same service code as above; outpatient procedure).[154] In sensitivity analysis, a proportion of procedures were assumed to be treated as day cases; the cost of a day case procedure was assumed to be £356 (NHS reference

costs 2012/13 BZ23Z, service code 130 Ophthalmology, minor vitreous retinal procedures; day case procedure).[154]

Based on clinical expert opinion (CS Appendix 14, pgs 647-665) bilateral treatment with a steroid was assumed to require two separate administration appointments on 75% of occasions and one administration appointment on the remaining 25% of occasions, giving an average of 1.75 appointments for bilateral treatment with a steroid. Clinical experts suggested that bilateral treatment with anti-VEGF might require two separate administration visits on 50% of occasions, and only one administration appointment on the remaining 50% of occasions, giving an average of 1.5 appointments for bilateral treatment with an anti-VEGF. Bilateral anti-VEGF treatment was assumed to require one appointment on a higher proportion of occasions compared with steroid treatment due to the less complex injection procedure associated with administration of an anti-VEGF compared with a steroid implant. Bilateral treatment with laser was assumed to be administered in the same visit on 100% of occasions, also based on clinical expert opinion. These assumptions were tested by the company in scenario analyses that are reported in Section 5.4.13.1.

The acquisition costs of each treatment and the total costs per round of treatment (including acquisition and administration costs) are provided for unilateral and bilateral DMO in Table 87. For bilateral treatment acquisition costs are doubled, as two units are needed to treat two eyes.

Table 87 Treatment costs including acquisition cost (list price) and administration costs associated with unilateral and bilateral treatment (adapted from CS, Tables 103 and 104)

Treatment	List price		Unilateral DMO	Bilateral DMO	
	Acquisition cost	Reference	Total cost per round of treatment	Number of appointments for bilateral treatment	Total cost per round of treatment
Dexamethasone	£870	MIMS (Accessed July 2014);[153] 700 microgram intravitreal implant in applicator	£987	1.75	£1,944
Watch and wait	£0	No treatment cost is associated with watch and wait	£0	1	£0
Ranibizumab	£742	MIMS (Accessed July 2014);[153] 10mg/ml solution for injection: 0.165ml prefilled syringe	£859	1.5	£1,659
Fluocinolone Acetonide	£5,500	MIMS (Accessed July 2014);[153] 190 microgram intravitreal implant in applicator	£5,617	1.75	£11,204
Bevacizumab	£50	Poku *et al.*, 2012 (NICE DSU)[159]; single pre-filled	£167	1.5	£275

		syringe			
Laser	£0	No acquisition cost is assumed for laser	£117	1	£117
Abbreviations used in the table: DMO, diabetic macular oedema; DSU, NICE Decision Support Unit; MIMS, Monthly Index of Medical Specialities; NICE, National Institute for Health and Care Excellence.					

ERG comment

Clinical expert advice confirmed that administration of treatments in an outpatient setting represents routine clinical practice. It was also noted that an increasing number of units are using nurses (not ophthalmologists) to inject anti-VEGF; however, although this change in staff reflects different resource use, it is believed that it would not have any impact on the standard NHS reference costs in the short term.

The ERG also confirmed with clinical experts that the assumptions used by the company in terms of visits required for bilateral treatment appear to be reasonable. One expert agreed with the company's assumptions, but another one expressed the opinion that bilateral treatment with anti-VEGF is more likely to happen in one visit on 75% of occasions and in two visits on 25% on occasions. Therefore the ERG conducted an additional analysis using this estimate (**Analysis C5**), which is discussed in Section 5.5.2.2 with results being provided in Section 6.1.2.2. The cost effectiveness of ranibizumab versus dexamethasone was not affected.

In addition to the administration costs considered by the company, the ERG's clinical experts highlighted that antiseptics are normally administered prior treatment to prepare the eye and topical antibiotics are routinely given post-treatment for 3 to 7 days. However, the associated costs are expected to be very low (for example, a 10mL vial of chloramphenicol eye drops 0.5% costs £1.39 according to BNF 68,[157] therefore the ERG did not undertake any further analysis to consider these costs as their impact on the cost effectiveness results is expected to be negligible.

The ERG finds useful the scenario analyses undertaken by the company which varied the discount prices of treatments subject to PAS to allow the Appraisal Committee to select the ICER that most closely represents the true cost to the NHS.

5.4.11.4 Monitoring and test costs

Patients with DMO were assumed to require regular monitoring visits and tests that may include OCT, fluorescein angiography and IOP checks. The unit costs of each type of visit and test incurred by patients in the model were taken from NHS Reference Costs 2012/13[154] and are shown in Table 88.

Table 88: Unit costs of monitoring and tests (reproduced from CS, Table 105, pg 405)

Resource	Unit cost	HRG code
Routine monitoring visit	£80.04	NHS Reference Costs 2012/13; WF01A code 130 Ophthalmology; consultant led non-admitted, face to face attendance, follow-up
OCT	£18.06	NHS Reference Costs 2012/13; RA23Z, service code 130 Ophthalmology, diagnostic imaging - direct access: ultrasound scan less than 20 minutes
Fluorescein angiography	£116.68	NHS Reference Costs 2012/13; BZ23Z, service code 130 Ophthalmology, minor vitreous retinal procedures (outpatient procedure)
IOP check	£80.04	NHS Reference Costs 2012/13; WF01A code 130 Ophthalmology; consultant led non-admitted, face to face attendance, follow-up
Abbreviations used in the table: HRG, health resource group; IOP, intraocular pressure; OCT, optical coherence tomography.		

The numbers of each type of visit and test required by patients with DMO varied according to the treatment they received. The company assumed all patients received a fluorescein angiography at baseline, with the exception of non-treated patients who were assumed to receive one per year. All patients required routine monitoring visits including OCT and only patients treated with dexamethasone were assumed to receive IOP checks. One of the key clinical assumptions used in the model regarding monitoring resource requirements is presented in Box 23. This assumption was presented and discussed with clinical experts at the company's advisory board meeting to determine if the company's assumptions on monitoring reflected standard clinical practice.

Box 23. Key clinical assumption 4 of the economic model presented and discussed at the advisory board meeting (CS; Appendix 14, pg 651)

Assumption 4: DMO patients are monitored for the entire time horizon of the model (15 years base case); with different resource requirements possible for those who are receiving each treatment and those who are receiving no treatment. Resource requirements are allowed to vary for the first 3 years with the third year requirements used in subsequent years. The monitoring of patients can vary for the first 3 years, depending on response, treatment regimen and capacity in the local service. On the whole, Years 1 and 2 were deemed to be more intensive than Year 3. However, from Year 4 onwards the monitoring schedule is likely to be constant.
Abbreviations used in the box: DMO, diabetic macular oedema.

The company estimated medical resource use associated with monitoring and testing for patients receiving dexamethasone based on the SPC and clinician opinion collected at the advisory board meeting (CS; Appendix 14, pgs 647-665). Previous TAs on other treatments for DMO were used to inform the medical resource use of the remaining treatments. For non-treated patients estimates were based on the TA271 company submission which included "optimised standard of care" as a comparator. TA271 was also used to inform the medical resource use for fluocinolone acetonide and laser, which were assumed to have equal monitoring requirements. The medical resource use for

ranibizumab was taken from the TA237 company submission and was also applied to bevacizumab. The numbers of each type of visit and test assumed to be required for each treatment are presented in Table 89 to Table 92.

Table 89. Monitoring visits and tests in patients with DMO receiving dexamethasone (reproduced from CS, Table 107)

Resource	Number required in		
	Year 1	Year 2	Year 3
Routine monitoring visit	4	4	4
OCT	4	4	4
Fluorescein angiography	1	0	0
IOP check	2	2	2
Total cost per patient	£669	£552	£552
Abbreviations used in the table: DMO, diabetic macular oedema; IOP, intraocular pressure; OCT, optical coherence tomography.			

Table 90. Monitoring visits and tests in patients with DMO not receiving treatment, including watch and wait patients (reproduced from CS, Table 106)

Resource	Number required in		
	Year 1	Year 2	Year 3
Routine monitoring visit	4	4	4
OCT	4	4	4
Fluorescein angiography	1	1	1
IOP check	0	0	0
Total cost per patient	£509	£509	£509
Abbreviations used in the table: DMO, diabetic macular oedema; IOP, intraocular pressure; OCT, optical coherence tomography.			

Table 91. Monitoring visits and tests in patients with DMO receiving either ranibizumab or bevacizumab (reproduced from CS, Tables 108 & 109)

Resource	Number required in		
	Year 1	Year 2	Year 3
Routine monitoring visit	12	10	4
OCT	12	10	4
Fluorescein angiography	1	0	0
IOP check	0	0	0
Total cost per patient	£1,294	£981	£392
Abbreviations used in the table: DMO, diabetic macular oedema; IOP, intraocular pressure; OCT, optical coherence tomography.			

Table 92. Monitoring visits and tests in patients with DMO receiving either fluocinolone acetonide or laser (reproduced from CS, Tables 110 & 111)

Resource	Number required in

	Year 1	Year 2	Year 3
Routine monitoring visit	4	4	4
OCT	4	4	4
Fluorescein angiography	1	0	0
IOP check	0	0	0
Total cost per patient	£509	£392	£392
Abbreviations used in the table: DMO, diabetic macular oedema; IOP, intraocular pressure; OCT, optical coherence tomography.			

As presented in Box 23, monitoring from Year 4 onwards was assumed to be constant for the remainder of the time horizon.

ERG comment

The ERG sought clinical expert opinion to determine whether unit costs associated with monitoring visits and tests appear to be relevant. The ERG is unclear as to why the company has used a HRG code relating to minor vitreous retinal procedures for a fluorescein angiography which is a diagnostic imaging test. The ERG has identified an alternative HRG code (RA17Z, Diagnostic Imaging, Service code 130 Ophthalmology, Contrast Fluoroscopy Procedures, 20 to 40 minutes, Outpatient) associated with a cost of £144 and considered this to be more appropriate.[154] The ERG has carried out an additional analysis using the cost of £144 for a fluorescein angiography (a**nalysis B4**) which is discussed in Section 5.5.2.1 with results presented in Section 6.1.2.1. The base case results of the economic analysis were not affected.

The ERG consulted with clinical experts to explore whether the number of monitoring vists and tests attached to each DMO treatment is reasonable and expresses routine clinical practice. Clinical expert opinion was that monitoring depends on the level of treatment response, which does not necessarily remain constant over time. Nevertheless, it was confirmed that the company's resource use estimates relating to monitoring and tests are broadly reflective of routine care.

Monitoring visits and tests for patients with DMO not receiving treatment was based on the "optimized standard of care" arm in FAME. The ERG believes this to be a reasonable proxy for "watch and wait" patients based on the published trial data available.

The ERG was advised that the treatment pathway for corticosteroids (i.e. dexamethasone and fluocinolone acetonide) is generally the same, with post-treatment monitoring occurring one month after the procedure (for IOP, visual acuity and CRT with OCT) and then approximately every 3 months.

Clinical experts expressed the view that the monitoring visits in the first year applied to anti-VEGF treatments (i.e. ranibizumab and bevacizumab) were overestimated, as the reported 12 visits were

based on trial data and may reflect optimal routine practice, but in reality a maximum of 10 monitoring visits per year is seen in clinical practice. The monitoring visits estimated for ranibizumab (and, consequently, for bevacizumab) were reported by the company to have been derived from the NICE TA237 on ranibizumab for the treatment of DMO.[43] However, the ERG notes that

- the numbers of ranibizumab monitoring visits in the Allergan submission correspond to the number of total visits (dedicated monitoring plus treatment visits) in the NICE TA237
- the number of total visits was amended to 12 visits in Year 1, 8 visits in Year 2 and 6 visits in Year 3 in the NICE TA274 (rapid review of TA237).[44]

It is also noted that in the NICE TA274 the number of total visits for laser treatment was 4 in each year (equal to the number of monitoring visits for laser in this company submission), and these included treatment visits and dedicated monitoring visits. The number of total visits for laser treatment was reduced from 16 in TA237 to 12 in TA274.

The reason for the amendments in the number of visits for ranibizumab and laser in TA274 compared with TA237 related to Appraisal Committee comments on whether treatment and monitoring visits should be counted separately, or whether some monitoring visits should be incorporated in treatment visits (without incurring extra costs). The conclusions drawn by the Appraisal Committee at the final appraisal determination (FAD) of TA274 are presented in Box 24.

Box 24. The Appraisal Committee's conclusions on the number of treatment and monitoring visits required for ranibizumab (TA274 FAD, pgs 58-59)[115]

The Committee was aware that in its original submission in NICE TA237, the company had assumed that a visit for treatment with ranibizumab would double as a monitoring visit and that people treated with laser photocoagulation would need a separate monitoring visit. The Committee was unaware of any clinical evidence to justify this difference, and the company had not explained the difference in its original submission or in consultation comments. The Committee noted that the company had addressed this issue in its rapid review submission by assuming that a treatment visit for people receiving ranibizumab or laser photocoagulation doubles as a monitoring visit. The Committee concluded that, compared with the company's original submission, the rapid review model provided a more plausible reflection of the number of treatment and monitoring visits that people receiving ranibizumab treatment or laser photocoagulation would need.
Abbreviations used in the box: FAD, final appraisal determination; NICE, National Institute for Health and Care Excellence.

Therefore, the Appraisal Committee of TA274 expressed the view that, for both ranibizumab and laser, at least some of the monitoring visits should be incorporated into treatment visits and not be counted separately, and agreed that the number of total visits (treatment and monitoring) in the CS for

TA274 was more reflective of routine clinical practice compared with the figures reported in the CS for TA237.

Clinical experts informed the ERG that if a patient undergoes different procedures associated with DMO management on the same day, the hospital receives payment only for one visit/procedure. For example, if a patient with DMO attends a monitoring visit and is administered an injection as a result of their assessment, the hospital receives payment only for one visit, that with the highest tariff. In some hospitals, this situation also includes diagnostic/monitoring tests, whereas in other hospitals undergoing diagnostic tests leads to a separate payment from that received for treatment/ monitoring visits. Nevertheless, the ERG notes that if visits to different specialists on the same day entail separate resource use each, then they should be costed separately (due to distinct opportunity costs), despite of the hospital potentially receiving one payment for more than one procedures.

On the other hand, the ERG believes that visits that include treatment administration and monitoring at the same time should be considered as one visit in terms of costing. The ERG notes that costs of treatment administration visits and monitoring visits have been applied separately in the model for all treatments, meaning that they have been implicitly considered as separate visits.

Given the views of the clinical experts consulting the ERG, the TA271 FAD, and the updated figures for ranibizumab total visits in the TA274, the ERG decided to amend the company's analysis as follows (**analysis C6**):

- For all treatments considered in the analysis, the numbers of monitoring visits considered by the company were deemed to reflect the total numbers of visits (treatment and monitoring), in accordance with TA274 (ranibizumab and laser) and TA237 (fluocinolone acetonide). One extra treatment visit was added in Year 1, to account for the initial treatment visit.
- The dedicated monitoring visits were subsequently estimated by subtracting the numbers of treatment visits (reported in Table 55 of this report) from the total numbers of visits.
- The total visits for ranibizumab (and bevacizumab) were amended in line with the updated figures used in the TA274.

The resulting number of visits following ERG amendments was presented to clinical experts to confirm the figures are consistent with clinical practice. The updated figures are shown in Table 93.

Table 93. Treatment and monitoring visits for all treatments included in the economic analysis – figures amended by ERG and included in Analysis C6

Treatment	Average number of treatments			Notes
	Year 1	Year 2	Year 3	

All DMO patients					
DEX700	Treatment	[redacted]	[redacted]	[redacted]	Company submission
	Dedicated monitoring	[redacted]	[redacted]	[redacted]	
	TOTAL	**5**	**4**	**4**	Company submission for monitoring visits; one extra visit assumed by ERG
Watch and wait	Treatment	0	0	0	Non-applicable
	Dedicated monitoring	4	4	4	
	TOTAL	**4**	**4**	**4**	Company submission
Fluocinolone acetonide	Treatment	1.00	0.26	0.036	Company submission – number for Year 3 corrected by ERG
	Dedicated monitoring	4	3.74	3.964	
	TOTAL	**5**	**4**	**4**	Company submission for monitoring visits; one extra visit assumed by ERG
DMO patients who are pseudophakic					
DEX700	Treatment	[redacted]	[redacted]	[redacted]	Company submission
	Dedicated monitoring	[redacted]	[redacted]	[redacted]	
	TOTAL	**5**	**4**	**4**	Company submission for monitoring visits; 1 extra visit assumed by ERG
Ranibizumab	Treatment	7.00	3.90	2.90	Company submission
	Dedicated monitoring	6	4.10	3.10	
	TOTAL	**13**	**8**	**6**	TA274 total number of visits for ranibizumab; 1 extra visit assumed by ERG in Year 1
Bevacizumab	Treatment	9.00	4.00	2.90	Company submission
	Dedicated monitoring	4	4	3.10	
	TOTAL	**13**	**8**	**6**	Assumed by company to equal to ranibizumab visits
Laser	Treatment	[redacted]	[redacted]	[redacted]	Company submission
	Dedicated monitoring	[redacted]	[redacted]	[redacted]	
	TOTAL	**5**	**4**	**4**	TA274 total number of visits; 1 extra visit assumed by ERG in Year 1
Watch and wait	Treatment	0	0	0	Non-applicable
	Dedicated monitoring	4	4	4	
	TOTAL	**4**	**4**	**4**	Company submission

Abbreviations used in table: DEX700, dexamethasone 700µ; DMO, diabetic macular oedema; ERG, evidence review group.

Note: monitoring visits assumed to incorporate treatment visits, with the exception of DEX700, fluocinolone acetate and laser, for which an extra treatment visit has been assumed

Analysis C6 is discussed in Section 5.5.2.2 with the results provided in 6.1.2.2. Use of alternative figures had no impact on the conclusions drawn from the base case analyses.

The ERG noted that no IOP checks were assumed for patients treated with fluocinolone acetonide, despite the fact that increase in IOP is an adverse event of corticosteroid treatment. Clinical experts advised that IOP would be checked at every monitoring visit following treatment with dexamethasone or fluocinolone acetonide, i.e. 4 IOP checks per year should be assumed for both corticosteroid treatments. During clarification the ERG asked the company to clarify why IOP checks were considered for dexamethasone but not for fluocinolone acetonide. The company's response is presented in

Box 25.

Box 25. Company's response regarding the absence of IOP checks for patients receiving fluocinolone acetonide (Company's response to clarification; pg47)

The resource use requirements for fluocinolone acetonide used within the economic model for this submission were assumed to be as per the company's submission for TA271, which did not include IOP checks. 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.
Abbreviations used in the Box: DEX700, dexamethasone 700µg; IOP, intraocular pressure.

Nevertheless, clinical experts advised the ERG that IOP checks are routinely done during monitoring visits, and therefore do not incude an extra cost. Potentially, this justifies the absence of an IOP cost for fluocinolone in TA271. For this reason, the ERG undertook an additional analysis (**Analysis C7**), which removed the cost of IOP checks for dexamethasone. This analysis is discussed in Section 5.5.2.2; its results are presented in Section 6.1.2.2. This scenario had no considerable impact on the base case results.

On the other hand, clinical expert opinion was that patients who experience raised IOP as an adverse event of treatment require additional IOP checks and therefore incur extra resource use. This issue is discussed further in Section 5.4.11.6.

5.4.11.5 Health state costs

Costs of treatment and monitoring were assumed to be equal across all health states.

If a patients' BCVA fell below 35 letters on the ETDRS chart they were classified as having severe vision loss. Patients with severe vision loss in the BSE (i.e. in both eyes) incurred additional costs associated with community care, residential care, hip replacement and depression, in line with Meads and Hyde[158] and Colquitt *et al*.[156]

In the base case analysis, the company excluded one-off costs associated with blind registration, low vision aids and low vision rehabilitation that are incurred when a patient first becomes blind; these costs were included in a scenario analysis, the results of which are reported in Section 5.4.13.1.

The proportion of patients assumed to require services associated with severe vision loss were taken from Colquitt *et al*.[156] and are presented in Table 94 alongside the unit costs of each service and the total NHS and personal social service costs associated with severe vision loss. Where national unit costs were available, these were utilised in the model; otherwise, costs reported by Colquitt *et al*. were used.

Table 94. Costs associated with severe vision loss that were utilised in the economic analysis

Resource	Unit cost	Unit cost reference	Cost type	% patients requiring service
Personal social care costs				
Community care	£10,958	Curtis (2013);[155] based on weekly cost of community care package for the elderly (excluding accommodation costs) of £210.	Annual	6%
Residential care	£52,283	Curtis (2013);[155] based on weekly cost of local authority residential care of £1002.		30%
Hip replacement	£4,222	NHS Reference Costs 2012/13;[154] HA13C, service code 110 Trauma and Orthopaedics, intermediate hip procedures for trauma, without CC (weighted by non-elective and elective, short and long stay data submissions).	Event	5% annual incidence
Depression	£517*	Colquitt *et al.* (2008);[156]	Annual	39%
Total cost per patient per year (base case)				£16,755
Blind registration	£138*	Colquitt *et al*. (2008);[156]	One-off	95%
Low vision aids	£180*			33%
Low vision rehabilitation	£311*			11%
Total cost per patient per year (scenario analysis; first year only)				£16,980
Abbreviations used in the table: CC, complication and comorbidity * Costs taken from Colquitt *et al*., 2008 were inflated to 2013 prices using the hospital & community health services pay and prices index taken from Curtis 2013				

ERG comment

The ERG notes that that the study by Colquitt *et al*.[156] was not included in the company's systematic review of resource use and costs. During clarification the ERG asked the company to clarify how Colquitt *et al*.[156] was identified and selected; the company's response was that the study was identified as reference that had been used in previous economic evaluations of treatments for DMO.

For transparency, the ERG notes that the costs of severe vision loss taken from Colquitt *et al*.[156] were sourced originally from other published literature. The cost of blind registration and low vision aids were originally sourced from Meads *et al*.,[160] the cost of depression from Knapp *et al*.[161] and the cost of low-vision rehabilitation from Curtis & Netten (2005).[162]

The ERG has identified a minor error in the company's uplifting the above unit costs from 2005 prices (as reported in Colquitt *et al*.) to 2013 prices. It appears that the company has used the 2005/06 inflation index instead of the 2004/05 one. Use of the correct inflation index resulted in slightly higher unit costs, which are presented in Table 95.

Table 95. Unit costs for severe vision loss, 2013 prices, uplifted from 2005 priced by ERG

Resource	Colquitt *et al*., 2008 2005 prices	Uplifted unit costs 2013 prices
Blind registration	£115	£143
Low vision aids	£150	£187
Low vision rehabilitation	£259	£322
Depression	£431	£536

NICE TA237 used Meads & Hyde[158] as the source of the cost associated with severe vision loss. The total cost of severe blindness used in the economic analysis was £6,067 for the first year and £5,936 for subsequent years (2009 prices). The total cost of severe vision loss used in the economic analysis for TA271 was £6,298 (2011 prices); this figure was based on the cost reported in TA237.

The ERG is concerned that the total cost of severe vision loss that was reported in the company submission for this STA (£16,755 in 2013 prices) is more than double the cost reported in previous TAs, after the latter were uplifted to 2013 prices. The ERG compared the cost elements, percentages of patients incurring each cost element, and respective unit costs that were used to estimate the cost of severe vision loss between the CS for this STA and the TA237, to explore reasons for the discrepancy in the reported total cost figures. The ERG identified minor discrepancies in unit costs and/or percentages of people incurring each cost element across most of the cost elements; these small discrepancies did not justify the substantial difference in total costs associated with severe vision loss between the two submissions. The only large discrepancy between the two submissions was observed in the estimation of the cost of residential care. The figures and assumptions used to estimate this cost in the two submissions are shown in Table 96.

Table 96. Comparison of the resource use and unit costs used in the CS for this STA and TA237 for the estimation of the cost of residential care associated with severe vision loss

Resource use for residential care	DEX CS (2013 prices)	TA237 (2009 prices)
% eligible for service	30%	15%
Eligibility source	Colquitt *et al*., 2008[156] (sourced originally from Meads *et al*., 2001)[163]	Assumption: Original data source (Mead & Hyde 2003)[158] is not AMD-specific; percentage reduced to take account of private payers
Unit cost (annual)	£52,253	£16,999
Mean annual cost per patient	£15,676	£2,550
Cost source	Curtis 2013; local authority residential care for older people, based on establishment cost per permanent resident week of £1002 (including capital costs, total local authority expenditure and agency overheads)	Curtis 2009; private residential care for older people, based on establishment costs per permanent resident week of £467 (including paid fees)
Abbreviations used in the table: AMD, age related macular degeneration; DEX, dexamethasone; CS, company submission		

The annual residential cost per patient was considerably different between the 2 submissions, with the cost figure estimated for this submission being more than 5.5 times higher than the cost figure estimated for the TA237, after the latter was uplifted to 2013 prices (resulting in a figure of £2,761). This was attributable to 2 factors:

a. The percentage of people receiving residential care was estimated to be 30% in this submission, but 15% in the TA237 submission;

b. The unit cost of residential care was based on local authority residential care in this submission, whereas in the TA237 submission was based on private residential care.

The ERG considers that it is reasonable to assume that 30% of patients with severe vision loss receive residential care, based on the review by Meads & Hyde[158]. On the other hand, the ERG is concerned with the use of the unit cost for local authority residential care by the company. This is inconsistent with the unit cost attached to residential care in the other TAs of treatments for DMO (TA237 and TA271), both of which utilised the unit cost of private residential care. Colquitt *et al*.[156] also utilised the unit cost of private residential care in order to estimate the total cost associated with severe vision loss.

The ERG conducted a brief review of previous NICE TAs of treatments for ocular diseases and notes that in TA229, which assessed dexamethasone for the treatment of macular oedema caused by retinal vein occlusion, the company also utilised a private residential care unit cost in order to estimate the

total cost associated with severe vision loss.[164] The total cost associated with severe vision loss in TA229 was estimated at £8,055 in 2009 prices. The economic analysis undertaken for that STA had also assumed that 30% of patients with severe vision loss receive residential care. The unit cost of private residential care was also used in TA297 on ocriplasmin for the treatment of vitreomacular traction,[165] resulting in an annual cost of blindness of £6,496 in 2012 prices. Finally, the ERG of TA298, which assessed ranibizumab for treating choroidal neovascularisation associated with pathological myopia, critiqued the company submission for using the unit cost of local authority residential care, as "it appears that the vast majority of residential care is now provided by the private sector" (ERG report for TA298, page 81).[166] The ERG of TA298 amended the cost of severe vision loss estimated by the company, after replacing the unit cost of local authority residential care by the unit cost of private residential care.

Following the review of the above economic analyses, the ERG's view was that the unit cost of private residential care should replace the unit cost of local authority residential care in the company's economic analysis. According to Curtis (2013)[155] this cost was £532 per week in 2013 prices, giving an annual cost of residential care of £27,664. The analysis undertaken using the private residential care cost instead of the local authority one (**analysis C8**) is discussed in Section 5.5.2.2, with results presented in Section 6.1.2.2. This scenario had a strong impact on the base case results in patients with DMO who are unsuitable for, or insufficiently responsive to non-corticosteroid therapy, as it reversed conclusions for dexamethasone (from being dominant in the base case analysis, under this scenario it demonstrated an ICER versus watch and wait of £30,366/QALY). Conclusions in pseudophakic patients with DMO were not affected.

Regarding the annual cost of depression, the ERG notes that this was based on a study of 28 people with affective disorders who had been recently discharged from a long stay psychiatric hospital in the UK that was published in 1995. A more recent estimate of the annual cost of depression has been reported in McCrone *et al.*, who conducted a modelling study using national epidemiological, service use and unit cost data, to estimate the costs of mental health care in England; the study was published in 2008.[167] The mean annual service cost of depression was reported to reach £2,085 in 2006 prices. This cost included psychiatric (10%) and non-psychiatric (17%) inpatient care, non-inpatient care (33%), GP contacts (9%), medication (1%), residential care (10%), social services (15%) and a small proportion of other small elements (5%).

The ERG felt that the study by McCrone *et al*. was more appropriate to use as the source of the cost of depression in the estimation of the cost associated with severe vision loss. The ERG noted that the cost figure reported in the report incorporated a residential care cost component, which needed to be excluded to avoid double-counting, as the cost of severe vision loss already included such a cost element. After excluding residential care cost and uplifting to 2013 prices using the hospital &

community health services index[155], the annual cost of depression (excluding residential care) reached £2,252. The ERG notes that the average annual cost reported in the study by McCrone *et al*. was the average annual cost across ages. In the report it was stated that the average service cost tended to increase with age, with substantially higher costs for those in the oldest age group. This means that the figure of £2,252 may be an underestimate for the study population of this TA. On the other hand, it is likely that the percentage of residential care in older people with depression is higher than 10%, meaning that a greater proportion (than %10) of the actual depression cost in older patients would be attributable to residential care and thus should be excluded from the actual estimate. **Analysis C9**, described in Section 5.5.2.2 with results presented in Section 6.1.2.2, utilises the figure of £2,252 for the annual cost of depression when estimating the annual cost of severe vision loss. This scenario had no substantial impact on the base case results.

After consideration of the amended unit cost of residential care and the updated cost of depression, the annual cost associated with severe vision loss, as estimated by the ERG, fell at £10,046 (£10,279 in the first year according to a scenario analysis). Details on unit costs, percentage of patients receiving the service, and data sources of the amended cost figures are reported in Table 97.

Table 97. Costs associated with severe vision loss following amendments by the ERG

Resource	Unit cost	Unit cost reference	Cost type	% patients requiring service
Personal social care costs				
Community care	£10,958	Curtis (2013)[155]; based on weekly cost of community care package for the elderly (excluding accommodation costs) of £210.	Annual	6%
Residential care	£27,664	Curtis (2013)[155]; based on weekly cost of private residential care of £532.		30%
Hip replacement	£4,222	NHS Reference Costs 2012/13[154];HA13C, service code 110 Trauma and Orthopaedics, intermediate hip procedures for trauma, without CC (weighted by non-elective and elective, short and long stay data submissions).	Event	5% annual incidence
Depression	£2,252	McCrone *et al*.[167]	Annual	39%
Total cost per patient per year (base case)				£10,046
Blind registration	£143	Colquitt *et al*.,[156] uplifted by ERG using the correct inflation indices	One-off	95%
Low vision aids	£187			33%
Low vision rehabilitation	£322			11%
Total cost per patient per year (scenario analysis; first year only)				£10,279
* Costs taken from Colquitt *et al*.[156] were inflated to 2013 prices using the hospital & community health services pay and prices index taken from Curtis 2013				

5.4.11.6 Adverse event costs

As described in Section 5.4.8, the economic analysis has incorporated five key adverse events that require medical or surgical intervention, depending on the type and severity of the adverse event. These are cataracts, raised IOP, retinal detachment, endophthalmitis and vitreous haemorrhage. The unit costs of these events with the exception of raised IOP were taken from the NHS Reference Costs 2012/13 and are presented in Table 98.

Table 98: Costs of four of the adverse events utilised in the economic analysis

Adverse event	Unit cost	NHS reference costs 2012/13[154]- HRG code
Cataract	£865.56	BZ02C, service code 130 Ophthalmology, Phacoemulsification cataract extraction and lens implant, with CC score 0-1, day case
Retinal detachment	£1,685.00	BZ22B, Service code 130 Ophthalmology, Intermediate vitreous retinal procedure, with CC score 0, day case
Endophthalmitis	£1,393.00	BZ23Z, Service code 130 Ophthalmology, Minor vitreous retinal procedure, non-elective inpatients, long stay
Vitreous haemorrhage	£1,685.00	BZ22B, Service code 130 Ophthalmology, Intermediate vitreous retinal procedure, with CC score 0, day case
Abbreviations used in the table: CC, complication and comorbidity; HRG, Health Resource Group		

Raised IOP may be treated by either medication or surgical intervention. The unit costs of medications and surgical procedures included for the treatment of raised IOP that were considered in the economic model are shown in Table 99 and Table 100, respectively. The unit costs of all medications were taken from the MIMS (Accessed July 2014)[153] and the unit costs of surgical procedures from the NHS Reference Costs 2012/13.[154] The average cost per patient of each medication was based on the mean number of days of medication expected to be required for a typical case of raised IOP and the maximum time (in days) one bottle of medication was expected to last. The total average cost per patient with raised IOP treated with medication was calculated assuming equal use of all medications. The total average cost per patient with raised IOP receiving surgical intervention was calculated assuming equal application of all surgical procedures. The proportions of cases of raised IOP that were assumed to be treated with medication or surgery have been reported in Section 5.4.8.2.

Table 99. Cost of medications for the treatment of raised IOP (adapted from CS; Table 114, pg 413)

Medication	Unit cost*	Mean number of days required	Maximum number of days per bottle	Average cost per patient

Beta-blockers; timolol 0.25%	£1.16	1096	28	£46.40
Prostaglandins; Xalatan	£12.48			£499.20
CA inhibitors; Azopt	£6.92			£276.80
Combination; Cospot	£10.05			£402.00
Brimonidine; Brimonidine tartrate	£2.19			£87.60
Total average cost per patient (assuming equal weighting for each treatment)				£262.40
Abbreviations used in the table: CA, carbonic anhydrase; IOP, intraocular pressure Notes: patients who have raised IOP are assumed to receive up to 3 years of treatment, consistent with the assumed duration of treatment for DMO; maximum number of days per bottle based on the maximum shelf-life being 28 days from opening. *based on eMIT,[168] MIMS[153]				

Table 100. Cost of surgical procedures for the treatment of raised IOP (adapted from CS; Table 115, pg 414)

Surgical procedure	NHS reference costs 2012/13[154] - HRG code	Unit cost
Trabeculectomy	BZ17B, Service code 130 Ophthalmology, Major glaucoma procedures, with CC score 0 (day case)	£1,422
Iridectomy	BZ18B, Service code 130 Ophthalmology, Intermediate glaucoma procedures, with CC score 0 (day case)	£1,123
Iridotomy	BZ18B, Service code 130 Ophthalmology, Intermediate glaucoma procedures, with CC score 0 (day case)	£1,123
Total average cost per patient (assuming equal weighting for each treatment)		£1,223
Abbreviations used in the table: CC, complication and comorbidity; HRG, Health Resource Group		

ERG comment

The ERG notes that the cost applied to retinal detachment and vitreous haemorrhage applied in the submission and the model is incorrect. The figure £1,685 used by the company refers to the correct code (BZ22B, Service code 130 Ophthalmology, Intermediate vitreous retinal procedure, with CC score 0-1) but corresponds to a non-elective inpatient short stay and not a day case procedure. The correct unit cost corresponding to an intermediate day case procedure is £989.

Clinical experts advised that management of retinal detachment may sometimes be a major (rather than intermediate) vitreous retinal procedure undertaken as a day-case, and in fewer cases it may even require hospital admission. The NHS Reference Cost of a major vitreous retinal procedure (BZ22B, Service code 130 Ophthalmology, Major vitreous retinal procedure, with CC score 0, day case) is £1,443.[154]

The ERG ran an analysis (**Analysis B5**) that amended the cost of intermediate vitreous retinal procedure (day case) to £989 (for both retinal detachment and vitreous haemorrhage), and also assumed that management of retinal detachment is achieved by intermediate vitreous retinal day-case procedure in 80% of cases, and by major vitreous retinal day-case procedure in the remaining 20% of cases, giving an average cost of management of retinal detachment at £1,080. This analysis is

described in Section 5.5.2.1, with results provided in Section 6.1.2.1. Base case results were not affected by the above corrections and assumptions.

The ERG's clinical experts expressed different opinions regarding pharmacological treatment for raised IOP: one expert considered equal use of medications as reasonable; however, another clinical expert expressed the opinion that generic prostaglandins comprise the most commonly used medication for treating raised IOP, followed by generic beta blockers, whereas the other treatments listed in the submission are less commonly used. The ERG notes that the average cost of medication for raised IOP assuming equal use of all medications that was reported by the company (£92.85) was incorrect. The correct figure (which was also applied in the submitted economic model) is £262.40, and this has been inserted by the ERG in Table 99 above.

The NICE guidance on the pricing of technologies for use in its Technology Appraisals[147] is presented in Box 26.

Box 26. NICE Guidance on the price of technologies

"The public list prices for technologies (for example, pharmaceuticals or medical devices) should be used in the reference-case analysis. When there are nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, then the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS. The Commercial Medicines Unit publishes information on the prices paid for some generic drugs by NHS trusts through its Electronic Marketing Information Tool (eMIT)"

Following NICE guidance, the ERG reviewed data contained within eMIT to identify the unit cost of generic prostaglandins, which was found to be £1.18 (Latanoprost, 50µg/ml eye drops, 2.5ml, excluding VAT).[168]

The ERG undertook an analysis (**Analysis C10**) that utilised the unit cost of generic latanoprost, and assumed that, of the patients with raised IOP that receive pharmacological treatment, 70% were treated with generic prostaglandins, 10% with generic beta-blockers, and the remaining 10% by equal use of the remaining treatments listed by the company. The mean cost of medication for raised IOP using these assumptions became £88.77. This analysis, which had no considerable impact on the base case results, is described in Section 5.5.2.2, with results provided in Section 6.1.2.2.

The ERG was also informed by clinical experts that iridectomy and iridotomy are not used for steroid-induced glaucoma and that trabeculectomy is the main surgical procedure used in routine clinical practice for this purpose. This view was also expressed at the company's advisory board meeting, as stated in the submission: "patients with IOP ≥40mmHg would be considered for surgical intervention,

which would likely be a Trabeculectomy" (CS; Appendix 14, pg 656). The ERG is unclear as to why the company considered iridectomy and iridotomy as additional treatment options.

The NHS reference unit cost for an intermediate glaucoma day case procedure is £1,123 (BZ18B, Service code 130 Ophthalmology, Intermediate glaucoma procedures, with CC score 0, day case).

The ERG undertook an analysis (**Analysis C11**) in which trabeculectomy was the only surgical procedure considered for the management of raised IOP; 50% of trabeculectomies were assumed to correspond to intermediate glaucoma day case procedures, and 50% to major glaucoma day case procedures. The mean cost of surgical intervention for raised IOP using these assumptions became £1273. This analysis is described in Section 5.5.2.2, with results provided in Section 6.1.2.2. The results of the base case analyses were practically unaffected.

Finally, the ERG was advised that patients who experience raised IOP as an adverse event of treatment require additional IOP checks and therefore incur extra resource use. It was estimated that patients with raised IOP require 2 additional IOP checks per year that IOP remains raised, on top of the routine IOP checks undertaken to all patients receiving DMO treatment with corticosteroids (as discussed in Section 5.4.11.4). It was noted that pharmacological treatment for raised IOP lasted 3 years in the company's model. Therefore, the total number of extra IOP checks required for patients with raised IOP that were treated with medication woud be 6. The same number of extra IOP checks was estimated to be required for patients treated surgically, because even if surgery occurred earlier than 3 years, it was estimated that extra IOP checks would be required post-surgically. Based on these estimates, the ERG ran an analysis (**Analysis C12**) that assumed that all patients with raised IOP in the economic analysis underwent 6 extra IOP checks in total. For simplicitly purposes regarding model reprogramming, all 6 checks were assumed to be occuring within the same year; as a consequence, no discounting on the associated costs was applied, and the total cost of extra IOP checks was £480. The ERG estimated that the effect of not discounting the costs associated with extra IOP checks was an overestimation of costs ranging between £16 (if IOP was raised in Year 1 of the model) and £47 (if IOP was raised in Year 3 of the model) per person with raised IOP. This analysis, which had no considerable impact on the base case results, is described in Section 5.5.2.2, with results provided in Section 6.1.2.2.

