NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Dexamethasone intravitreal implant for treating diabetic macular oedema

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List of Abbreviations

AE	Adverse event
AUC	Area under the curve
BCVA	Best corrected visual acuity
BEV	bevacizumab
BRB	Blood retinal barrier
BRVO	Branch retinal vein occlusion
BSE	Better seeing eye
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence internal
CRT	Central retinal thickness
CSDMO	Clinically significant diabetic macular oedema
CSMO	Clinically significant macular oedema
CV	Cardiovascular
DDS	Drug delivery system
DEX	Dexamethasone
DM	Diabetes mellitus
DMO	Diabetic macular oedema
DR	Diabetic retinopathy
EMA	European Medicines Agency
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
HbA1c	Glycosylated haemoglobin
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
MIMS	Monthly Index of Medical Specialities
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NMB	Net monetary benefit
OCT	Optical coherence tomography
OS	Overall survival
OSC	Optimised standard of care
PFS	Progression free survival

PRN	*Pro re nata*
PS DDS	Posterior segment drug delivery system
PSS	Personal social services
QALY(s)	Progression-adjusted life year(s)
RCO	Royal College of Ophthalmologists
RCT	Randomised controlled trials
RVO	Retinal vein occlusion
SAE	Serious adverse event
SD	Standard deviation
SMC	Scottish Medicines Consortium
TPM	Transition probability matrices
TTP	Time to progression
UK	United kingdom
US	United States of America
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VFQ	Visual functioning questionnaire
WSE	Worse-seeing eye

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 10.1 to 10.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices

should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126]’ rather than ‘One trial[126]’).

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, section 11.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

Effective management of diabetes and the associated complications of this chronic disease pose a significant challenge to the NHS. Diabetic macular oedema (DMO) is one such complication that can result in permanent retinal damage and irreversible vision loss if insufficiently treated. Therapeutic options currently available to treat DMO in the UK have limitations regarding variability of response, the intensity of administration schedules, safety and restrictions on use (licence, guideline and/or HTA restrictions) and thus cannot be used to successfully manage all patients with DMO and associated visual impairment that present in clinical practice. There is a continued unmet medical need for additional therapeutic options that allow clinicians to successfully treat more patients presenting with visual impairment due to DMO based on their individual requirements.

Introduction to DEX700 for DMO

Dexamethasone 700µg (DEX700) intravitreal implant in applicator (Ozurdex®) is an injectable intravitreal implant that delivers active treatment to the posterior segment of the eye through an innovative NOVADUR solid polymer drug delivery system (DDS) over a period of 6 months or more; remaining in the vitreous for up to 270 days before fully dissolving.

Dexamethasone is a potent corticosteroid that reduces the levels of multiple inflammatory mediators (including the production of vascular endothelial growth factor (VEGF)) which are involved in the multifactorial pathophysiology of DMO. As a result, dexamethasone improves visual acuity through resolution of macular oedema: the key to effective long-term management of this condition.

In the UK, DEX700 has existing market authorisations for use in retinal vein occlusion (RVO) and uveitis and has recently been granted market authorisation for use in diabetic macular oedema (DMO). The approved indication for DEX700 in DMO is 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.

DEX700 is provided as a single intravitreal implant in applicator, containing 700µg of dexamethasone at an acquisition cost of £870.00.

The recommended course of treatment is one DEX700 implant at approximately six month intervals for patients who experience a response to treatment followed subsequently by a loss in visual acuity or increase in macular oedema and in the physician's opinion may benefit from retreatment without being exposed to significant risk.

Patients who experience and retain improved vision should not be retreated but treatment may be reinitiated if patients experience a loss in vision or increase in macular oedema at a later stage. Patients who experience deterioration in vision, which is not slowed by DEX700, should not be retreated.

Current clinical pathway of care

Therapies currently available for use in DMO are: laser photocoagulation therapy, anti-VEGF agents (bevacizumab; ranibizumab, Lucentis®) and a corticosteroid implant (fluocinolone acetonide, Iluvien®). Laser photocoagulation therapy has generally been shown to slow the deterioration in vision, rather than improve vision and importantly should only be considered when the centre of the macular is not involved (~20% of all patients with DMO) due to the destructive nature of the treatment. Anti-VEGF agents demonstrate superior efficacy to laser photocoagulation therapy in randomised controlled trials (RCT) and are safe for use in centre-involved DMO but require frequent administration to achieve optimum efficacy which poses a significant burden to both patients and care providers. In addition, anti-VEGF agents only target a single component of the inflammatory pathway of DMO and a number of patients demonstrate insufficient response to such therapy in clinical practice. Corticosteroid therapies target the multifactorial pathophysiology of DMO and implant developments allow long-term treatment to be administered in a single injection.

The primary comparator to DEX700 for the treatment of adult patients with visual impairment due to DMO, who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy, is “watch and wait” as there are no alternative active therapy options for the majority of such patients in England and Wales.

The primary comparator to DEX700 for the treatment of adult patients with visual impairment due to DMO, who are pseudophakic, is ranibizumab 0.5mg (Lucentis®)

therapy as this is the preferred first-line treatment option for such patients in England and Wales. Ranibizumab may be given as monotherapy or in combination with laser photocoagulation.

The fluocinolone acetonide implant (Iluvien) is included in the submission as a secondary comparator to DEX700 for the treatment of adult patients with visual impairment due to DMO, who are considered insufficiently responsive to non-corticosteroid. This implant is licensed for use in chronic DMO who are considered insufficiently responsive to available therapies and is further restricted to use in pseudophakic patients in England and Wales by NICE. It is therefore viewed as a last line therapy in clinical practice that is only available to a small DMO cohort.

Laser monotherapy and bevacizumab are included in the submission as secondary comparators to DEX700 for the treatment of adult patients with visual impairment due to DMO, who are pseudophakic. 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. Laser monotherapy for the treatment of DMO is not common practice since more effective pharmaceutical treatment options became available and the implications of its destructive nature coupled with limitations of patient types in which it can not be used (e.g. patients with lesions close to the centre of the macular, patients with ischaemia) are better understood (appendix 14, section 10.14). Bevacizumab is not licensed for use in DMO; it is not formulated for intraocular use and there are no large-scale RCTs providing long-term clinical and safety evidence of its use in DMO. Clinical experts have indicated that since the availability of licensed pharmaceutical treatment options with large-scale RCT evidence, its use has declined and it is not available for intraocular use in the majority of UK hospitals (appendix 14, section 10.14).

Clinical evidence base

Key clinical evidence in the submission comes from head-to-head RCTs which include at least a proportion of patients in which DEX700 is directly compared with the appropriate comparator with reference to the decision problem.

The regulatory trial programme, MEAD, provides phase III RCT evidence of DEX700 compared to sham therapy, intended as a proxy for watch and wait in clinical

practice. These trials recruited patients who had previously received prior medical or laser therapy or were considered unsuitable for laser photocoagulation therapy. An additional phase IIIb RCT provides direct evidence of DEX700 compared to ranibizumab therapy.

A phase II RCT provides direct evidence of DEX700 addition to laser therapy and a further phase II RCT provides direct evidence of DEX700 compared to bevacizumab.

A significant proportion of patients in all studies presented with a pseudophakic lens.

No head-to-head trials are available that compare DEX700 to the fluocinolone acetonide implant. In addition, the phase II and IIIb trials adopt dosing regimens for DEX700 that are not in line with the recommended course of treatment in the confirmed marketing authorisation.

A mixed treatment comparison is therefore also presented alongside the RCT evidence that estimates comparative efficacy of DEX700 in line with the recommended course of treatment (as per MEAD) to all primary and secondary comparators in population's representative of those of relevance to the decision problem. There are however a number of limitations with this analysis, primarily caused by heterogeneity between trials, that need to be considered when interpreting results.

Clinical Effectiveness and Safety

In the regulatory trial programme, MEAD, DEX700 resulted in rapid and sustained anatomical and VA improvements in patients with DMO and associated visual impairment. With a mean of 4-5 injections over three years, DEX700 demonstrated statistically significant superiority over sham treatment in primary and key secondary efficacy outcomes despite a sham result which is considered to be superior to the outcomes expected without treatment in true clinical practice.

Over the three year MEAD study period, DEX700 resulted in a mean BCVA average change (AUC approach) of 3.5 letters compared with 2.0 letters in the sham arm ($p=0.023$). At study end, 38.7% and 22.1% of DEX700 treated patients achieved at least a 10-letter and at least a 15-letter gain in ETDRS letters from baseline compared with 23.0% and 13.3% of sham treated patients ($p<0.05$). Over the three year MEAD study period, DEX700 resulted in a mean central retinal thickness (CRT) change of -111.6 µm compared with -41.9 µm in the sham arm ($p<0.001$). The mean

CRT change from baseline was statistically significantly superior with DEX700 compared to sham at all visits throughout the study as well as at study end.