5.4.11.7 Costs following discontinuation

The company's economic model assumed no further treatment following discontinuation. The justification for this assumption was that modelling an explicit next line of treatment following discontinuation would address a different decision problem and the purpose of the current model was not to assess sequences of treatments (CS, page 347). Treatment received following discontinuation was one of the key clinical assumptions considered in the model. This assumption, which is shown in

Box 27, was presented and discussed with clinical experts at the company's advisory board meeting to determine whether it reflected clinical practice.

Box 27. Key clinical assumption 1 of the economic model presented and discussed at the advisory board meeting (CS; Appendix 14, pg 651)

Assumption 1: Following discontinuation from initial treatment (either due to adverse events or other non-efficacy related reasons or due to lack [or loss] of efficacy) patients are assumed to receive a "basket" of next-line treatment options with an associated average cost and average efficacy.

Following the discussion, the company reported that "Attendees felt that in practice, the initial therapy and reason for discontinuation would dictate the next line of treatment… […] Attendees confirmed that patients may not necessarily/always receive another treatment after discontinuation" (CS; Appendix 14, pg650). Therefore treatment costs following discontinuation in the economic model were assumed to be zero. However, people discontinuing treatment still incurred costs associated with monitoring of DMO; monitoring visits followed the same schedule with monitoring visits in patients receiving no treatment (i.e. in the watch and wait arm of the model), incurring a cost of £509 per year.

ERG comment

The opinions described at the advisory board meeting surrounding the assumption following discontinuation reflect the opinions of the clinical experts consulting the ERG. Consequently the ERG finds reasonable the assumption that, following discontinuation, no treatment costs are incurred, but patients would still incur monitoring costs.

5.4.12 Cost effectiveness results

The company presented deterministic and probabilistic results for each of the three populations of DMO patients. The base case results were calculated deterministically (using mean parameter values only) as well as probabilistically (assessing the simultaneous effect of parameter uncertainty). All probabilistic analyses were based on the average results of 5,000 simulations.

Since there was no difference in the model structure between DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy, the results for these two populations are presented simultaneously to avoid repetition, unless otherwise stated.

Section 5.4.12.1 outlines the base case results of DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy and Section 5.4.12.2 outlines the results for DMO patients who are pseudophakic.

5.4.12.1 Cost effectiveness results – DMO patients who are considered unsuitable or insufficiently responsive for non-corticosteroid therapy

Results presented by the company for the population of DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy are provided in Table 101.

Table 101. Base case results: DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy (adapted from CS, Tables 129-132, pgs 439-440)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Deterministic results					
DEX	£20,413	5.7420	-	-	-
Watch and wait	£21,882	5.6764	£1,469	-0.0656	Dexamethasone dominates
Probabilistic results					
DEX	£20,827	5.7789	-	-	-
Watch and wait	£22,536	5.7230	£1,708	-0.0559	Dexamethasone dominates
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Dexamethasone dominated watch and wait in both the deterministic and probabilistic base case analyses as treatment with dexamethasone was associated with a lower cost and greater QALYs than watch and wait. Therefore dexamethasone was cost-effective compared with watch and wait in DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy.

Disagregated costs for each intervention are shown in Table 102.

Table 102. Summary of costs by component, dexamethasone versus watch and wait (adapted from CS, Tables 122 and 125, pgs 434-435)

Item	DEX cost	Watch and wait cost	Incremental cost
Treatment acquisition	£4,861	£0	£4,861
Treatment administration (including laser administrations)	£619	£0	£619
Severe vision loss	£8,971	£16,777	-£7,806
Adverse events	£863	£258	£605
Medical resource use (monitoring)	£5,100	£4,847	£253
Total	£20,413	£21,882	-£1,469
Abbreviations used in table: DEX, dexamethasone			

Detailed deterministic estimates of costs and QALYs of each treatment by DMO status (unilateral DMO in the BSE or WSE, or bilateral DMO) were also presented in the company submission (CS, Tables 120-121, 123-124, pgs 433-435).

5.4.12.2 Cost effectiveness results –DMO patients who are pseudophakic

Results presented by the company for DMO patients who are pseudophakic based on the list price for ranibizumab are provided in Table 103.

Table 103. Base case results; DMO patients who are pseudophakic – list price for ranibizumab (adapted from CS, Tables 133 and 134, pg 441)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Deterministic results					
DEX	£15,720	5.0886	-	-	-
Ranibizumab (list price)	£21,724	5.2066	£6,004	0.1179	£50,905 *
Probabilistic results					
DEX	£16,053	5.1422	-	-	-
Ranibizumab (list price)	£22,762	5.2172	£6,710	0.0749	£89,531*
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. * Ranibizumab vs dexamethasone;.dexamethasone is less costly and less effective than ranibizumab					

When ranibizumab was assumed to be available at list price, dexamethasone was less effective and less costly than ranibizumab in both deterministic and probabilistic analysis. Ranibizumab was not cost-effective compared with dexamethasone at a cost effectiveness threshold of £20,000/QALY.

The company also presented a base case for DMO patients who are pseudophakic where a 50% discount to the price of ranibizumab was applied, to account for the agreed (but unknown) PAS discount available to the NHS. Results are shown in Table 104.

Table 104. Base case results; DMO patients who are pseudophakic - 50% discount for ranibizumab (adapted from CS, 135 and 136, pg 442)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Deterministic results					
Ranibizumab (50% discount)	£15,004	5.2066			
DEX	£15,720	5.0886	£716	-0.1179	Ranibizumab dominates
Probabilistic results					
Ranibizumab (50% discount)	£16,037	5.2172			
DEX	£16,053	5.1422	£15	-0.0749	Ranibizumab dominates
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

When a 50% discount was applied to the price of ranibizumab, ranibizumab dominated dexamethasone (i.e. it was more effective and less costly than dexamethasone) in both the deterministic and probabilistic base case analyses. The company stated that dexamethasone was found to be more cost-effective than ranibizumab when using the list price of ranibizumab and up to a discount of 27% to the list price of ranibizumab.

Disagregated costs for each intervention are shown in Table 105.

Table 105. Summary of costs by component, DEX vs ranibizumab – list price (adapted from CS, Table 128, pg 437)

Item	DEX cost	Ranibizumab cost	Incremental cost
Treatment acquisition	£4,337	£13,439	-£9,102
Treatment administration (including laser administrations)	£549	£1,884	-£1,336
Severe vision loss	£5,894	£850	£5,044
Adverse events	£424	£3	£420
Medical resource use (monitoring)	£4,516	£5,547	-£1,031
Total	£15,720	£21,724	-£6,004
Abbreviations used in table: DEX, dexamethasone.			

Detailed deterministic estimates of costs and QALYs of each treatment by DMO status (unilateral DMO in the BSE or WSE, or bilateral DMO) were also presented in the company submission (CS, Tables 126-127, pg 436).

5.4.13 Sensitivity analyses

The company carried out one-way sensitivity analyses (OWSA) and scenario analyses to assess the impact of parameter and structural uncertainty on the deterministic cost-effectiveness results. Section 5.4.13.1 and Section 5.4.13.2 describe the scenario analyses and OWSA undertaken in each population, respectively. In addition, probabilistic sensitivity analysis (PSA) that was incorporated into the company's model is described in Section 5.4.13.3.

5.4.13.1 Scenario analyses

The company carried out a series of scenario analyses to test the robustness of model results to changes in model parameters. Table 106 summarises the scenarios explored, and the company's justification for each scenario.

Table 106. Scenario analyses performed, relevant to all populations under consideration unless stated (taken from CS, Table 116, pgs 317-425)

Scenario number	Base case assumption	Scenario considered	Justification
1*	List price for RAN, FA not included in base case analyses for all DMO patients	Variable discount between 0% (list price) and 50%	A confidential PAS is available to the NHS for RAN and FA. This analysis will allow the committee to select the most plausible ICER.
2*	RAN is the only comparator for DMO patients who are pseudophakic	Comparators are RAN, laser, BEV and watch and wait	RAN is the most appropriate comparator in this population as it is the most commonly used 1st line treatment; however there is minimal use of laser and BEV in practice so these have been included as a scenario analysis. Watch and wait has been included for completeness.
3**	Utility regression equation derived from VFQ-UI collected in MEAD	Utility regression equation derived from EQ-5D collected in MEAD	EQ-5D meets the NICE reference case but has been shown not to be sensitive to changes in vision; EQ-5D was collected at baseline only in the MEAD studies whereas NEI VFQ-25 was collected throughout, giving more data from which to derive the base case utility regression.
4	No age-adjusted utilities	Age-adjustment included using a coefficient of -0.00029 per year from Sullivan *et al.,* 2011[143]	The regression equation does not include a coefficient for age; therefore a sensitivity analysis including an age-adjustment has been included.
5	Maximum duration of treatment 3 years	Maximum 5 years of treatment, including 1 maintenance treatment per year (or a maximum of 1 additional fluocinolone acetonide treatment), applying LOCF to efficacy outcomes	The base case analysis is 3 years to avoid the need for extrapolating beyond the longest study duration. However, the duration of treatment for DMO is uncertain, so a scenario has been included to extend the duration to 5 years, with two alternative assumptions for the efficacy beyond the MEAD study duration due to the uncertainty as to what these outcomes should be.
6		Maximum 5 years of treatment, including 1 maintenance treatment per year (or a maximum of 1 additional fluocinolone acetonide treatment), assuming stable vision following this	
7	No change in vision upon development of fellow eye DMO	Vision decline equal to 1 cycle of natural history of vision with DMO (Mitchell *et al*., 2012)[31]	Base case assumption is no change in vision as it is assumed given the frequent visit schedule for DMO patients this would be caught early. Scenario of 1 cycle of natural history of vision with DMO to reflect that in practice treatment often is not initiated until some vision loss occurs.
8	Natural history of DMO applied	Stable vision (identity matrix) applied following	Base case assumption is that DMO is a chronic condition and that

	following treatment cessation Mitchell *et al.,* 2012[31]	treatment cessation	once treatment ceases vision will decline at a rate equal to natural history. Alternative scenario is that treatment ceases because the vision has stabilised and therefore no further treatment is required, given the uncertainty around the long-term treatment for DMO.
9	15 year time horizon	1 year	To determine the impact of varying the time horizon on the results.
10		5 years	
11		10 years	
12		20 years	
13	Baseline distribution of patients across unilateral BSE, unilateral WSE and bilateral DMO obtained from the MEAD studies	100% unilateral DMO in the BSE; no FEI	To assess the impact of treating only DMO in the BSE.
14		100% unilateral DMO in the WSE; no FEI	To assess the impact of treating only DMO in the WSE.
15		100% bilateral DMO	To assess the impact of treating only bilateral DMO.
16	HR of 2.45, applying both the risk of death due to DM (1.93; Mulnier *et al.*, 2006)[132] and due to DMO (1.27; Hirai *et al*., 2008)[34]	Only HR due to DM (1.93; Mulnier *et al*., 2006)[132] applied	It is unclear whether there is double-counting as the DM population who informed the hazard ratio due to DM may have included some patients with DMO.
17		Only HR due to DMO (1.27; Hirai *et al*., 2008)[34] applied	
18	No additional mortality due to severe vision loss	RR of 1.54 (Christ *et al*., 2008)[130] applied to patients whose BSE falls below 35 letters	Not included in base case analysis as the hazard ratio for DMO is likely to include some patients with severe vision loss. However, it has been included in previous retinal technology appraisals (e.g. DEX700 for RVO, TA229) and so has been included as a scenario analysis.
19	One-off costs associated with severe vision not included	Include the one-off costs in Year 1 of the model only	Given the memory-less property of the model it is not possible to track whom moves into severe vision loss for the first time in each cycle (as patients may have moved in a previous cycle and then improved vision but then lost it again). Therefore as a simplifying assumption the one-off costs have been excluded in the base case and in a sensitivity analysis included only in Year 1 of the model.
20	All intravitreal injection treatments administered as an outpatient procedure 100% of the time	All intravitreal injection treatments administered as day case procedures 100% of the time	Reflects the variability of service provision.
21		All intravitreal injection treatments administered as day case procedures 50% of the time	
22		DEX700 administered as a day case procedure 50% of the time; all other intravitreal injection treatments	

		administered as an outpatient procedure 100% of the time	
23	Bilateral treatment on the same day 50% of the time for anti-VEGF and 25% of the time for steroids	Bilateral treatment on the same day 100% of the time for anti-VEGF (average of 1 appointment for bilateral treatment) and 0% of the time for steroids (average of 2 appointments for bilateral treatment)	Reflects the variability of service provision and the uncertainty around the number of appointments that would be required for bilateral treatment in practice; as this is likely to be determined by clinician preference.
24		Bilateral treatment on the same day 50% of the time for anti-VEGF (average of 1.5 appointment for bilateral treatment) and 0% of the time for steroids (average of 2 appointments for bilateral treatment)	
25		Bilateral treatment on the same day 50% of the time for anti-VEGF (average of 1.5 appointment for bilateral treatment) and 50% of the time for steroids (average of 1.5 appointments for bilateral treatment)	
26	Risk of FEI based on analysis using a broad definition of DMO in the non-study eye in the MEAD clinical trials. Annual rate of [redacted] in Year 1 and Year 2	Risk of FEI based on specific definition of DMO reported in the non-study eye in the MEAD clinical trials. Annual rate of [redacted] in Year 1 and Year 2	Use of escape therapy in the MEAD studies was recorded as treatment for either DMO or DMO-related diagnosis and this definition was used in the base case to define fellow eye incidence of DMO. However, this includes a range of diagnoses which are not specifically "DMO" so a scenario has been performed using the rate observed if a strict definition of incidence of DMO is applied.
27		No risk of FEI	To determine the impact of excluding FEI
28	Discontinuation from watch and wait only due to lack or loss of efficacy.	Discontinuation from watch and wait is due to either a lack or loss of efficacy, or due to adverse events and other non-efficacy related reasons.	In the base case it was assumed that patients who discontinued from sham arm of the MEAD studies would be likely to have same efficacy as those who remained in the study in the absence of a sham procedure in clinical practice. However the true BCVA evolution of these patients is unknown and therefore a scenario analysis including discontinuation from watch and wait due to adverse events and other non-efficacy related reasons whereby BCVA is assumed to follow natural history for these patients is felt appropriate to consider.

Abbreviations used in the table: BEV, bevacizumab; BSE, best-seeing eye; DEX 700, dexamethasone 700µg; DM, diabetes mellitus; DMO, diabetic macular oedema; FA, fluocinolone acetonide; FEI fellow eye involvement; ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward; NEI-VFQ, National Eye Institute Visual Functioning Questionnaire-25; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; RAN, ranibizumab; RVO, retinal vein occlusion; VFQ-UI, Visual Function Questionnaire Utility Index; WSE, worst-seeing eye

*Not applicable to the population of DMO patients who were considered unsuitable for non-corticosteroid therapy

**Not applicable to the population of DMO patients who are considered insufficiently responsive to non-corticosteroid therapy

Due to the high number of scenario analyses, which were conducted separately in each patient population, the ERG presents here only scenarios which had had a significant impact on the ICER to avoid repetition with the submission. Results for each individual scenario analysis are presented in the submission separately for each population (CS; pgs 459-489).

Scenario analyses - DMO patients who are considered unsuitable or insufficiently responsive for non-corticosteroid therapy

There were four scenarios in which dexamethasone no longer dominated watch and wait in the population of DMO patients who were considered unsuitable for or insufficiently responsive to non-corticosteroid therapy; these included:

- shorter time horizons of 1, 5 and 10 years (scenarios 9, 10 and 11);
- 100% unilateral treatment in the WSE (scenario 14).

The results of these four analyses are presented in Table 107 and

Table 108. Note that in

Table 108 the results are different from the respective tables in the company submission (Table 148, pg 463 and Table 180, pg 473), because the ERG has identified a discrepancy between the figures reported in the submission and the electronic copy of the economic model. The figures reported in

Table 108 are consistent with those included in the electronic copy of the model.

Table 107. Results of scenario analyses varying the time horizon (adapted from CS; Tables 143-145, pgs 461-462 and Tables 175-177, pg 472)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Time horizon = 1 year (scenario 9)					
Watch and wait	£711	0.6012	-	-	-
DEX	£3,435	0.6027	£2,724	0.0015	£1,822,946
Time horizon = 5 years (scenario 10)					
Watch and wait	£7,214	2.6290	-	-	-
DEX	£10,785	2.6571	£3,571	0.0281	£127,034
Time horizon = 10 years (scenario 11)					
Watch and wait	£15,649	4.4869	-	-	-
DEX	£15,985	4.5398	£337	0.0529	£6,365
Abbreviations used in the table: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Table 108. Results of Scenario 14 – 100% unilateral treatment in WSE (based on the results reported in the electronic copy of the model)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Watch and wait	£11,630	5.7491	-	-	-
DEX	£14,042	5.7947	£2,411	0.0456	£52,858
Abbreviations used in the table: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; WSE, worst seeing eye.					

Out of those four scenarios, there were three in which dexamethasone was no longer considered cost-effective compared with watch and wait at a willingness-to-pay (WTP) threshold of £20,000 per QALY gained. These included shorter time horizons of 1 and 5 years, and the scenario in which treatment was assumed to be administered only to patients affected in their WSE.

In the scenario where the time horizon was reduced to 10 years dexamethasone no longer dominated watch and wait, however it remained cost-effective at a WTP threshold of £20,000 per QALY with an ICER of £6,365 per QALY gained.

All remaining scenario analyses conducted by the company in the population of DMO patients who are considered unsuitable for non-corticosteroid therapy had minimal impact on the results. However for the population of DMO patients who are considered insufficiently responsive to non-corticosteroid therapy, scenario 1 considered flucinolone acetonide as a comparator. In addition, the price of fluocinolone acetonide was varied using a 10%, 20%, 30%, 40% and 50% discount to reflect the potential PAS discount available to the NHS.

Regarding scenario 1, dexamethasone was cost-effective if no discount was applied to fluocinolone acetonide i.e. using its list price. When a 10% discount price was applied to fluocinolone acetonide, dexamethasone became less costly and less effective than fluocinolone acetonide. For all higher discounted assessed, fluocinolone acetonide dominated dexamethasone i.e. it was less costly and more effective. The results of scenario analysis 1 for each discount are presented in Table 109.

Table 109**.** Results of Scenario 1 - Inclusion of fluocinolone acetonide; variation of price of fluocinolone acetonide (adapted from CS; Tables 163-168, pgs 468-70)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER	ICER vs Baseline
List price for fluocinolone acetonide						
Dexamethasone	£20,413	5.7420	-	-	-	-
Watch and wait	£21,877	5.6765	£1,464	-0.0655	Dexamethasone dominates	Dexamethasone dominates
Fluocinolone	£22,365	5.8214	£1,953	0.0794	£24,591*	£24,591*
10% discount to price for fluocinolone acetonide						
Dexamethasone	£20,413	5.7420	-	-	-	-

Fluocinolone	£21,226	5.8214	£813	0.0794	£10,241*	£10,241*
Watch and wait	£21,877	5.6765	£651	-0.1449	Fluocinolone dominates	Dexamethasone dominates
20% discount to price for fluocinolone acetonide						
Fluocinolone	£20,086	5.8214	-	-	-	-
Dexamethasone	£20,413	5.7420	£326	-0.0794	Fluocinolone dominates	Fluocinolone dominates
Watch and wait	£21,877	5.6765	£1,790	-0.1449	Fluocinolone dominates	Fluocinolone dominates
30% discount to price for fluocinolone acetonide						
Fluocinolone	£18,947	5.8214	-	-	-	-
Dexamethasone	£20,413	5.7420	£1,466	-0.0794	Fluocinolone dominates	Fluocinolone dominates
Watch and wait	£21,877	5.6765	£2,930	-0.1449	Fluocinolone dominates	Fluocinolone dominates
40% discount to price for fluocinolone acetonide						
Fluocinolone	£17,808	5.8214	-	-	-	-
Dexamethasone	£20,413	5.7420	£2,605	-0.0794	Fluocinolone dominates	Fluocinolone dominates
Watch and wait	£21,877	5.6765	£4,069	-0.1449	Fluocinolone dominates	Fluocinolone dominates
50% discount to price for fluocinolone acetonide						
Fluocinolone	£16,668	5.8214	-	-	-	-
Dexamethasone	£20,413	5.7420	£3,745	-0.0794	Fluocinolone dominates	Fluocinolone dominates
Watch and wait	£21,877	5.6765	£5,209	-0.1449	Fluocinolone dominates	Fluocinolone dominates
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years *Fluocinolone acetonide vs dexamethasone						

Scenario analyses - DMO patients who are pseudophakic

In the population of DMO patients who are pseudophakic, the company considered ranibizumab as the most appropriate comparator in the base case analysis. Scenario analysis 1 applied discounts to the price of ranibizumab to reflect the PAS discount that is available to the NHS (which was unknown to the company); these included discounts of 0% (list price), 10%, 20%, 30%, 40% and 50%. For all remaining scenario analyses performed by the company in the pseudophakic population, the incremental analysis was presented at a 50% discount for ranibizumab which was intended to provide the most pessimistic view of cost-effectiveness for dexamethasone.

In scenario 1 dexamethasone was less costly and less effective (i.e. in the south-west quadrant) than ranibizumab for all discounts except 50%. When a 50% discount price was applied to ranibizumab, ranibizumab dominated dexmaethasone (i.e. it was less costly and more effective than dexamethasone). The results of scenario 1 for each discount are presented in .Table 110.

Table 110. Results of Scenario 1 – changes in price of ranibizumab (adapted from CS; Tables 195-200, pgs 478-479)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
List price for ranibizumab					
DEX	£15,720	5.0886	-	-	-
Ranibizumab	£21,724	5.2066	£6,004	0.1179	£50,905*
10% discount to price for ranibizumab					
DEX	£15,720	5.0886	-	-	-
Ranibizumab	£20,380	5.2066	£4,660	0.1179	£39,510*
20% discount to price for ranibizumab					
DEX	£15,720	5.0886	-	-	-
Ranibizumab	£19,036	5.2066	£3,316	0.1179	£28,116*
30% discount to price for ranibizumab					
DEX	£15,720	5.0886	-	-	-
Ranibizumab	£17,692	5.2066	£1,972	0.1179	£16,721*
40% discount to price for ranibizumab					
DEX	£15,720	5.0886	-	-	-
Ranibizumab	£16,348	5.2066	£628	0.1179	£5,327*
50% discount to price for ranibizumab					
Ranibizumab	£15,004	5.2066	-	-	-
DEX	£15,720	5.0886	£716	-0.1179	Ranibizumab dominates

Abbreviations used in the table: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

*Ranibizumab vs dexamethasone; dexamethasone is less costly and less effective than ranibizumab

In scenario 2, laser, bevacizumab and watch and wait were included in the analysis of DMO patients who are pseudophakic. Both dexamethasone and ranibizumab were shown to be dominated by bevacizumab. Dexamethasone was also dominated by laser. Results are presented in Table 111.

Table 111. Results of Scenario 2: Inclusion of laser, bevacizumab and watch and wait in incremental; 50% PAS discount assumed for ranibizumab (taken from CS; Table 201, pg 479)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER	ICER vs baseline (laser)
Laser	£8,361	5.1368	-	-	-	-
Bevacizumab	£9,402	5.2377	£1,041	0.1010	£10,310*	£10,310
Ranibizumab	£15,004	5.2066	£5,602	-0.0312	Bevacizumab dominates	£95,180
DEX	£15,720	5.0886	£6,318	-0.1419	Bevacizumab dominates	-£152,857
Watch and wait	£21,823	4.9824	£12,421	-0.2553	Bevacizumab dominates	-£87,199

Abbreviations used in the table: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

*Bevacizumab vs laser

There were only seven scenarios in which ranibizumab (at 50% list price discount) no longer dominated dexamethasone in the population of DMO patients who are pseudophakic; these included:

- stable vision following treatment cessation (scenario 8);
- shorter time horizons of 1, 5 and 10 years (scenarios 9, 10 and 11);
- 100% unilateral treatment in the WSE (scenario 14);
- all intravitreal injection procedures administered as a day case procedure 100% of the time (scenario 20);
- all intravitreal injection procedures administered as a day case procedure 50% of the time (scenario 21).

The results of these analyses are presented in Table 112 to Table 115. All remaining scenario analyses in the population of DMO patients who are pseudophakic had little impact on the results, with ranibizumab remaining the dominant option (at 50% discount) (CS; pgs478-489). In all these remaining scenarios, dexamethasone became cost-effective compared with ranibizumab at a WTP threshold of £20,000 per QALY if the discount to ranibizumab was reduced by at least a range of 14%-36%, depending on the scenario.

Table 112. Results of Scenario 8 – Stable vision following treatment cessation; 50% PAS discount assumed for ranibizumab (taken from CS; Table 207, pg 481)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
DEX	£14,498	5.0981	-	-	-
Ranibizumab	£14,718	5.2393	£219	0.1412	£1,554*
Abbreviations used in the table: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years. *Ranibizumab vs dexamethasone; dexamethasone is less costly and less effective than ranibizumab					

In this scenario the company reported that dexamethasone was cost-effective at a WTP threshold of £20,000 per QALY if the discount for ranibizumab was 30% or less.

Table 113. Results of Scenarios 9, 10 and 11, which varied the time horizon of the analysis; 50% PAS discount assumed for ranibizumab (adapted from CS; Tables 208-210, pg 482)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Time horizon = 1 year (scenario 9)					
DEX	£3,555	0.5986	-	-	-
Ranibizumab	£5,966	0.6020	£2,412	0.0035	£697,936*
Time horizon = 5 years (scenario 10)					

DEX	£9,456	2.5789	-	-	-
Ranibizumab	£12,327	2.6390	£2,871	0.0601	£47,729*
Time horizon = 10 years (scenario 11)					
DEX	£13,132	4.2223	-	-	-
Ranibizumab	£13,896	4.3233	£764	0.1010	£7,564*
Abbreviations used in the table: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years. *Ranibizumab vs dexamethasone; dexamethasone is less costly and less effective than ranibizumab					

At a time horizon of 10 years (Scenario 11), the company reported that dexamethasone was cost-effective at a WTP threshold of £20,000 per QALY if the discount for ranibizumab was 40% or less.

Table 114. Results of Scenario 14 – 100% unilateral treatment in WSE; 50% PAS discount assumed for ranibizumab (taken from CS; Table 213, pg 483)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
DEX	£8,134	5.1530	-	-	-
Ranibizumab	£11,403	5.2099	£3,269	0.0570	£57,384*
Abbreviations used in the table: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years. *Ranibizumab vs dexamethasone; dexamethasone is less costly and less effective than ranibizumab					

Table 115. Results of Scenarios 20 and 21, which varied the setting and percentage of intravitreal injection administrations; 50% PAS discount assumed for ranibizumab (adapted from CS; Tables 219 and 220, pg 486)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Scenario 20: All intravitreal injection procedures administered as a day case procedure 100% of the time					
DEX	£16,847	5.0886	-	-	-
Ranibizumab	£18,773	5.2066	£1,925	0.1179	£16,323*
Scenario 21: All intravitreal injection procedures administered as a day case procedure 50% of the time					
DEX	£16,284	5.0886	-	-	-
Ranibizumab	£16,889	5.2066	£605	0.1179	£5,128*
Abbreviations used in the table: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years. *Ranibizumab vs dexamethasone; dexamethasone is less costly and less effective than ranibizumab					

The company reported that, under Scenario 20, dexamethasone became cost-effective at a WTP threshold of £20,000 per QALY if the discount for ranibizumab was 46% or less; under Scenario 21, dexamethasone became cost-effective if the discount for ranibizumab was 36% or less.

ERG comment

In all populations shortening the time horizon of the analysis had a large influence on the results. The company stated that "this is because treatment costs are incurred upfront, whereas the costs of blindness are either incurred or avoided over the longer term" (CS; pg490). The ERG agrees with the company but does not consider shortening the time horizon to less than 10-15 years to be appropriate, as a short time horizon would not allow the long-term impact of treatment on outcomes to be taken into account. On the other hand, in order to consider a time horizon of 15 years, the company had to make a number of assumptions on the natural progression of DMO and on the visual functioning in non-DMO affected eyes, due to lack of relevant data and the complexity of the model that would be otherwise required. It is noted that, although the base case analysis assumed 3 years of treatment according to the duration of key trials that informed the model, the duration of treatment is likely to extend beyond 3 years in UK clinical practice as discussed previously in Section 0. The ERG also notes that increasing the time horizon to 20 years did not have any impact on the results.

Treatment according to DMO status (i.e. unilateral treatment of the BSE or WSE or bilateral treatment) appeared to be an important driver of cost-effectiveness in all populations. The company stated that "this is because patients who are treated in their BSE only and patients who are treated bilaterally have a greater capacity for improvements in utility than patients treated in their WSE" (CS; pg 490). However the ERG notes that when 100% unilateral treatment in the WSE was assumed in DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy, dexamethasone demonstrated lower QALY gains compared with base case analysis, but also was no longer less costly than watch and wait. The ERG checked the detailed cost components associated with each intervention in the electronic copy of the model, and found that this result was due to a smaller difference in costs associated with severe vision loss between dexamethasone and watch and wait (i.e. a smaller difference in patients residing in the lowest health state 1 over the model duration) compared with the base case analysis, which was not adequate to fully offset the dexamethasone acquisition cost (in the base case analysis the cost-savings from prevention of severe vision loss associated with dexamethasone relative to watch and wait offset dexamethasone the acquisition cost, leading to dexamethasone being overall less costly than watch and wait).

For the population of DMO patients who are insufficiently responsive to non-corticosteroid therapy, the results were sensitive to the inclusion of fluocinolone acetonide within the analysis, particularly when a discount was applied to its list price. Results of this analysis indicate that dexamethasone is not cost-effective in DMO patients who are insufficiently responsive to non-corticosteroid therapy, if flucinolone acetonide is available at a discounted price to the NHS (even at 10%). However, as discussed previously in Section 5.4.6.2, the analysis including fluocinolone acetonide is characterised by important limitations, so the respective results should be interpreted with caution.

Results on the pseudophakic population were sensitive to changes in the price of ranibizumab. Dexamethasone was found to be less effective than ranibizumab, but also overall less costly until a 50% discount in the price of ranibizumab was assumed. At the list price for ranibizumab, dexamethasone was more cost-effective. When the discount to the price for ranibizumab fell between 20-30%, ranibizumab became the cost-effective option. It needs to be noted that the exact PAS discount is not known either to the company, or to the ERG, and therefore no safe conclusions on the cost effectiveness of dexamethasone relative to ranibizumab can be made, especially considering the flaws relating to the application of the NMA results into the economic model.

In the scenario including bevacizumab, laser and watch and wait as treatment options for DMO patients who are pseudophakic, dexamethasone was dominated by both bevacizumab and laser; ranibizumab was also dominated by bevacizumab. Both treatments were included in the NICE scope as relevant comparators. Nevertheless, clinical experts consulting the ERG agreed with the company that "neither treatment is routinely used as first line therapy in current clinical practice but may be used to treat patients who do not meet NICE restrictions for use of ranibizumab (CRT ≥400 μm) in England and Wales or are considered unsuitable for ranibizumab therapy" (CS, pg 22).

In the pseudophakic population the results were sensitive to the proportion of intravitreal injection procedures being performed in the outpatient versus the day case setting. The company stated this was because "an increasing proportion of day case procedures lead to increased costs, disadvantaging ranibizumab which is associated with higher numbers of injections" (CS, pg490). The ERG agrees with the company that since ranibizumab requires more frequent treatment visits compared with dexamethasone, increasing the proportion of day case procedures disadvantages ranibizumab more than dexamethasone. However the ERG was informed by clinical experts that DMO treatment with corticosteroid or anti-VEGF injections would be administered in an outpatient setting in the vast majority of patients; therefore Scenarios 20 and 21 do not appear to be relevant to the UK clinical practice.

The ERG was surprised that increasing the duration of treatment from 3 to 5 years had no impact on the results in any population. However, there were restrictions applied to each of these scenarios which limited the impact of extra treatment for 2 more years on costs and outcomes. Firstly, only one maintenance treatment per year (or a maximum of 1 additional fluocinolone acetonide treatment) was allowed. Secondly, extrapolation beyond 3 years was based on the LOCF and stable vision in scenarios 5 and 6, respectively, which is unlikely to reflect outcomes in DMO patients observed in the UK clinical practice. However, the ERG is aware that this is a limitation of the data available that is outside the company's control.

5.4.13.2 One way sensitivity analysis (OWSA)

The company carried out OWSA on all model parameters considered to be associated with uncertainty. A full list of parameters used to inform the company's analysis is presented in Appendix 9.11. In order to determine the lower and upper bounds for each parameter, the company either utilitised the 95% confidence intervals from the distributions fitted for the probabilistic analyses, or used high and low values reported in the sources from which the parameter was obtained. On various occasions, when no other data were available to determine 95% confidence intervals, these were estimated by assuming a standard error as a proportion of the mean value used in the distribution. In the case of NHS Reference Costs, upper and lower quartiles were extracted to inform the upper and lower bounds. Where clinician opinion was used to inform the number of outpatient procedures, extremes of 0% and 100% were used.

In the submission, the company presented tornado diagrams illustrating the impact on the Net Monetary Benefit (NMB) for the 10 most influential parameters. This was provided for pair-wise comparisons of dexamethasone with watch and wait in the populations of DMO patients who are considered unsuitable for or insufficiently responsive non-corticosteroid therapy and with ranibizumab in the population of DMO patients who are pseudophakic (CS, pgs 443-448). A summary of the results is presented in the sections that follow.

OWSA - DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy

Under extreme values of all parameters dexamethasone remained cost-effective compared with watch and wait as the NMB remained positive under all extreme values. The parameters with the largest influence on the results were the unit cost of, and proportion of patients requiring residential care to be funded by the NHS (but their influence was not adequate to reverse conclusions).

OWSA - DMO patients who are pseudophakic

Dexamethasone remained cost-effective compared with ranibizumab under extreme values of all parameters when ranibizumab was at list price. When a 50% discount was applied to the price of ranibizumab, ranibizumab remained cost-effective compared with dexamethasone under most extreme values applied, with two exceptions: when the upper bound of the relative risk of worsening vision of ranibizumab versus dexamethasone was applied, or when the lower bound for the proportion of ranibizumab procedures that were undertaken in an outpatient setting was applied, dexamethasone became more cost-effective than ranibizumab. Apart from those two parameters, other parameters with influence on the results (which was inadequate to reverse conclusions) were the relative risk of improving vision for ranibizumab versus dexamethasone, and the cost of residential care.

ERG comment

The ERG regards the sensitivity analysis conducted by the company to be comprehensive, but believes that important causes of uncertainty in the analysis lie in the structural assumptions of the economic model, described in Section 5.4.2.

OWSA suggested that the results of the base case analyses were robust to parameter variation, with conclusions remaining unchanged under the vast majority of parameters being varied.

Results in pseudophakic patients, when a 50% discount in the price of ranibizumab was applied, were sensitive to the efficacy data derived from the NMA. This is not surprising, as NMA outputs were characterised by wide credible intervals (in particular the comparison between dexamethasone and ranibizumab), and treatment efficacy is the main QALY driver; in addition, treatment efficacy in this model influenced the number of people moving to the most severe health state 1, affecting the magnitude of costs associated with severe vision loss. Nevertheless, as stated in Section 5.4.6.2, there are various limitations in the way NMA outputs were applied into the model, which make the validity of the model questionable.

Ranibizumab is associated with a higher treatment burden than dexamethasone, hence it was not unexpected that increasing the proportion of procedures that are treated as day cases, which are more expensive, improved the cost-effectiveness of dexamethasone as additional costs were incurred for ranibizumab. However, clinical experts advising the ERG expressed the view that the majority of anti-VEGF as well as corticosteroid administrations will be performed in an outpatient setting, therefore an increased proportion of day cases is unlikely to reflect UK routine clinical practice.

The ERG was not surprised to see that the cost of residential care was among the parameters that were most influential on the results, as this was by far the largest component of the cost of severe vision loss. The ERG notes that there is a discrepancy between the cost of residential care applied in previous TAs with that applied by the company; hence the ERG undertook an additional analysis (**analysis C8**), described in Section 5.5.2.2, using alternative residential care costs; results of these analysis are provided in Section 6.1.2.2.

5.4.13.3 Probabilistic sensitivity analysis (PSA)

Parameter uncertainty was explored using PSA. Individual parameters within the model were assigned a probability distribution from which estimates were simultaneously sampled for 5,000 simulations. This was deemed to produce stable results based on five runs of 10,000 simulations obtained from the total costs and QALYs for each intervention.

The probabilistic analysis varied costs using a gamma distribution, probabilities using a beta-distribution and continuous variables using a normal distribution. Transition probability matrices for the baseline treatment were also varied in probabilistic analysis using the Dirichlet probability

distribution. In addition, the relative risks of improving, worsening or maintaining stable vision were sampled at random from their posterior distribution of 10,000 samples obtained directly from the NMA output. This was achieved by sampling a random number at each PSA iteration, multiplying this by 10,000 and looking up the corresponding row of the posterior distribution output (CS; pg426).

Table 116 summarises the company estimates of probability of cost-effectiveness at a WTP threshold of £20,000 and £30,000. In addition, the results of the PSA as presented upon the cost-effectiveness plane are replicated in Figure 35 for DMO patients who are considered unsuitable or insufficiently responsive to non-corticosteroid therapy and Figure 36, Figure 37 for DMO patients who are pseudophakic with ranibizumab at list price and at a 50% discounted price, respectively. Cost-effectiveness acceptability curves and 95% confidence ellipses of costs and QALYs are also presented in the submission for each population under consideration.

Table 116. Probability of cost-effectiveness of dexamethasone in base case analyses

Dexamethasone versus:	**Probability of dexamethasone being considered cost-effective at a WTP threshold of:**	
	£20,000 per additional QALY	**£30,000 per additional QALY***
DMO patients who are considered unsuitable or insufficiently responsive to non-corticosteroid therapy		
Watch and wait	60.8%	61.1%
DMO patients who are pseudophakic		
Ranibizumab (list price)	75.6%	65.6%
Ranibizumab (50% discount)	40.9%	41.2%
Abbreviations used in table: DMO, diabetic macular oedema; QALY, quality-adjusted life year; WTP, willingness-to-pay. *Taken from the company's model		

Figure 35. Cost-effectiveness plane for dexamethasone versus watch and wait (reproduced from CS; Figure 78, pg 450, and Figure 82, pg 453)

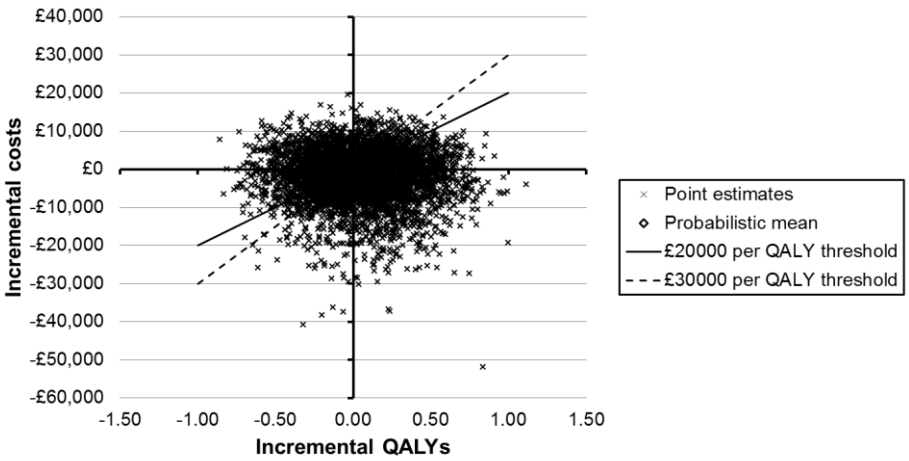


Figure 36. Cost-effectiveness plane for dexamethasone versus ranibizumab (list price) (reproduced from CS; Figure 86, pg 455)

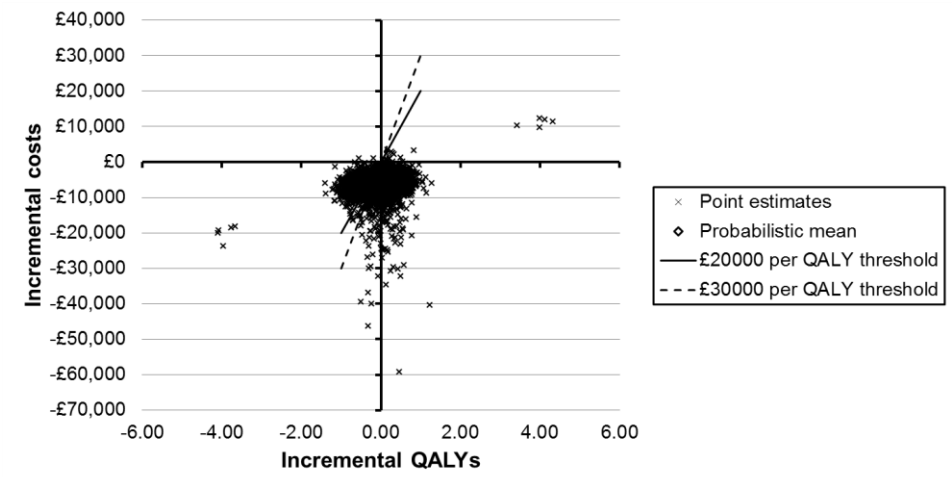
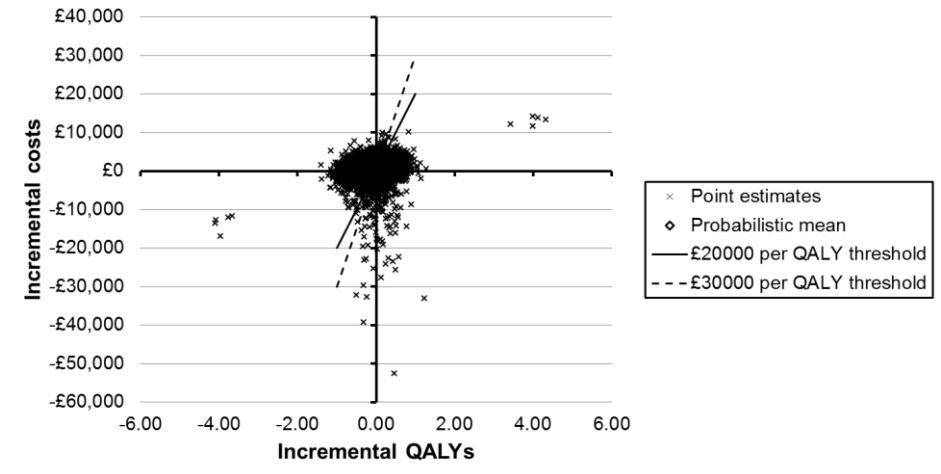


Figure 37. Cost-effectiveness plane for dexamethasone versus ranibizumab (50% discount) (reproduced from CS; Figure 90, pg 458)



The incremental costs and QALYs fell into all four quadrants of the cost-effectiveness plane in Figure 35 for the population of DMO patients who are considered unsuitable or insufficiently responsive to non-corticosteroid therapy. For DMO patients who are pseudophakic almost all probabilistic simulations indicated that dexamethasone was cheaper than ranibizumab when the cost of ranibizumab was based on the list price, with the majority of simulations spanning the south-east and south-west quadrants (Figure 36). However, when a 50% discount was applied to the cost of ranibizumab the incremental costs decreased, as expected. This is illustrated in an upward shift of the incremental costs and QALYs which spanned all four quadrants of the cost-effectiveness plane in Figure 37.

ERG comment

The ERG considers the method used to determine the stability of 5,000 simulations to be sufficient, especially when taking into account the complexities of the model and the resulting time to run the PSA. The probability distributions which were used to sample model parameters were overall

appropriate. The ERG agrees with the company that the correlation present in parameters estimated through NMA was potentially maintained, since parameters were sampled from the same NMA iteration. However, as discussed in Section 5.4.6.2,

a. the correlations in each NMA iteration characterised mutually exclusive outcomes (absolute effects) of every treatment (i.e. probability of improving vision, probability of deteriorating, probability of retaining stable vision), and not multiple relative outcomes between treatments. Sampling of relative risks for all treatments from the same NMA iteration by the company did not maintain the correlation across absolute outcomes; on the other hand, the correlation across relative effects, which is claimed to have been retained by the company, is probably meaningless.
b. 'Normalisation' of absolute (mutually exclusive) outcomes so that their summed probabilities equal 1, implicitly 'broke' any underlying correlation between the relative risks obtained from each NMA iteration.

One point to note is that incremental costs and QALYs in all cost effectiveness planes lay across all 4 quadrants, indicating high uncertainty and making results difficult to interpret. For example, whilst dexamethasone dominated watch and wait in the base case for DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy, the incremental costs and QALYs of dexamethasone versus watch and wait lay across all quadrants of the cost effectiveness plane close to the origin (Figure 35), implying that treatments were similar in terms of costs and effectiveness.

5.4.14 Model validation and face validity check

The company took a number of measures for model quality assurance and validation, which are summarised in Box 28.

Box 28. Company's economic model validation and face validity assessments (CS; pg492)

The *de novo* economic model was quality assured by a health economist with experience in model validation. The following areas of the model were checked:

- Plausibility and accuracy of inputs and assumptions
- Programming of formulae and macros
- Logic of model inputs vs model outputs

Additionally, the model structure and assumptions were validated with key opinion leaders, and the suitability of inputs was reviewed by clinical experts at advisory boards.

The ERG considers that the company's validation process was reasonable.

The ERG regards the discussions held at the advisory board meetings and interviews to be described in detail within the submission and does not consider the questions asked to be open ended or misleading. The inputs of the economic model were compared against previous NICE TAs for the

treatment of DMO in order to ensure consistency. Furthermore, the company undertook a wide range of structural and parameter sensitivity analyses to test the robustness of the model results.

The ERG checked all model input parameters in the electronic copy of the model against data sources to identify potential errors in the data utilised. A number of errors were identified and corrected without considerably changing the results of the analysis. All model assumptions were discussed with clinical experts to confirm they were plausible and reflective of the disease natural history and of UK clinical practice. In addition, the ERG performed a number of checks in the model:

- costs and QALYs, both aggregated and disaggregated, were checked for their plausibility; differences in clinical and cost inputs between treatments were checked to identify potential drivers of the results;
- efficacy and cost parameters were altered to check whether results changed in the expected direction; sensitivity analyses using zero and extreme values wereundertaken to check whether results changed as expected;
- input parameters in all arms of the model were set at the same value to check whether ouputs (costs and QALYs) in all arms became equal;
- model formulae were not checked systematically, due to the number of submitted models, their size and complexity. However, important input parameters were tracked to check whether they were correctly applied within formulae.

The ERG considers the submitted model overall well constructed; the description of the model structure and assumptions was transparent. However, the ERG identified a number of flaws in the model structure and assumptions, described in respective sections of this report, which may have introduced bias in the analysis. In particular, the ERG considers the methodology and the assumptions underpinning the application of the NMA efficacy data into the model as an important limitation of the model, which limits the validity of the results.

5.5 Exploratory and sensitivity analyses requested by the ERG and undertaken by the company or undertaken by the ERG

Following review of the CS and the submitted economic model, the ERG requested a number of additional analyses to be carried out by the company during the clarification process; moreover, the ERG undertook a number of additional analyses. The purpose of the analyses requested from the company was to explore the cost effectiveness of dexamethasone after removing a number of assumptions underlying the base case analysis, some of which were inherent in the methodology applied to the NMA and the application of the NMA outputs onto the economic model. These analyses requested patient-level data from the MEAD trials, therefore it was not possible for the ERG to undertake them without access to these data. The purpose of the analyses undertaken by the ERG

was to both correct a number of potential model errors, and to test the robustness of model results to changes in parameters. An outline of the additional analyses carried out by the company following ERG request is provided in Section **Error! Reference source not found.**; an outline of the additional analyses carried out by ERG is presented in Section 5.5.2**Error! Reference source not found.**. Section 6 presents the results of each of these analyses.

5.5.1 Additional analyses carried out by the company, following ERG requests at clarification

The company carried out the following analyses in response to ERG requests at clarification:

- **Analysis A1:** This analysis was not requested directly by the ERG. During clarification, the ERG asked the company to clarify why the baseline BCVA distribution of BSE and WSE in bilateral DMO appeared to be taken from respective DMO eyes in unilateral DMO and was not determined directly from data on the sub-group of patients with bilateral DMO (ERG clarification question B5b). The company's response was that 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). However, at clarification the company provided the baseline BCVA distributions observed in dexamethasone patients with unilateral as well as bilateral DMO (shown in Table 53 and Table 54 of this report, respectively); based on these distributions, the company reported alternative results (company's response to clarification, pgs 35-41).
- **Analysis A2:** this analysis used the outputs of the updated NMA, as requested by the ERG at clarification (Priority question B4, pg 31).
- **Analysis A3**: at clarification, the ERG requested an analysis that would utilise 3-month transition probabilities for watch and wait (as well as for dexamethasone) directly from the pooled MEAD trials (i.e. without utilising the NMA outputs), using the assumption that improvement or deterioration of vision by at least 10-letters is restricted to moving up or down by one health state, respectively (which was the assumption used in the original model submitted) (Priority question B1a, pg 11). The rationale for this analysis was the ERG's concern about the validity of the company's assumption, which was central to the model design, that the 12-month relative risks derived form the network meta-analyses remained constant from baseline to year 3; using this assumption, the company applied the 12-month relative risks derived from the NMA onto 3-month baseline transition probabilities over the whole 3-year duration of the model. The ERG believes that this assumption is incorrect, because clinical data demonstrate that the relative effect of dexamethasone versus sham is not stable over 3 years in the MEAD trials, at least not for the whole DMO population. Moreover, normalisation of resulting transition probabilities introduced bias in the submitted analyses, although the direction and magnitude of bias is not known and cannot be predicted. The ERG felt that this method of analysis (use of efficacy data directly from the MEAD trials) was more appropriate and reflective of the relative effects of dexamethasone versus sham (which was used as a proxy for watch and wait).

- **Analysis A4**: at clarification, the ERG requested an analysis that would utilise 3-month transition probabilities for watch and wait (as well as for dexamethasone) directly from the pooled MEAD trials (i.e. without utilising the NMA outputs), but without transitions being restricted by maximum one health state (Priority question B1b, pg 12). This analysis utilised the actual transitions of patients as observed in the MEAD trials, so, like Analysis A3 it removed the assumptions and flaws associated with the use of 12-month NMA data and with normalisation, and, in addition, removed the assumption of restriction in transitions. Therefore this analysis was regarded by the ERG as the one that best reflected the relative effects of dexamethasone and watch and wait, after removing bias and assumptions associated with the application of the NMA outputs into the model, as well as the assumption of restricted transitions.
- **Analysis A5:** the ERG requested an analysis where mean utilities for each health state were estimated directly from patients' responses on VFQ-UI in the MEAD trials, rather than from the regression model reported in the company submission (Priority question B1c, pg 13). The rationale for this request was to explore the impact on the results of using the VFQ-UI regression model versus the actual utility values obtained from the patients, as the regression model appeared to produce a narrow range of values. In response, the company undertook an analysis that used transition probabilities based on actual patient-level data for both dexamethasone and watch and wait/sham, without imposing restrictions on transitions, and mean utility data as shown in Table 76 of this report.
- **Analysis A6:** in response to ERG's request for mean utilities being estimated directly from patients' responses on VFQ-UI in the MEAD trials, this analysis used the outputs of the updated NMA and mean utility data for each health state as shown in Table 76.

5.5.2 Additional analyses carried out by the ERG

5.5.2.1 ERG model corrections

The ERG identified the following potential errors in the company's model:

- **Analysis B1:** for FEI, the model utilised a rate of [redacted], estimated from the 2-year probability of [redacted]; this is an instantaneous rate and should be converted to an annual probability of [redacted] before it is applied into the model.
- **Analysis B2:** the mean number of re-treatments for fluocinolone acetonide in Year 3 was estimated to be 0.26 in the economic model, based on LOCF. However, cumulative data for Years 2 and 3 were available and allowed estimation of the mean number of re-treatments for Year 3 for fluocinolone acetonide, which was amended to 0.036.
- **Analysis B3**: the probability of cataract for dexamethasone in Years 1, 2 and 3 has been amended from 8.40%, 19.17% and 2.94%, respectively, to 11.83%, 37.66%, and 26.39%, respectively, based on ERG calculations. The annual probability of cataract for patients with DMO receiving no treatment or watch and wait has also been slightly amended from 2.34% to 2.32%.
- **Analysis B4**: the cost of £117 for a fluorescein angiography, based on NHS reference costs 2012/13, HRG code BZ23Z, service code 130 Ophthalmology, minor vitreous retinal procedures (outpatient procedure) was replaced by £144, based on NHS reference costs

2012/13, HRG code RA17Z, Diagnostic Imaging, Service code 130 Ophthalmology, Contrast Fluoroscopy Procedures, 20 to 40 minutes, Outpatient.

- **Analysis B5**: the unit cost of intermediate vitreous procedures applied to the management of vitreous haemorrhage and retinal detachment was amended from £1,685 to £989; the management of retinal detachment was estimated to be achieved by intermediate vitreous procedure (day case) in 80% of cases, and by major vitreous procedure (day case) in 20% of cases. The total cost of management of retinal detachment became £1,080 under these assumptions.

5.5.2.2 ERG additional scenario analyses

In addition to the model corrections detailed in Section 5.5.2.1, the ERG carried out the following scenario analyses:

- **Analysis C1:** a higher annual probability of FEI of 55.28% was used in Years 1 and 2; this gives an estimated probability of FEI over 2 years of 80.00%, which was used to account for an assumed increased risk for FEI over the 15-year time horizon of the model. This analysis has overestimated any impact of FEI on the results, as it brings forward, i.e. earlier in time, the additional costs and outcomes associated with the risk of FEI over the 15 years of the model, but this was necessary due to the structural assumption of the company's model that FEI occurs only up to 2 years from treatment initiation
- **Analysis C2**: a higher 3-month probability of deterioration of vision by at least 10 letters for those ending or discontinuing treatment was assumed; a figure of 5.5% was used, with 3.5% of patients assumed to improve vision and 91% to remain in stable vision.
- **Analysis C3**: Discontinuation rates for all treatment options were set at zero.
- **Analysis C4**: an overall hazard ratio of mortality of 3.5 for DMO vs the general population was applied
- **Analysis C5**: Bilateral treatment with anti-VEGF was assumed to require one administration visit on 75% of the occasions and 2 administration visits on 25% of the occasions.
- **Analysis C6**: the numbers of total visits associated with treatment and monitoring each year were amended to take into account that some monitoring visits are incorporating into treatment visits and do not incur extra (separate) monitoring costs.
- **Analysis C7**: costs associated with IOP checks were removed from analysis, as IOP checks are normaly included in monitoring visits.
- **Analysis C8**: the unit cost of private residential care (£532 per week) was utilised instead of the cost of local authority residential care (£1002 per week) in order to estimate the annual cost associated with severe vision loss.
- **Analysis C9**: the cost of depression taken from McCrone *et al*.[167] after excluding the cost of residential care (£2,252) was utilised in the estimation of the annual cost of severe vision loss
- **Analysis C10:** the average cost of pharmacological treatment for raised IOP has been estimated using the unit cost of generic prostaglandins (taken from eMIT) and assuming that, of the patients with raised IOP that receive pharmacological treatment, 70% are treated with

generic prostaglandins; 10% with generic beta-blockers; and the remaining 20% by equal use of the remaining treatments listed by the company. The mean cost of medication for raised IOP using these assumptions is £88.77.

- **Analysis C11:** trabeculectomy was the only surgical procedure considered for the management of raised IOP; 50% of trabeculectomies were assumed to correspond to intermediate glaucoma day case procedures, and 50% to major glaucoma day case procedures. The mean cost of surgical intervention for raised IOP using these assumptions became £1273.
- **Analysis C12**: additional IOP checks were assumed for patients who experienced raised IOP. 2 extra IOP checks per year, over 3 years were assumed. For simplicitly purposes regarding model reprogramming, all 6 checks were assumed to be occuring within the same year; as a consequence, no discounting on the associated costs was applied, and the total cost of the 6 extra IOP checks was £480.
- **Analysis C13**: application of utility data from Czoski-Murray et al.[99] in the original analysis submitted by the company using the NMA outputs. This analysis assumed that the contribution of WSE and BSE to the overall utility was 3/13 and 10/13, respectively, based on the assumption that the impact of WSE on overall utility equalled 30% of the impact of the BSE. This assumption is broadly in line with the approach preferred by the committees for TA274 and TA301, according to which treating the WSE had 30% of the HRQL impact for the same change in vision from treating the BSE. The utility values used in this analysis, modified to correspond to the model's health states, are shown in Table 84.
- **Analysis C14:** application of utility data from Czoski-Murray et al.[99] in the analysis undertaken by the company during clarification, which utilised transition probabilities derived directly from the MEAD trials, assuming unrestricted transitions. This analysis assumed that the contribution of WSE and BSE to the overall utility was 3/13 and 10/13, respectively, based on the assumption that the impact of WSE on overall utility equalled 30% of the impact of the BSE. This assumption is broadly in line with the approach preferred by the committees for TA274 and TA301, according to which treating the WSE had 30% of the HRQL impact for the same change in vision from treating the BSE. The utility values used in this analysis, modified to correspond to the model's health states, are shown in Table 84. Application of the utility data from Czoski-Murray et al.[99] in the population of DMO patients who are pseudophakic was not attempted, due to the need for model re-programming and time constraints.

5.6 Conclusions of the cost effectiveness section

The company submitted an economic evaluation comparing dexamethasone versus watch and wait (and fluocinolone acetonide in a scenario analysis) for patients with DMO who are considered unsuitable for, or insufficiently responsive to, non-corticosteroid therapy; and an economic evaluation comparing dexamethasone versus ranibizumab (and laser, bevacizumab and watch and wait in a scenario analysis) for DMO patients who are pseudophakic. The ERG considers the comparison and populations submitted to be appropriate to inform the decision problem that is the focus of this STA.

The ERG notes that the study population in the MEAD trials (which were included in the NMA that informed the economic model) was not directly relevant to the study populations considered in the economic analuses. Moreover, clinical efficacy for watch and wait was based on data obtained from the pooled sham arms in the MEAD trials; this means that the relative effect of dexamethasone versus watch and wait is likely to have been underestimated, although the extent of underestimation is unclear.

The economic analysis adopted a number of assumptions and approaches to analyse the clinical data which are likely to have biased the results, including the assumption that the baseline distributions of BSE and WSE across BCVA states are independent from each other; the application of 12-month relative effects from initiation of treatment and up to 3 years of treatment duration (assuming that these are stable over time); the 'normalisation' of transition probabilities in order to ensure that these add up to 1, which resulted in the relative risks being effectively and consistently altered from their original values obtained from the NMA; the restriction of transitions by a maximum of one BCVA state per cycle, which, as further analyses showed, does not reflect trial evidence; and the naïve synthesis of discontinuation trial data. In addition, the ERG identified a few areas of inaccuracy or uncertainty in the base case model assumptions and parameters used.

Following ERG corrections and amendments in the model data, the deterministic ICER of dexamethasone versus watch and wait in patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, became £22,049/QALY when NMA outputs were utilised; and £1,166,271/QALY when data from the MEAD trials from both dexamethasone and watch and wait (sham) were utilised, without transitions being restricted by one health state up or down. These findings are very different from the company's base case analysis, and indicate the considerable impact of the company's assumptions on the results of the economic analysis.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1.1 Additional analyses carried out by the company, following ERG request at clarification

This section presents the results of all the analyses undertaken by the company at clarification, mostly in response to ERG requests.

Analysis A1.

Table 117. Results of Analysis A1, using baseline BCVA distributions as per Table 53; DMO patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy (Company's response to clarification, pg 38)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Watch and wait	£17,610	5.4357			
DEX	£17,627	5.4944	£17	0.0587	£287*
Abbreviations used in the table: BCVA, best corrected visual acuity; DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years *Dexamethasone versus watch and wait					

Table 118. Results of Analysis A1, using baseline BCVA distributions as per Table 53; DMO patients who are pseudophakic (Company's response to clarification, pg 39)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Ranibizumab at list price					
DEX	£13,370	4.9370			
Ranibizumab	£20,565	5.0440	£7,195	0.1070	£67,245*
Ranibizumab at 50% discount					
DEX	£13,370	4.9370			
Ranibizumab	£14,142	5.0440	£771	0.1070	£7,208*
Abbreviations used in the table: BCVA, best corrected visual acuity; DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. *Ranibizumab vs DEX					

After changing the baseline BCVA distribution, dexamethasone remained cost-effective compared with watch and wait in DMO patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, although in this analysis dexamethasone was associated with an additional cost of £287/QALY. In pseudophakic DMO patients, the cost effectiveness of dexamethasone was improved, as, according to the company, it remained cost-effective at higher discount to the price of ranibizumab (up to 39% of the list price). Ranibizumab at 50% discount price was not dominant anymore, although it was still cost-effective compared with dexamethasone at an ICER of £7,208/QALY.

Analysis A2.

Table 119. Results of Analysis A2, using efficacy data from the updated NMA; patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid treatment (company's response to clarification, pgs 31-34)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
DEX	£20,413	5.7420	-	-	-
Watch and wait	£21,571	5.6785	£1,158	-0.0635	DEX dominates
Abbreviations used in the table: DEX, dexamethasone DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALYs, quality-adjusted life years.					

Table 120: Results of Analysis A2, using efficacy data fmor the updated NMA; DMO patients who are pseudophakic (company's response to clarification, pgs 31-34)

Technologies	Total		Incremental		ICER
	Cost	QALY	Cost	QALY	
Ranibizumab at list price					
DEX	£15,720	5.0886	-	-	-
Ranibizumab	£21,639	5.2119	£5,919	0.1233	£48,026*
Ranibizumab at 50% discount					
Ranibizumab	£14,920	5.2119	-	-	-
DEX	£15,720	5.0886	£800	-0.1233	Ranibizumab dominates
Abbreviations used in the table: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALYs, quality-adjusted life years. *Ranibizumab vs dexamethasone					

Results based on the updated NMA outputs were very similar to the company's base case analysis.Scenario analyses including all relevant comparators were also presented by the company and are provided in Appendix 9.12. Total costs and QALYs were marginally different from the values presented in the submission using the original NMA; however the difference was very small and the conclusion of the analyses remained unchanged.

Analysis A3.

Table 121. Results of Analysis A3, using MEAD trial efficacy data for both dexamethasone and watch and wait, with movements between health states restricted to a maximum of one state; patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid treatment (Company's response to clarification, pg 11)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Watch and wait	£12,091	5.7528	-	-	-
DEX	£20,413	5.7420	£8,322	-0.0108	Watch and wait dominates
Abbreviations used in the table: DEX, dexamethasone DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

The company commented on the results of this analysis, as shown in Box 29.

Box 29. Company's comment regarding Analysis A3 that was requested by the ERG (Company's response to clatificaition, pgs 11-12)

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 [note: this refers to Analysis A4 and the company's response presented in Box 30.]
Abbreviations used in the box: DEX700, dexamethasone 700µg; ERG, evidence review group; MTC, mixed treatement comparison.

The ERG notes that results for watch and wait in this analysis are considerably better compared with the company's base case analysis: watch and wait results in a higher number of QALYs and is associated with lower total costs in this analysis, implying that a lower number of patients incurred costs associated with the severe vision loss state (which is the main cost component of watch and wait) compared with the company's base case analysis. The ERG's critique of the company's comment is provided after presentation of analysis A4 undertaken by the company and company's related statement.

Analysis A4.

Table 122. Results of Analysis A4, using MEAD trial efficacy data for both dexamethasone and watch and wait, with unrestricted movements between health states; patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid treatment (Company's response to clarification, pg 12)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Watch and wait	£13,607	5.7517	-	-	-
DEX	£21,241	5.7571	£7,635	0.0054	£1,411,676*

Abbreviations used in the table: DEX, dexamethasone DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
*DEX vs watch and wait

The company made a statement regarding this analysis, presented in Box 30.

Box 30. Company's comment regarding Analysis A4 that was requested by the ERG (Company's response to clarification, pgs 12-13)

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 [i.e. Analysis A3]. 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 [redacted] 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.[112] 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,[31] 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 ([redacted] 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[67,91] 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[67] allowed deferred laser treatment in the no treatment arm meaning that the study by Olk[91] 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.
Abbreviations used in the box: DEX700, dexamethasone 700µg; ERG, evidence review group; ETDRS, Early Treatment Diabetic Retinopathy Study; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

The ERG's comments on the points raised by the company are as follows:

The company claimed that this analysis demonstrated that the restriction of movements between health states to a maximum of one state up or down (which was necessary in order to use the NMA output) biases against dexamethasone, in favour of watch and wait. The ERG fully agrees with this statement.

The company argued that using data from the sham arm of the MEAD studies to represent watch and wait was not appropriate as the MEAD sham arm was likely to over-estimate the true efficacy of a watch and wait strategy. As discussed in Section 5.4.6.1, the ERG agrees that use of the MEAD pooled sham arms as a proxy for watch and wait is likely to have overestimated the true efficacy for watch and wait, and, consequently, to have underestimated the efficacy of dexamethasone. However, this underestimation of the true relative effect of dexamethasone versus watch and wait is a limitation inherent to the MEAD trial design, and is not possible to remove from any analysis incorporating the MEAD trial data, including the NMA.

As the sham arms of the MEAD studies were not representative of a true "watch and wait" treatment arm, the company argued that the originally submitted economic analysis that used the NMA to estimate the relative efficacy of watch and wait compared with dexamethasone was more appropriate than analysis A4, which used directly the outcomes of the MEAD sham treatment arms in order to estimate the watch and wait effect. To support this argument, the company highlighted the fact that

the base case NMA incorporated data from two additional studies that included a sham/no treatment arm and was 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, the ERG notes that this argument is not valid. The relative effect of dexamethasone versus sham in the NMA was exclusively informed by the relative effect in the MEAD trials (as these were the only trials connecting the two treatment options, and no indirect comparisons were made between these two treatments in the network). Therefore, the relative effect derived from the NMA should be identical to the treatment effect observed in their head-to-head comparison in the MEAD trials (and should be underestimated to exactly the same extent). The fact that more studies in the network included a sham/no treatment arm is not relevant, as these studies did not contribute to the estimation of the relative effect between dexamethasone and sham. Moreover, these studies did not even contribute to the absolute effect of sham used in the economic analysis; this is because the economic analysis used dexamethasone as baseline treatment and the absolute effect of sham was estimated by applying the relative effect of sham versus dexamethasone (derived from the NMA, but exclusively informed by the pooled MEAD trials) onto the dexamethasone baseline data. So, the effect of watch and wait estimated in the economic analysis that utilised the NMA outputs should be in theory identical to the sham effect as observed in the pooled MEAD trials.

Based on the above, the ERG argues that, in principle, the results of the economic analysis between dexamethasone and watch and wait should be effectively the same, whether the relative effect is taken directly from the MEAD trials (Analysis A4) or from the NMA (company's base case analysis). However this is not the case; possible factors contributing to the large discrepancies between the results of the two analyses are:

- The application of the relative risks derived from the NMA estimated using 12-month data, onto 3-month baseline transition probabilities in the economic model, from initiation of treatment and up to 3 years of treatment duration. This application was based on the assumption that relative effects of treatments were constant over the 3 years of treatment duration; however, as evidence from MEAD trials suggests (discussed in Section 5.4.6.2), this assumption may not hold. The relative effect between dexamethasone and watch and wait appears to be considerably reduced in the second year of treatment, and resumed towards the end of the third.
- The normalisation of transition probabilities, which was required so that the probabilities summed up to 1, is likely to have introduced bias in the company's analysis, as demonstrated in Section 5.4.6.2, although the direction and magnitude of bias is not known and cannot be predicted.

The ERG therefore, feels that the company's base case economic analysis that utilised NMA data suffers from severe limitations and therefore its results are unlikely to be robust. In contrast, the analysis A4, which uses data directly from the MEAD trials, appears to be more reflective of relative clinical effects between dexamethasone and sham, and is the one that ERG regards as the most appropriate for the estimation of the cost effectiveness of dexamethasone versus watch and wait for patients with DMO who are unsuitable for, or insufficiently responsive to non-corticosteroid therapy.

Analysis A5.

Table 123. Results of Analysis A5, using MEAD trial efficacy data for both dexamethasone and watch and wait, with unrestricted movements between health states, and utilities estimated directly from patients' responses on VFQ-UI in MEAD trials; patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid treatment (Company's response to clarification, pgs 13-15)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Watch and wait	£13,607	6.7960	-	-	-
DEX	£21,241	6.8108	£7,635	0.00149	£513,797*
Abbreviations used in the table: DEX, dexamethasone DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years *DEX vs watch and wait.					

The company described the approach adopted in this analysis, shown in Box 31.

Box 31. Company's description on the approach adopted in Analysis A5 that was requested by the ERG (Company's response to clarification, pg 14)

The mean utility values in each health state for the BSE and for the WSE have been utilised 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 [as shown in Table 76]. 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.
Abbreviations used in the box: BSE, best seeing eye; ERG, evidence review group; WSE, worst seeing eye.

The ERG requested that the company use mean utilities estimated directly from patients' responses on the VFQ-UI in the MEAD trials. The ERG wanted the company to estimate QALYs directly from the VFQ-UI data collected over 3 years in the MEAD trials, without linking the VFQ-UI data to modelled health states. However, the ERG acknowledges that its request may have not been clear enough. In response, the company applied utility data from the MEAD trials in the model using the approach described above. This approach was characterised by two major limitations:

- The utility data for BSE and WSE were not estimated in isolation from each other. Utility data corresponding to BCVA health states of the BSE were affected by the BCVA of the WSE, and vice versa. This resulted in the mean utilities of the WSA appearing to be higher than the utilities of the BSE (because the vision of the BSE 'pulled up' the utility associated with the WSE, whereas the vision of the WSE 'pulled down' the utility associated with the

BSE), implying that the utility associated with the WSE is higher than the utility associated with the BSE, which does not seem realistic.

- The approach gave equal weight to BSE and WSE (since each was assumed to account for 50% of the patient's vision and utility), which is in conflict with the perception that the BCVA of the BSE contributes to a higher degree to the patient's utility; this perception is supported by the company's VFQ-UI regression model, in which the coefficient for the BCVA of the BSE was almost twice as high as the coefficient for the BCVA of the WSE.

In this analysis conducted by the company, the WSE effectively contributed more than the BSE to the overall person's utility, because both eyes were considered to be equally contributing (by 50%) to the person's utility, but WSE was associated with a higher utility compared with the BSE for the same BCVA health state. The ERG felt that this approach lacked face validity and therefore did not consider this analysis further.

Analysis A6.

Table 124. Results of Analysis A6, using NMA outputs for the efficacy of watch and wait, and utilities estimated directly from patients' responses on VFQ-UI in MEAD trials; patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid treatment (Company's response to clarification, pgs 13-15)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Watch and wait	£21,571	6.5962	-	-	-
DEX	£20,413	6.7702	-£1,158	0.1740	DEX dominates
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALYs, quality-adjusted life years; VFQ-UI, Visual Functioning Questionnaire Utility Index.					

The ERG has not considered this analysis further, as finds the approach adopted by the company for the estimation of utilities to be problematic; the approach adopted by the company and the ERG's critique are provided under analysis A5.

6.1.2 Additional analyses carried out by the ERG

The ERG carried out a series of model corrections (Section 6.1.2.1), and scenario analyses (Section 6.1.2.2) on the company's model. In addition, the ERG presents a most plausible base case ICER estimate for each population considered in this STA (Section 6.1.2.3).

All the additional analyses undertaken by the ERG were deterministic. The ERG did not undertake probabilistic analyses. This was decided because of time constraints, and also because the model results in the company submission were shown to be overall consistent between deterministic and probabilistic estimates.

The additional analyses B1-B5 and C1-C12 undertaken by the ERG were carried out on the following electronic versions of the company's models (where relevant):

- DMO_NICE_Oct2014_All DMO [base case analysis of dexamethasone versus watch and wait for patients with DMO who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy]
- DMO_NICE_Oct2014_All DMO_incl.FAME [scenario analysis for patients with DMO who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy, including fluocinolone acetonide]
- DMO_NICE_Oct2014_Pseudophakic_All_Tx [base case analysis of dexamethasone versus ranibizumab for pseudophakic patients with DMO, including the scenario analysis that considers laser, bevacizumab and watch and wait as well]
- DMO_NICE_Oct2014_All DMO_No MTC_All movements [analysis of dexamethasone versus watch and wait for patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, with transitions based on the MEAD trial data and unrestricted movements, undertaken by the company following ERG request]

Analysis C13 was undertaken on the following electronic version of the model:

- DMO_NICE_Oct2014_All DMO_RevisedMTC_Utility update [analysis of dexamethasone versus watch and wait for patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, with transitions for watch and wait based on the updated NMA]

This version was selected because it already considered utility values relating to each health state, so no substantial model re-progarmming was required. The ERG set the NMA outputs back to the outputs that were used in the originally submitted model. It is noted that all other model aspects are identical to model version DMO_NICE_Oct2014_All DMO.

Analysis C14 was undertaken on the following electronic version of the model:

- DMO_NICE_Oct2014_All DMO_No MTC_All movements_Utility update [analysis of dexamethasone versus watch and wait for patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, with transitions based on the MEAD trial data and unrestricted movements, with utility data taken directly from patients' responses to VFQ-UI, undertaken by the company following ERG request]

This version was selected because it already considered utility values relating to each health state, so no substantial model re-structuring was required. It is noted that all other model aspects are identical to model version DMO_NICE_Oct2014_All DMO_No MTC_All movements.

All Calculation sheets showing the changes made by the ERG in the company's economic models in order to perform additional analyses are provided in Appendix 9.13.

6.1.2.1 ERG model corrections

Table 125 presents a summary of all model corrections performed by the ERG and the resulting ICERs for the base case analyses. It can be seen that none of the corrections had a substantial impact on the results. Detailed results of the model corrections performed by the ERG are provided in Appendix 9.14

Table 125. Impact of ERG corrections on the company's base case comparisons (analyses using NMA efficacy data)

Analyses	**ICER (cost/QALY)**		
Deterministic analyses	**All patients with DMO**	**DMO patients who are pseudophakic**	
DEX700 versus	**Watch and wait**	**Ranibizumab list price**	**Ranibizumab 50% discount**
Base case ICER (deterministic)	DEX700 dominant	£50,905*	Ranibizumab Dominant

Analysis B1: annual probability of FEI corrected to [redacted]	DEX700 dominant	£51,644*	Ranibizumab Dominant
Analysis B2: mean number of re-treatments for fluocinolone acetonide in Year 3 amended to 0.036	Not relevant	Not relevant	Not relevant
Analysis B3: the probability of cataract for DEX700 in Years 1, 2 and 3 was amended to [redacted], [redacted], and [redacted], respectively; the annual probability of cataract for patients with DMO receiving no treatment or watch and wait was amended to 2.32%	DEX700 dominant	Not relevant	Not relevant
Analysis B4: the cost of fluorescein angiography was amended to £144	DEX700 dominant	£50,849*	Ranibizumab Dominant
Analysis B5: the unit cost of vitreous haemorrhage and retinal detachment was amended from £1685 to £989; management of retinal detachment was estimated to be an intermediate / major vitreous day case procedure in 80% and 20% of cases, respectively, with a mean cost of £1,080	DEX700 dominant	£51,807*	Ranibizumab Dominant
Combination: analyses B1 to B5	DEX700 dominant	£52,494*	Ranibizumab Dominant
Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, evidence review group; FEI, fellow eye involvement; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. *Ranibizumab vs dexamethasone; dexamethasone is less costly and less effective than ranibizumab			

6.1.2.2 ERG additional scenario analyses

Table 126 presents a summary of all additional scenario analyses performed by the ERG and the resulting ICERs for the base case analyses. It can be seen that the only scenario that had a considerable impact on the results was the one utilising the unit cost of private residential care in the estimation of the cost associated with severe vision loss. Under this scenario, dexamethasone became more costly than watch and wait, at an ICER of £30,366/QALY. Detailed results of the additional scenario analyses carried out by the ERG are provided in Appendix 9.14.