The positive results observed in the sham treated patients were not expected. One factor that is likely to have contributed to these observations is that 56.7% of the sham group discontinued during the study, often as a consequence of vision loss, and many of these discontinuations were early within the study period. This meant that the study was not able to capture any subsequent deterioration in the clinical condition of this significant cohort of patients and left patients with a favourable natural history in the study.

In the subgroup of patients enrolled in MEAD who presented with pseudophakic lens at baseline, DEX700 continued to demonstrate statistically significant superiority over sham treatment but with a greater magnitude of effect in cumulative BCVA analysis: mean BCVA average change (AUC approach), DEX700 =6.5, Sham = 1.7 ($p<0.001$); ≥15-letter gain at study end, DEX700 = 23.3%, Sham = 10.9% ($p=0.024$). Intravitreal corticosteroid therapies are associated with progression of lens opacification and primary cataract formation that impair visual acuity alongside visual impairment due to progression of oedema. In patients with pseudophakic lens, such adverse events are not of concern; therefore visual acuity is not influenced by such factors.

In the phase IIIb RCT, study 024, DEX700 was [redacted] mean injection frequency of [redacted] respectively within the 12 month study period. In primary efficacy analysis, DEX700 resulted in a mean BCVA average change of [redacted] letters compared with [redacted] letters in the ranibizumab arm. The lower bound CI value in the between group [redacted] difference between the DEX700 and ranibizumab treatment groups in the mean change from baseline in foveal thickness of the central subfield at study end [redacted] was seen in the mean change from baseline in total leakage area (mm^2) [redacted]

In all RCTs, DEX700 demonstrated a stable and clearly characterised safety profile, medically manageable in line with standard clinical practice. Typical of intravitreal steroid, common adverse events associated with DEX700 therapy were related to IOP elevation and cataract. Both were anticipated *a priori* and did not exceed expected levels in any of the DEX700 trials.

Cost Effectiveness

A cost-utility analysis was conducted, in line with the NICE reference case. A cohort model with a Markov structure was chosen to model changes in BCVA resulting from the treatment of DMO over a 15-year time horizon. The model allows BCVA changes in both eyes to be modelled independently; with the better-seeing eye (BSE) and worse-seeing eye (WSE) defined at baseline and fixed throughout the time horizon. Treatment may be modelled in both eyes (bilateral DMO) or in either the BSE or WSE (unilateral DMO). Changes in BCVA are modelled as transitions between six visual acuity states of 10-letter increments.

Efficacy of treatment is modelled using the relative risks of improving vision (moving up one visual acuity state), worsening vision (moving down one visual acuity state) or retaining stable vision (remaining in the same visual acuity state) for each treatment relative to DEX700 PRN treatment obtained from the network meta-analysis.

The baseline distribution of patients across unilateral treatment in either the BSE or WSE, or bilateral treatment was taken from the MEAD clinical trials. Patients within the cohort who are unilaterally affected at baseline are assumed to be at risk of developing DMO in their fellow eye (fellow eye involvement) and moving on to bilateral treatment at the end of Year 1 or Year 2 at a rate of [redacted] per year, a further simplifying assumption of the economic model. Eyes without DMO are assumed to have stable vision.

Patients within the cohort are assumed to be at risk of discontinuing from treatment due to either:

- adverse events and other non-efficacy-related reasons, or,
- lack (or loss) of efficacy of treatment

All patients who discontinue from treatment are assumed to receive no further treatment costs and their vision is assumed to follow the natural history of vision in eyes with DMO.

Maximum treatment duration of 3 years is applied in the base case analysis, consistent with the maximum duration of clinical trials in DMO. Following the initial 3-year treatment period any patients within the cohort who have not discontinued from treatment are assumed to then receive no further treatment costs and their vision is assumed to follow the natural history of vision in eyes with DMO.

Utility data were estimated from the MEAD clinical trial data. In the base case analysis linear regression analyses performed on Visual Function Questionnaire – utility index (VFQ-UI) data obtained from the MEAD clinical trials were used to provide an algorithm for the estimation of whole person utility from the BCVA in both the BSE and the WSE.

Costs were estimated from the perspective of the NHS and PSS in England and were taken from NHS reference costs and the Monthly Index of Medical Specialities (MIMS) where appropriate. Costs included were the costs of treatment acquisition and administration, the cost of medical monitoring and tests, the cost of treatment of adverse events and the costs associated with severe vision loss. It is noted that treatment acquisition costs are based on the list price or an assumed patient access scheme discount where applicable as the exact details of the discount are confidential and hence unknown.

All-cause mortality for adults in England was adjusted for DMO using hazard ratios for diabetes mellitus (DM) relative to the general population and for DMO relative to a DM population. No additional mortality due to severe vision loss is assumed in the base case analysis to avoid double-counting as it is likely that the hazard ratio for DMO relative to the DM population would include some patients with severe vision loss.

Costs and QALYs are discounted at a rate of 3.5% per year, consistent with the NICE reference case.

The economic evaluation includes analyses that cover the licensed indication for DEX700 as follows:

Patients with DMO and associated visual impairment who are considered unsuitable for non-corticosteroid therapy

- DEX700 PRN considered as a first-line treatment option
- The comparator for this analysis is watch and wait in the base case as there is an unmet need for an active treatment option in this patient population
- This analysis is based on evidence for the whole DMO population as a proxy for the population of patients with DMO who are considered unsuitable for non-corticosteroid therapy
  - There is no available evidence for DEX700 or sham in this specific population; therefore the assumption has been made that there is no differential efficacy of DEX700 or sham in the population of DMO patients who are considered unsuitable for non-corticosteroid therapy compared with the whole DMO population

Patients with DMO and associated visual impairment who are considered insufficiently responsive to non-corticosteroid therapy

- DEX700 PRN considered as a second-line treatment option.
- The comparator for this analysis is watch and wait in the base case as there is an unmet need for a treatment option in this patient population.
  - A scenario analysis has been presented including fluocinolone acetonide in an incremental analysis
  - Fluocinolone acetonide has been excluded from the base case analysis because
    - Market share data indicates minimal use of this treatment in clinical practice, likely due to the restrictions placed on its use by its marketing authorisation and by NICE guidance
    - The network meta-analysis including the FAME trial is subject to a number of limitations making it difficult to draw any meaningful conclusions from an analysis based on an analysis including fluocinolone acetonide

- This analysis is based on evidence for the whole DMO population as a proxy for the population of patients with DMO who are considered insufficiently responsive to non-corticosteroid therapy
  - Available evidence does not suggest that there is a differential efficacy of DEX700 treatment in patients who are considered insufficiently responsive to non-corticosteroid therapy compared with the whole population

Patients with DMO and associated visual impairment who are pseudophakic

- DEX700 PRN considered as a first-line treatment option
- The comparator for this analysis is ranibizumab in the base case as this is the most common first-line treatment for DMO used in practice
  - Scenario analyses have been presented including laser, bevacizumab and watch and wait in an incremental analysis
- This analysis is based on the subgroup of pseudophakic patients in the pooled MEAD clinical studies
  - Where possible, data for other treatments in the network of evidence are also for the pseudophakic subgroup, but where this was not possible data for the whole DMO population has been used as a proxy

The base case results are presented in Table 1 and Table 2 for each population covered by the marketing authorisation for DEX700. Ranibizumab is subject to a confidential patient access scheme (PAS) so results have been presented at list price and a 50% discount to the price of ranibizumab to show the most optimistic and most pessimistic estimates of cost-effectiveness for DEX700 compared with ranibizumab.

Table 1: Base-case cost-effectiveness results – Patients with DMO and associated visual impairment who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy

	DEX700 PRN	Watch and wait
Technology acquisition cost	£4,861	£0
Other costs	£15,552	£21,882
Total costs	£20,413	£21,882
Difference in total costs	N/A	-£1,469*
LYG	11.7964	11.7964
LYG difference	N/A	0.0000*
QALYs	5.7420	5.6764
QALY difference	N/A	0.0656*
ICER	N/A	DEX700 dominates

Key: DEX, dexamethasone; DMO, Diabetic macular oedema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PRN, *pro re nata*; QALY(s), quality-adjusted life year(s).
Notes: *DEX700 vs. watch and wait

Table 2: Base-case cost-effectiveness results – Patients with DMO and associated visual impairment who are pseudophakic, ranibizumab at list price (ranibizumab at 50% discount)