Table 126. Impact of ERG additional scenario analyses on the company's base-case comparisons (analyses using NMA efficacy data)

Analyses	**ICER (cost/QALY)**		
Deterministic analyses	**All patients with DMO**	**DMO patients who are pseudophakic**	
DEX700 versus	**Watch and wait**	**Ranibizumab list price**	**Ranibizumab 50% discount**
Base case ICER (deterministic)	DEX700 dominant	£50,905 *	Ranibizumab Dominant
Analysis C1: annual probability of FEI 55.28%	DEX700 dominant	£46,307*	Ranibizumab

			Dominant
Analysis C2: a 5.5% 3-month probability of deterioration of vision for those ending or discontinuing treatment was assumed; 3.5% of patients improved vision and 91% remained stable	DEX700 dominant	£43,787*	Ranibizumab Dominant
Analysis C3: Discontinuation rates for all treatment options were set at zero	DEX700 dominant	£55,252*	Ranibizumab Dominant
Analysis C4: an overall 3.5 HR of mortality for DMO vs the general population was applied	DEX700 dominant	£63,296*	£197*
Analysis C5: Bilateral treatment with anti-VEGF was assumed to require 1 vs 2 administration visits on 75% and 25% of the occasions, respectively	Not relevant	£49,423*	Ranibizumab Dominant
Analysis C6: the numbers of total visits associated with treatment and monitoring each year were amended to take into account that some re-treatment visits included monitoring visits	DEX700 dominant	£43,759*	Ranibizumab Dominant
Analysis C7: costs associated with IOP checks were removed from analysis	DEX700 dominant	£54,284*	Ranibizumab Dominant
Analysis C8: the unit cost of private residential care (£532 weekly) was used.	£30,366	£69,862*	£12,889*
Analysis C9: a cost of depression of £2,252 was utilised	DEX700 dominant	£49,162*	Ranibizumab Dominant
Analysis C10: a mean cost of medication for raised IOP of £88.77 was used, using the cost of generic prostaglandins and assuming that, medication for raised IOP comprises 70% generic prostaglandins; 10% generic beta-blockers; and 20% equal use of remaining treatments listed by the company	DEX700 dominant	£51,193*	Ranibizumab Dominant
Analysis C11: trabeculectomy was the only surgical procedure considered for the management of raised IOP; 50% of procedures were assumed to be intermediate and 50% major glaucoma day case procedures; cost was £1273	DEX700 dominant	£50,872*	Ranibizumab Dominant
Analysis C12: 6 extra IOP visits were added to patients with DMO who were treated for raised IOP	DEX700 dominant	£49,786*	Ranibizumab Dominant
Analysis C13: use of utility data from Czoski-Murray *et al*.2009[99]	DEX700 dominant	Scenario not applied in this population	
Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, evidence review group; FEI, fellow eye involvement; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure; QALYs, quality-adjusted life years. *Ranibizumab vs dexamethasone; dexamethasone is less costly and less effective than ranibizumab			

The ERG notes that under analysis C3 (discontinuation rates for all treatment options set at zero), in patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroids, the number of QALYs for both dexamethasone and watch and wait was reduced, while the total costs for both interventions increased compared with the base case analysis, as shown in Table 127. The impact was more significant for watch and wait than for dexamethasone, as incremental costs of watch and wait versus dexamethasone increased and incremental QALYs

decreased. This finding was rather unexpected, as it implied that patients who discontinue treatment (either dexamethasone or sham, which was used as a proxy for watch and wait) have higher benefits and incur lower costs compared with those who continue treatment, in particular those receiving sham. This is at odds with the company's claim that the watch and wait arm in the MEAD trials consisted of 'super-responders', due to the high discontinuation rates imposed by the study protocol, who are "not likely to represent what we would expect to observe with no active treatment in clinical practice" and who "potentially overestimate the effect of sham treatment" (company's argument provided in Box 30). The ERG is not clear what the cause of this finding might be. It could be potentially an error in the model programming, but the ERG could not identify such an error. A potential alternative explanation could be that the overall effects of both dexamethasone and watch and wait in the MEAD trials were worse than the 'effect' of natural progression on patients with DMO. In any case, these results indicate that the patient group in sham/watch and wait in the MEAD trials may not consist of 'super responders' and the company's argument that the MEAD trials have overestimated the effect of sham (and thus the effect of watch and wait) and, consequently, have underestimated the relative treatment effect of dexamethasone, may not appear robust.

Table 127. Comparison of the results of the base case analysis and Analysis C3 undertaken by the ERG in patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroids

Analysis	Total cost		Incremental cost per patient	Total QALYs		Incremental QALYs per patient	ICER
	DEX700	Watch & wait		DEX700	Watch & wait		
Base case	£20,413	£21,882	£1,469	5.7420	5.6764	-0.0656	Watch & wait dominated
C3: zero discontinuation	£21,511	£25,178	£3,667	5.7394	5.6536	-0.0858	Watch & wait dominated
Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure.							

Further to analyses C1-C13, the results for analysis C14 (use of utility data from Czoski Murray *et al*.[99] and transition probabilities derived directly from the MEAD trials, assuming unrestricted transitions) are reported in Table 128. It can be seen that use of alternative utility data from Czoski-Murray et al.[99] considerably favoured dexamethasone by increasing the incremental QALYs versus watch and wait, resulting in an ICER of £257,136/QALY; this ICER is greately reduced compared with analysis A4, which also utilised exclusively MEAD trial data, did not impose restrictions in transitions, and utilised the VFQ-UI regression model for the estimation of QALYs. The ICER in

analysis A4 was £1,411,676/QALY. However, the ERG notes that the utility values reported in Czoski-Murray et al.[99] are likely less relevant (and thus less appropriate to use) than those reported by the company, which were based on the VFQ-UI and obtained directly from patients with DMO.

Table 128. Results of revised base-case analysis by ERG: patients with DMO who are considered to be unsuitable for, or insufficiently responsive to non-corticosteroids; efficacy data based on MEAD trials, no restrictions on movements by one health state up or down imposed

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
DEX	£17,065	5.9550	£6,727	0.0262	£257,136
Watch and wait	£10,338	5.9288	-	-	-
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

6.1.2.3 ERG base case ICER

Based upon the model corrections and a selection of the scenario analyses outlined in Sections 6.1.2.1 and 6.1.2.2, respectively, the ERG has estimated a revised base case ICER for the comparison of dexamethasone versus watch and wait in patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy. The revised base case ICER has been estimated after combining all model corrections undertaken by the ERG (analyses B1-B5) and additional scenarios considered in the analyses C5-C12 performed by the ERG.

The ERG considers the derivation of efficacy data from watch and wait directly from the pooled MEAD trials as the most robust, due to the severe limitations associated with the application of the NMA outputs in the model, including the assumption that the 12-month relative risks estimated in the NMA are stable and can be applied from initiation of treatment to 3 years of treatment duration, the effect of normalisation on the transition probabilities, and the restriction of transitions by one health state up or down in every cycle of the model. This issue has been discussed in more detail in Section 6.1.1, under Analysis A4 (pgs 159-162). The revised base case analysis by the ERG, for patients with DMO who are considered to be unsuitable for, or insufficiently responsive to non-corticosteroids, when the efficacy of watch and wait was based on patient-level data from the pooled MEAD sham arms, resulted in an ICER of £1,166,271/QALY, as shown in Table 129.

Table 129. Results of revised base case analysis by ERG: patients with DMO who are considered to be unsuitable for, or insufficiently responsive to non-corticosteroids; efficacy data based on MEAD trials, no restrictions on movements by one health state up or down imposed

Intervention	Total cost	Total QALYs	Incremental	Incremental	ICER

			cost	QALYs	
DEX	£17,065	5.7589	£6,727	0.0058	£1,166,271
Watch and wait	£10,338	5.7531			
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Nevertheless, the ERG also estimated revised base case ICERs for all populations and comparators, after utilising the NMA ouputs. This was unavoidable in the case of DMO patients who are pseudophakic, as the NMA outputs were the only source of efficacy data that could be utilised for any comparison in this population apart from that between dexamethasone and watch and wait. However, as already discussed in Section 5.4.6.2, the ERG believes that application of NMA outputs in the model was characterised be considerable flaws, and therefore has serious concerns about the validity of the results of these analyses.

The revised results for DMO patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy are provided in Table 130 (base case analysis) and Table 131 (analysis including fluocinolone acetonide). Results indicated that dexamethasone is more costly than watch and wait at an additional cost of £22,049/QALY. Fluocinolone acetonide at a 50% discount price dominated dexamethasone.

Table 130. Results of revised base-case analysis by ERG: patients with DMO who are considered to be unsuitable for, or insufficiently responsive to non-corticosteroids; efficacy data based on NMA

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
DEX	£16,601	5.7438	£1,428	0.0648	£22,049
Watch and wait	£15,174	5.6791			
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Table 131: Results of revised scenario analysis by ERG: patients with DMO who are considered to be unsuitable for, or insufficiently responsive to non-corticosteroids; scenario including fluocinolone acetonide

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs baseline
	Cost	QALY	Cost	QALY		
Fluocinolone acetonide at list price						
Watch and wait	£15,171	5.6791	-	-	-	-
DEX	£16,601	5.7438	£1,431	0.0647	£22,105	£22,105
Fluocinolone acetonide	£20,170	5.8220	£3,569	0.0781	£45,684*	£35,000
Fluocinolone acetonide at 50% discount						
Watch and wait	£15,171	5.6791				
Fluocinolone acetonide	£15,235	5.8220	£64	0.1428	£446	£446
DEX	£16,601	5.7438	£1,367	-0.0781	Fluocinolone acetonide dominates	£22,105
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. *Fluocinolone acetonide vs dexamethasone						

The revised results for DMO patients who are pseudophakic are presented in Table 130 (base case analysis) and Table 131 (analysis including bevacizumab, laser and watch and wait). Conclusions were not affected, as ranibizumab at list price was not cost-effective compared with dexamethasone, but became cost-effective compared with dexamethasone when a 50% discount to its list price was assumed. Bevacizumab dominated both ranibizumab (even at 50% discount) and dexamethasone. Laser also dominated dexamethasone.

Table 132. Results of revised base-case analysis by ERG: DMO patients who are pseudophakic; efficacy data based on NMA

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Ranibizumab list price					
DEX	£12,841	5.0894			
Ranibizumab	£20,219	5.2054	£7,378	0.1160	£63,609*
Ranibizumab 50% discount price					
DEX	£12,841	5.0894			
Ranibizumab	£13,556	5.2054	£715	0.1160	£6,162*
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. * Ranibizumab vsdexamethasone;.dexamethasone is less costly and less effective than ranibizumab					

Table 133. Results of revised scenario analysis by ERG: patients with DMO who are pseudophakic; scenario including laser, bevacizumab and watch and wait

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER	ICER vs baseline (laser)
Laser	£6,831	5.1369				
Bevacizumab	£7,915	5.2359	£1,084	0.0990	£10,736*	£10,945
DEX	£12,841	5.0894	£4,926	-0.1465	Bevacizumab dominates	-£126,595
Ranibizumab (50% discount)	£13,556	5.2054	£5,640	-0.0305	Bevacizumab dominates	£98,134
Watch and wait	£14,544	4.9851	£6,628	-0.2509	Bevacizumab dominates	-£50,804

Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
*Bevacizumab vs laser

Nevertheless, the ERG wishes to emphasise the fact that results based on the NMA are characterised by severe flaws (including the assumption that relative risks between all treatments of improving vision, stable vision and worsening vision are equal to 12-month relative risks and stable over the whole 3-year duration of treatment and the normalisation approach) and therefore results obtained from these analyses should be interpreted with great caution.

7 OVERALL CONCLUSIONS

7.1 Summary of clinical effectiveness issues

The EU marketing authorisation for dexamethasone restricts it use to the treatment of adult patients with visual impairment due to DMO, who are pseudophakic (have an artificial lens implant, or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. However, the ERG considers that in terms of the actual populations in the six RCTs presented in the CS for dexamethasone, none of them directly addressed the populations covered by the EU marketing authorisation for dexamethasone. All six RCTs had inclusion criteria designed to assess broader populations to the one of interest. The ERG thus considers that the results presented in the CS are limited in their specificity for addressing the populations for whom dexamethasone has EU marketing authorisation.

The ERG notes that two of the RCTs reported in the CS used treatment regimens that are not approved for use in the UK (BEVORDEX and 024). These two studies both allowed re-treatment with dexamethasone more frequently than the 6-month minimum re-treatment period specified in the EU licence. The ERG thus does not consider these trials of relevance to the decision problem.

In terms of the comparators, the ERG notes that the company did not include data for fluocinolone acetonide in combination with laser photocoagulation or bevacizumab in combination with laser photocoagulation within the CS. The ERG also notes that the company included data for an additional comparator, watch and wait, within the submission and that the company used an NMA to provide data for some of the comparators in the CS where there were no head-to-head studies. The ERG has concerns over the validity of the results from the NMA due to the presence of both clinical and statistical heterogeneity within the network of trials.

Regarding outcomes, the ERG notes that not all of the outcomes requested in the NICE final scope were covered within the CS in each of the six dexamethasone RCTs. Results were not available for all of the outcomes in terms of the comparison of dexamethasone with each of the specified comparators in the NICE final scope. However, in terms of actual outcomes reported in the CS, the ERG considers the key clinical outcomes are reported in the CS although the ERG has concerns around the populations in which the outcome data are reported; i.e. not addressing the EU licensed populations for dexamethasone in DMO.

The ERG notes that missing data in the MEAD studies were handled using last observation carried forward (LOCF) methodology and thus considers that the high discontinuation rates in the MEAD studies could potentially confound the results of the trials. The ERG is unable to ascertain in which direction this bias might affect the results. The ERG is also concerned as to why the discontinuation rates in the dexamethasone arm of the MEAD studies were so high compared with discontinuation rates seen with dexamethasone in the other trials reported in the CS.

The mean BCVA change from baseline, the proportion of patients achieving at least a 10-letter improvement in visual acuity at study end and the HRQL analyses in PLACID demonstrated no significant difference between dexamethasone + laser versus laser alone. However, these outcomes were assessed at 12 months and so the results for dexamethasone + laser may be confounded by cataract AE development.

In the MEAD studies, the ERG notes that whilst dexamethasone generally resulted in favourable efficacy outcomes compared with sham, clinical experts reported that they were not reflected in clinically significant changes in BCVA. In addition, from month 15 onwards in the MEAD studies the improvement in BCVA provided by dexamethasone 700µg relative to sham was reduced and didn't recover until after 36 months. The ERG notes that this trend coincides with cataract adverse effects during the second year of the study in the dexamethasone group which must be considered when considering dexamethasone as a treatment option in phakic DMO patients. In addition the ERG consider there to be a lack of long term safety and efficacy data for dexamethasone in DMO as the RCT data presented in the CS has a maximum follow-up duration of 39 months.

The ERG acknowledges that the pseudophakic patients in the dexamethasone group of the MEAD studies achieved a much greater improvement in BCVA compared to the whole trial ITT population (6.5 letters in the pseudophakic subgroup compared with 3.5 in the whole trial ITT population). However, clinical experts reported that this difference of 3 letters between the treatment groups may not represent a clinically meaningful change in BCVA to the patient. The ERG's clinical experts reported that a change of 5 or more letters is more likely to represent a clinically significant change to the patient.

In terms of the NMA, the ERG are concerned that the populations of the RCTs do not address the EU licensed populations for dexamethasone and in addition that there are clinical differences in terms of the baseline characteristics of the patients in the RCTs, i.e. a potential source of clinical heterogeneity. The company's statistical assessment of heterogeneity in the NMA suggest that there are high levels of statistical heterogeneity present and that the chosen model is a poor fit for the underlying data. The ERG is thus concerned about the validity of the results from the NMA. The ERG also notes that there is a considerable amount of uncertainty around some of the efficacy estimates from the NMA.

In addition, the pair wise meta-analysis from MEAD-010 and MEAD-011 which the company qualitatively compared with the results from the NMA for dexamethasone versus sham/no treatment resulted in substantially different efficacy estimates for this comparison. The ERG finds this to be another reason to be concerned about the validity of the results from the NMA.

7.2 Summary of cost-effectiveness issues

The ERG considers the company's modelling approach to be in principle appropriate. The model structure was consistent with the progression of the disease and reflective of patient presentation and treatment in clinical practice. Modelling transitions in BCVA states in each eye independently was an improvement over previous economic models assessing treatments for DMO, as it allowed a more realistic representation of patient experience and enabled a more accurate estimation of HRQL, as it considered the impact of each of the BSE and the WSE on HRQL separately. The economic model was well constructed and transparent, with only few errors and inconsistencies in data between the model and the company's submission. Estimation of QALYs was based on utility data collected from patients with DMO participating in the MEAD trials using a vision-specific preference-based measure (VFQ-UI). Utility in each patient was estimated using a regression model, which considered BCVA in the BSE and the WSE independently, with BSE contributing to a higher degree to the final utility compared with the WSE, which appears to be reasonable.

The ERG's main concerns with the company's economic analysis are:

The mismatch between the study population in the MEAD trials and the licensed DMO populations that were considered in the economic models

Efficacy data on dexamethasone for patients with DMO who are considered unsuitable for, or insufficiently responsive to, non-corticosteroid therapy were taken from the whole DMO population in the MEAD trials. However, participants in the MEAD trials were not representative of these patient sub-groups examined in the economic analysis, as a substantial proportion (more than 25%) were treatment naïve, and less than 7% had previously received anti-VEGF treatment. The ERG notes that a patient who has not previously responded to anti-VEGF or laser treatment, may be overall treatment-resistant and less likely to respond to other treatments as well; this means that consideration of the MEAD population as a proxy for patients with DMO who are insufficiently responsive to non-corticosteroid therapy has likely overestimated the treatment effect in favour of dexamethasone.

Moreover, efficacy data for pseudophakic patients with DMO were based on NMA outputs resulting from a synthesis of data on pseudophakic (dexamethasone) and mixed (anti-VEGF and laser) DMO populations, as no (or very limited) data on pseudophakic patients were available for anti-VEGF and laser treatments. The ERG notes that pseudophakic patients with DMO may have a slightly higher BCVA compared with the whole DMO population and are not at risk for cataract formation, which is a condition that negatively affects BCVA outcomes and is associated with the presence of diabetes mellitus (DM). Therefore, use of efficacy data for anti-VEGF and laser treatments from the whole DMO population as a proxy for the pseudophakic population with DMO is likely to have underestimated the effect of these treatments on pseudophakic DMO patients relative to dexamethasone (for which data on pseudophakic populations were available and used in the NMA).

The assumption that the baseline distributions of BSE and WSE across BCVA states are independent from each other

This assumption may have important implications, as it allowed the WSE to have a non-trivial probability to be in a better BCVA state than the BSE at baseline, and potentially throughout the duration of the model, considering that the BSE and WSE were fixed at initiation of treatment and throughout the model duration. Considering that both eyes contribute to the patient's utility, with the visual acuity of the BSE having a greater impact than that of the WSE, this assumption may have introduced bias into the analysis. However, the ERG was unable to assess the magnitude and direction of bias resulting from this assumption.

The application in the economic model of relative risks from the NMA (which synthesised 12-month efficacy data) onto 3-month baseline transition probabilities, over the whole 3-year duration of all treatments.

The ERG has major concerns with the application in the economic model of relative risks from the NMA (which synthesised 12-month efficacy data) onto 3-month baseline transition probabilities, over the maximum 3-year duration of all treatments. This application was based on the assumption that relative effects of all treatments considered in the NMA remain stable from initiation of treatment and up to 3 years of treatment duration; however, evidence from the MEAD trials suggests that this

assumption is unlikely to hold, at least not in the whole DMO population. The assumption appears to be more consistent with evidence on pseudophakic patients treated with dexamethasone, but the available evidence did not allow assessment of its applicability in pseudophakic DMO populations receiving other treatments.

An analysis undertaken by the company following the ERG's request, showed that when efficacy data from the MEAD trials were utilised for both dexamethasone and watch and wait (sham) instead of the NMA outputs and without any restrictions imposed on transitions, then the cost effectiveness of dexamethasone was substantially reduced, and its ICER versus watch and wait changed from being dominant (according to the company's base case analysis) to £1,166,271/QALY. The ERG attributes the discrepancy between the results of the two analyses to the application in the economic model of 12-month relative risks assuming they are stable over 3 years, and, potentially, to the normalisation of transition probabilities, as discussed below. The results suggest that the analysis that utilised the NMA outputs is likely to have overestimated the efficacy of dexamethasone versus watch and wait in patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy.

The 'normalisation' of transition probabilities in the economic model, in order to ensure that these add up to 1

The ERG notes that this approach effectively resulted in the relative risks being consistently altered from their original values obtained from the NMA, thus potentially introducing bias into the analysis, the direction and magnitude of which were not possible to ascertain or predict.

The assumption that transitions between health states are restricted by a maximum of one BCVA state per cycle

This assumption was required, according to the company, in order to utilise the relative effects obtained from the NMA. However, as further analyses (requested by the ERG and undertaken by the company) showed, the assumption does not appear to reflect trial evidence and in fact has underestimated the effect of dexamethasone relative to watch and wait.

An overestimate of the cost associated with severe vision loss (i.e. BCVA <35 letters), due to overestimation of the cost of residential care

The ERG notes that the cost associated with severe vision loss (i.e. BCVA <35 letters) is likely to have been overestimated by the company, due to overestimation of the cost of residential care, which was one of its components. The company has utilised the unit cost of residential care provided by local authority. However, economic analyses in previous TAs have utilised the unit cost of private residential care, with views expressed that the private sector appears to be the main provider of residential care in the UK. The unit cost of private residential care is almost 50% lower than the unit cost of residential care provided by local authority. If private sector is the main provider of residential

care, then use of the unit cost of local authority residential care by the company has seriously overestimated the cost associated with severe vision loss.

Following ERG corrections and amendments in the company's model data, the deterministic ICER of dexamethasone versus watch and wait in patients who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy, became £22,049/QALY when NMA outputs were utilised; and £1,166,271/QALY when data from the MEAD trials for both dexamethasone and watch and wait (sham) were utilised, without transitions being restricted by one health state up or down.

The discrepancy between the ERG's ICER and the company's ICER when NMA data were utilised was driven by the different unit cost of residential care used: the ERG utilised the unit cost of private residential care whereas the company utilised the unit cost of residential care provided by local authority.

In patients with DMO who are pseudophakic, ranibizumab at list price was not cost-effective compared with dexamethasone, but became cost-effective compared with dexamethasone when a 50% discount to its list price was assumed. Bevacizumab and laser both dominated dexamethasone.

Conclusively, the ERG feels that the company's base case economic analysis that utilised NMA data suffers from severe limitations as described above and therefore its results are unlikely to be robust. On the other hand, the ERG considers the analysis which utilised efficacy data from the MEAD trials for both dexamethasone and sham to be more reflective of the relative efficacy between dexamethasone and sham, and is the one that ERG regards as the most appropriate for the estimation of the cost effectiveness of dexamethasone versus watch and wait in patients with DMO who are unsuitable for, or insufficiently responsive to non-corticosteroid therapy.

7.3 Implications for research

The ERG considers that there is a need for further research into:

- the safety and efficacy of the 700µg dexamethasone intravitreal implant in the treatment of adult patients with visual impairment due to DMO, who are pseudophakic (have an artificial lens implant), or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy;
- the long term safety and clinical benefit of dexamethasone in DMO;
- further head-to-head trials comparing dexamethasone alone and in combination with laser to laser photocoagulation alone, ranibizumab alone or in combination with laser photocoagulation, fluocinolone acetonide intravitreal implant alone or in combination with laser photocoagulation and watch and wait.

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9 APPENDICES

9.1 Company's clinical search strategies

The initial searches were performed in Medline and Medline In-Process and other non-indexed citations, Embase and The Cochrane Library on 13th February 2014 for RCT evidence and on 18th July 2014 for non-RCT evidence. The complete search strategies used, including all the search terms: text words (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean) are presented below for each database. For the updated searches (17th July 2014) a date limit of 2014 was applied to the initial search terms.

A. Search strategy for RCT clinical evidence base; adapted from CS, Appendix 2, pgs 541-552

Box 32: Search strategy for identification of RCT studies: Medline and Medline in Process & Other Non-Indexed citations: Ovid. 1946 to Present

1. exp Diabetes Mellitus/
2. diabetic retinopathy/
3. diabet$.tw.
4. or/1-3
5. Macular Edema/
6. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.
7. maculopath$.tw.
8. (dme or dmo).tw.
9. or/5-8
10. 4 and 9
11. exp Dexamethasone/
12. dexamethasone.tw.
13. ozurdex.tw.
14. 50-02-2.rn.
15. aflibercept.tw.
16. eylea.tw.
17. 845771-78-0.rn.
18. bevacizumab.tw.
19. avastin.tw.
20. 216974-75-3.rn.
21. ranibizumab.tw.
22. lucentis.tw.
23. 347396-82-1.rn.
24. Triamcinolone Acetonide/

25. triamcinolone acetonide or ivta.tw.
26. taiftol.tw.
27. trigon.tw.
28. 76-25-5.rn.
29. exp Fluocinolone Acetonide/
30. fluocinolone acetonide.tw.
31. iluvien.tw.
32. 67-73-2.rn.
33. Laser Coagulation/
34. photocoagulat$.tw.
35. (photo and coagulat$).tw.
36. ((focal or grid) adj3 laser$).tw.
37. ((argon or diode or micropulse) adj3 (coagulat$ or laser$)).tw.
38. or/11-37
39. 10 and 38
40. randomized controlled trial.pt.
41. controlled clinical trial.pt.
42. randomized.ab.
43. placebo.ab.
44. drug therapy.fs.
45. randomly.ab.
46. trial.ab.
47. groups.ab.
48. or/40-47
49. exp animals/ not humans.sh.
50. 48 not 49
51. 39 and 50
52. meta-analysis as topic/
53. (meta analy$ or metaanaly$).tw.
54. Meta-Analysis/
55. (systematic adj (review$1 or overview$1)).tw.
56. "Review Literature as Topic"/
57. or/52-56
58. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
59. ((reference adj list$) or bibliograph$ or hand-search$ or (relevant adj journals) or (manual adj search$)).ab.
60. ((selection adj criteria) or (data adj extraction)).ab.
61. "review"/
62. 60 and 61

63. comment/ or editorial/ or letter/
64. Animals/
65. Humans/
66. 64 not (64 and 65)
67. 63 or 66
68. 57 or 58 or 59 or 62
69. 68 not 67
70. 39 and 69

Box 33: Search strategy for identification of RCT studies: Embase: Ovid.

1. exp diabetes mellitus/
2. diabetic retinopathy/
3. diabet$.tw.
4. or/1-3
5. exp retina macular edema/
6. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.
7. maculopath$.tw.
8. (dme or dmo).tw.
9. or/5-8
10. 4 and 9
11. dexamethasone/
12. dexamethasone.tw.
13. ozurdex.tw.
14. 50-02-2.rn.
15. aflibercept/
16. aflibercept.tw.
17. eylea.tw.
18. 845771-78-0.rn.
19. bevacizumab/
20. bevacizumab.tw.
21. avastin.tw.
22. 216974-75-3.rn.
23. ranibizumab/
24. ranibizumab.tw.
25. lucentis.tw.
26. 347396-82-1.rn.
27. triamcinolone acetonide/
28. triamcinolone acetonide or ivta.tw.
29. taiftol.tw.

30. trigon.tw.
31. 76-25-5.rn.
32. fluocinolone acetonide/
33. fluocinolone acetonide.tw.
34. iluvien.tw.
35. 67-73-2.rn.
36. exp laser coagulation/
37. photocoagulat$.tw.
38. (photo and coagulat$).tw.
39. ((focal or grid) adj3 laser$).tw.
40. ((argon or diode or micropulse) adj3 (coagulat$ or laser$)).tw.
41. or/11-40
42. 10 and 41
43. Clinical trial/
44. Randomized controlled trial/
45. Randomization/
46. Single blind procedure/
47. Double blind procedure/
48. Crossover procedure/
49. Placebo/
50. Randomi?ed controlled trial$.tw.
51. Rct.tw.
52. Random allocation.tw.
53. Randomly allocated.tw.
54. Allocated randomly.tw.
55. (allocated adj2 random).tw.
56. Single blind$.tw.
57. Double blind$.tw.
58. ((treble or triple) adj blind$).tw.
59. Placebo$.tw.
60. Prospective study/
61. or/43-60
62. Case study/
63. Case report.tw.
64. Abstract report/ or letter/
65. or/62-64
66. 61 not 65
67. 42 and 66
68. exp Meta Analysis/
69. ((meta adj analy$) or metaanalys$).tw.

70. (systematic adj (review$1 or overview$1)).tw.
71. or/68-70
72. cancerlit.ab.
73. cochrane.ab.
74. embase.ab.
75. (psychlit or psyclit).ab.
76. (psychinfo or psycinfo).ab.
77. (cinahl or cinhal).ab.
78. science citation index.ab.
79. bids.ab.
80. or/72-79
81. reference lists.ab.
82. bibliograph$.ab.
83. hand-search$.ab.
84. manual search$.ab.
85. relevant journals.ab.
86. or/81-85
87. data extraction.ab.
88. selection criteria.ab.
89. 87 or 88
90. review.pt.
91. 89 and 90
92. letter.pt.
93. editorial.pt.
94. animal/
95. human/
96. 94 not (94 and 95)
97. or/92-93,96
98. 71 or 80 or 86 or 91
99. 98 not 97
100. 42 and 99

Box 34: Search strategy for identification of RCT studies: Cochrane Library: Wiley Interscience. Cochrane Database of Systematic Reviews (CDSR): Wiley Interscience. 1996-present; Cochrane Central Register of Controlled Trials (CCRT): Wiley Interscience. 1898-present; Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present; Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees
#2 MeSH descriptor: [Diabetic Retinopathy] this term only
#3 diabet*:ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Macular Edema] this term only

#6 ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) next/3 (edema* or oedema*)):ti,ab,kw

#7 maculopath*:ti,ab,kw

#8 (dme or dmo):ti,ab,kw

#9 #5 or #6 or #7 or #8

#10 #4 and #9

#11 MeSH descriptor: [Dexamethasone] explode all trees

#12 dexamethasone:ti,ab,kw

#13 50-02-2:ti,ab,kw

#14 aflibercept:ti,ab,kw

#15 eylea:ti,ab,kw

#16 845771-78-0:ti,ab,kw

#17 bevacizumab:ti,ab,kw

#18 avastin:ti,ab,kw

#19 216974-75-3:ti,ab,kw

#20 ranibizumab:ti,ab,kw

#21 lucentis:ti,ab,kw

#22 347396-82-1:ti,ab,kw

#23 MeSH descriptor: [Triamcinolone Acetonide] this term only

#24 (triamcinolone acetonide or ivta):ti,ab,kw

#25 taiftol:ti,ab,kw

#26 trigon:ti,ab,kw

#27 76-25-5:ti,ab,kw

#28 MeSH descriptor: [Fluocinolone Acetonide] explode all trees

#29 fluocinolone acetonide

#30 iluvien:ti,ab,kw

#31 67-73-2:ti,ab,kw

#32 MeSH descriptor: [Laser Coagulation] this term only

#33 photocoagulat*:ti,ab,kw

#34 (photo and coagulat*):ti,ab,kw

#35 ((focal or grid) next/3 laser*):ti,ab,kw

#36 ((argon or diode or micropulse) next/3 (coagulat* or laser*)):ti,ab,kw

#37 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36

#38 #10 and #37

Box 35: Search strategy for identification of RCT studies: CINAHL: EBSCO

S60 S37 AND S59

S59 S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58

S58 TI clinic* N1 trial* or AB clinic* N1 trial*

S57 TI ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) or AB ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*))

S56 TI Placebos or AB Placebos

S55 TI Placebo* or AB Placebo*

S54 TI Random* allocat* or AB Random* allocat*

S53 TI Allocat* random* or AB Allocat* random*

S52 (MH "Quantitative Studies")

S51 (MH "Random Assignment")

S50 TI Randomi?ed control* trial* or AB Randomi?ed control* trial*

S49 PT Clinical trial

S48 (MH "Clinical Trials+")

S47 S37 AND S46

S46 S42 not S45

S45 S43 or S44

S44 (MH "Animals")

S43 PT Commentary or PT Letter or PT Editorial

S42 S38 or S39 or S40 or S41

S41 systematic N2 review or systematic N2 overview

S40 (MH "Literature Review+")

S39 TI ((Meta analys* or Metaanaly*)) or AB ((Meta analys* or Metaanaly*))

S38 (MH "Meta Analysis")

S37 S9 AND S36

S36 S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35

S35 ((argon or diode or micropulse) N3 (coagulat* or laser*))

S34 ((focal or grid) N3 laser*)

S33 (photo and coagulat*)

S32 photocoagulat*

S31 (MH "Laser Therapy+")

S30 67-73-2

S29 iluvien

S28 fluocinolone acetonide

S27 76-25-5

S26 trigon

S25 taiftol

S24 (triamcinolone acetonide or ivta)

S23 (MH "Triamcinolone")

S22 347396-82-1

S21 lucentis

S20 ranibizumab

S19 216974-75-3

S18 avastin

S17 bevacizumab

S16 845771-78-0

S15 eylea

S14 aflibercept

S13 50-02-2

S12 ozurdex

S11 dexamethasone

S10 (MH "Dexamethasone+")

S9 S4 and S8

S8 S5 or S6 or S7

S7 (dme or dmo)

S6 maculopath*

S5 ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) N3 (edema* or oedema*))

S4 S1 or S2 or S3

S3 diabet*

S2 (MH "Diabetic Retinopathy")

S1 (MH "Diabetes Mellitus+")

B. Search strategy non-RCT evidence; adapted from CS, Appendix 6, pgs 568-572

Box 36: Search strategy for non-RCT evidence: Medline and Medline in Process & Other Non-Indexed citations: Ovid. 1946 to Present

1. exp Diabetes Mellitus/

2. diabetic retinopathy/

3. diabet$.tw.

4. or/1-3

5. Macular Edema/

6. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.

7. maculopath$.tw.

8. (dme or dmo).tw.

9. or/5-8

10. 4 and 9

11. exp Dexamethasone/
12. dexamethasone.tw.
13. ozurdex.tw.
14. 50-02-2.rn
15. or/11-14
16. 10 and 15

Box 37: Search strategy for non-RCT evidence: Embase: Ovid.

1. exp diabetes mellitus/
2. diabetic retinopathy/
3. diabet$.tw.
4. or/1-3
5. exp retina macular edema/
6. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.
7. maculopath$.tw.
8. (dme or dmo).tw.
9. or/5-8
10. 4 and 9
11. dexamethasone/
12. dexamethasone.tw.
13. ozurdex.tw.
14. 50-02-2.rn.
15. or/11-14
16. 10 and 15

Box 38: Search strategy for non-RCT evidence: Cochrane Library: Wiley Interscience. Cochrane Database of Systematic Reviews (CDSR): Wiley Interscience. 1996-present; Cochrane Central Register of Controlled Trials (CCRT): Wiley Interscience. 1898-present; Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present; Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees
#2 MeSH descriptor: [Diabetic Retinopathy] this term only
#3 diabet*:ti,ab,kw
#4 #1 or #2 or #3
#5 MeSH descriptor: [Macular Edema] this term only
#6 ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) next/3 (edema* or oedema*)):ti,ab,kw
#7 maculopath*:ti,ab,kw
#8 (dme or dmo):ti,ab,kw

#9 #5 or #6 or #7 or #8
#10 #4 and #9
#11 MeSH descriptor: [Dexamethasone] explode all trees
#12 dexamethasone:ti,ab,kw
#13 ozurdex:ti,ab,kw
#14 50-02-2:ti,ab,kw
#15 {or #11#14}
#16 #10 and #15

Box 39: Search strategy for non-RCT evidence: CINAHL: EBSCO

S15 S9 AND S14
S14 S10 or S11 or S12 or S13
S13 50-02-2
S12 ozurdex
S11 dexamethasone
S10 (MH "Dexamethasone+")
S9 S4 and S8
S8 S5 or S6 or S7
S7 (dme or dmo)
S6 maculopath*
S5 ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) N3 (edema* or oedema*))
S4 S1 or S2 or S3
S3 diabet*
S2 (MH "Diabetic Retinopathy")
S1 (MH "Diabetes Mellitus+")

9.2 Clinical trials.gov search results

Table 134: Clinical trials.gov search results for dexamethasone in DMO studies for which no results have been made available to date (adapted from CS appendix 24)

Study ID	Study Type	Intervention	Control	Enrolment	Study start date	Study Completion Date	Primary Completion Date	Status
NCT01698749	Single arm trial	DEX700	NA	61	December 2011	February 2012	January 2012	Completed
NCT00308542	Phase 1/2, single arm trial	DEX700	NA	N	NR	NR	NR	Completed
NCT01787669	Phase 2, non-	DEX700	Bevacizumab PRN	50	June 2013	December 2015	October 2014	Currently recruiting

	randomised							
NCT01571232	Phase 2, open-label	DEX700 4 monthly	Bevacizumab monthly	20	April 2012	June 2013	June 2013	Currently recruiting
NCT01613716	Phase 4, single arm trial	DEX700	NA	30	July 2012	December 2014	September 2014	Currently recruiting
NCT02036424	Phase 4	DEX700 3 monthly	Bevacizumab monthly	60	January 2014	June 2015	June 2015	Currently recruiting
NCT01951066	Phase 2, single arm trial	DEX700	NA	20	October 2013	NR	September 2015	Currently recruiting
NCT01892163	Phase 3	DEX700 PRN	DEX700 CNT	100	March 2013	December 2014	December 2014	Currently recruiting
NCT01748487	Phase 3, single arm trial	DEX700	NA	24	December 2012	NR	June 2014	Currently recruiting
NCT01788475	RCT	DEX700 6 monthly	SHAM Sham implant	15	December 2012	May 2016	May 2016	Currently recruiting
NCT02121197	Retrospective cohort study	DEX700	NA	300	May 2014	November 2014	November 2014	Not yet open for participation
NCT02188173	Prospective cohort study	DEX700	NA	1000	July 2014	March 2017	December 2016	Not yet open for recruitment
Key: DEX700, dexamethasone 700µg; NA, not applicable; NR, not reported								

9.3 Company's quality assessment of RCTs

Table 135: Company's quality assessment of the dexamethasone RCTs (Reproduced from CS Table 242)

MEAD		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Adequate: a series of patient randomisation numbers were provided by a validated automated system. Patients were randomised in a 1:1:1 ratio.	Yes
Was the concealment of treatment allocation adequate?	Adequate: sites used either the interactive voice response system or the interactive web response system to assign each qualified patient to a randomisation number.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Adequate: participants and outcome assessors blind to treatment allocation. Care providers not blinded given the sham nature of control arm but there is no predicted impact on the risk of bias as a result.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: study completion rates were higher in the DEX implant 0.7 mg (64.1%) and 0.35 mg (66.3%) groups than in the sham group (43.4%) because of a >3-fold higher rate of discontinuations owing to lack of efficacy in the sham group.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes made available.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: Efficacy outcomes were evaluated in the intent-to-treat population of all randomised patients where appropriate. The last-observation-carried-forward method was used for imputation of missing values.	Yes

Study 024		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Adequate: patients were randomised in a 1:1 ratio. Randomisation was stratified by BCVA score at baseline (≥34 to ≤49 and ≥50 to ≤70).	Yes
Was the concealment of treatment allocation adequate?	Adequate: an automated interactive voice response system/interactive web response system was used.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Adequate: outcome assessors blind to treatment allocation. Care providers and participants not blinded given the different administration methods of active treatment arms but there is no predicted impact on the risk of bias as a result.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: discontinuation rate comparable across treatment arms.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes made available.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: Efficacy outcomes were evaluated in the intent-to-treat population of all randomised patients where appropriate. The last-observation-carried-forward method was used for imputation of missing values.	Yes

PLACID		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Adequate: randomisation was stratified by baseline BCVA. Patients were randomised in a 1:1 ratio.	Yes
Was the concealment of treatment allocation adequate?	Adequate: the randomisation schedule was computer generated and stored in a locked cabinet until the study ended.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Adequate: participants and outcome assessors blind to treatment allocation. Care providers not blinded given the sham nature of control arm but there is no predicted impact on the risk of bias as a result.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: discontinuation rate comparable across treatment arms.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes made available.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: Efficacy outcomes were evaluated in the intent-to-treat population of all randomised patients. The last-observation-carried-forward method was used for imputation of missing values.	Yes

NCT00035906		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Adequate: patients were randomised using a 1:1:1 allocation generated by the study sponsor.	Yes
Was the concealment of treatment allocation adequate?	Unclear: no further details reported.	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Adequate: outcome assessors blind to treatment allocation. Care providers and participants not blinded given the observation (no treatment) control arm but there is no predicted impact on the risk of bias as a result.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: discontinuation rate comparable across treatment arms.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all key outcomes made available in publication.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: Efficacy outcomes were evaluated in the intent-to-treat population of all randomised patients. The last-observation-carried-forward method was used for imputation of missing values.	Yes