	DEX700 PRN	Ranibizumab
Technology acquisition cost	£4,337	£13,439 (£6,720)
Other costs	£11,383	£8,285
Total costs	£15,720	£21,724 (£15,004)
Difference in total costs	N/A	-£6,004 (-£)*
LYG	10.2207	10.2207
LYG difference	N/A	0.0000*
QALYs	5.0886	5.2066
QALY difference	N/A	-0.1179*
ICER	N/A	£50,905 (ranibizumab dominates)*
Incremental NMB	N/A	£3,645 (-£6,068)*

Key: DEX, dexamethasone; DMO, Diabetic macular oedema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PRN, *pro re nata*; QALY(s), quality-adjusted life year(s).
Notes: *DEX700 vs. ranibizumab

Clinical Benefit

DEX700 provides a favourable benefit/harm profile in the populations of relevance to the decision problem. In patients with DMO and associated visual impairment who

are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy, DEX700 offers a treatment option that acts to prevent permanent retinal damage and irreversible vision loss due to insufficiently treated oedema. This is extremely important in the context of the diabetic patient for whom self-management is the key to successful disease management and should help to reduce the overall burden of this condition on the patient, the health system and society.

In patients with DMO and associated visual impairment who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy, DEX700 offers a cost-effective treatment option compared with watch and wait, as treatment with DEX700 PRN results in additional QALYs at a lower cost than a strategy of watch and wait. This result is robust to sensitivity analyses. In these populations DEX700 PRN is considered cost-effective compared with watch and wait at a willingness to pay threshold of £20,000 per QALY gained in 61% of 5,000 probabilistic simulations. Further, in the population of patients with DMO and associated visual impairment who are pseudophakic, DEX700 PRN is cost-effective up to a discount of 27% to the list price of ranibizumab in the base case analysis.

In conclusion, DEX700 provides a clinically and cost-effective treatment option for the population of patients with DMO and associated visual impairment who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy, populations in which there is a clear unmet need for a treatment option. The introduction of DEX700 into the clinical pathway for these populations would result in fewer patients becoming clinically blind as a result of DMO remaining untreated due to a lack of available therapies. Given the high annual cost per patient with clinical blindness the introduction of DEX700 where currently there is an unmet need for a treatment option could result in considerable cost savings for the NHS.

DEX700 additionally provides a clinically effective treatment option in the population of patients with DMO and associated visual impairment who are pseudophakic and may be considered cost-effective in this population dependent on the level of discount applied to the list price of ranibizumab. The introduction of DEX700 into the treatment pathway for these patients may achieve substantial cost savings to the NHS, and reduce the burden to both the patient and the NHS due to the reduced injection and monitoring frequency associated with DEX700 compared with ranibizumab.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Ozurdex®
Approved name: Dexamethasone 700µg intravitreal implant in applicator
Therapeutic class: Ophthalmologicals, anti-inflammatory agents, corticosteroid
ATC code: S01BA01

1.2 What is the principal mechanism of action of the technology?

Ozurdex contains the active treatment: dexamethasone; a potent corticosteroid that has been shown to suppress inflammation by inhibiting fibrin deposition, capillary leakage and phagocytic migration of the inflammatory response, and thus reduce macular oedema due to various causes.[1-3] As with other corticosteroids, dexamethasone is a glucocorticoid agonist that binds to cytoplasmic glucocorticoid receptors, resulting in decreased production of pro-inflammatory mediators that are over-expressed as part of the pathogenic pathway of diabetic macular oedema (DMO) through hyperglycaemia.[3-9]

Dexamethasone not only decreases synthesis of vascular endothelial growth factor, (VEGF) which promotes breakdown of the blood retinal barrier (BRB) and retinal neovascularisation, stimulates leukostasis and increases vascular permeability; it also prevents the release of other inflammatory factors involved in DMO

development.[3] These factors include intercellular adhesion molecule-1(ICAM-1), which facilitates leukocyte adhesion to endothelial cells; interleukin-6 (IL-6), which increases VEGF production; tumour necrosis factor-α (TNF-α), which promotes breakdown of the BRB and ICAM-1 expression; angiopoietin-2 (ANG-2), which promotes breakdown of the BRB and sensitises endothelial cells to TNF-α; and chemokines ligand-2, which induces leukocyte recruitment and activation.[4, 6-9]

As a result, dexamethasone can revert vessel dilation and altered flow and prohibit exudation of fluids and leukocyte accumulation; directly resolving macular oedema and stabilising the BRB.[2, 3, 10]

Ozurdex is an injectable intravitreal implant that delivers 700µg dexamethasone (DEX700) to the posterior segment of the eye through an innovative NOVADUR solid polymer drug delivery system (DDS) over a period of 6 months or more.[2, 3] This DDS was developed to prolong the duration of effect of dexamethasone in the eye and overcome ocular drug delivery barriers.