BEVORDEX		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Adequate: patients were randomised using a series of serially numbered envelopes. Randomisation was stratified by phakic or pseudophakic lens status and a history or vitrectomy or not.	Yes
Was the concealment of treatment allocation adequate?	Adequate: treatment assignments were compiled using a list of computer generated pseudo-random numbers in permuted blocks of variable size.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Adequate: outcome assessors blind to treatment allocation. Care providers and participants not blinded given the different administration methods of active treatment arms but there is no predicted impact on the risk of bias as a result.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: discontinuation rate comparable across treatment arms.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all key outcomes made available in publication.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: Efficacy outcomes were evaluated in the intent-to-treat population of all randomised patients. The last-observation-carried-forward method was used for imputation of missing values.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table 136. Company's quality assessment of the comparator RCTs (Reproduced from CS Table 244)

BOLT		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Adequate: randomisation was stratified for BCVA	Yes
Was the concealment of treatment allocation adequate?	Adequate: randomisation used an in-house computerized randomization program	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Adequate: the patient and the study physician were not masked to the therapeutic modality, the study optometrist, OCT technician, photographer, graders performing assessment of the FAZ and ETDRS retinopathy grading, and study statistician were all masked to the patient randomization	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: study completion rates were similar between treatment groups	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes made available.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: Efficacy outcomes were evaluated in the intent-to-treat population of all randomised patients where appropriate. The last-observation-carried-forward method was used for imputation of missing values.	Yes

ETDRS		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Unclear: no detail of randomization provided	Not Clear
Was the concealment of treatment allocation adequate?	Unclear: no detail of treatment allocation provided	Not Clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Unclear: no baseline demographic characteristics provided	Not Clear
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Unclear: no detail of blinding provided	No Clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear: no detail of drop-outs provided	Not Clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes made available.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unclear: no detail provided	Not Clear

FAME		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Unclear: patients were randomized in a 2:2:1 ratio. No details on methods of randomisation are provided	Not Clear
Was the concealment of treatment allocation adequate?	Unclear: no detail of treatment allocation provided	Not Clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Unclear: a double-masked study, no detail provided on who was blind to treatment allocation	Not Clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: study completion rates to the week 24 primary end point were similar in all groups	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes made available.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: An intent-to-treat population is presented in which all patients randomized are included and missing data are imputed by the method of last observation carried forward	Yes

Olk et al. 1986		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Unclear: no details of method of randomization provided	Not Clear
Was the concealment of treatment allocation adequate?	Unclear: no details of treatment allocation provided	Not Clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Unclear: no details on blinding provided	Not Clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: study completion rates to the week 24 primary end point were similar in all groups	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes made available.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unclear: no details on statistical analysis methods provided	Not Clear

PROTOCOL I		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Adequate: randomization was carried out using a permuted blocks design stratified by study eye visual acuity. Randomization was in a 1:1:1:1 ratio	Yes
Was the concealment of treatment allocation adequate?	Adequate: eyes were randomly assigned to treatment on the DRCR.net website	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Adequate: Study participants in the 3 groups receiving laser were masked to treatment assignment through the primary outcome visit, whereas the ranibizumab + deferred laser group was not masked. Visual acuity examiners and OCT technicians were masked to treatment group.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: study completion rates to the week 24 primary end point were similar in all groups	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes made available.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes: primary analysis followed the intent-to-treat principle. For eyes without 1 year data the last-observation-carried forward method was used to impute data for the primary analysis	Yes

RESTORE		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Adequate: randomization was carried out using a randomization list that automated assignment of treatment arms into the specified ratio 1:1:1	Yes
Was the concealment of treatment allocation adequate?	Adequate: a randomization list was produced by Novartis Drug Supply Management using a validated system	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Adequate: participants and outcome assessors were masked to treatment assignment. Care providers are unmasked however this would not likely impact on bias	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Adequate: study completion rates to the week 24 primary end point were similar in all groups	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes made available.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: the primary analysis was performed on the full analysis set and used the last observation carried forward	Yes

REVEAL		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Unclear: no details on method of randomization provided	Not Clear
Was the concealment of treatment allocation adequate?	Unclear: no details on treatment allocation provided	Not Clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Adequate: there were no differences in baseline demographic or study eye characteristics among the treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Adequate: a double masked study with the participants and investigators blinded to treatment	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear: no details on drop-outs provided	Not Clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Adequate: results for all outcomes made available	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: a full analysis set was used for the analysis, this consisted of all randomized patients who received at least 1 application of study treatment	Not Clear
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.4 Company's quality assessment of non-RCT's

Table 137: Company's quality assessment of the non-RCTs (Reproduced from CS Table 247)

CHAMPLAIN		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)

Do the selected patients represent the eligible population for the intervention?	Adequate: vitrectomised patients with DMO and visual impairment relevant to the unsuitable for non-corticosteroid therapy population of the decision problem.	Yes
How was selection bias minimised?	Adequate: patients enrolled based on explicit inclusion/exclusion criteria across 13 study centres.	Yes
Were the patients enrolled similar at the outset of the study in terms of prognostic factors, for example, severity of disease to the eligible population?	Adequate: baseline characteristics comparable to that we would expect in clinical practice.	Yes
Did the setting reflect UK practice?	Adequate: Australian and US study sites but treatment administered and effect monitored in line with UK practice.	Yes
Were outcome measures clinically relevant and reliable? Were outcomes assessed using objective criteria?	Adequate: clinically relevant BCVA and anatomical outcomes reported and assessed using reliable methods and objective criteria.	Yes
Was outcome assessment blind to exposure status?	Not applicable: single treatment	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: efficacy outcomes were evaluated in the intent-to-treat population of all randomised patients. The last-observation-carried-forward method was used for imputation of missing values.	Yes

Medeiros et al. 2014		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Do the selected patients represent the eligible population for the intervention?	Adequate: patients with refractory DMO and visual impairment relevant to the insufficiently responsive to non-corticosteroid therapy population of the decision problem.	Yes
How was selection bias minimised?	Adequate: patients enrolled based on explicit inclusion/exclusion criteria	Yes
Were the patients enrolled similar at the outset of the study in terms of prognostic factors, for example, severity of disease to the eligible population?	Adequate: baseline characteristics comparable to that we would expect in clinical practice.	Yes
Did the setting reflect UK practice?	Adequate: Spanish study site but treatment administered and effect monitored in line with UK practice.	Yes
Were outcome measures clinically relevant and reliable? Were outcomes assessed using objective criteria?	Adequate: clinically relevant BCVA and anatomical outcomes reported and assessed using reliable methods and objective criteria.	Yes
Was outcome assessment blind to exposure status?	Not applicable: single treatment	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not applicable: all patients completed the study and thus were included in the final analysis	N/A
MOZART		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Do the selected patients represent the eligible population for the intervention?	Adequate: patients with DMO and visual impairment, 80% of which had received prior therapy, relevant to the insufficiently responsive to non-corticosteroid therapy population of the decision problem.	Yes
How was selection bias minimised?	Adequate: patients enrolled based on explicit inclusion/exclusion criteria across 5 study centres	Yes
Were the patients enrolled similar at the outset of the study in terms of prognostic factors, for example, severity of disease to the eligible population?	Adequate: baseline characteristics comparable to that we would expect in clinical practice.	Yes

Did the setting reflect UK practice?	Adequate: French study sites but treatment administered and effect monitored in line with UK practice.	Yes
Were outcome measures clinically relevant and reliable? Were outcomes assessed using objective criteria?	Adequate: clinically relevant BCVA and anatomical outcomes reported and assessed using reliable methods and objective criteria.	Yes
Was outcome assessment blind to exposure status?	Adequate: outcome assessments conducted monthly. Treatment exposure monitored alongside outcome assessments.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not applicable: all patients completed the study and thus were included in the final analysis	N/A
OCTOME		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Do the selected patients represent the eligible population for the intervention?	Adequate: subgroup of patients with DMO and visual impairment, 60% of which had received prior therapy, relevant to the insufficiently responsive to non-corticosteroid therapy population of the decision problem.	Yes
How was selection bias minimised?	Adequate: patients enrolled based on explicit inclusion/exclusion criteria.	Yes
Were the patients enrolled similar at the outset of the study in terms of prognostic factors, for example, severity of disease to the eligible population?	Adequate: baseline characteristics comparable to that we would expect in clinical practice.	Yes
Did the setting reflect UK practice?	Adequate: UK study site with retreatment eligibility assessed from week 16	Yes
Were outcome measures clinically relevant and reliable? Were outcomes assessed using objective criteria?	Adequate: clinically relevant BCVA and anatomical outcomes reported and assessed using reliable methods and objective criteria.	Yes
Was outcome assessment blind to exposure status?	Adequate: outcome assessments conducted monthly. Treatment exposure monitored alongside outcome assessments.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Adequate: efficacy outcomes were evaluated in the intent-to-treat population of all randomised patients. The last-observation-carried-forward method was used for imputation of missing values.	Yes

Pacella et al. 2013		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Do the selected patients represent the eligible population for the intervention?	Adequate: patients with persistent DMO and visual impairment relevant to the insufficiently responsive to non-corticosteroid therapy population of the decision problem.	Yes
How was selection bias minimised?	Adequate: patients enrolled based on explicit inclusion/exclusion criteria.	Yes
Were the patients enrolled similar at the outset of the study in terms of prognostic factors, for example, severity of disease to the eligible population?	Adequate: baseline characteristics comparable to that we would expect in clinical practice.	Yes
Did the setting reflect UK practice?	Adequate: Italian study site but treatment administered and effect monitored in line with UK practice.	Yes
Were outcome measures clinically relevant and reliable? Were outcomes assessed using objective criteria?	Adequate: clinically relevant BCVA and anatomical outcomes reported and assessed using reliable methods and objective criteria.	Yes
Was outcome assessment blind to exposure status?	Not applicable: single treatment	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not applicable: all patients completed the study and thus were included in the final analysis	N/A
Zucchiatti et al. 2014		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Do the selected patients represent the eligible population for the intervention?	Adequate: patients with persistent DMO and visual impairment relevant to the insufficiently responsive to non-corticosteroid therapy population of the decision problem.	Yes
How was selection bias minimised?	Adequate: patients enrolled based on explicit inclusion/exclusion criteria.	Yes
Were the patients enrolled similar at the outset of the study in terms of prognostic factors, for example, severity of disease to the eligible population?	Adequate: baseline characteristics comparable to that we would expect in clinical practice.	Yes

Did the setting reflect UK practice?	Adequate: Italian study site but treatment administered and effect monitored in line with UK practice.	Yes
Were outcome measures clinically relevant and reliable? Were outcomes assessed using objective criteria?	Adequate: clinically relevant BCVA and anatomical outcomes reported and assessed using reliable methods and objective criteria.	Yes
Was outcome assessment blind to exposure status?	Not applicable: single treatment	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not applicable: all patients completed the study and thus were included in the final analysis	N/A

Giralt et al. 2014		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Do the selected patients represent the eligible population for the intervention?	Adequate: patients with refractory DMO and visual impairment relevant to the insufficiently responsive to non-corticosteroid therapy population of the decision problem.	Yes
How was selection bias minimised?	Unclear: patient eligibility criteria not detailed (abstract only).	Not clear
Were the patients enrolled similar at the outset of the study in terms of prognostic factors, for example, severity of disease to the eligible population?	Unclear: baseline characteristics not detailed (abstract only).	Not clear
Did the setting reflect UK practice?	Adequate: Spanish study site but treatment appears to be administered and effect monitored in line with UK practice.	Yes
Were outcome measures clinically relevant and reliable? Were outcomes assessed using objective criteria?	Not clear: clinically relevant BCVA and anatomical outcomes reported but assessment method not detailed (abstract only).	Not clear
Was outcome assessment blind to exposure status?	Not applicable: single treatment	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not applicable: all patients completed the study and thus were included in the final analysis	N/A
Gusson et al. 2013		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Do the selected patients represent the eligible population for the intervention?	Adequate: patients with DMO and visual impairment undergoing cataract surgery, relevant to the pseudophakic population of the decision problem.	Yes
How was selection bias minimised?	Unclear: patient eligibility criteria not detailed (abstract only).	Not clear
Were the patients enrolled similar at the outset of the study in terms of prognostic factors, for example, severity of disease to the eligible population?	Unclear: baseline characteristics not detailed (abstract only).	Not clear

Did the setting reflect UK practice?	Adequate: Italian study site but treatment appears to be administered and effect monitored in line with UK practice.	Yes
Were outcome measures clinically relevant and reliable? Were outcomes assessed using objective criteria?	Not clear: clinically relevant BCVA and anatomical outcomes reported but assessment method not detailed (abstract only).	Not clear
Was outcome assessment blind to exposure status?	Not applicable: single treatment	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not applicable: all patients completed the study and thus were included in the final analysis	N/A
Bonet-Fernandez et al. 2014		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Do the selected patients represent the eligible population for the intervention?	Adequate: patients with refractory DMO and visual impairment relevant to the insufficiently responsive to non-corticosteroid therapy population of the decision problem.	Yes
How was selection bias minimised?	Unclear: patient eligibility criteria not detailed (poster only).	Not clear
Were the patients enrolled similar at the outset of the study in terms of prognostic factors, for example, severity of disease to the eligible population?	Unclear: baseline characteristics not detailed (posteronly).	Not clear
Did the setting reflect UK practice?	Adequate: Spanish study site but treatment appears to be administered and effect monitored in line with UK practice. Retreatment eligibility assessed from week 12	Yes
Were outcome measures clinically relevant and reliable? Were outcomes assessed using objective criteria?	Adequate: clinically relevant BCVA and anatomical outcomes reported and assessed using reliable methods and objective criteria.	Yes
Was outcome assessment blind to exposure status?	Adequate: outcome assessments conducted monthly. Treatment exposure monitored alongside outcome assessments.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not applicable: all patients completed the study and thus were included in the final analysis	N/A

9.5 Results of company's non-RCT evidence review

Box 40. Results of the review of non-RCT evidence as reported in the CS pgs X

Prospective Studies

The largest prospective study that included significant numbers of treatment resistant patients followed 76 DMO patients for 9 months. Patients were included with DMO with macular thickness of >300 um and visual acuity 15-72 ETDRS. After initial DEX700 treatment, retreatment with DEX700 was performed if after 3 months CRT was >150um or a VA loss of >10 letters was observed. Laser photocoagulation therapy was permitted alongside DEX700 treatment after day 21. In this study, 40 patients fulfilled the criteria of treatment resistance which was defined as >6 months not responding to other treatments. Reinjection was performed in 32 of the refractory patients with an average time to reinjection of 4.9 months. Laser photocoagulation was performed in 18 of the refractory patients and 29 of the naïve patients (Bonet et al. 2014).

In the treatment resistant group the visual gains were 6.2 ETDRS letters at 9 months accompanied with a retinal thickness reduction of 287um. The peak acuity gain was at 2 months with a steady decline thereafter.[141]

From a safety perspective a transient rise in intraocular pressure was noted in 7.9% and observed cataract in 2.6% of the total study population.[141]

In the second largest prospective study, CHAMPLAIN, clinical efficacy and safety of DEX700 in DMO patients with a previous pars plana vitrectomy was investigated. In total, 55 patients were recruited with macular thickness >275um and baseline VA between 24-70 ETDRS letters. They were treated with a single DEX700 implant at baseline and followed for 26 weeks. The average VA at baseline was 56 ETDRS letters and the duration of DMO was 43 months, representing a resistant patient group. 55% of patients had been previously treated with anti-VEGF, 66% had been previously treated with laser photocoagulation, 55% had received previous steroid treatment and 84% of patients had received at least 2 types of previous treatment.[132]

The primary endpoint of central retinal thickness was significantly reduced at all timepoints in the study with reductions of -156um at week 8 and -39um at week 26. Correspondingly, the improvements in VA were significant with +6 letters at week 8 and +3 letters at week 26.[132]

In safety analysis, two of the phakic patients (17%) had cataract progression and 17% of patients initiated topical IOP lowering therapy during the study period.[132]

In post-hoc HRQL analysis of vitrectomised patients treated with DEX700 in CHAMPLAIN, general vision and near vision activities improvements, measured using the NEI-VFQ-25 tool, were observed as soon as week 4 and maintained through week 26. Peak HRQL effect was observed at week 20 with statistically significant improvement observed for general vision and the five subscales: near vision activities, distance vision activities, social functioning, role limitations and mental health.[170]

In the open-label study, OCTOME, 30 patients treated with DEX700 for macular oedema of varied origin (not exclusively DMO) were prospectively followed for 36 weeks. 24 of the patients had macular oedema secondary to diabetes. Patients were retreated at weeks 16, 20 and 24 if there was an increase in macular thickness of 50um or a reduction in visual acuity of >5 ETDRS letters from the previous visit. 60% of patients had had previous laser treatment.[135]

Retreatment was carried out in 6/30 patients (all DMO) at weeks 16 (x2), week 30 (x1) and week 24 (x2).The primary endpoint of change in macular thickness showed a significant reduction from 527um at all timepoints to 32 weeks. This was reported as similar for diabetic and non-diabetic patients. The patients had visual acuity improvements of +8, +9, +9, +8 letters at weeks 4, 8, 12 and 28 respectively (all significant) and numerical improvements +5.5, +4, +5.5, +3.6, +4.2 at weeks 16, 20 24, 32 and 36.[135]

Two patient's required IOP lowering therapy and a single patient developed a vitreous haemorrhage.[135]

In a further prospective study, persistent DMO patients were followed for 6 months after DEX700 administration. Patients who had a visual acuity of 1.0 logMAR and 0.3 logMAR and macular thickness of >275um were included. At baseline, the average BCVA was 0.67 logMAR and duration of DMO was 46.3 months. Of the 17 DMO patients included, 13 had received previous anti-VEGF treatment. Retreatment with DEX700 was permitted after month 4 if visual acuity worsened by >10 ETDRS letters or there was an increase in macular thickness of >150um. This occurred in 2 patients.[136]

The visual acuity significantly increased to 0.525, 0.52 logMAR at months 1 and 3, and non-significantly at month 4 and 6 to 0.56 and 0.76 logMAR respectively. The central macular thickness improved from 519um to 292um, 347um at months 1 and 3 and was numerically lower at months 4 and 6 respectively (476um and 494um).[136]

The safety profile was reported as consistent with the phase II and III registration studies.[136]

The final prospective study was a small case series reporting on the results of 7 patients with chronic diffuse DMO undergoing cataract surgery and receiving simultaneous DEX700 at time of surgery. The primary observation reported was that BCVA was increased during the 6 months of follow up and the mean foveal thickness was reduced for 4-5 months in patients receiving DEX700 compared to those undergoing cataract surgeries without DEX700 treatment.[140]

Retrospective studies

The largest retrospective study identified, MOZART, examined the records of 74 DMO patients (resistant and naïve) with at least 6 months of follow up after initial DEX700 treatment. Patients were included with central retinal thickness of >350um and visual acuity between 25-70 ETDRS letters. Of the total population, 86% of the patients were previously treated. Reinjection with DEX700 occurred in 14 patients and the average time to reinjection was 5.4 months.[134]

The BCVA at baseline was 55 letters. This increased to a plateau of +8.5 letters at 2-4 months and then gradually decreased to +7.6 letters after 6 months. The central retinal thickness decreased by -239um in month 2 and -134 at month 6.[134]

There was no worsening of cataract observed and IOP treatment was increased in 17% of patients during the study.[134]

A further three retrospective studies investigated the clinical efficacy of DEX700 exclusively in patients with persistent / chronic refractory DMO.

The largest of these examined patients with persistent DMO (defined as foveal thickness >250um despite laser, anti-VEGF or steroid treatment) with at least 6 months of follow up from a single

DEX700 treatment. Of the 58 patients examined, 88% had received previous focal laser therapy, 74% had received previous panretinal photocoagulation therapy, 76% had received previous anti-VEGF therapy, 67% had received previous intra-vitreal triamcinolone therapy and 41% had a previous pars plana vitrectomy.[133]

The foveal thickness decreased significantly by 196um, 202um and 123um at months 1, 3, 6 respectively. The improvements in BCVA were also significant throughout the study with 0.66 logMAR at baseline and 0.52 logMAR, 0.44 logMAR, and 0.51 logMAR at months 1, 3, 6 respectively. [133]

A smaller retrospective study followed 9 patients with persistent DMO for 6 months. All patients had been previously treated and had CRT of >300um at least 90 days after the treatment. The previous treatment consisted of grid laser therapy (9/9), anti-VEGF therapy (7/9), steroid therapy (3/9) and pan retinal photocoagulation (2/9). Average duration of DMO at baseline was 50 months and BCVA at baseline was 0.74 logMAR. This improved to 0.62 logMAR (p=0.02), 0.59 logMAR (0.02)and 0.63 logMAR (p=0.06) and 0.73 logMAR (p=0.4) at months 1, 3, 4, 6 respectively. The CRT decreased from 502um at baseline to 271um (p=0.007), 325um (p=0.03), 462um and 537um (p=0.33), at months 1, 3, 4, 6 respectively (Zucchiatti et al. 2014).

One patient required topical IOP lowering therapy and there was no report of cataract progression.[137]

A final retrospective study followed 33 patients with chronic refractory DMO for 6 months. The patients included had all received at least one prior treatment of laser, anti-VEGF or steroid therapy. The central macular thickness reduced from 497um at baseline to 295um (p<0.0001) at month 3 and 357um (p=0.0015) at month 6.[139]

In summary, the non-RCT data set supports the RCT evidence base conclusions that DEX700 provides significant benefits in patients with DMO for 6 months or more post implantation though some patients do appear to benefit from more frequent retreatment intervals to maximise outcomes.

9.6 Details of 024 and BEVORDEX

Table 138: Eligibility criteria in the 024 and BEVORDEX trials (adapted from CS Table 14, pg115)

Trial number	Inclusion criteria	Exclusion criteria
[redacted]	[redacted]	[redacted]

		[redacted]
BEV ORD EX	>18 years; diagnosis of DM Type 1 or 2; DMO affecting the fovea in one or both eyes for which laser treatment is unlikely to be helpful; BCVA 17-72 letters; retinal thickness >250 micron in 1mm subfield on OCT; previous macular laser treatment, or the investigator believes laser treatment is unlikely to be helpful; IOP <22mmHg; women of childbearing potential to have negative pregnancy test at screening and prior to treatment; written informed consent.	Known allergy to agents used in the study; women who are pregnant, nursing or planning a pregnancy or not using reliable contraception; uncontrolled glaucoma or controlled with more than 1 medication or with 1 medication and glaucomatous field defects; loss of vision due to any other cause; any ocular condition that would prevent VA improvement despite resolution of oedema; treatment with IVTA within the last 6 months or peribulbar TA within the last 3 months or anti vascular endothelial growth factor drugs: bevacizumab, ranibizumab and pegaptanib within the last 2 months; cataract surgery within the last 6 months; retinal laser treatment within the last 3 months; history of herpes virus infection in the study eye; media opacity including cataract that already precludes adequate macular photography and laser treatment, or cataract that is likely to require surgery within 2 years; known allergies to dexamethasone or bevacizumab; receiving systemic steroid treatment >5mg prednisolone daily or equivalent; intercurrent severe disease such as septicemia, any condition which would affect follow-up or photographic documentation; history of chronic renal failure requiring dialysis or renal transplant; blood pressure >180/110; condition or is in a situation that in the investigators opinion may put the patient at significant risk, may confound the study results or may interfere significantly with the patients participation in the study.

Abbreviations used in the table **:** BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; DEX700, dexamethasone; DM, diabetes mellitus; DMO, diabetic macular oedema; ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, fluocinolone acetonide; GFR, glomerular filtration rate; HRQL, health-related quality of life; IOP, intraocular pressure; IVTA, intravitreal triamcinolone; OCT, optical coherence tomography; PS DDS, posterior segment drug delivery system; TA, triamcinolone; VA, visual acuity; YAG, yttrium aluminium garnet.

Notes: Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Source: Boyer et al. 2014[67]; Callanan et al. 2013[125]; CSR 206207-010[121]; CSR 206207-011[123]; CSR 206207-012[126]; CSR 206207-024[124]; Gillies et al. 2010[117]; Gillies et al. 2014b[127]; Haller et al. 2010[5]; Kuppermann et al. 2007[1]

Table 139: Baseline characteristics of participants in 024 and BEVORDEX (reproduced from CS Table 16, pg124)

	024				BEVORDEX				
	[redacted]	[redacted]			DEX700 (n=46)	BEV (n=42)			
Demographics									
Age, mean (years (SD)	[redacted]	[redacted]			61.4 (9.0)	62.2 (10.5)			
Male, n (%)	[redacted]	[redacted]			30 (65.2)	26 (61.9)			
Caucasian, n (%)	[redacted]	[redacted]			NR	NR			
Disease Characteristics									
Duration of DM, mean years (SD)	[redacted]	[redacted]			16.7 (10.3)	16.7 (10.7)			
Type 2 DM, n (%)	[redacted]	[redacted]			NR	NR			
Baseline HbA1c, mean % (SD)	[redacted]	[redacted]			7.7 (2.5)	7.8 (2.1)			
IOP in study eye, mean mmHg (SD)	[redacted]	[redacted]			14.8 (3.0)	14.5 (2.4)			
Duration of DMO, mean months (SD)	[redacted]	[redacted]			NR	NR			
Duration of DMO ≥3 years, n (%)*	[redacted]	[redacted]			NR	NR			
Pseudophakic lens, n (%)	[redacted]	[redacted]			16 (34.8)	10 (23.8)			
Baseline VA, mean letters (SD)	[redacted]	[redacted]			55.5 (12.5)	56.3 (11.9)			
Baseline CRT, mean µm (SD)	[redacted]	[redacted]			474.3 (95.9)	503 (140.9)			
CRT ≥400 µm, n (%)*	[redacted]	[redacted]			NR	NR			
Study eye was BSE, n (%)	[redacted]	[redacted]			NR	NR			
Bilateral DMO, n (%)	[redacted]	[redacted]			NR	NR			
Treatment history for DMO in the study eye									
Treatment naïve, n (%)	[redacted]	[redacted]			NR	NR			
Prior laser, n	[redacted]	[redacted]			NR	NR			

(%)									
Prior anti-VEGF, n (%)	[redacted]	[redacted]			NR	NR			
Prior steroid, n (%)	[redacted]	[redacted]			NR	NR			

Abbreviations used in the table **:** BEV, bevacizumab; BSE, best seeing eye; CRT, central retinal thickness; DEX700, dexamethasone; DM, diabetes mellitus; DMO, diabetic macular oedema; DR, diabetic retinopathy; HbA1c, glycosylated haemoglobin; IOP, intraocular pressure; NR, not reported; OCT, ocular computed tomography; RAN, ranibizumab; RCT, randomised clinical trial; SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor.

Note: *analysed *post-hoc* due to licence/HTA restrictions on use of comparator therapies.

Source: Callanan et al. 2013[125]; CSR 206207-012[126]; CSR 206207-024[124]; Clinical Story PLACID final[143]; Clinical Story 024 fina[144]l; Haller et al. 2010; Gillies et al. 2014b[127]

Table 140: Primary and secondary outcomes of 024 and BEVORDEX (Reproduced from CS Table 17, pg129)

Trial number	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
024	The primary outcome was mean BCVA average change from baseline through Month 12 (final analysis). BCVA was measured using the ETDRS method. Average change was measured using the arithmetic mean of individual change from baseline BCVA values across the follow-up period.	[redacted]	[redacted]	[redacted]
BEVORDEX	The comparison of the proportion of eyes gaining 10 letters of visual acuity between the bevacizumab and dexamethasone	BCVA is a clinically relevant endpoint used to guide treatment decisions and is directly referenced in the decision problem.	Secondary outcomes included change from baseline in BCVA at all post-baseline timepoints and the proportion of patients with improving/worsening vision based on various	BCVA is a clinically relevant endpoint used to guide treatment decisions and is directly referenced in the decision problem.

	implant arms. BCVA was measured using the ETDRS method.	Change in BCVA using an ETDRS eye chart is globally accepted as the gold standard for VA measurements in clinical trials and is adopted in clinical practice.	categorisations. BCVA was measured using the ETDRS method. Anatomical outcomes included the change in CRT. CRT was assessed by OCT. Patient satisfaction was measured through a treatment satisfaction questionnaire. Throughout the course of the study, all adverse events were monitored and reported, including seriousness, severity, action taken and relationship to study drug.	CRT is a clinically relevant endpoint used to guide treatment decisions. Health-related quality of life and safety are clinically relevant endpoints, directly referenced in the decision problem. All outcomes are consistent with other studies of therapeutic agents for DMO.

Abbreviations used in the table: AUC, area under the curve; BCVA, best corrected visual acuity; CRT, central retinal thickness; DEX700, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study; DMO, diabetic macular oedema; OCT, ocular computed tomography; VA, visual acuity.

Source: Boyer et al. 201467; Callanan et al. 2013125; CSR 206207-010121; CSR 206207-011123; CSR 206207-012126; CSR 206207-024124; Gillies et al. 2010; Gillies et al. 2014b127; Haller et al. 20105.

Table 141: Summary of statistical analyses in 024 and BEVORDEX (Reproduced from CS Table 18, pg136)

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
024	[redacted]	[redacted]	[redacted]	[redacted]

			[redacted]	
BEV ORD EX	That there is a difference in change in visual acuity resulting from treatment with intravitreal bevacizumab compared with dexamethasone implant in eyes with advanced macular oedema; that there is a difference in degree of resolution of macular oedema resulting from treatment with intravitreal bevacizumab compared with dexamethasone implant in eyes with advanced macular oedema; that both intravitreal bevacizumab and dexamethasone implants have a manageable	The statistical analysis of the incidence of improved visual acuity at 24 months will be performed using logistic regression with generalised estimating equations to take account of the correlation between data from participants with both eyes in the study.	A minimum of 35 eyes per group is required for 80% power of detecting this difference as significant at the two-sided 5% level. Adjusting for an estimated loss to follow up of 12% of eyes, we aim to recruit a minimum of 40 eyes per group, if time permits we will aim to recruit 50 eyes per group in order to increase the power of the study.	Data was analysed on the basis of intention to treat. The last observation carried forward method was used when patients were lost to follow-up. A sensitivity analysis was performed for the primary outcome, improvement of 10 letters, to investigate the potential effect of the missing data, by alternately assuming that all missing eyes had actually improved by 10 letters or that all missing eyes had not improved by 10 letters.

	and acceptable safety profile in eyes with DMO.			

Abbreviations used in the table: ANCOVA, analysis of covariance; ANOVA, analysis of variance; AUC, area under the curve; BCVA, best corrected visual acuity; CI, confidence interval; DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ITT, intend to treat; OCT, ocular computed tomography; PS DDS, posterior segment drug delivery system; RVO, retinal vein occlusion.

Source: Boyer et al. 2014[67]; Callanan et al. 2013[125]; CSR 206207-010[121]; CSR 206207-011[123]; CSR 206207-012[126]; CSR 206207-024[124]; Gillies et al. 2010[117]; Gillies et al. 2014b[127]; Haller et al. 2010[5]; Kuppermann et al. 2007[1]

[redacted]

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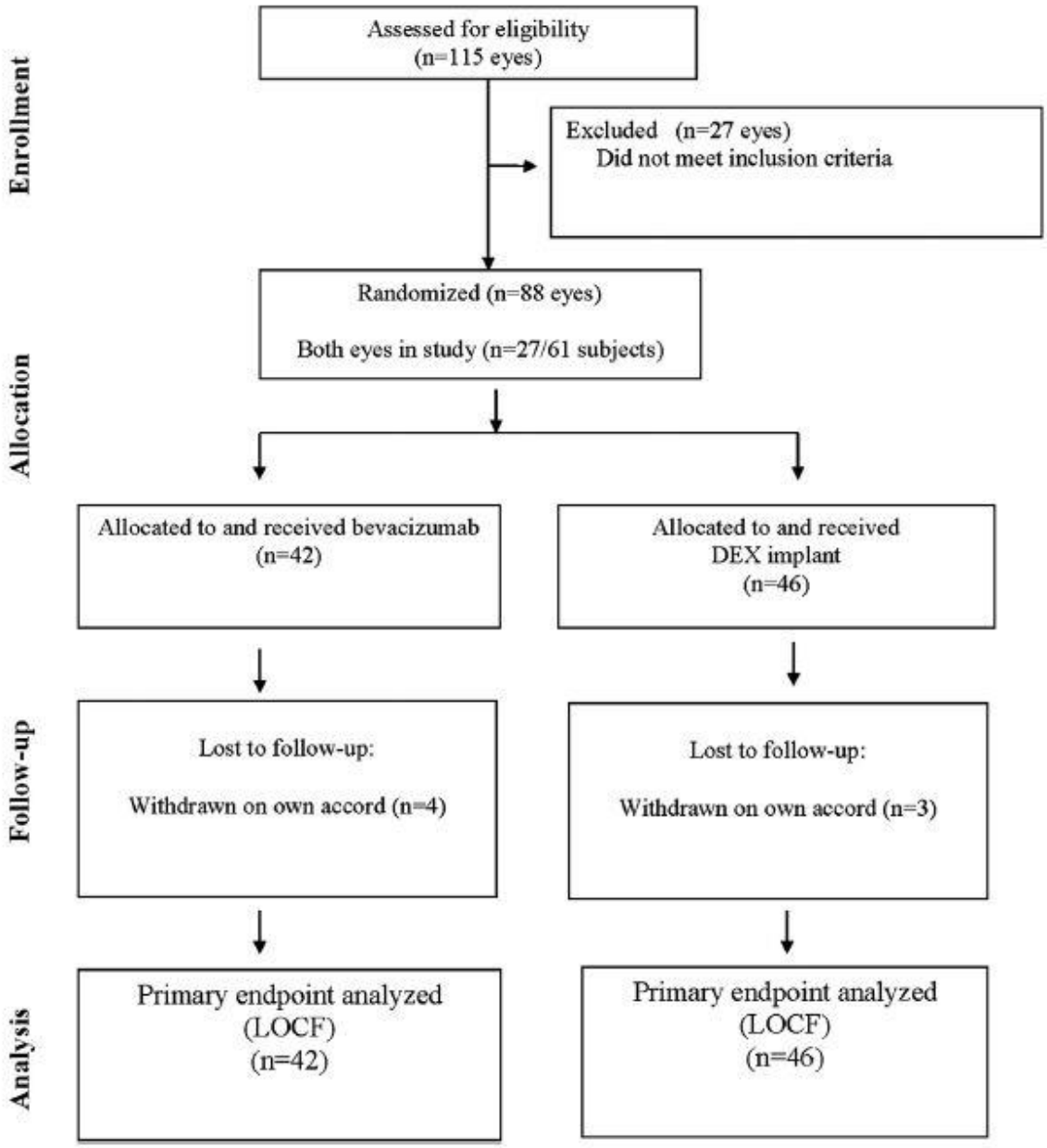
Source: [redacted]

Figure 39: BEVORDEX interim CONSORT flow chart (BEVRODEX is ongoing and the CONSORT flow chart presented is that for patient flow at 12 months [Reproduced from CS Figure 13, pg148]).



Source: Gillies et al. 2014b[127]

[redacted]

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9.6.1 [redacted] BEVORDEX treatment effectiveness results

Box 41. BEVORDEX BCVA outcomes (reproduced from CS pg181)

In ITT analysis at 12 months of the proportion of eyes achieving at least a 10-letter improvement in visual acuity, no significant difference was observed between DEX700 and bevacizumab treatment arms: 41% (19/46) versus 40% (17/42); p=0.99. Sensitivity analysis showed that results from this analysis were robust to the presence of missing data.[127]

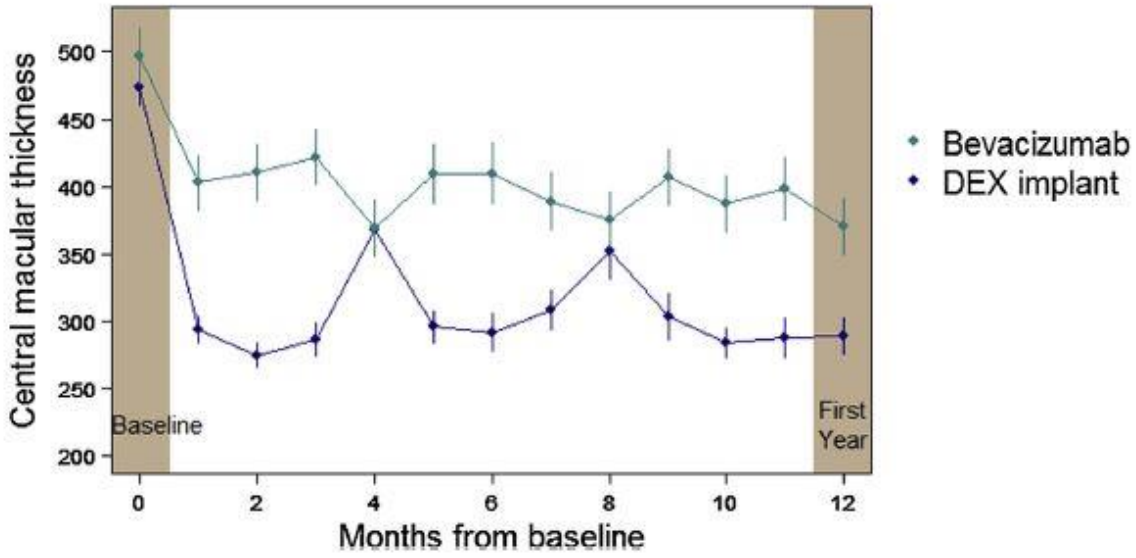
For patients with both eyes in the study (treated with DEX700 in one eye and bevacizumab in the other), there was no correlation in the change in BCVA at 12 months between each eye (p=0.006). [127]

Five of the 46 (11%) of DEX700 treated eyes have lost ≥10 letters from baseline at 12 months compared with none of the bevacizumab treated eyes. The authors note this is mostly due to un-operated cataract with four of the five cases attributed to cataract density.[128] [127]

The mean improvement in BCVA in ITT analysis at 12 months was 8.9 letters (95% CI, 6.27-11.6) for eyes treated with bevacizumab and 5.6 letters (95% CI, 0.90-10.4) for eyes treated with DEX700. This difference did not reach statistical significance at the 95% level, p=0.24. Median gain in BCVA was 6.5 letters for bevacizumab treated eyes compared with 7.5 letters for DEX700 treated eyes.[127]

In patients who were pseudophakic at baseline, a numerically greater mean change in BCVA from baseline at 12 months was observed with DEX700 (n=16) at 10.4 letters compared with bevacizumab treatment (n =10) at 7.7 letters. This difference failed to reach statistical significance (p=0.47) but was not powered to detect statistical significance.[127]

Figure 42: Mean central macular thickness for each month of follow-up in BEVORDEX, µm (reproduced from CS Table 28 pg182)



Source: Gillies et al. 2014b[127]

Box 42. BEVORDEX HRQL and mortality results (reproduced from CS pg182)

HRQL Outcomes

Bilateral DMO patients (n=27) treated with randomised treatment in the right eye and the reverse treatment in the left eye stated their treatment preference with the use of a standardised questionnaire. Of the 24 responding patients, 11 (46%) preferred DEX700, 8 (33%) preferred bevacizumab and 5 (21%) had no preference (p>0.1).[127]

Mortality

No deaths have been reported from the BEVORDEX trial to date.[127]

9.6.2 BEVORDEX treatment exposure and safety results

Box 43. Company summary of treatment exposure and adverse events in BEVORDEX (reproduced from CS pg261)

Treatment Exposure

At 12 months, the mean number of DEX700 injections administered was 2.7. Further details have not been reported to date but this suggests a number of eyes randomised to DEX700 treatment did not require retreatment every 4 months. At the same time point, the mean number of bevacizumab injections administered was markedly higher at 8.6.

Safety Profile

IOP elevation and cataract were the most common AE associated with DEX700 treatment and intravitreal injection associated adverse events most commonly associated with bevacizumab treatment. Both treatments were well tolerated systemically during the first year of the study. The most frequent systemic adverse event was the worsening of hypertension, which occurred in 6.7% (1/15), 10.5% (2/19), and 14.8% (4/27) of patients who received BEV only, DEX700 only and both treatments, respectively.

IOP Adverse Events

In the first 12 months of the study, 12 eyes demonstrated an IOP of more than 25 mmHg at least once; all 12 eyes had been treated with DEX700. Generally IOP elevations were managed successfully with either observation or topical IOP-lowering medications. One eye from each group required selective laser trabeculopathy to control IOP but both eyes were from the same patient.

Cataract Adverse Events

Of the 88 eyes randomised in BEVORDEX, 62 had a phakic lens at baseline. Of these eyes, 4 required cataract surgery during the first 12 months of the study: 1 treated with BEV and 3 treated with DEX700. The same number of patients again experienced an increase in cataract by >2 grades but have not received cataract surgery to date.

Table 151: Ocular adverse events across the BEVORDEX trial, n (%) (reproduced from CS Table 55, pg261)

	DEX700 (n=46)	**BEV (n=42)**
IOP elevation ≥5 mmHg	21 (45.7)	8 (19.0)
IOP elevation ≥10 mmHg	9 (19.6)	0
Increase in cataract by >2 grades	6 (13.0)	2 (4.8)
Cataract surgery	3 (6.5)	1 (2.4)
Vision decrease of >10 letters	5 (10.9)	0
Vitreous haemorrhage	2 (4.3)	0
Floaters	5 (10.9)	0
Subconjunctival haemorrhage	2 (4.3)	3 (7.1)
Eye pain	1 (2.2)	3 (7.1)
Itching	3 (6.5)	0
Blepharitis	1 (2.2)	1 (2.4)
Epiphora	0	2 (4.8)

Abbreviations used in the table: BEV, bevacizumab; DEX700, dexamethasone 700µg; IOP, intraocular pressure.
Source: Gillies et al. 2014b [127]

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Abbreviations used in the table [redacted]						

9.7 Company's economic search strategies

The initial searches were performed in Medline and Medline In-Process and other non-indexed citations, Embase, Health Technology Assessment Database (HTA), NHS Economic evaluation database (NHS EED), Database of Abstracts of Review and Effects (DARE), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and EconLit on 24th February 2014. The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean) for each database are presented below. For the updated searches (17th July 2014) a date limit of 2014 was applied to the initial search terms.

A. Search strategies developed by the company for identification of economic evidence; adapted from CS, Appendix 10, pgs 583-597

Box 44. Search strategy for cost-effectiveness studies: Medline and Medline in Process & Other Non-Indexed citations: Ovid. 1946 to Present

1. exp Diabetes Mellitus/
2. diabetic retinopathy/
3. diabet$.tw.

4. or/1-3
5. Macular Edema/
6. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.
7. maculopath$.tw.
8. (dme or dmo).tw.
9. or/5-8
10. 4 and 9
11. exp Dexamethasone/
12. dexamethasone.tw.
13. DEX700.tw.
14. 50-02-2.rn.
15. aflibercept.tw.
16. eylea.tw.
17. 845771-78-0.rn.
18. bevacizumab.tw.
19. avastin.tw.
20. 216974-75-3.rn.
21. ranibizumab.tw.
22. lucentis.tw.
23. 347396-82-1.rn.
24. Triamcinolone Acetonide/
25. (triamcinolone acetonide or ivta).tw.
26. taiftol.tw.
27. trigon.tw.
28. 76-25-5.rn.
29. exp Fluocinolone Acetonide/
30. fluocinolone acetonide.tw.
31. iluvien.tw.
32. 67-73-2.rn.
33. Laser Coagulation/
34. photocoagulat$.tw.
35. (photo and coagulat$).tw.
36. ((focal or grid) adj3 laser$).tw.
37. ((argon or diode or micropulse) adj3 (coagulat$ or laser$)).tw.
38. or/11-37
39. 10 and 38
40. exp "Costs and Cost Analysis"/
41. Economics/
42. exp Economics, Hospital/

43. exp Economics, Medical/
44. Economics, Nursing/
45. exp models, economic/
46. Economics, Pharmaceutical/
47. exp "Fees and Charges"/
48. exp Budgets/
49. budget$.tw.
50. ec.fs.
51. cost$.ti.
52. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
53. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
54. (price$ or pricing$).tw.
55. (financial or finance or finances or financed).tw.
56. (fee or fees).tw.
57. (value adj2 (money or monetary)).tw.
58. quality-adjusted life years/
59. (qaly or qalys).af.
60. (quality adjusted life year or quality adjusted life years).af.
61. or/40-60
62. 39 and 61

Box 45. Search strategy for cost-effectiveness studies: Embase: Ovid.

1. exp diabetes mellitus/
2. diabetic retinopathy/
3. diabet$.tw.
4. or/1-3
5. exp retina macular edema/
6. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.
7. maculopath$.tw.
8. (dme or dmo).tw.
9. or/5-8
10. 4 and 9
11. dexamethasone/
12. 50-02-2.rn.
13. aflibercept/
14. aflibercept.tw.
15. eylea.tw.
16. 845771-78-0.rn.

17. bevacizumab/
18. bevacizumab.tw.
19. avastin.tw.
20. 216974-75-3.rn.
21. ranibizumab/
22. ranibizumab.tw.
23. lucentis.tw.
24. 347396-82-1.rn.
25. triamcinolone acetonide/
26. (triamcinolone acetonide or ivta).tw.
27. taiftol.tw.
28. trigon.tw.
29. 76-25-5.rn.
30. fluocinolone acetonide/
31. fluocinolone acetonide.tw.
32. iluvien.tw.
33. 67-73-2.rn.
34. exp laser coagulation/
35. photocoagulat$.tw.
36. (photo and coagulat$).tw.
37. ((focal or grid) adj3 laser$).tw.
38. ((argon or diode or micropulse) adj3 (coagulat$ or laser$)).tw.
39. or/11-38
40. 10 and 39
41. Socioeconomics/
42. Cost benefit analysis/
43. Cost effectiveness analysis/
44. Cost of illness/
45. Cost control/
46. Economic aspect/
47. Financial management/
48. Health care cost/
49. Health care financing/
50. Health economics/
51. Hospital cost/
52. (fiscal or financial or finance or funding).tw.
53. Cost minimization analysis/
54. (cost adj estimate$).mp.
55. (cost adj variable$).mp.
56. (unit adj cost$).mp.

57. or/41-56

58. 40 and 57

Box 46. Search strategy for cost-effectiveness studies: Cochrane Library: Wiley Interscience; NHS EED: Wiley Interscience. 1995-present; HTA: Wiley Interscience. 1995-present; DARE: Wiley Interscience. 1995-present

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees

#2 MeSH descriptor: [Diabetic Retinopathy] this term only

#3 diabet*:ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Macular Edema] this term only

#6 ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) next/3 (edema* or oedema*)):ti,ab,kw

#7 maculopath*:ti,ab,kw

#8 (dme or dmo):ti,ab,kw

#9 #5 or #6 or #7 or #8

#10 #4 and #9

#11 MeSH descriptor: [Dexamethasone] explode all trees

#12 dexamethasone:ti,ab,kw

#13 50-02-2:ti,ab,kw

#14 aflibercept:ti,ab,kw

#15 eylea:ti,ab,kw

#16 845771-78-0:ti,ab,kw

#17 bevacizumab:ti,ab,kw

#18 avastin:ti,ab,kw

#19 216974-75-3:ti,ab,kw

#20 ranibizumab:ti,ab,kw

#21 lucentis:ti,ab,kw

#22 347396-82-1:ti,ab,kw

#23 MeSH descriptor: [Triamcinolone Acetonide] this term only

#24 (triamcinolone acetonide or ivta):ti,ab,kw

#25 taiftol:ti,ab,kw

#26 trigon:ti,ab,kw

#27 76-25-5:ti,ab,kw

#28 MeSH descriptor: [Fluocinolone Acetonide] explode all trees

#29 fluocinolone acetonide

#30 iluvien:ti,ab,kw

#31 67-73-2:ti,ab,kw

#32 MeSH descriptor: [Laser Coagulation] this term only

#33 photocoagulat*:ti,ab,kw

#34 (photo and coagulat*):ti,ab,kw

#35 ((focal or grid) next/3 laser*):ti,ab,kw

#36 ((argon or diode or micropulse) next/3 (coagulat* or laser*)):ti,ab,kw

#37 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36

#38 #10 and #37

Box 47. Search strategy for cost-effectiveness studies: CINAHL: EBSCO

S54 S37 AND S53

S53 S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S52

S52 quality adjusted life year or quality adjusted life years

S51 qaly or qalys

S50 value and (money or monetary)

S49 fee or fees

S48 financial or finance or finances or financed

S47 price* or pricing*

S46 TI economic* or pharmacoeconomic* or pharmaco-economic*

S45 AB cost* and (effective* or utilit* or benefit* or minimi*)

S44 cost*

S43 budget*

S42 (MH "Budgets")

S41 (MH "Fees and Charges+")

S40 (MH "Economics, Pharmaceutical")

S39 (MH "Economics")

S38 (MH "Costs and Cost Analysis+")

S37 S9 AND S36

S36 S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35

S35 ((argon or diode or micropulse) N3 (coagulat* or laser*))

S34 ((focal or grid) N3 laser*)

S33 (photo and coagulat*)

S32 photocoagulat*

S31 (MH "Laser Therapy+")

S30 67-73-2

S29 iluvien

S28 fluocinolone acetonide

S27 76-25-5

S26 trigon

S25 taiftol
S24 (triamcinolone acetonide or ivta)
S23 (MH "Triamcinolone")
S22 347396-82-1
S21 lucentis
S20 ranibizumab
S19 216974-75-3
S18 avastin
S17 bevacizumab
S16 845771-78-0
S15 eylea
S14 aflibercept
S13 50-02-2
S12 DEX700
S11 dexamethasone
S10 (MH "Dexamethasone+")
S9 S4 and S8
S8 S5 or S6 or S7
S7 (dme or dmo)
S6 maculopath*
S5 ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) N3 (edema* or oedema*))
S4 S1 or S2 or S3
S3 diabet*
S2 (MH "Diabetic Retinopathy")
S1 (MH "Diabetes Mellitus+")

Box 48. Search strategy for cost-effectiveness studies: EconLit: Ovid.

1. dexamethasone.tw.
2. DEX700.tw.
3. aflibercept.tw.
4. eylea.tw.
5. bevacizumab.tw.
6. avastin.tw.
7. ranibizumab.tw.
8. lucentis.tw.
9. (triamcinolone acetonide or ivta).tw.
10. taiftol.tw.
11. trigon.tw.

12. fluocinolone acetonide.tw.

13. iluvien.tw.

14. photocoagulat$.tw.

15. (photo and coagulat$).tw.

16. ((focal or grid) adj3 laser$).tw.

17. ((argon or diode or micropulse) adj3 (coagulat$ or laser$)).tw.

18. or/1-17

B. Search strategy developed by the company for identification of data on health related quality of life; adapted from CS, Appendix 12, pgs 624- 632

Box 49. Search strategy for utility studies: Medline and Medline in Process & Other Non-Indexed citations: Ovid. 1946 to Present

1. exp Diabetes Mellitus/

2. diabetic retinopathy/

3. diabet$.tw.

4. or/1-3

5. Macular Edema/

6. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.

7. maculopath$.tw.

8. (dme or dmo).tw.

9. or/5-8

10. 4 and 9

11. "Quality of Life"/

12. (qol or (quality adj2 life)).ab,ti.

13. (value adj2 (money or monetary)).tw.

14. value of life/

15. quality adjusted life year/

16. quality adjusted life.tw.

17. (qaly$ or qald$ or qale$ or qtime$).tw.

18. disability adjusted life.tw.

19. daly$.tw.

20. health status indicators/

21. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

22. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

23. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

24. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
25. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
26. (euroqol or euro qol or eq5d or eq 5d).tw.
27. (hql or hqol or h qol or HRQL or hr qol).tw.
28. (hye or hyes).tw.
29. health$ year$ equivalent$.tw.
30. health utilit$.tw.
31. (hui or hui1 or hui2 or hui3).tw.
32. disutilit$.tw.
33. rosser.tw.
34. (quality adj2 wellbeing).tw.
35. qwb.tw.
36. (willingness adj2 pay).tw.
37. standard gamble$.tw.
38. time trade off.tw.
39. time tradeoff.tw.
40. tto.tw.
41. letter.pt.
42. editorial.pt.
43. comment.pt.
44. 41 or 42 or 43
45. or/11-40
46. 45 not 44
47. 10 and 46

Box 50. Search strategy for utility studies: Embase: Ovid.

1. exp diabetes mellitus/
2. diabetic retinopathy/
3. diabet$.tw.
4. or/1-3
5. exp retina macular edema/
6. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.
7. maculopath$.tw.
8. (dme or dmo).tw.
9. or/5-8
10. 4 and 9

11. "Quality of Life"/
12. (qol or (quality adj2 life)).ti,ab.
13. (value adj2 (money or monetary)).tw.
14. socioeconomics/
15. quality adjusted life year/
16. (qaly$ or qald$ or qale$ or qtime$).tw.
17. disability adjusted life.tw.
18. daly$.tw.
19. health survey/
20. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
21. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
22. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
23. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
24. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
25. (euroqol or euro qol or eq5d or eq 5d).tw.
26. (hql or hqol or h qol or HRQL or hr qol).tw.
27. (hye or hyes).tw.
28. health$ year$ equivalent$.tw.
29. health utilit$.tw.
30. (hui or hui1 or hui2 or hui3).tw.
31. disutilit$.tw.
32. rosser.tw.
33. (quality adj2 wellbeing).tw.
34. qwb.tw.
35. (willingness adj2 pay).tw.
36. standard gamble$.tw.
37. time trade off.tw.
38. time tradeoff.tw.
39. tto.tw.
40. letter.pt.
41. editorial.pt.
42. comment.pt.
43. 40 or 41 or 42
44. or/11-39
45. 44 not 43
46. 10 and 45

Box 51. Search strategy for utility studies: Cochrane Library: Wiley Interscience; NHS EED: Wiley Interscience. 1995-present; HTA: Wiley Interscience. 1995-present; DARE: Wiley Interscience. 1995-present

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees

MeSH descriptor: [Diabetic Retinopathy] this term only

diabet*:ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Macular Edema] this term only

#6 ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) next/3 (edema* or oedema*)):ti,ab,kw

#7 maculopath*:ti,ab,kw

#8 (dme or dmo):ti,ab,kw

#9 #5 or #6 or #7 or #8

#10 #4 and #9

#11 MeSH descriptor: [Quality of Life] explode all trees

#12 (qol or (quality next/2 life)):ti,ab,kw

#13 MeSH descriptor: [Value of Life] this term only

#14 value and (money or monetary):ti,ab,kw

#15 MeSH descriptor: [Quality-Adjusted Life Years] this term only

#16 (quality adjusted life):ti,ab,kw

#17 (qaly* or qald* or qale* or qtime*):ti,ab,kw

#18 disability adjusted life:ti,ab,kw

#19 daly*:ti,ab,kw

#20 MeSH descriptor: [Health Status Indicators] explode all trees

#21 sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six:ti,ab,kw

#22 sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six:ti,ab,kw

#23 sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve:ti,ab,kw

#24 sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen:ti,ab,kw

#25 shortfrom sixteen or short form sixteen:ti,ab,kw

#26 sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty:ti,ab,kw

#27 euroqol or euro qol or eq5d or eq 5deuroqol or euro qol or eq5d or eq 5d:ti,ab,kw

#28 5d:ti,ab,kw

#29 hql or hqol or h qol or HRQL or hr qol:ti,ab,kw

#30 hye or hyes:ti,ab,kw

#31 health* year* equivalent*:ti,ab,kw

#32 health utilit*:ti,ab,kw

#33 hui or hui1 or hui2 or hui3:ti,ab,kw

#34 disutilit*:ti,ab,kw

#35 rosser:ti,ab,kw

#36 qwb:ti,ab,kw

#37 willingness to pay:ti,ab,kw

#38 quality of wellbeing:ti,ab,kw

#39 time trade off:ti,ab,kw

#40 time tradeoff:ti,ab,kw

#41 tto:ti,ab,kw

#42 letter:pt

editorial:pt

comment:pt

#43 #40 or #41 or #42

#44 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39

#45 #44 not #43

#46 #10 and #45

Box 52. Search strategy for utility studies: CINAHL: EBSCO

S45 S9 AND S44

S44 S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39

S43 S40 or S41 or S42

S42 PT comment

S41 PT editorial

S40 PT letter

S39 TI tto or AB tto

S38 TI time tradeoff or AB time tradeoff

S37 TI time trade off or AB time trade off

S36 TI standard gamble* or AB standard gamble*

S35 TI willingness N2 pay or AB willingness N2 pay

S34 TI qwb or AB qwb

S33 TI quality N2 wellbeing or AB quality N2 wellbeing

S32 TI rosser or AB rosser

S31 TI disutilit* or AB disutilit*

S30 TI (hui or hui1 or hui2 or hui3) or AB (hui or hui1 or hui2 or hui3)

S29 TI health utilit* or AB health utilit*

S28 TI health* year* equivalent* or AB health* year* equivalent*

S27 TI (hye or hyes) or AB (hye or hyes)

S26 TI (hql or hqol or h qol or HRQL or hr qol) or AB (hql or hqol or h qol or HRQL or hr qol)

S25 TI (euroqol or euro qol or eq5d or eq 5d) or AB (euroqol or euro qol or eq5d or eq 5d)

S24 TI (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or AB (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)

S23 TI (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) or AB (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)

S22 TI (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or AB (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)

S21 TI quality adjusted life or AB quality adjusted life

S20 TI (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or AB (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)

S19 TI (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or AB (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)

S18 (MH "Health Status Indicators")

S17 TI daly* or AB daly*

S16 TI disability adjusted life or AB disability adjusted life

S15 TI (qaly* or qald* or qale* or qtime*) or AB (qaly* or qald* or qale* or qtime*)

S14 (MH "Quality-Adjusted Life Years")

S13 (MH "Economic Value of Life")

S12 TI value and TI (money or monetary) or AB value and AB (money or monetary)

S11 TI (qol or (quality N2 life)) or AB (qol or (quality N2 life))

S10 (MH "Quality of Life")

S9 S4 and S8

S8 S5 or S6 or S7

S7 (dme or dmo)

S6 maculopath*

S5 ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) N3 (edema* or oedema*))

S4 S1 or S2 or S3

S3 diabet*

S2 (MH "Diabetic Retinopathy")

S1 (MH "Diabetes Mellitus+")

Box 53. Search strategy for utility studies: EconLit: Ovid

1. diabet$.tw.
2. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.
3. maculopath$.tw.
4. (dme or dmo).tw.
5. 2 or 3 or 4
6. 1 and 5

C. Search strategy developed by the company for identification of data on relevant resource use and costs; adapted from CS, Appendix 13, pgs 638-645

Box 54. Search strategy for resource identification, measurement and valuation: Medline and Medline in Process & Other Non-Indexed citations: Ovid. 1946 to Present

1. exp Diabetes Mellitus/
2. diabetic retinopathy/
3. diabet$.tw.
4. or/1-3
5. Macular Edema/
6. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.
7. maculopath$.tw.
8. (dme or dmo).tw.
9. or/5-8
10. 4 and 9
11. exp "Costs and Cost Analysis"/
12. Economics/
13. exp Economics, Hospital/
14. exp Economics, Medical/
15. Economics, Nursing/
16. exp models, economic/
17. Economics, Pharmaceutical/
18. exp "Fees and Charges"/
19. exp Budgets/
20. budget$.tw.
21. ec.fs.
22. cost$.ti.
23. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.

24. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
25. (price$ or pricing$).tw.
26. (financial or finance or finances or financed).tw.
27. (fee or fees).tw.
28. (value adj2 (money or monetary)).tw.
29. quality-adjusted life years/
30. (qaly or qalys).af.
31. (quality adjusted life year or quality adjusted life years).af.
32. Resource Allocation/
33. health care rationing/
34. (resource$ adj2 (allocat$ or utili$ or usage or use$)).tw.
35. or/11-34
36. 10 and 35

Box 55. Search strategy for resource identification, measurement and valuation: Embase: Ovid

1. exp diabetes mellitus/
2. diabetic retinopathy/
3. diabet$.tw.
4. or/1-3
5. exp retina macular edema/
6. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.
7. maculopath$.tw.
8. (dme or dmo).tw.
9. or/5-8
10. 4 and 9
11. Socioeconomics/
12. Cost benefit analysis/
13. Cost effectiveness analysis/
14. Cost of illness/
15. Cost control/
16. Economic aspect/
17. Financial management/
18. Health care cost/
19. Health care financing/
20. Health economics/
21. Hospital cost/
22. (fiscal or financial or finance or funding).tw.

23. Cost minimization analysis/

24. (cost adj estimate$).mp.

25. (cost adj variable$).mp.

26. (unit adj cost$).mp.

27. resource allocation/

28. (resource$ adj2 (allocat$ or utili$ or usage or use$)).tw.

29. or/11-28

30. 10 and 29

Box 56. Search strategy for resource identification, measurement and valuation: Cochrane Library: Wiley Interscience. NHS EED: Wiley Interscience. 1995-present; HTA: Wiley Interscience. 1995-present; DARE: Wiley Interscience. 1995-present

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees

#2 MeSH descriptor: [Diabetic Retinopathy] this term only

#3 diabet*:ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Macular Edema] this term only

#6 ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) next/3 (edema* or oedema*)):ti,ab,kw

#7 maculopath*:ti,ab,kw

#8 (dme or dmo):ti,ab,kw

#9 #5 or #6 or #7 or #8

#10 #4 and #9

Box 57. Search strategy for resource identification, measurement and valuation: CINAHL: EBSCO

S28 S9 AND S27

S27 S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26

S26 (resource* N2 (allocat* or utili* or usage or use*))

S25 (MH "Resource Allocation+")

S24 quality adjusted life year or quality adjusted life years

S23 qaly or qalys

S22 value and (money or monetary)

S21 fee or fees

S20 financial or finance or finances or financed

S19 price* or pricing*

S18 TI economic* or pharmacoeconomic* or pharmaco-economic*

S17 AB cost* and (effective* or utilit* or benefit* or minimi*)

S16 cost*

S15 budget*

S14 (MH "Budgets")

S13 (MH "Fees and Charges+")

S12 (MH "Economics, Pharmaceutical")

S11 (MH "Economics")

S10 (MH "Costs and Cost Analysis+")

S9 S4 and S8

S8 S5 or S6 or S7

S7 (dme or dmo)

S6 maculopath*

S5 ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) N3 (edema* or oedema*))

S4 S1 or S2 or S3

S3 diabet*

S2 (MH "Diabetic Retinopathy")

S1 (MH "Diabetes Mellitus+")

Box 58. Search strategy for resource identification, measurement and valuation: EconLit: Ovid.

1. diabet$.tw.

2. ((central or diabetes or diabetic or fovea or macular or macular or retina or retinal) adj3 (edema$ or oedema$)).tw.

3. maculopath$.tw.

4. (dme or dmo).tw.

5. 2 or 3 or 4

6. 1 and 5

9.8 Regression analyses undertaken by the company on VFQ-UI and EQ-5D data

A. Results of the regression analyses undertaken by the company on VFQ-UI and EQ-5D data, including goodness-of-fit statistics

Table 154. Covariate-adjusted linear regression of VFQ-UI scores at baseline (Table 12 in company clarification response)

Parameters	Specifications								
	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]	

Parameters	Specifications														
	Main model + 1 covariate			Main model + 2 covariates			Main model + 3 covariates			Main model + 4 covariates			Main model + 5 covariates		
	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							
Gen Health – Very Good vs. Poor							
Gen Health - Good vs. Poor							
Gen Health - Fair vs. Poor							
N							
R-square							

Abbreviations used in the table: BCVA, best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; Gen, general; SE, standard error; VFQ-UI, Visual Functioning Questionnaire Utility Index; WSE, worse-seeing eye.

Note: Bold entries indicate $p<0.05$

Table 154 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 R2 (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 βBCVA_BSE >βBCVA_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. Alternate Model 1 which included only BCVA_BSE had a similar coefficient on BCVA_BSE (β=0.005) and R2 compared with the Main Model; however, Alternate Model 2 which included BCVA_WSE only fit the data less well (R2 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 R2 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. 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 155: Covariate-adjusted mixed effects* analysis of VFQ-UI scores across all time points (Table 13 in company clarification response)

Parameters	Specifications								
	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]	

Parameters	Specifications														
	Main model + 1 covariate			Main model + 2 covariates			Main model + 3 covariates			Main model + 4 covariates			Main model + 5 covariates		
	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]
Gen Health – Very Good vs. Poor					[redacted]
Gen Health - Good vs. Poor					[redacted]
Gen Health - Fair vs. Poor					[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Likelihood Ratio test for Fit vs Main Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: 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; VFQ-UI, Visual Functioning Questionnaire Utility Index; WSE, worse-seeing eye.

Note: * Patient, Treatment and Study (010 vs 011) included as random effects; Bold entries indicate $p<0.05$

Table 155 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.

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 βBCVA_BSE >βBCVA_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 βBCVA_BSE and βBCVA_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 156: Covariate-adjusted mixed effects* analysis of VFQ-UI scores adjusting for ocular adverse events (Table 14 in company clarification response)

Parameters	Specifications								
	Main model			Main model + cataract			Main model + cataract surgery		
	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]
Cataract_BSE				[redacted]	[redacted]	[redacted]			
Cataract_WSE				[redacted]	[redacted]	[redacted]			
Cataract Surgery							[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]	

Parameters	Specifications								
	Main model			Main model + IOP change ≥10mmHg			Main model + IOP ≥30mmHg		
	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]

Abbreviations used in the table: 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; VFQ-UI, Visual Functioning Questionnaire Utility Index; WSE, worse-seeing eye.

Note: * Patient, Treatment and Study (010 vs 011) included as random effects; Bold entries indicate $p<0.05$

Table 156 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.

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 the 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.

Table 157: Covariate-adjusted linear regression of EQ-5D utility scores at baseline (Table 15 in company clarification response)

Parameters	Specifications								
	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]	

Parameters	Specifications														
	Main model + 1 covariate			Main model + 2 covariates			Main model + 3 covariates			Main model + 4 covariates			Main model + 5 covariates		
	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													[redacted]	[redacted]	[redacted]

Good vs. Poor					
Gen Health - Good vs. Poor					
Gen Health - Fair vs. Poor					
N					
R-square					

Abbreviations used in the table: BCVA, best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; Gen, general; SE, standard error; WSE, worse-seeing eye.

Note: Bold entries indicate p<0.05

Table 157 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.

B. Impact of adverse events on utility – extra analyses provided by the company in response to clarification question B3b; amended by the ERG

The proportion of the total population experiencing cataract extraction was calculated as per Table 158.

Table 158: Cataract extraction (based on data reported in Table 70)

Treatment	% Phakic			% phakic patients with cataract extraction			% total population with cataract extraction*		
	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%

Abbreviations used in table: DEX700, dexamethasone 700µ; ERG, evidence review group.
Note: *Calculated as % phakic patients with cataract extraction multiplied by % phakic.

According to the company, multiplying the % total population with cataract extraction by the coefficient for cataract surgery (-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 159. 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 159: 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**

Abbreviations used in the table: DEX700, dexamethasone 700µ; ERG, evidence review group; QALY, quality-adjusted life year.

The ERG amended the above figures using the corrected figures for the annual risk of cataract in patients with DMO treated with DEX700, as estimated by the ERG in Table 72. The amended figures for cataract extraction and for QALY decrement due to cataract extraction are shown in Table 160 and Table 161, respectively.

Table 160: Cataract extraction (amended by ERG, based on data reported in Table 70)

Treatment	% Phakic	% phakic patients with	% total population with

				cataract extraction			cataract extraction*		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
DEX700	75.50%	66.57%	41.50%	11.83%	37.66%	26.39%	8.9%	25.1%	11.0%
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%
Abbreviations used in the table: DEX700, dexamethasone 700µ; ERG, evidence review group. **Note**: *Calculated as % phakic patients with cataract extraction multiplied by % phakic.									

Table 161: QALY decrement due to cataract extraction, amended by ERG

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**	**-0.000338**
Fluocinolone acetonide	0.000000	-0.000421	-0.000093	**-0.000513**	**0.000131**
Abbreviations used in the table: DEX700, dexamethasone 700µ; ERG, evidence review group; QALY, quality-adjusted life year.					

It is noted that the amended figures double the QALY decrement due to cataract extraction, but the QALY difference between DEX700 and its comparators due to cataract extraction remains minimal.

The proportion of the total population experiencing raised IOP ≥30mmHg or initiation of IOP medication is assumed to be as per Table 162.

Table 162: Raised IOP (based on data reported in Table 71)

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%
Abbreviations used in the table: DEX700, dexamethasone 700µ; IOP, intraocular pressure; QALY, quality-adjusted life year.			

According to the company, multiplying the % total population with raised IOP by the coefficient for raised IOP ≥30mmHg or initiation of IOP medication (-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 163. 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.

Table 163: 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
Abbreviations used in the table: DEX700, dexamethasone 700µ; IOP, intraocular pressure; QALY, quality-adjusted life year.					

9.9 Results of one-way sensitivity analysis

Table 164. Results of OWSA on the Net Monetary Benefit (NMB), illustrating the parameters considered comparing dexamethasone with watch and wait in the population of DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy.

Base case NMB, DEX700 PRN vs. watch and wait: £2,780 (DEX700 PRN dominates)			
Parameter		**Lower**	**Upper**
1	Unit cost residential care	£1,406	£4,295
2	% patients with SVL requiring residential care	£1,376	£4,265
3	Discount rate – costs	£4,079	£1,778
4	Proportion outpatient procedures: DEX700 PRN	£1,509	£2,780
5	Probability of improving vision: Natural history	£3,382	£2,182
6	Probability of worsening vision: Natural history	£3,176	£2,307
7	Mortality hazard ratio due to DMO	£2,330	£3,196
8	Proportion treated unilaterally in BSE	£3,105	£2,407
9	Proportion discontinuing due to loss of efficacy watch and wait: Month 9	£2,501	£3,081
10	Discount rate - benefits	£2,506	£3,064
11	Proportion treated bilaterally	£3,000	£2,511
12	Proportion discontinuing due to loss of efficacy watch and wait: Month 6	£3,021	£2,600
13	Bilateral BSE baseline % patients in HS4	£3,003	£2,604
14	Utility equation coefficient BSE	£2,944	£2,584
15	Proportion discontinuing due to loss of efficacy watch and wait: Month 15	£2,932	£2,595
16	Bilateral BSE baseline % patients in HS2	£2,616	£2,944
17	Proportion discontinuing due to loss of efficacy watch and wait: Month 12	£2,597	£2,912
18	Proportion discontinuing due to AEs DEX700 PRN: Month 9	£2,661	£2,935
19	Proportion of fellow eyes developing DMO	£2,658	£2,903
20	Number of appointments for bilateral treatment: DEX700 PRN	£2,943	£2,726
21	Unit cost outpatient procedure	£2,908	£2,695
22	Unilateral WSE baseline % patients in HS4	£2,694	£2,900
23	Utility equation coefficient WSE	£2,707	£2,901
24	% patients with vitreous haemorrhage DEX700 PRN: Year 3	£2,691	£2,870
25	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 9	£2,959	£2,780
26	Bilateral BSE baseline % patients in HS1	£2,852	£2,675
27	% patients receiving treatment DEX700 PRN: Month 12	£2,714	£2,883
28	Routine monitoring visits DEX700 PRN re-tx from Month 6 : Year 1	£2,696	£2,850
29	% patients receiving treatment DEX700 PRN: Month 6	£2,868	£2,715
30	Proportion discontinuing due to AEs DEX700 PRN: Month 6	£2,723	£2,874
31	Routine monitoring visits watch and wait : Year 1	£2,856	£2,707
32	Bilateral WSE baseline % patients in HS4	£2,855	£2,706
33	% patients receiving treatment DEX700 PRN: Month 18	£2,856	£2,708
34	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 6	£2,716	£2,863
35	Proportion discontinuing due to AEs DEX700 PRN: Month 15	£2,708	£2,853
36	Baseline age	£2,840	£2,703
37	% patients receiving treatment DEX700 PRN: Month 24	£2,848	£2,713

38	Unit cost community care	£2,841	£2,719
39	% patients with SVL requiring community care	£2,723	£2,844
40	Unit cost IOP check	£2,723	£2,844
41	Routine monitoring visits DEX700 PRN re-tx from Month 6 : Year 2	£2,711	£2,830
42	Unilateral BSE baseline % patients in HS4	£2,849	£2,735
43	% patients with vitreous haemorrhage DEX700 PRN: Year 1	£2,834	£2,727
44	% patients receiving treatment DEX700 PRN: Month 30	£2,737	£2,843
45	Proportion discontinuing due to loss of efficacy watch and wait: Month 21	£2,824	£2,718
46	Unilateral BSE baseline % patients in HS2	£2,826	£2,722
47	Routine monitoring visits watch and wait : Year 2	£2,723	£2,827
48	% patients receiving treatment DEX700 PRN: Month 21	£2,831	£2,727
49	% patients receiving treatment DEX700 PRN: Month 33	£2,732	£2,829
50	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 15	£2,742	£2,838
51	% patients receiving treatment DEX700 PRN: Month 15	£2,826	£2,730
52	% patients receiving treatment DEX700 PRN: Month 27	£2,826	£2,732
53	% patients receiving treatment DEX700 PRN: Month 9	£2,824	£2,731
54	Proportion discontinuing due to AEs DEX700 PRN: Month 12	£2,825	£2,732
55	Unit cost vitrectomy	£2,722	£2,814
56	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 12	£2,823	£2,731
57	Unilateral WSE baseline % patients in HS1	£2,746	£2,833
58	Proportion discontinuing due to loss of efficacy watch and wait: Month 18	£2,847	£2,763
59	Routine monitoring visits DEX700 PRN re-tx from Month 6 : Year 3	£2,822	£2,740
60	Cataract extraction rate DEX700 PRN: Year 3	£2,819	£2,742
61	IOP checks DEX700 PRN re-tx from Month 6 : Year 1	£2,818	£2,742
62	Unit cost cataract extraction procedure	£2,809	£2,733
63	% patients with retinal detachment DEX700 PRN: Year 3	£2,818	£2,743
64	Routine monitoring visits watch and wait : Year 3	£2,752	£2,826
65	Cataract extraction rate DEX700 PRN: Year 2	£2,817	£2,747
66	Unilateral BSE baseline % patients in HS1	£2,744	£2,813
67	Unilateral WSE baseline % patients in HS2	£2,799	£2,730
68	Bilateral BSE baseline % patients in HS5	£2,747	£2,814
69	Unilateral WSE baseline % patients in HS5	£2,811	£2,746
70	Unit cost Fluorescein angiography	£2,750	£2,813
71	Proportion male	£2,812	£2,752
72	Untreated BSE baseline % patients in HS3	£2,745	£2,804
73	% patients with raised IOP DEX700 PRN: Year 1	£2,806	£2,752
74	Fluorescein angiographys DEX700 PRN re-tx from Month 6 : Year 1	£2,807	£2,753
75	Mortality hazard ratio due to diabetes	£2,807	£2,754
76	IOP checks DEX700 PRN re-tx from Month 6 : Year 2	£2,802	£2,749
77	Bilateral WSE baseline % patients in HS1	£2,801	£2,748
78	% patients with vitreous haemorrhage DEX700 PRN: Year 2	£2,754	£2,807
79	Fluorescein angiographys watch and wait : Year 1	£2,668	£2,721
80	% cases of raised IOP treated with medications: DEX700 PRN	£2,759	£2,809
81	Untreated BSE baseline % patients in HS2	£2,806	£2,760

82	Proportion discontinuing due to AEs DEX700 PRN: Month 21	£2,806	£2,760
83	% patients with raised IOP DEX700 PRN: Year 3	£2,798	£2,753
84	Bilateral WSE baseline % patients in HS2	£2,799	£2,758
85	Cataract extraction rate DEX700 PRN: Year 1	£2,802	£2,761
86	Proportion discontinuing due to loss of efficacy watch and wait: Month 27	£2,801	£2,761
87	Bilateral WSE baseline % patients in HS5	£2,799	£2,761
88	IOP checks DEX700 PRN re-tx from Month 6 : Year 3	£2,763	£2,800
89	Unit cost depression	£2,762	£2,799
90	% patients with SVL requiring treatment for depression	£2,793	£2,758
91	Fluorescein angiographys watch and wait : Year 2	£2,763	£2,798
92	Proportion discontinuing due to AEs DEX700 PRN: Month 18	£2,767	£2,801
93	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 18	£2,767	£2,801
94	Optical coherence tomographys DEX700 PRN re-tx from Month 6 : Year 1	£2,797	£2,764
95	% patients with raised IOP DEX700 PRN: Year 2	£2,795	£2,762
96	Optical coherence tomographys watch and wait : Year 1	£2,764	£2,797
97	Proportion discontinuing due to loss of efficacy watch and wait: Month 33	£2,760	£2,792
98	Untreated BSE baseline % patients in HS5	£2,798	£2,767
99	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 21	£2,798	£2,767
100	% patients with retinal detachment DEX700 PRN: Year 2	£2,796	£2,766
101	Optical coherence tomographys DEX700 PRN re-tx from Month 6 : Year 2	£2,770	£2,798
102	Fluorescein angiographys watch and wait : Year 3	£2,765	£2,792
103	% patients with endophthalmitis DEX700 PRN: Year 1	£2,787	£2,762
104	Optical coherence tomographys watch and wait : Year 2	£2,793	£2,768
105	Untreated BSE baseline % patients in HS6	£2,768	£2,793
106	% patients with endophthalmitis DEX700 PRN: Year 2	£2,786	£2,764
107	Untreated BSE baseline % patients in HS4	£2,770	£2,791
108	Unilateral BSE baseline % patients in HS5	£2,786	£2,765
109	Proportion phakic eyes at baseline	£2,791	£2,771
110	Unit cost Iridectomy	£2,789	£2,769
111	Unit cost Iridotomy	£2,784	£2,765
112	Cataract extraction rate watch and wait: Year 3	£2,784	£2,765
113	Optical coherence tomographys DEX700 PRN re-tx from Month 6 : Year 3	£2,772	£2,790
114	Optical coherence tomographys watch and wait : Year 3	£2,789	£2,772
115	Proportion discontinuing due to AEs DEX700 PRN: Month 30	£2,787	£2,771
116	Bilateral BSE baseline % patients in HS3	£2,758	£2,774
117	Annual risk of cataract extraction DMO population	£2,773	£2,788
118	Proportion discontinuing due to AEs DEX700 PRN: Month 27	£2,786	£2,773
119	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 27	£2,774	£2,787
120	Unit cost endophthalmitis procedure	£2,784	£2,773
121	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 30	£2,775	£2,786
122	Routine monitoring visits no treatment : Year 3	£2,784	£2,774
123	% patients with SVL requiring hip replacement	£2,776	£2,786

124	Untreated WSE baseline % patients in HS4	£2,775	£2,785
125	Unit cost hip fracture	£2,776	£2,785
126	Routine monitoring visits no treatment : Year 2	£2,815	£2,806
127	Unit cost Trabeculectomy	£2,787	£2,779
128	Unit cost procedure for attachment of retina	£2,777	£2,785
129	Mean days of Prostaglandins required	£2,783	£2,775
130	Cataract extraction rate watch and wait: Year 1	£2,785	£2,777
131	Mean days of Combination required	£2,777	£2,785
132	Cataract extraction rate watch and wait: Year 2	£2,777	£2,784
133	Unilateral WSE baseline % patients in HS3	£2,784	£2,777
134	Proportion discontinuing due to loss of efficacy watch and wait: Month 24	£2,777	£2,784
135	Unilateral BSE baseline % patients in HS3	£2,772	£2,778
136	Mean days of CA inhibitors required	£2,777	£2,783
137	Untreated WSE baseline % patients in HS5	£2,783	£2,778
138	Bilateral WSE baseline % patients in HS3	£2,784	£2,780
139	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 33	£2,779	£2,782
140	Proportion discontinuing due to AEs DEX700 PRN: Month 33	£2,779	£2,782
141	Fluorescein angiographys no treatment : Year 3	£2,783	£2,780
142	Proportion discontinuing due to AEs DEX700 PRN: Month 24	£2,779	£2,782
143	Untreated WSE baseline % patients in HS3	£2,781	£2,779
144	Fluorescein angiographys no treatment : Year 2	£2,779	£2,782
145	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 24	£2,779	£2,782
146	Routine monitoring visits no treatment : Year 4	£2,779	£2,782
147	Optical coherence tomographys no treatment : Year 3	£2,779	£2,781
148	Optical coherence tomographys no treatment : Year 2	£2,782	£2,780
149	Untreated WSE baseline % patients in HS1	£2,781	£2,780
150	Proportion discontinuing due to loss of efficacy watch and wait: Month 30	£2,780	£2,781
151	Mean days of Brimonidine required	£2,780	£2,781
152	Routine monitoring visits no treatment : Year 5	£2,781	£2,780
153	Fluorescein angiographys no treatment : Year 4	£2,781	£2,780
154	Mean days of Beta-blockers required	£2,780	£2,781
155	Optical coherence tomographys no treatment : Year 4	£2,780	£2,781
156	Fluorescein angiographys no treatment : Year 5	£2,780	£2,781
157	Routine monitoring visits no treatment : Year 1	£2,780	£2,781
158	Optical coherence tomographys no treatment : Year 5	£2,780	£2,781
159	Fluorescein angiographys no treatment : Year 1	£2,780	£2,781
160	Optical coherence tomographys no treatment : Year 1	£2,780	£2,780
161	Untreated WSE baseline % patients in HS2	£2,781	£2,781
162	Utility equation constant	£2,780	£2,780
163	Discount rate - life years	£2,780	£2,780
164	Unilateral BSE baseline % patients in HS6	£2,780	£2,780
165	Untreated WSE baseline % patients in HS6	£2,780	£2,780
166	Unilateral WSE baseline % patients in HS6	£2,780	£2,780
167	Untreated BSE baseline % patients in HS1	£2,780	£2,780

168	Bilateral BSE baseline % patients in HS6	£2,780	£2,780
169	Bilateral WSE baseline % patients in HS6	£2,780	£2,780
170	Mean BCVA in HS1	£2,780	£2,780
171	Mean BCVA in HS2	£2,780	£2,780
172	Mean BCVA in HS3	£2,780	£2,780
173	Mean BCVA in HS4	£2,780	£2,780
174	Mean BCVA in HS5	£2,780	£2,780
175	Mean BCVA in HS6	£2,780	£2,780
176	Unit cost day case procedure	£2,780	£2,780
177	Unit cost laser procedure	£2,780	£2,780
178	Average cost of next line treatment (discontinue due to AEs): Initial treatment DEX700 PRN	£2,780	£2,780
179	Average cost of next line treatment (discontinue due to AEs): Initial treatment watch and wait	£2,780	£2,780
180	Average cost of next line treatment (discontinue due to Rescue): Initial treatment DEX700 PRN	£2,780	£2,780
181	Average cost of next line treatment (discontinue due to Rescue): Initial treatment watch and wait	£2,780	£2,780
182	Unit cost Routine monitoring visit	£2,780	£2,780
183	Unit cost Optical coherence tomography	£2,780	£2,780
184	Unit cost blind registration	£2,780	£2,780
185	Unit cost low vision aids	£2,780	£2,780
186	Unit cost low vision rehabilitation	£2,780	£2,780
187	Proportion outpatient procedures: watch and wait	£2,780	£2,780
188	Number of appointments for bilateral treatment: watch and wait	£2,780	£2,780
189	% patients receiving treatment DEX700 PRN: Month 0	£2,780	£2,780
190	% patients receiving treatment DEX700 PRN: Month 36	£2,780	£2,780
191	% patients receiving treatment DEX700 PRN: Month 39	£2,780	£2,780
192	% patients receiving treatment DEX700 PRN: Month 42	£2,780	£2,780
193	% patients receiving treatment DEX700 PRN: Month 45	£2,780	£2,780
194	% patients receiving treatment DEX700 PRN: Month 48	£2,780	£2,780
195	% patients receiving treatment DEX700 PRN: Month 51	£2,780	£2,780
196	% patients receiving treatment DEX700 PRN: Month 54	£2,780	£2,780
197	% patients receiving treatment DEX700 PRN: Month 57	£2,780	£2,780
198	Proportion discontinuing due to AEs DEX700 PRN: Month 36	£2,780	£2,780
199	Proportion discontinuing due to AEs DEX700 PRN: Month 39	£2,780	£2,780
200	Proportion discontinuing due to AEs DEX700 PRN: Month 42	£2,780	£2,780
201	Proportion discontinuing due to AEs DEX700 PRN: Month 45	£2,780	£2,780
202	Proportion discontinuing due to AEs DEX700 PRN: Month 48	£2,780	£2,780
203	Proportion discontinuing due to AEs DEX700 PRN: Month 51	£2,780	£2,780
204	Proportion discontinuing due to AEs DEX700 PRN: Month 54	£2,780	£2,780
205	Proportion discontinuing due to AEs DEX700 PRN: Month 57	£2,780	£2,780
206	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 36	£2,780	£2,780
207	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 39	£2,780	£2,780
208	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 42	£2,780	£2,780

209	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 45	£2,780	£2,780
210	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 48	£2,780	£2,780
211	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 51	£2,780	£2,780
212	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 54	£2,780	£2,780
213	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 57	£2,780	£2,780
214	Proportion discontinuing due to loss of efficacy watch and wait: Month 36	£2,780	£2,780
215	Proportion discontinuing due to loss of efficacy watch and wait: Month 39	£2,780	£2,780
216	Proportion discontinuing due to loss of efficacy watch and wait: Month 42	£2,780	£2,780
217	Proportion discontinuing due to loss of efficacy watch and wait: Month 45	£2,780	£2,780
218	Proportion discontinuing due to loss of efficacy watch and wait: Month 48	£2,780	£2,780
219	Proportion discontinuing due to loss of efficacy watch and wait: Month 51	£2,780	£2,780
220	Proportion discontinuing due to loss of efficacy watch and wait: Month 54	£2,780	£2,780
221	Proportion discontinuing due to loss of efficacy watch and wait: Month 57	£2,780	£2,780
222	IOP checks no treatment : Year 1	£2,780	£2,780
223	IOP checks no treatment : Year 2	£2,780	£2,780
224	IOP checks no treatment : Year 3	£2,780	£2,780
225	IOP checks no treatment : Year 4	£2,780	£2,780
226	IOP checks no treatment : Year 5	£2,780	£2,780
227	Routine monitoring visits DEX700 PRN re-tx from Month 6 : Year 4	£2,780	£2,780
228	Routine monitoring visits DEX700 PRN re-tx from Month 6 : Year 5	£2,780	£2,780
229	Optical coherence tomographys DEX700 PRN re-tx from Month 6 : Year 4	£2,780	£2,780
230	Optical coherence tomographys DEX700 PRN re-tx from Month 6 : Year 5	£2,780	£2,780
231	Fluorescein angiographys DEX700 PRN re-tx from Month 6 : Year 2	£2,780	£2,780
232	Fluorescein angiographys DEX700 PRN re-tx from Month 6 : Year 3	£2,780	£2,780
233	Fluorescein angiographys DEX700 PRN re-tx from Month 6 : Year 4	£2,780	£2,780
234	Fluorescein angiographys DEX700 PRN re-tx from Month 6 : Year 5	£2,780	£2,780
235	IOP checks DEX700 PRN re-tx from Month 6 : Year 4	£2,780	£2,780
236	IOP checks DEX700 PRN re-tx from Month 6 : Year 5	£2,780	£2,780
237	Routine monitoring visits watch and wait : Year 4	£2,780	£2,780
238	Routine monitoring visits watch and wait : Year 5	£2,780	£2,780
239	Optical coherence tomographys watch and wait : Year 4	£2,780	£2,780
240	Optical coherence tomographys watch and wait : Year 5	£2,780	£2,780
241	Fluorescein angiographys watch and wait : Year 4	£2,780	£2,780
242	Fluorescein angiographys watch and wait : Year 5	£2,780	£2,780
243	IOP checks watch and wait : Year 1	£2,780	£2,780
244	IOP checks watch and wait : Year 2	£2,780	£2,780
245	IOP checks watch and wait : Year 3	£2,780	£2,780
246	IOP checks watch and wait : Year 4	£2,780	£2,780
247	IOP checks watch and wait : Year 5	£2,780	£2,780
248	% patients with SVL requiring blind registration	£2,780	£2,780
249	% patients with SVL requiring low vision aids	£2,780	£2,780
250	% patients with SVL requiring low vision rehabilitation	£2,780	£2,780
251	% patients with raised IOP watch and wait: Year 1	£2,780	£2,780

252	% patients with raised IOP watch and wait: Year 2	£2,780	£2,780
253	% patients with raised IOP watch and wait: Year 3	£2,780	£2,780
254	% cases of raised IOP treated with medications: watch and wait	£2,780	£2,780
255	% patients with retinal detachment DEX700 PRN: Year 1	£2,780	£2,780
256	% patients with retinal detachment watch and wait: Year 1	£2,780	£2,780
257	% patients with retinal detachment watch and wait: Year 2	£2,780	£2,780
258	% patients with retinal detachment watch and wait: Year 3	£2,780	£2,780
259	% patients with endophthalmitis DEX700 PRN: Year 3	£2,780	£2,780
260	% patients with endophthalmitis watch and wait: Year 1	£2,780	£2,780
261	% patients with endophthalmitis watch and wait: Year 2	£2,780	£2,780
262	% patients with endophthalmitis watch and wait: Year 3	£2,780	£2,780
263	% patients with vitreous haemorrhage watch and wait: Year 1	£2,780	£2,780
264	% patients with vitreous haemorrhage watch and wait: Year 2	£2,780	£2,780
265	% patients with vitreous haemorrhage watch and wait: Year 3	£2,780	£2,780
Abbreviations used in the table: AE, adverse event; BCVA, best corrected visual acuity; BSE, better-seeing eye; CA, carbonic anhydrase**;** DEX700 PRN, dexamethasone 700 *pro ne rata*; DMO, diabetic macular oedema; HS, health state; IOP, intraocular pressure; NMB, net monetary benefit; OWSA, one-way sensitivity analysis; re-tx, re-treatment; SVL, severe vision loss; WSE, worse-seeing eye.			

Table 165. Results of OWSA on the Net Monetary Benefit (NMB), illustrating the parameters considered comparing dexamethasone with ranibizumab (list price) in the population of DMO patients who are pseudophakic

Base case NMB, DEX700 PRN vs. ranibizumab: £3,645			
Parameter		**Lower**	**Upper**
1	Relative risk of worsening vision, DEX700 PRN as reference treatment, ranibizumab	£2,968	£7,406
2	Relative risk of improving vision, DEX700 PRN as reference treatment, ranibizumab	£7,413	£3,645
3	Proportion outpatient procedures: ranibizumab	£4,861	£2,931
4	Unit cost residential care	£4,533	£2,666
5	% patients with SVL requiring residential care	£4,552	£2,686
6	Mortality hazard ratio due to DMO	£4,356	£2,860
7	Discount rate - benefits	£2,840	£4,237
8	Probability of worsening vision: Natural history	£3,110	£4,239
9	Discount rate - costs	£2,518	£3,645
10	Probability of improving vision: Natural history	£3,114	£4,167
11	Utility equation coefficient BSE	£4,047	£3,186
12	Proportion outpatient procedures: DEX700 PRN	£3,142	£3,912
13	Baseline age	£3,295	£3,995
14	Proportion treated unilaterally in BSE	£3,983	£3,311
15	Bilateral BSE baseline % patients in HS4	£3,293	£3,929
16	Bilateral BSE baseline % patients in HS1	£3,896	£3,325
17	Utility equation coefficient WSE	£3,968	£3,450
18	Number of appointments for bilateral treatment: ranibizumab	£3,421	£3,869
19	Proportion treated bilaterally	£3,868	£3,422

20	Bilateral BSE baseline % patients in HS2	£3,380	£3,822
21	Relative risk of stable vision, DEX700 PRN as reference treatment, ranibizumab	£3,889	£3,472
22	Routine monitoring visits ranibizumab : Year 1	£3,514	£3,898
23	Unit cost outpatient procedure	£3,452	£3,774
24	Unit cost Routine monitoring visit	£3,322	£3,641
25	Unilateral WSE baseline % patients in HS4	£3,803	£3,487
26	Unilateral BSE baseline % patients in HS1	£3,792	£3,489
27	Proportion discontinuing due to AEs ranibizumab: Month 11	£3,795	£3,499
28	% patients receiving treatment DEX700 PRN: Month 12	£3,799	£3,505
29	Proportion male	£3,505	£3,785
30	% patients receiving treatment DEX700 PRN: Month 6	£3,801	£3,535
31	Routine monitoring visits ranibizumab : Year 2	£3,778	£3,518
32	Proportion of fellow eyes developing DMO	£3,774	£3,516
33	% patients receiving treatment DEX700 PRN: Month 18	£3,531	£3,762
34	Unilateral BSE baseline % patients in HS2	£3,531	£3,762
35	% patients receiving treatment ranibizumab: Month 6	£3,531	£3,762
36	% patients receiving treatment ranibizumab: Month 7	£3,532	£3,761
37	% patients receiving treatment ranibizumab: Month 8	£3,532	£3,761
38	% patients receiving treatment ranibizumab: Month 9	£3,532	£3,761
39	% patients receiving treatment ranibizumab: Month 10	£3,557	£3,784
40	% patients receiving treatment ranibizumab: Month 11	£3,754	£3,528
41	% patients receiving treatment DEX700 PRN: Month 24	£3,538	£3,754
42	% patients receiving treatment ranibizumab: Month 3	£3,538	£3,754
43	% patients receiving treatment ranibizumab: Month 4	£3,538	£3,754
44	% patients receiving treatment ranibizumab: Month 5	£3,539	£3,746
45	Proportion discontinuing due to AEs DEX700 PRN: Month 9	£3,735	£3,544
46	Bilateral WSE baseline % patients in HS4	£3,721	£3,531
47	% patients receiving treatment DEX700 PRN: Month 30	£3,787	£3,598
48	Number of appointments for bilateral treatment: DEX700 PRN	£3,545	£3,733
49	Untreated BSE baseline % patients in HS2	£3,769	£3,582
50	% patients receiving treatment DEX700 PRN: Month 33	£3,536	£3,719
51	% patients with vitreous haemorrhage DEX700 PRN: Year 3	£3,722	£3,554
52	% patients receiving treatment DEX700 PRN: Month 9	£3,713	£3,545
53	% patients receiving treatment DEX700 PRN: Month 15	£3,714	£3,550
54	Untreated BSE baseline % patients in HS3	£3,712	£3,549
55	Unilateral WSE baseline % patients in HS3	£3,712	£3,554
56	% patients receiving treatment ranibizumab: Month 12	£3,686	£3,532
57	% patients receiving treatment ranibizumab: Month 13	£3,571	£3,723
58	% patients receiving treatment ranibizumab: Month 14	£3,571	£3,723
59	% patients receiving treatment DEX700 PRN: Month 27	£3,571	£3,723
60	Routine monitoring visits DEX700 PRN : Year 1	£3,711	£3,560
61	Mortality hazard ratio due to diabetes	£3,553	£3,704
62	Unilateral WSE baseline % patients in HS5	£3,594	£3,745
63	% patients receiving treatment DEX700 PRN: Month 21	£3,713	£3,564

64	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 9	£3,718	£3,572
65	% patients receiving treatment ranibizumab: Month 15	£3,704	£3,561
66	% patients receiving treatment ranibizumab: Month 16	£3,580	£3,714
67	% patients receiving treatment ranibizumab: Month 17	£3,580	£3,714
68	% patients receiving treatment ranibizumab: Month 18	£3,580	£3,714
69	% patients receiving treatment ranibizumab: Month 19	£3,581	£3,712
70	% patients receiving treatment ranibizumab: Month 20	£3,581	£3,712
71	% patients receiving treatment ranibizumab: Month 21	£3,581	£3,712
72	% patients receiving treatment ranibizumab: Month 22	£3,583	£3,710
73	% patients receiving treatment ranibizumab: Month 23	£3,583	£3,710
74	Unilateral WSE baseline % patients in HS1	£3,583	£3,710
75	Proportion discontinuing due to AEs ranibizumab: Month 23	£3,715	£3,592
76	Unit cost IOP check	£3,581	£3,700
77	% patients with vitreous haemorrhage DEX700 PRN: Year 1	£3,575	£3,692
78	Optical coherence tomographys ranibizumab : Year 1	£3,710	£3,602
79	Routine monitoring visits DEX700 PRN : Year 2	£3,691	£3,587
80	Unilateral WSE baseline % patients in HS2	£3,595	£3,696
81	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 27	£3,594	£3,695
82	% patients receiving treatment ranibizumab: Month 24	£3,695	£3,595
83	% patients receiving treatment ranibizumab: Month 25	£3,588	£3,682
84	% patients receiving treatment ranibizumab: Month 26	£3,601	£3,692
85	Bilateral WSE baseline % patients in HS5	£3,601	£3,692
86	Routine monitoring visits ranibizumab : Year 3	£3,601	£3,692
87	Proportion discontinuing due to loss of efficacy ranibizumab: Month 11	£3,603	£3,687
88	Unit cost vitrectomy	£3,709	£3,628
89	Proportion discontinuing due to AEs DEX700 PRN: Month 27	£3,688	£3,609
90	% patients receiving treatment ranibizumab: Month 27	£3,684	£3,605
91	% patients receiving treatment ranibizumab: Month 28	£3,607	£3,686
92	% patients receiving treatment ranibizumab: Month 29	£3,607	£3,686
93	Unit cost community care	£3,607	£3,686
94	% patients with SVL requiring community care	£3,682	£3,604
95	% patients receiving treatment ranibizumab: Month 30	£3,682	£3,604
96	% patients receiving treatment ranibizumab: Month 31	£3,608	£3,685
97	% patients receiving treatment ranibizumab: Month 32	£3,608	£3,685
98	Unilateral BSE baseline % patients in HS4	£3,608	£3,685
99	% patients receiving treatment ranibizumab: Month 33	£3,609	£3,684
100	% patients receiving treatment ranibizumab: Month 34	£3,609	£3,684
101	% patients receiving treatment ranibizumab: Month 35	£3,609	£3,684
102	IOP checks DEX700 PRN : Year 1	£3,607	£3,681
103	Bilateral WSE baseline % patients in HS1	£3,620	£3,694
104	Routine monitoring visits DEX700 PRN : Year 3	£3,681	£3,609
105	% patients with retinal detachment DEX700 PRN: Year 3	£3,671	£3,604
106	Optical coherence tomographys ranibizumab : Year 2	£3,678	£3,612
107	Proportion discontinuing due to AEs DEX700 PRN: Month 18	£3,662	£3,597

108	Fluorescein angiographys ranibizumab : Year 1	£3,613	£3,677
109	% patients with raised IOP DEX700 PRN: Year 1	£3,666	£3,609
110	Fluorescein angiographys DEX700 PRN : Year 1	£3,618	£3,672
111	Bilateral WSE baseline % patients in HS3	£3,670	£3,616
112	% patients with vitreous haemorrhage DEX700 PRN: Year 2	£3,672	£3,618
113	% cases of raised IOP treated with medications: DEX700 PRN	£3,665	£3,613
114	Bilateral WSE baseline % patients in HS2	£3,535	£3,587
115	IOP checks DEX700 PRN : Year 2	£3,631	£3,682
116	Proportion discontinuing due to AEs DEX700 PRN: Month 15	£3,670	£3,620
117	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 15	£3,622	£3,671
118	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 24	£3,661	£3,619
119	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 18	£3,669	£3,628
120	% patients with raised IOP DEX700 PRN: Year 3	£3,661	£3,629
121	Proportion discontinuing due to AEs ranibizumab: Month 35	£3,661	£3,629
122	Bilateral BSE baseline % patients in HS3	£3,633	£3,665
123	IOP checks DEX700 PRN : Year 3	£3,659	£3,627
124	Optical coherence tomographys DEX700 PRN : Year 1	£3,635	£3,664
125	% patients with raised IOP DEX700 PRN: Year 2	£3,635	£3,664
126	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 6	£3,652	£3,626
127	% patients with retinal detachment DEX700 PRN: Year 2	£3,636	£3,662
128	Unit cost depression	£3,652	£3,627
129	% patients with SVL requiring treatment for depression	£3,656	£3,632
130	Unilateral BSE baseline % patients in HS5	£3,657	£3,633
131	Optical coherence tomographys DEX700 PRN : Year 2	£3,656	£3,634
132	% patients with endophthalmitis DEX700 PRN: Year 1	£3,651	£3,629
133	Untreated BSE baseline % patients in HS6	£3,650	£3,630
134	% patients with endophthalmitis DEX700 PRN: Year 2	£3,638	£3,657
135	Optical coherence tomographys ranibizumab : Year 3	£3,635	£3,655
136	Untreated BSE baseline % patients in HS4	£3,656	£3,675
137	Proportion discontinuing due to AEs DEX700 PRN: Month 30	£3,648	£3,630
138	Unit cost Iridectomy	£3,648	£3,630
139	Unit cost Iridotomy	£3,635	£3,652
140	Proportion discontinuing due to AEs DEX700 PRN: Month 6	£3,654	£3,636
141	Unit cost laser procedure	£3,641	£3,657
142	Routine monitoring visits no treatment : Year 3	£3,652	£3,638
143	Optical coherence tomographys DEX700 PRN : Year 3	£3,650	£3,635
144	Unilateral BSE baseline % patients in HS3	£3,650	£3,635
145	% patients with raised IOP ranibizumab: Year 1	£3,650	£3,637
146	Number of laser ranibizumab: Month 35	£3,642	£3,654
147	Routine monitoring visits no treatment : Year 4	£3,639	£3,651
148	Proportion discontinuing due to AEs DEX700 PRN: Month 33	£3,651	£3,639
149	Unit cost endophthalmitis procedure	£3,642	£3,653
150	Unit cost Fluorescein angiography	£3,649	£3,638
151	Unit cost Trabeculectomy	£3,649	£3,638

152	Unit cost procedure for attachment of retina	£3,651	£3,641
153	Proportion discontinuing due to AEs DEX700 PRN: Month 21	£3,678	£3,670
154	Number of laser ranibizumab: Month 23	£3,638	£3,647
155	Mean days of Prostaglandins required	£3,652	£3,643
156	Untreated WSE baseline % patients in HS2	£3,641	£3,649
157	% patients with SVL requiring hip replacement	£3,649	£3,642
158	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 21	£3,648	£3,642
159	Unit cost hip fracture	£3,649	£3,643
160	Fluorescein angiographys no treatment : Year 3	£3,649	£3,642
161	Routine monitoring visits no treatment : Year 2	£3,648	£3,642
162	Mean days of Combination required	£3,648	£3,642
163	Fluorescein angiographys no treatment : Year 4	£3,648	£3,642
164	Mean days of CA inhibitors required	£3,648	£3,654
165	Optical coherence tomographys no treatment : Year 3	£3,647	£3,641
166	Proportion discontinuing due to AEs DEX700 PRN: Month 12	£3,647	£3,643
167	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 12	£3,647	£3,643
168	Untreated BSE baseline % patients in HS5	£3,647	£3,643
169	Optical coherence tomographys no treatment : Year 4	£3,646	£3,644
170	Fluorescein angiographys no treatment : Year 2	£3,646	£3,644
171	Routine monitoring visits no treatment : Year 5	£3,644	£3,646
172	Optical coherence tomographys no treatment : Year 2	£3,644	£3,643
173	Mean days of Brimonidine required	£3,646	£3,647
174	Bilateral BSE baseline % patients in HS5	£3,646	£3,644
175	Untreated WSE baseline % patients in HS1	£3,646	£3,644
176	Fluorescein angiographys no treatment : Year 5	£3,645	£3,645
177	Mean days of Beta-blockers required	£3,645	£3,645
178	Routine monitoring visits no treatment : Year 1	£3,645	£3,645
179	Optical coherence tomographys no treatment : Year 5	£3,645	£3,645
180	Fluorescein angiographys no treatment : Year 1	£3,645	£3,645
181	Untreated WSE baseline % patients in HS4	£3,645	£3,645
182	Optical coherence tomographys no treatment : Year 1	£3,645	£3,645
183	Untreated WSE baseline % patients in HS3	£3,645	£3,645
184	Discount rate - life years	£3,645	£3,645
185	Proportion phakic eyes at baseline	£3,645	£3,645
186	Unilateral BSE baseline % patients in HS6	£3,645	£3,645
187	Untreated WSE baseline % patients in HS5	£3,645	£3,645
188	Untreated WSE baseline % patients in HS6	£3,645	£3,645
189	Unilateral WSE baseline % patients in HS6	£3,645	£3,645
190	Untreated BSE baseline % patients in HS1	£3,645	£3,645
191	Bilateral BSE baseline % patients in HS6	£3,645	£3,645
192	Bilateral WSE baseline % patients in HS6	£3,645	£3,645
193	Mean BCVA in HS1	£3,645	£3,645
194	Mean BCVA in HS2	£3,645	£3,645
195	Mean BCVA in HS3	£3,645	£3,645

196	Mean BCVA in HS4	£3,645	£3,645
197	Mean BCVA in HS5	£3,645	£3,645
198	Mean BCVA in HS6	£3,645	£3,645
199	Unit cost day case procedure	£3,645	£3,645
200	Average cost of next line treatment (discontinue due to AEs): Initial treatment DEX700 PRN	£3,645	£3,645
201	Average cost of next line treatment (discontinue due to AEs): Initial treatment ranibizumab	£3,645	£3,645
202	Average cost of next line treatment (discontinue due to Rescue): Initial treatment DEX700 PRN	£3,645	£3,645
203	Average cost of next line treatment (discontinue due to Rescue): Initial treatment ranibizumab	£3,645	£3,645
204	Unit cost Optical coherence tomography	£3,645	£3,645
205	Unit cost blind registration	£3,645	£3,645
206	Unit cost low vision aids	£3,645	£3,645
207	Unit cost low vision rehabilitation	£3,645	£3,645
208	Unit cost cataract extraction procedure	£3,645	£3,645
209	% patients receiving treatment DEX700 PRN: Month 0	£3,645	£3,645
210	% patients receiving treatment DEX700 PRN: Month 36	£3,645	£3,645
211	% patients receiving treatment DEX700 PRN: Month 39	£3,645	£3,645
212	% patients receiving treatment DEX700 PRN: Month 42	£3,645	£3,645
213	% patients receiving treatment DEX700 PRN: Month 45	£3,645	£3,645
214	% patients receiving treatment DEX700 PRN: Month 48	£3,645	£3,645
215	% patients receiving treatment DEX700 PRN: Month 51	£3,645	£3,645
216	% patients receiving treatment DEX700 PRN: Month 54	£3,645	£3,645
217	% patients receiving treatment DEX700 PRN: Month 57	£3,645	£3,645
218	% patients receiving treatment ranibizumab: Month 0	£3,645	£3,645
219	% patients receiving treatment ranibizumab: Month 1	£3,645	£3,645
220	% patients receiving treatment ranibizumab: Month 2	£3,645	£3,645
221	% patients receiving treatment ranibizumab: Month 36	£3,645	£3,645
222	% patients receiving treatment ranibizumab: Month 37	£3,645	£3,645
223	% patients receiving treatment ranibizumab: Month 38	£3,645	£3,645
224	% patients receiving treatment ranibizumab: Month 39	£3,645	£3,645
225	% patients receiving treatment ranibizumab: Month 40	£3,645	£3,645
226	% patients receiving treatment ranibizumab: Month 41	£3,645	£3,645
227	% patients receiving treatment ranibizumab: Month 42	£3,645	£3,645
228	% patients receiving treatment ranibizumab: Month 43	£3,645	£3,645
229	% patients receiving treatment ranibizumab: Month 44	£3,645	£3,645
230	% patients receiving treatment ranibizumab: Month 45	£3,645	£3,645
231	% patients receiving treatment ranibizumab: Month 46	£3,645	£3,645
232	% patients receiving treatment ranibizumab: Month 47	£3,645	£3,645
233	% patients receiving treatment ranibizumab: Month 48	£3,645	£3,645
234	% patients receiving treatment ranibizumab: Month 49	£3,645	£3,645
235	% patients receiving treatment ranibizumab: Month 50	£3,645	£3,645
236	% patients receiving treatment ranibizumab: Month 51	£3,645	£3,645

237	% patients receiving treatment ranibizumab: Month 52	£3,645	£3,645
238	% patients receiving treatment ranibizumab: Month 53	£3,645	£3,645
239	% patients receiving treatment ranibizumab: Month 54	£3,645	£3,645
240	% patients receiving treatment ranibizumab: Month 55	£3,645	£3,645
241	% patients receiving treatment ranibizumab: Month 56	£3,645	£3,645
242	% patients receiving treatment ranibizumab: Month 57	£3,645	£3,645
243	% patients receiving treatment ranibizumab: Month 58	£3,645	£3,645
244	% patients receiving treatment ranibizumab: Month 59	£3,645	£3,645
245	Number of laser ranibizumab: Month 0	£3,645	£3,645
246	Number of laser ranibizumab: Month 1	£3,645	£3,645
247	Number of laser ranibizumab: Month 2	£3,645	£3,645
248	Number of laser ranibizumab: Month 3	£3,645	£3,645
249	Number of laser ranibizumab: Month 4	£3,645	£3,645
250	Number of laser ranibizumab: Month 5	£3,645	£3,645
251	Number of laser ranibizumab: Month 6	£3,645	£3,645
252	Number of laser ranibizumab: Month 7	£3,645	£3,645
253	Number of laser ranibizumab: Month 8	£3,645	£3,645
254	Number of laser ranibizumab: Month 9	£3,645	£3,645
255	Number of laser ranibizumab: Month 10	£3,645	£3,645
256	Number of laser ranibizumab: Month 11	£3,645	£3,645
257	Number of laser ranibizumab: Month 12	£3,645	£3,645
258	Number of laser ranibizumab: Month 13	£3,645	£3,645
259	Number of laser ranibizumab: Month 14	£3,645	£3,645
260	Number of laser ranibizumab: Month 15	£3,645	£3,645
261	Number of laser ranibizumab: Month 16	£3,645	£3,645
262	Number of laser ranibizumab: Month 17	£3,645	£3,645
263	Number of laser ranibizumab: Month 18	£3,645	£3,645
264	Number of laser ranibizumab: Month 19	£3,645	£3,645
265	Number of laser ranibizumab: Month 20	£3,645	£3,645
266	Number of laser ranibizumab: Month 21	£3,645	£3,645
267	Number of laser ranibizumab: Month 22	£3,645	£3,645
268	Number of laser ranibizumab: Month 24	£3,645	£3,645
269	Number of laser ranibizumab: Month 25	£3,645	£3,645
270	Number of laser ranibizumab: Month 26	£3,645	£3,645
271	Number of laser ranibizumab: Month 27	£3,645	£3,645
272	Number of laser ranibizumab: Month 28	£3,645	£3,645
273	Number of laser ranibizumab: Month 29	£3,645	£3,645
274	Number of laser ranibizumab: Month 30	£3,645	£3,645
275	Number of laser ranibizumab: Month 31	£3,645	£3,645
276	Number of laser ranibizumab: Month 32	£3,645	£3,645
277	Number of laser ranibizumab: Month 33	£3,645	£3,645
278	Number of laser ranibizumab: Month 34	£3,645	£3,645
279	Number of laser ranibizumab: Month 36	£3,645	£3,645
280	Number of laser ranibizumab: Month 37	£3,645	£3,645

281	Number of laser ranibizumab: Month 38	£3,645	£3,645
282	Number of laser ranibizumab: Month 39	£3,645	£3,645
283	Number of laser ranibizumab: Month 40	£3,645	£3,645
284	Number of laser ranibizumab: Month 41	£3,645	£3,645
285	Number of laser ranibizumab: Month 42	£3,645	£3,645
286	Number of laser ranibizumab: Month 43	£3,645	£3,645
287	Number of laser ranibizumab: Month 44	£3,645	£3,645
288	Number of laser ranibizumab: Month 45	£3,645	£3,645
289	Number of laser ranibizumab: Month 46	£3,645	£3,645
290	Number of laser ranibizumab: Month 47	£3,645	£3,645
291	Number of laser ranibizumab: Month 48	£3,645	£3,645
292	Number of laser ranibizumab: Month 49	£3,645	£3,645
293	Number of laser ranibizumab: Month 50	£3,645	£3,645
294	Number of laser ranibizumab: Month 51	£3,645	£3,645
295	Number of laser ranibizumab: Month 52	£3,645	£3,645
296	Number of laser ranibizumab: Month 53	£3,645	£3,645
297	Number of laser ranibizumab: Month 54	£3,645	£3,645
298	Number of laser ranibizumab: Month 55	£3,645	£3,645
299	Number of laser ranibizumab: Month 56	£3,645	£3,645
300	Number of laser ranibizumab: Month 57	£3,645	£3,645
301	Number of laser ranibizumab: Month 58	£3,645	£3,645
302	Number of laser ranibizumab: Month 59	£3,645	£3,645
303	Proportion discontinuing due to AEs DEX700 PRN: Month 24	£3,645	£3,645
304	Proportion discontinuing due to AEs DEX700 PRN: Month 36	£3,645	£3,645
305	Proportion discontinuing due to AEs DEX700 PRN: Month 39	£3,645	£3,645
306	Proportion discontinuing due to AEs DEX700 PRN: Month 42	£3,645	£3,645
307	Proportion discontinuing due to AEs DEX700 PRN: Month 45	£3,645	£3,645
308	Proportion discontinuing due to AEs DEX700 PRN: Month 48	£3,645	£3,645
309	Proportion discontinuing due to AEs DEX700 PRN: Month 51	£3,645	£3,645
310	Proportion discontinuing due to AEs DEX700 PRN: Month 54	£3,645	£3,645
311	Proportion discontinuing due to AEs DEX700 PRN: Month 57	£3,645	£3,645
312	Proportion discontinuing due to AEs ranibizumab: Month 0	£3,645	£3,645
313	Proportion discontinuing due to AEs ranibizumab: Month 1	£3,645	£3,645
314	Proportion discontinuing due to AEs ranibizumab: Month 2	£3,645	£3,645
315	Proportion discontinuing due to AEs ranibizumab: Month 3	£3,645	£3,645
316	Proportion discontinuing due to AEs ranibizumab: Month 4	£3,645	£3,645
317	Proportion discontinuing due to AEs ranibizumab: Month 5	£3,645	£3,645
318	Proportion discontinuing due to AEs ranibizumab: Month 6	£3,645	£3,645
319	Proportion discontinuing due to AEs ranibizumab: Month 7	£3,645	£3,645
320	Proportion discontinuing due to AEs ranibizumab: Month 8	£3,645	£3,645
321	Proportion discontinuing due to AEs ranibizumab: Month 9	£3,645	£3,645
322	Proportion discontinuing due to AEs ranibizumab: Month 10	£3,645	£3,645
323	Proportion discontinuing due to AEs ranibizumab: Month 12	£3,645	£3,645
324	Proportion discontinuing due to AEs ranibizumab: Month 13	£3,645	£3,645

325	Proportion discontinuing due to AEs ranibizumab: Month 14	£3,645	£3,645
326	Proportion discontinuing due to AEs ranibizumab: Month 15	£3,645	£3,645
327	Proportion discontinuing due to AEs ranibizumab: Month 16	£3,645	£3,645
328	Proportion discontinuing due to AEs ranibizumab: Month 17	£3,645	£3,645
329	Proportion discontinuing due to AEs ranibizumab: Month 18	£3,645	£3,645
330	Proportion discontinuing due to AEs ranibizumab: Month 19	£3,645	£3,645
331	Proportion discontinuing due to AEs ranibizumab: Month 20	£3,645	£3,645
332	Proportion discontinuing due to AEs ranibizumab: Month 21	£3,645	£3,645
333	Proportion discontinuing due to AEs ranibizumab: Month 22	£3,645	£3,645
334	Proportion discontinuing due to AEs ranibizumab: Month 24	£3,645	£3,645
335	Proportion discontinuing due to AEs ranibizumab: Month 25	£3,645	£3,645
336	Proportion discontinuing due to AEs ranibizumab: Month 26	£3,645	£3,645
337	Proportion discontinuing due to AEs ranibizumab: Month 27	£3,645	£3,645
338	Proportion discontinuing due to AEs ranibizumab: Month 28	£3,645	£3,645
339	Proportion discontinuing due to AEs ranibizumab: Month 29	£3,645	£3,645
340	Proportion discontinuing due to AEs ranibizumab: Month 30	£3,645	£3,645
341	Proportion discontinuing due to AEs ranibizumab: Month 31	£3,645	£3,645
342	Proportion discontinuing due to AEs ranibizumab: Month 32	£3,645	£3,645
343	Proportion discontinuing due to AEs ranibizumab: Month 33	£3,645	£3,645
344	Proportion discontinuing due to AEs ranibizumab: Month 34	£3,645	£3,645
345	Proportion discontinuing due to AEs ranibizumab: Month 36	£3,645	£3,645
346	Proportion discontinuing due to AEs ranibizumab: Month 37	£3,645	£3,645
347	Proportion discontinuing due to AEs ranibizumab: Month 38	£3,645	£3,645
348	Proportion discontinuing due to AEs ranibizumab: Month 39	£3,645	£3,645
349	Proportion discontinuing due to AEs ranibizumab: Month 40	£3,645	£3,645
350	Proportion discontinuing due to AEs ranibizumab: Month 41	£3,645	£3,645
351	Proportion discontinuing due to AEs ranibizumab: Month 42	£3,645	£3,645
352	Proportion discontinuing due to AEs ranibizumab: Month 43	£3,645	£3,645
353	Proportion discontinuing due to AEs ranibizumab: Month 44	£3,645	£3,645
354	Proportion discontinuing due to AEs ranibizumab: Month 45	£3,645	£3,645
355	Proportion discontinuing due to AEs ranibizumab: Month 46	£3,645	£3,645
356	Proportion discontinuing due to AEs ranibizumab: Month 47	£3,645	£3,645
357	Proportion discontinuing due to AEs ranibizumab: Month 48	£3,645	£3,645
358	Proportion discontinuing due to AEs ranibizumab: Month 49	£3,645	£3,645
359	Proportion discontinuing due to AEs ranibizumab: Month 50	£3,645	£3,645
360	Proportion discontinuing due to AEs ranibizumab: Month 51	£3,645	£3,645
361	Proportion discontinuing due to AEs ranibizumab: Month 52	£3,645	£3,645
362	Proportion discontinuing due to AEs ranibizumab: Month 53	£3,645	£3,645
363	Proportion discontinuing due to AEs ranibizumab: Month 54	£3,645	£3,645
364	Proportion discontinuing due to AEs ranibizumab: Month 55	£3,645	£3,645
365	Proportion discontinuing due to AEs ranibizumab: Month 56	£3,645	£3,645
366	Proportion discontinuing due to AEs ranibizumab: Month 57	£3,645	£3,645
367	Proportion discontinuing due to AEs ranibizumab: Month 58	£3,645	£3,645
368	Proportion discontinuing due to AEs ranibizumab: Month 59	£3,645	£3,645

369	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 30	£3,645	£3,645
370	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 33	£3,645	£3,645
371	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 36	£3,645	£3,645
372	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 39	£3,645	£3,645
373	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 42	£3,645	£3,645
374	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 45	£3,645	£3,645
375	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 48	£3,645	£3,645
376	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 51	£3,645	£3,645
377	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 54	£3,645	£3,645
378	Proportion discontinuing due to loss of efficacy DEX700 PRN: Month 57	£3,645	£3,645
379	Proportion discontinuing due to loss of efficacy ranibizumab: Month 0	£3,645	£3,645
380	Proportion discontinuing due to loss of efficacy ranibizumab: Month 1	£3,645	£3,645
381	Proportion discontinuing due to loss of efficacy ranibizumab: Month 2	£3,645	£3,645
382	Proportion discontinuing due to loss of efficacy ranibizumab: Month 3	£3,645	£3,645
383	Proportion discontinuing due to loss of efficacy ranibizumab: Month 4	£3,645	£3,645
384	Proportion discontinuing due to loss of efficacy ranibizumab: Month 5	£3,645	£3,645
385	Proportion discontinuing due to loss of efficacy ranibizumab: Month 6	£3,645	£3,645
386	Proportion discontinuing due to loss of efficacy ranibizumab: Month 7	£3,645	£3,645
387	Proportion discontinuing due to loss of efficacy ranibizumab: Month 8	£3,645	£3,645
388	Proportion discontinuing due to loss of efficacy ranibizumab: Month 9	£3,645	£3,645
389	Proportion discontinuing due to loss of efficacy ranibizumab: Month 10	£3,645	£3,645
390	Proportion discontinuing due to loss of efficacy ranibizumab: Month 12	£3,645	£3,645
391	Proportion discontinuing due to loss of efficacy ranibizumab: Month 13	£3,645	£3,645
392	Proportion discontinuing due to loss of efficacy ranibizumab: Month 14	£3,645	£3,645
393	Proportion discontinuing due to loss of efficacy ranibizumab: Month 15	£3,645	£3,645
394	Proportion discontinuing due to loss of efficacy ranibizumab: Month 16	£3,645	£3,645
395	Proportion discontinuing due to loss of efficacy ranibizumab: Month 17	£3,645	£3,645
396	Proportion discontinuing due to loss of efficacy ranibizumab: Month 18	£3,645	£3,645
397	Proportion discontinuing due to loss of efficacy ranibizumab: Month 19	£3,645	£3,645
398	Proportion discontinuing due to loss of efficacy ranibizumab: Month 20	£3,645	£3,645
399	Proportion discontinuing due to loss of efficacy ranibizumab: Month 21	£3,645	£3,645
400	Proportion discontinuing due to loss of efficacy ranibizumab: Month 22	£3,645	£3,645
401	Proportion discontinuing due to loss of efficacy ranibizumab: Month 23	£3,645	£3,645
402	Proportion discontinuing due to loss of efficacy ranibizumab: Month 24	£3,645	£3,645
403	Proportion discontinuing due to loss of efficacy ranibizumab: Month 25	£3,645	£3,645
404	Proportion discontinuing due to loss of efficacy ranibizumab: Month 26	£3,645	£3,645
405	Proportion discontinuing due to loss of efficacy ranibizumab: Month 27	£3,645	£3,645
406	Proportion discontinuing due to loss of efficacy ranibizumab: Month 28	£3,645	£3,645
407	Proportion discontinuing due to loss of efficacy ranibizumab: Month 29	£3,645	£3,645
408	Proportion discontinuing due to loss of efficacy ranibizumab: Month 30	£3,645	£3,645
409	Proportion discontinuing due to loss of efficacy ranibizumab: Month 31	£3,645	£3,645
410	Proportion discontinuing due to loss of efficacy ranibizumab: Month 32	£3,645	£3,645
411	Proportion discontinuing due to loss of efficacy ranibizumab: Month 33	£3,645	£3,645
412	Proportion discontinuing due to loss of efficacy ranibizumab: Month 34	£3,645	£3,645

413	Proportion discontinuing due to loss of efficacy ranibizumab: Month 35	£3,645	£3,645
414	Proportion discontinuing due to loss of efficacy ranibizumab: Month 36	£3,645	£3,645
415	Proportion discontinuing due to loss of efficacy ranibizumab: Month 37	£3,645	£3,645
416	Proportion discontinuing due to loss of efficacy ranibizumab: Month 38	£3,645	£3,645
417	Proportion discontinuing due to loss of efficacy ranibizumab: Month 39	£3,645	£3,645
418	Proportion discontinuing due to loss of efficacy ranibizumab: Month 40	£3,645	£3,645
419	Proportion discontinuing due to loss of efficacy ranibizumab: Month 41	£3,645	£3,645
420	Proportion discontinuing due to loss of efficacy ranibizumab: Month 42	£3,645	£3,645
421	Proportion discontinuing due to loss of efficacy ranibizumab: Month 43	£3,645	£3,645
422	Proportion discontinuing due to loss of efficacy ranibizumab: Month 44	£3,645	£3,645
423	Proportion discontinuing due to loss of efficacy ranibizumab: Month 45	£3,645	£3,645
424	Proportion discontinuing due to loss of efficacy ranibizumab: Month 46	£3,645	£3,645
425	Proportion discontinuing due to loss of efficacy ranibizumab: Month 47	£3,645	£3,645
426	Proportion discontinuing due to loss of efficacy ranibizumab: Month 48	£3,645	£3,645
427	Proportion discontinuing due to loss of efficacy ranibizumab: Month 49	£3,645	£3,645
428	Proportion discontinuing due to loss of efficacy ranibizumab: Month 50	£3,645	£3,645
429	Proportion discontinuing due to loss of efficacy ranibizumab: Month 51	£3,645	£3,645
430	Proportion discontinuing due to loss of efficacy ranibizumab: Month 52	£3,645	£3,645
431	Proportion discontinuing due to loss of efficacy ranibizumab: Month 53	£3,645	£3,645
432	Proportion discontinuing due to loss of efficacy ranibizumab: Month 54	£3,645	£3,645
433	Proportion discontinuing due to loss of efficacy ranibizumab: Month 55	£3,645	£3,645
434	Proportion discontinuing due to loss of efficacy ranibizumab: Month 56	£3,645	£3,645
435	Proportion discontinuing due to loss of efficacy ranibizumab: Month 57	£3,645	£3,645
436	Proportion discontinuing due to loss of efficacy ranibizumab: Month 58	£3,645	£3,645
437	Proportion discontinuing due to loss of efficacy ranibizumab: Month 59	£3,645	£3,645
438	IOP checks no treatment : Year 1	£3,645	£3,645
439	IOP checks no treatment : Year 2	£3,645	£3,645
440	IOP checks no treatment : Year 3	£3,645	£3,645
441	IOP checks no treatment : Year 4	£3,645	£3,645
442	IOP checks no treatment : Year 5	£3,645	£3,645
443	Routine monitoring visits DEX700 PRN : Year 4	£3,645	£3,645
444	Routine monitoring visits DEX700 PRN : Year 5	£3,645	£3,645
445	Optical coherence tomographys DEX700 PRN : Year 4	£3,645	£3,645
446	Optical coherence tomographys DEX700 PRN : Year 5	£3,645	£3,645
447	Fluorescein angiographys DEX700 PRN : Year 2	£3,645	£3,645
448	Fluorescein angiographys DEX700 PRN : Year 3	£3,645	£3,645
449	Fluorescein angiographys DEX700 PRN : Year 4	£3,645	£3,645
450	Fluorescein angiographys DEX700 PRN : Year 5	£3,645	£3,645
451	IOP checks DEX700 PRN : Year 4	£3,645	£3,645
452	IOP checks DEX700 PRN : Year 5	£3,645	£3,645
453	Routine monitoring visits ranibizumab : Year 4	£3,645	£3,645
454	Routine monitoring visits ranibizumab : Year 5	£3,645	£3,645
455	Optical coherence tomographys ranibizumab : Year 4	£3,645	£3,645
456	Optical coherence tomographys ranibizumab : Year 5	£3,645	£3,645

457	Fluorescein angiographys ranibizumab : Year 2	£3,645	£3,645
458	Fluorescein angiographys ranibizumab : Year 3	£3,645	£3,645
459	Fluorescein angiographys ranibizumab : Year 4	£3,645	£3,645
460	Fluorescein angiographys ranibizumab : Year 5	£3,645	£3,645
461	IOP checks ranibizumab : Year 1	£3,645	£3,645
462	IOP checks ranibizumab : Year 2	£3,645	£3,645
463	IOP checks ranibizumab : Year 3	£3,645	£3,645
464	IOP checks ranibizumab : Year 4	£3,645	£3,645
465	IOP checks ranibizumab : Year 5	£3,645	£3,645
466	% patients with SVL requiring blind registration	£3,645	£3,645
467	% patients with SVL requiring low vision aids	£3,645	£3,645
468	% patients with SVL requiring low vision rehabilitation	£3,645	£3,645
469	Annual risk of cataract extraction DMO population	£3,645	£3,645
470	% patients with raised IOP ranibizumab: Year 2	£3,645	£3,645
471	% patients with raised IOP ranibizumab: Year 3	£3,645	£3,645
472	% cases of raised IOP treated with medications: ranibizumab	£3,645	£3,645
473	% patients with retinal detachment DEX700 PRN: Year 1	£3,645	£3,645
474	% patients with retinal detachment ranibizumab: Year 1	£3,645	£3,645
475	% patients with retinal detachment ranibizumab: Year 2	£3,645	£3,645
476	% patients with retinal detachment ranibizumab: Year 3	£3,645	£3,645
477	% patients with endophthalmitis DEX700 PRN: Year 3	£3,645	£3,645
478	% patients with endophthalmitis ranibizumab: Year 1	£3,645	£3,645
479	% patients with endophthalmitis ranibizumab: Year 2	£3,645	£3,645
480	% patients with endophthalmitis ranibizumab: Year 3	£3,645	£3,645
481	% patients with vitreous haemorrhage ranibizumab: Year 1	£3,645	£3,645
482	% patients with vitreous haemorrhage ranibizumab: Year 2	£3,645	£3,645
483	% patients with vitreous haemorrhage ranibizumab: Year 3	£3,645	£3,645
484	Utility equation constant	£3,645	£3,645
485	Relative risk of improving vision, DEX700 PRN as reference treatment, DEX700 PRN	£3,645	£3,645
486	Relative risk of stable vision, DEX700 PRN as reference treatment, DEX700 PRN	£3,645	£3,645
487	Relative risk of worsening vision, DEX700 PRN as reference treatment, DEX700 PRN	£3,645	£3,645
Abbreviations used in the table: AE, adverse event; BCVA, best corrected visual acuity; BSE, better-seeing eye; CA, carbonic anhydrase**;** DEX700 PRN, dexamethasone 700 *pro ne rata*; DMO, diabetic macular oedema; HS, health state; IOP, intraocular pressure; NMB, net monetary benefit; OWSA, one-way sensitivity analysis; re-tx, re-treatment; SVL, severe vision loss; WSE, worse-seeing eye.			

Results of scenario analyses using efficacy data from the updated NMA

Table 131Table 166 and Table 167 report the results of scenario analyses using efficacy data from the updated NMA, carried out by the company following the ERG's request during clarification.

Table 166: Scenario analysis results using efficacy data from the updated NMA; DMO patients who are considered insufficiently responsive to non-corticosteroid therapy (scenario analysis including fluocinolone acetonide) (Company's response to clarification, pgs 31-34)

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. baseline
	Cost	QALY	Cost	QALY		
Fluocinolone acetonide at list price						
DEX700	£20,413	5.7420	-	-	-	-
Watch and wait	£21,512	5.6789	£1,100	-0.0631	DEX700 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	£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

Abbreviations used in table: DEX700, dexamethasone 700µ; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALYs, quality-adjusted life years.

*Fluocinolone acetonide vs. dexamethasone

Table 167: Scenario analysis results using efficacy data from updated NMA; DMO patients who are pseudophakic (scenario analysis including bevacizumab, laser and watch and wait) (company's response to clarification, pgs 31-34)

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	£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	£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

Abbreviations used in the table: DEX700, dexamethasone 700µg; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

*Bevacizumab vs. laser.

9.10 Calculation sheets

Calculation sheets showing the changes made by the ERG in the company's economic models, in order to perform additional analyses

DMO_NICE_OCT2014_ALL DMO_ERG

Analysis number	Model worksheet affected	Description of ERG changes
B1	Inp_FEI	[redacted]
B2	Not relevant	Not relevant
B3	Inp_AE	[redacted]
B4	Inp_Costs	Cell C71 amended from 116.68 to =IF('ERG analysis'!$E$7=TRUE,144,116.68)
B5	Inp_Costs	Cell C145 amended from 1685 to =IF('ERG analysis'!$E$13=TRUE,(989*0.8)+(1443*0.2),1685) Cell C159 amended from 1685 to =IF('ERG analysis'!$E$13=TRUE,989,1685)
Analysis number	**Model worksheet affected**	**Description of ERG changes**
C1	Inp_FEI	[redacted]
C2	Inp_Efficacy	Cell G84 amended from 4.5% to =IF('ERG analysis'!$E$22=TRUE,5.5%,4.5%)
C3	Sub_data	Cells G1835 to G1874; G2402 to G2435, G2591 to G2630 changed from their initial value "x" to =IF('ERG analysis'!E13=TRUE,0,"x")
C4	Inp_Mortality	Cells E28:F120 amended from [E28 for example]: MIN(1,(1-(1-C28)^(p_Mortality_HR_Diabetes*p_Mortality_HR_DMO))) to =IF('ERG analysis'!$E$24=TRUE, MIN(1,(1-(1-C28)^3.5)), MIN(1,(1-(1-C28)^(p_Mortality_HR_Diabetes*p_Mortality_HR_DMO))))
C5	Not relevant	Not relevant

C6	Inp_MRU	Cell C29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,5-p_Doses_Dex_6m_Y1,4) Cell D29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y2,4) Cell E29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y3,4)
C7	Inp_MRU	Cells 'Inp_MRU'!C32:C36 amended from 2 to =IF('ERG analysis'!$E$9=TRUE,0,2)
C8	Inp_Costs	Cell C94 amended from 52282.93 to =IF('ERG analysis'!$E$10=TRUE,(532*(365.25/7)),52282.93)
C9	Inp_Costs	Cell C104 amended from 517.24 to =IF('ERG analysis'!$E$11=TRUE,2252,517.24)
C10	Inp_Costs	Cell C134 amended from 12.48 to =IF('ERG analysis'!$E$20=TRUE,1.18,12.48) Cell F138 amended from =AVERAGEIF(F133:F137,">0",F133:F137) to =IF('ERG analysis'!$E$20=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))
C11	Inp_Costs	Cell C120 amended from 1421.92 to =IF('ERG analysis'!$E$15=TRUE,(1123*0.5)+(1422*0.5),1421.92) Cell C126 amended from =SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125) to =IF('ERG analysis'!$E$15=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125))
C12	Inp_Costs	Additional cell to account for extra 6 visits: C138 =IF('ERG analysis'!E22=TRUE,6*Cost_Resource_4,0) F138 amended further to =C138+(IF('ERG analysis'!$E$20=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))) C126 amended further to: =C138+(IF('ERG analysis'!$E$21=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125)))
C13	Inp_Efficacy	[redacted]

	Inp_Utility	[redacted]

DMO_NICE_OCT2014_ALL DMO_INCL.FAME_ERG

Analysis number	Model worksheet affected (ALL DMO_INCL.FAME)	Description of ERG changes
B1	Inp_FEI	[redacted]
B2	Sub_Data	Cell E977 amended from =E965 to =IF('ERG analysis'!$E$5=TRUE,0.036, E965)
B3	Inp_AE	[redacted]
B4	Inp_Costs	Cell C71 amended from 116.68 to =IF('ERG analysis'!$E$7=TRUE,144,116.68)
B5	Inp_Costs	Cell C145 amended from 1685 to =IF('ERG analysis'!$E$13=TRUE,(989*0.8)+(1443*0.2),1685) Cell C159 amended from 1685 to =IF('ERG analysis'!$E$13=TRUE,989,1685)
Analysis number	**Model worksheet affected (ALL DMO_INCL.FAME)**	**Description of ERG changes**
C1	Inp_FEI	[redacted]
C2	Inp_Efficacy	Cell G84 amended from 4.5% to =IF('ERG analysis'!$E$22=TRUE,5.5%,4.5%)
C3	Sub_data	Cells G1835 to G1874; G2402 to G2435, G2591 to G2630, E2087 to E2146 changed from their initial value “x” to =IF('ERG analysis'!E13=TRUE,0,”x”)
C4	‘Inp_Mortality’	Cells E28:F120 amended from [E28 for example]: MIN(1,(1-(1-C28)^(p_Mortality_HR_Diabetes*p_Mortality_HR_DMO))) to =IF('ERG analysis'!$E$24=TRUE, MIN(1,(1-(1-C28)^3.5)), MIN(1,(1-(1-C28)^(p_Mortality_HR_Diabetes*p_Mortality_HR_DMO))))

C5	Not relevant	Not relevant
C6	Inp_MRU	Cell C29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,5-p_Doses_Dex_6m_Y1,4) Cell D29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y2,4) Cell E29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y3,4) Cell C73 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,5-p_Doses_Tx2_Y1,4) Cell D73 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Tx2_Y2,4) Cell E73 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Tx2_Y3,4)
C7	Inp_MRU	Cells 'Inp_MRU'!C32:C36 amended from 2 to =IF('ERG analysis'!$E$9=TRUE,0,2)
C8	Inp_Costs	Cell C94 amended from 52282.93 to =IF('ERG analysis'!$E$10=TRUE,(532*(365.25/7)), 52282.93)
C9	Inp_Costs	Cell C104 amended from 517.24 to =IF('ERG analysis'!$E$11=TRUE,2252,517.24)
C10	Inp_Costs	Cell C134 amended from 12.48 to =IF('ERG analysis'!$E$14=TRUE,1.18,12.48) Cell F138 amended from =AVERAGEIF(F133:F137,">0",F133:F137) to =IF('ERG analysis'!$E$14=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))
C11	Inp_Costs	Cell C120 amended from 1421.92 to =IF('ERG analysis'!$E$15=TRUE,(1123*0.5)+(1422*0.5),1421.92) Cell C126 amended from =SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125) to =IF('ERG analysis'!$E$15=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125))
C12	Inp_Costs	Additional cell to account for extra 6 visits: C138 =IF('ERG analysis'!E22=TRUE,6*Cost_Resource_4,0) F138 amended further to =C138+(IF('ERG analysis'!$E$20=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))) C126 amended further to: =C138+(IF('ERG analysis'!$E$21=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125)))

DMO_NICE_OCT2014_PSEUDOPHAKIC_ALL_TX_ERG

Analysis number	Model worksheet affected (PSEUDOPHAKIC_ALL _TX)	Description of ERG changes
B1	Inp_FEI	[redacted]
B2	N/A	N/A
B3	N/A	N/A
B4	Inp_Costs	Cell C71 amended from 116.68 to =IF('ERG analysis'!$E$7=TRUE,144,116.68)
B5	Inp_Costs	Cell C145 amended from 1685 to =IF('ERG analysis'!$E$13=TRUE,(989*0.8)+(1443*0.2),1685) Cell C159 amended from 1685 to =IF('ERG analysis'!$E$13=TRUE,989,1685)
Analysis number	**Model worksheet affected (Pseudophakic_All_Tx)**	**Description of ERG changes**
C1	Inp_FEI	[redacted]
C2	Inp_Efficacy	Cell G84 amended from 4.5% to =IF('ERG analysis'!$E$22=TRUE,5.5%,4.5%)
C3	Sub_data	Cells G1835 to G1874; G2213 to G2237; G2402 to G2435, G2591 to G2630, E2087 to E2209; E2665 to E2689; E2780 to E2804 changed, where needed, from their initial value “x” to =IF('ERG analysis'!E13=TRUE,0,”x”)
C4	‘Inp_Mortality’	Cells E28:F120 amended from [E28 for example]: MIN(1,(1-(1-C28)^(p_Mortality_HR_Diabetes*p_Mortality_HR_DMO))) to =IF('ERG analysis'!$E$24=TRUE, MIN(1,(1-(1-C28)^3.5)), MIN(1,(1-(1-C28)^(p_Mortality_HR_Diabetes*p_Mortality_HR_DMO))))

C5	Inp_Treatment	Cells E25 & E26 amended from 1.5 to =IF('ERG analysis'!$E$15=TRUE,1.25,1.5)
C6	Inp_MRU	Cell C29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,5-p_Doses_Dex_6m_Y1,4) Cell D29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y2,4) Cell E29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y3,4) Cell C73 amended from 12 to =IF('ERG analysis'!$E$16=TRUE,13-p_Doses_Tx2_Y1,12) Cell D73 amended from 10 to =IF('ERG analysis'!$E$16=TRUE,8-p_Doses_Tx2_Y2,10) Cell E73 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,6-p_Doses_Tx2_Y3,4) Cell C84 amended from 12 to =IF('ERG analysis'!$E$16=TRUE,13-p_Doses_Tx3_Y1,12) Cell D84 amended from 10 to =IF('ERG analysis'!$E$16=TRUE,8-p_Doses_Tx3_Y2,10) Cell E84 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,6-p_Doses_Tx3_Y3,4) Cell C95 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,5-p_Laser_Tx4_Y1,4) Cell D95 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Laser_Tx4_Y2,4) Cell E95 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Laser_Tx4_Y3,4)
C7	Inp_MRU	Cells 'Inp_MRU'!C32:C36 amended from 2 to =IF('ERG analysis'!$E$9=TRUE,0,2)
C8	Inp_Costs	Cell C94 amended from 52282.93 to =IF('ERG analysis'!$E$10=TRUE,(532*(365.25/7)),52282.93)
C9	Inp_Costs	Cell C104 amended from 517.24 to =IF('ERG analysis'!$E$11=TRUE,2252,517.24)
C10	Inp_Costs	Cell C134 amended from 12.48 to =IF('ERG analysis'!$E$14=TRUE,1.18,12.48) Cell F138 amended from =AVERAGEIF(F133:F137,">0",F133:F137) to =IF('ERG analysis'!$E$14=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))
C11	Inp_Costs	Sheet 'Inp_Costs' cell C120 amended from 1421.92 to =IF('ERG analysis'!$E$15=TRUE,(1123*0.5)+(1422*0.5),1421.92) Sheet 'Inp_Costs' cell C126 amended from =SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125) to =IF('ERG analysis'!$E$15=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125))
C12	Inp_Costs	Additional cell to account for extra 6 visits: C138 =IF('ERG analysis'!E22=TRUE,6*Cost_Resource_4,0) F138 amended further to =C138+(IF('ERG analysis'!$E$20=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))) C126 amended further to: =C138+(IF('ERG analysis'!$E$21=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_

		6)/COUNTA(C120:C125)))

DMO_NICE_OCT2014_ALL DMO_NO MTC_ALL MOVEMENTS_ERG

Same calculation sheet as in DMO_NICE_OCT2014_ALL DMO_ERG

DMO_NICE_OCT2014_ALL DMO_NO MTC_All MOVEMENTS_UTILITY UPDATE_ERG

Same calculation sheet as in DMO_NICE_OCT2014_ALL DMO_ERG. In addition the following amendments were made:

Analysis number	Model worksheet affected	Description of ERG changes
C14	Inp_Utility	[redacted]

9.11 Full results of additional analyses carried out by the ERG

Table 168. Patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy

Scenario	Total cost (DEX700)	Total cost (watch and wait)	Incremental cost per patient	Total QALYs (DEX700)	Total QALYs (watch and wait)	Incremental QALYs per patient	ICER (watch and wait vs DEX700)
Base case ICER	£20,413	£21,882	£1,469	5.7420	5.6764	-0.0656	Dominated
Model corrections							
B1: FEI rate set to 23.77%	£20,146	£21,525	£1,379	5.7438	5.6791	-0.0648	Dominated
B2: NA							
B3: Cataract extraction to amended ERG figures	£20,837	£21,879	£1,042	5.7420	5.6764	-0.0656	Dominated
B4: Cost of fluorescein angiography at £144	£20,633	£22,142	£1,509	5.7420	5.6764	-0.0656	Dominated
B5: Vitreous haemorrhage cost at £989 & retinal detachment cost at £1,080	£20,302	£21,882	£1,579	5.7420	5.6764	-0.0656	Dominated
All model corrections	£20,674	£21,783	£1,108	5.7438	5.6791	-0.0648	Dominated
Additional scenario analyses							
C1: Annual probability of FEI of 55.28%	£22,267	£24,335	£2,068	5.7294	5.6583	-0.0711	Dominated
C2: Probability of deterioration of vision increased to 5.5%; improvement 3.5% and stable 91%	£22,341	£24,289	£1,947	5.7287	5.6647	-0.0640	Dominated
C3: Discontinuation set at zero	£21,511	£25,178	£3,667	5.7394	5.6536	-0.0858	Dominated
C4: HR of mortality 3.5 for DMO vs.	£18,948	£19,786	£839	5.2991	5.2387	-0.0604	Dominated

general population							
C5: NA	-	-	-	-	-	-	-
C6: Monitoring visits are incorporated into treatment visits	£20,179	£21,882	£1,703	5.7420	5.6764	-0.0656	Dominated
C7: IOP checks removed from model	£19,989	£21,882	£1,893	5.7420	5.6764	-0.0656	Dominated
C8: Private residential care at £532 per week	£16,436	£14,445	£1,991	5.7420	5.6764	0.0656	£30,366.30
C9: Cost of depression at £2252	£20,778	£22,566	£1,787	5.7420	5.6764	-0.0656	Dominated
C10: Mean cost of raised IOP (medication) at £88.77	£20,376	£21,882	£1,506	5.7420	5.6764	-0.0656	Dominated
C11: Mean cost of raised IOP (surgical) at £1273	£20,417	£21,882	£1,465	5.7420	5.6764	-0.0656	Dominated
C12: Add 6 extra IOP visits for those with raised IOP	£20,554	£21,882	£1,328	5.7420	5.6764	-0.0656	Dominated
C13: Application of utility data from Czoski-Murray et al. 2009	£20,413	£21,882	£1,469	5.9095	5.6000	-0.3095	Dominated
Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; FEI, fellow eye involvement; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure; NA, not applicable.							

Table 169. Patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy – scenario analysis including fluocinolone acetonide

Analysis	Intervention / Comparator	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
Base case	DEX700	£20,413	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,464	-0.0655	Dominated
	fluocinolone acetonide	£22,383	5.8214	£1,971	0.0794	£24,817

Model corrections						
B1: FEI rate set to 23.77%	DEX700	£20,146	5.7438	-	-	-
	watch and wait	£21,520	5.6791	£1,374	-0.0647	Dominated
	fluocinolone acetonide	£22,193	5.8220	£2,047	0.0781	£26,203
B2: Re-treatments for fluocinolone not based on LOCF	DEX700	£20,413	5.7420	-	-	-
	fluocinolone acetonide	£20,871	5.8214	£459	0.0794	£5,777
	watch and wait	£21,878	5.6765	£1,005	-0.1449	Dominated
B3: Cataract extraction to amended ERG figures	DEX700	£20,837	5.7420	-	-	-
	watch and wait	£21,874	5.6765	£1,037	-0.0655	Dominated
	fluocinolone acetonide	£22,383	5.8214	£1,546	0.0794	£19,467
B4: Cost of fluorescein angiography at £144	DEX700	£20,633	5.7420	-	-	-
	watch and wait	£22,137	5.6765	£1,504	-0.0655	Dominated
	fluocinolone acetonide	£22,598	5.8214	£1,965	0.0794	£24,754
B5: Vitreous haemorrhage cost at £989 & retinal detachment cost at £1,080	DEX700	£20,302	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,574	-0.0655	Dominated
	fluocinolone acetonide	£22,383	5.8214	£2,081	0.0794	£26,205
All model corrections	DEX700	£20,674	5.7438	-	-	-
	fluocinolone acetonide	£20,913	5.8220	£238	0.0781	£3,053
	watch and wait	£21,778	5.6791	£865	-0.1428	Dominated
Additional scenario analyses						
C1: Annual probability of FEI of 55.28%	DEX700	£22,267	5.7294	-	-	-
	fluocinolone acetonide	£23,747	5.8174	£1,480	0.0880	£16,807
	watch and wait	£24,330	5.6583	£583	-0.1591	Dominated
C2: Probability of deterioration of vision increased to 5.5%; improveme	DEX700	£22,342	5.7287	-	-	-
	fluocinolone acetonide	£23,600	5.8073	£1,258	0.0786	£16,012
	watch and wait	£24,284	5.6648	£684	-0.1426	Dominated

nt 3.5% and stable 91%						
C3: Discontinuation set at zero	DEX700	£21,511	5.7394	-	-	-
	fluocinolone acetonide	£22,399	5.8275	£887	0.0881	£10,067
	watch and wait	£25,171	5.6536	£2,773	-0.1739	Dominated
C4: HR of mortality 3.5 for DMO vs. general population	DEX700	£18,948	5.2991	-	-	-
	watch and wait	£19,7812	5.2388	£834	-0.0603	Dominated
	fluocinolone acetonide	£21,427	5.3721	£2,480	0.0730	£33,970
C5: NA	-	-	-	-	-	-
C6: Monitoring visits are incorporated into treatment visits	DEX700	£20,179	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,698	-0.0655	Dominated
	fluocinolone acetonide	£22,349	5.8214	£2,170	0.0794	£27,326
C7: IOP checks removed from model	DEX700	£19,989	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,888	-0.0655	Dominated
	fluocinolone acetonide	£22,383	5.8214	£2,394	0.0794	£30,154
C8: Private residential care at £532 per week	watch and wait	£14,443	5.6765	-	-	-
	DEX700	£16,436	5.7420	£1,994	0.0655	£30,424
	fluocinolone acetonide	£20,818	5.8214	£4,381	0.0794	£55,178
C9: Cost of depression at £2252	DEX700	£20,778	5.7420	-	-	-
	fluocinolone acetonide	£22,527	5.8214	£1,749	0.0794	£22,025
	watch and wait	£22,560	5.6765	£33	-0.1449	Dominated
C10: Mean cost of raised IOP (medication) at £88.77	DEX700	£20,376	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,501	-0.0655	Dominated
	fluocinolone acetonide	£22,357	5.8214	£1,982	0.0794	£24,959
C11: Mean cost of raised IOP (surgical) at £1273	DEX700	£20,417	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,460	-0.0655	Dominated
	fluocinolone acetonide	£22,442	5.8214	£2,025	0.0794	£25,508
C12: Add 6 extra IOP visits for those with raised IOP	DEX700	£20,554	5.7420	-	-	-
	watch and wait	£21,877	5.6765	£1,323	-0.0655	Dominated
	fluocinolone acetonide	£23,025	5.8214	£2,471	0.0794	£31,114

C13: NA	-	-	-	-	-	-
Abbreviations used in the table: Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; FEI, fellow eye involvement; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure; NA, not applicable.						

Table 170. Patients with DMO who are pseudophakic – all comparators considered by the company for this population

All calculations below based on list price for ranibizumab

Analysis	Treatment	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
Base case (CS, Table 201)	laser	£8,361	5.1368	-	-	-
	bevacizumab	£9,402	5.2377	£1,041	0.1010	£10,310
	DEX700	£15,720	5.0886	£6,318	-0.1491	Dominated
	ranibizumab	£21,724	5.2066	£12,322	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,421	-0.2553	Dominated
Model corrections						
B1: FEI rate set to 23.77%	laser	£8,289	5.1369			
	bevacizumab	£9,340	5.2359	£1,052	0.0990	£10,618
	DEX700	£15,573	5.0894	£6,232	-0.1465	Dominated
	watch and wait	£21,506	4.9847	£12,166	-0.2512	Dominated
	ranibizumab	£21,564	5.2054	£12,223	-0.0305	Dominated
B2: NA	-	-	-	-	-	-
B3: NA	-	-	-	-	-	-
B4: Cost of fluorescein angiography at £144	laser	£8,553	5.1368	-	-	-
	bevacizumab	£9,586	5.2377	£1,033	0.1010	£10,228
	DEX700	£15,913	5.0886	£6,327	-0.1491	Dominated
	ranibizumab	£21,910	5.2066	£12,325	-0.0312	Dominated
	watch and wait	£22,052	4.9824	£12,466	-0.2553	Dominated
B5: Vitreous haemorrhage cost at £989 & retinal detachment cost at £1,080	laser	£8,083	5.1368	-	-	-
	bevacizumab	£9,402	5.2377	£1,319	0.1010	£13,061
	DEX700	£15,614	5.0886	£6,212	-0.1491	Dominated
	ranibizumab	£21,724	5.2066	£12,322	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,421	-0.2553	Dominated
All model corrections	laser	£8,207	5.1369			
	bevacizumab	£9,524	5.2359	£1,317	0.0990	£13,301
	DEX700	£15,661	5.0894	£6,137	-0.1465	Dominated
	watch and wait	£21,309	4.9851	£11,785	-0.2509	Dominated
	ranibizumab	£21,750	5.2054	£12,226	-0.0305	Dominated
Additional scenario analyses						
C1: Annual probability	laser	£8,887	5.1357	-	-	-
	bevacizumab	£9,814	5.2500	£927	0.1143	£8,106

of FEI of 55.28%	DEX700	£16,763	5.0830	£6,950	-0.1670	Dominated
	ranibizumab	£22,847	5.2143	£13,033	-0.0357	Dominated
	watch and wait	£24,006	4.9664	£14,193	-0.2836	Dominated
C2: Probability of deterioration of vision increased to 5.5%; improvement 3.5% and stable 91%	laser	£9,288	5.1248	-	-	-
	bevacizumab	£9,677	5.2260	£389	0.1012	£3,842
	DEX700	£17,001	5.0774	£7,325	-0.1487	Dominated
	ranibizumab	£22,144	5.1948	£12,468	-0.0312	Dominated
	watch and wait	£23,756	4.9739	£14,080	-0.2522	Dominated
C3: Discontinuation set at zero	laser	£7,640	5.1527	-	-	-
	bevacizumab	£9,483	5.2421	£1,843	0.0894	£20,621
	DEX700	£16,025	5.0979	£6,542	-0.1442	Dominated
	ranibizumab	£22,641	5.2176	£13,157	-0.0244	Dominated
	watch and wait	£23,728	4.9706	£14,245	-0.2715	Dominated
C4: HR of mortality 3.5 for DMO vs. general population	laser	£7,339	4.5665	-	-	-
	bevacizumab	£8,792	4.6572	£1,453	0.0907	£16,028
	DEX700	£14,225	4.5238	£5,433	-0.1334	Dominated
	watch and wait	£18,861	4.4300	£10,068	-0.2272	Dominated
	ranibizumab	£20,871	4.6288	£12,079	-0.0284	Dominated
C5: Bilateral treatment with anti-VEGF 75% 1 admin visit	laser	£8,361	5.1368	-	-	-
	bevacizumab	£9,191	5.2377	£830	0.1010	£8,219
	DEX700	£15,720	5.0886	£6,529	-0.1491	Dominated
	watch and wait	£21,381	4.9828	£12,190	-0.2549	Dominated
	ranibizumab	£21,549	5.2066	£12,358	-0.0312	Dominated
C6: Monitoring visits are incorporated into treatment visits	bevacizumab	£8,110	5.2377	-	-	-
	laser	£8,157	5.1368	£48	-0.1010	Dominated
	DEX700	£15,522	5.0886	£7,413	-0.1491	Dominated
	ranibizumab	£20,683	5.2066	£12,574	-0.0312	Dominated
	watch and wait	£21,381	4.9828	£13,272	-0.2549	Dominated
C7: IOP checks removed from model	laser	£8,361	5.1368	-	-	-
	bevacizumab	£9,402	5.2377	£1,041	0.1010	£10,310
	DEX700 PRN	£15,322	5.0886	£5,920	-0.1491	Dominated
	ranibizumab	£21,724	5.2066	£12,322	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,421	-0.2553	Dominated
C8: Private residential care at £532 per week	laser	£6,996	5.1368	-	-	-
	bevacizumab	£9,208	5.2377	£2,213	0.1010	£21,915
	DEX700	£13,107	5.0886	£3,899	-0.1491	Dominated
	watch and wait	£14,043	4.9824	£4,835	-0.2553	Dominated
	ranibizumab	£21,347	5.2066	£12,139	-0.0312	Dominated
C9: Cost of	laser	£8,487	5.1368	-	-	-

depression at £2252	bevacizumab	£9,420	5.2377	£933	0.1010	£9,243
	DEX700	£15,960	5.0886	£6,541	-0.1491	Dominated
	ranibizumab	£21,759	5.2066	£12,339	-0.0312	Dominated
	watch and wait	£22,538	4.9824	£13,118	-0.2553	Dominated
C10: Mean cost of raised IOP (medication) at £88.77	laser	£8,352	5.1368	-	-	-
	bevacizumab	£9,377	5.2377	£1,024	0.1010	£10,147
	DEX700	£15,684	5.0886	£6,307	-0.1491	Dominated
	ranibizumab	£21,722	5.2066	£12,345	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,446	-0.2553	Dominated
C11: Mean cost of raised IOP (surgical) at £1273	laser	£8,364	5.1368	-	-	-
	bevacizumab	£9,402	5.2377	£1,038	0.1010	£10,285
	DEX700	£15,724	5.0886	£6,322	-0.1491	Dominated
	watch and wait	£21,381	4.9828	£11,979	-0.2549	Dominated
	ranibizumab	£21,724	5.2066	£12,322	-0.0312	Dominated
C12: Add 6 extra IOP visits for those with raised IOP	laser	£8,410	5.1368	-	-	-
	bevacizumab	£9,472	5.2377	£1,062	0.1010	£10,518
	DEX700	£15,858	5.0886	£6,386	-0.1491	Dominated
	watch and wait	£21,381	4.9828	£11,909	-0.2549	Dominated
	ranibizumab	£21,730	5.2066	£12,258	-0.0312	Dominated
C13: NA	-	-	-	-	-	-
Abbreviations used in the table: Abbreviations used in table: CS, company submission; DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; FEI, fellow eye involvement; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure; NA, not applicable.						