Bolus intravitreal administration of dexamethasone has been associated with suboptimal durability, due to a short half-life of approximately 3 hours.[11, 12] The DEX700 implant is characterised by dual-phase pharmacokinetics; initially releasing a burst of dexamethasone to rapidly achieve a therapeutic concentration; then gradually releasing the remaining total dose over several months.[2, 13] This allows long-term treatment of DMO through a single application.

The innovative DDS contains a material (copolymer, poly(lactic-co-glycolic) acid) similar to that used in dissolvable sutures, which dissolves and degrades into CO_2 and water over time.[2, 14] In total, the DEX700 implant remains in the vitreous for up to 270 days before fully dissolving.[3, 13] This alleviates any concerns regarding the long-term safety of implant retention.

In response to physician concerns about the pressure required to insert the original DDS needle, the DDS applicator is now supplied with a sharper needle. The geometry, mechanical penetration force and cutting profile of this new needle was shown to be superior to that of the old needle in an recently reported study.[15] Clinicians report that it has helped to achieve a smooth and painless penetration through the human sclera.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Application for extension of the indication for DEX700 to include DMO patients was submitted to the European Medicines Agency (EMA) on 21 June 2013.

DEX700 received a positive Committee for Medicinal Products for Human Use (CHMP) opinion 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 was approved by the European Commission for a marketing authorisation on 24 August 2014.

DEX700 already 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.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

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]

Whilst the CHMP acknowledged the visual outcomes were impacted by the occurrence of cataract events in the majority of patients treated with DEX700, it was deemed misleading to discount the loss of vision experienced as a result of cataract. They concluded that the majority of patients will experience cataract after treatment with DEX700 and will lose vision as a result, albeit temporarily. 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. Such a short-acting implant would allow physicians to evaluate the safety and efficacy response of patients to steroid treatment and make re-treatment decisions accordingly.[16]

In regard to perceived risk, the CHMP noted the most frequent adverse drug reactions observed with DEX700 in clinical trials for DMO (raised IOP, cataract, and injection-related events) were not unexpected, and were known adverse reactions already listed in the SPC for other indications that are manageable. With regards to the subgroups of pseudophakic patients and patients with prior DMO treatment, the CHMP considered that the safety of DEX700 was not markedly different to that in the overall population other than there being no risk of steroid-induced cataract in pseudophakic patients.[16]

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]

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The approved indication for DEX700 in DMO is:

To treat adult patients with visual impairment due to DMO, who are pseudophakic, or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Of the studies from which evidence is presented in section 6, interim data only are available for one study at this time. Final analyses (24 month data) of the BEVORDEX trial should become available within the next 12 months.

In addition, a search on clinicaltrials.gov identified 12 studies for which no results have been made available to date that would potentially meet the eligibility criteria of the systematic reviews designed to identify evidence of effectiveness of DEX700 in DMO (outlined in section 6). Details of these trials are presented in Appendix 23.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

DEX700 is already available in the UK, due to the existing marketing authorisations in RVO and uveitis and its recent marketing authorisation in DMO.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

DEX 700 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.

DEX700 has regulatory approval from the US Food and Drug Administration (FDA) for the treatment of DMO. DEX700 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). Based on an ongoing review of clinical data demonstrating efficacy and safety, the FDA has now approved DEX700 for use in the general DMO population (29th September 2014).

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

DEX700 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 is scheduled for a health technology appraisal by the Scottish Medicines Consortium (SMC) in December 2014.

NICE have already completed a technology appraisal of DEX700 for the treatment of macular oedema secondary to retinal vein occlusion (RVO) [TA229]. In July 2011, NICE recommended dexamethasone intravitreal implant as a possible treatment for people with macular oedema due to RVO if they have macular oedema due to blockage of the central retinal vein or a branch retinal vein and laser treatment has not helped or is not suitable. The SMC also gave a positive recommendation in this indication with the same restrictions in June 2012 [652/10].

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 3: Unit costs of technology being appraised

Pharmaceutical formulation	Intravitreal implant in applicator
Acquisition cost (excluding VAT)	£870.00
Method of administration	Intravitreal injection
Doses	700µg
Dosing frequency	Repeat doses should be considered when a patient experiences a response to treatment followed by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk
Average length of a course of treatment	A maximum of three years of treatment has been assumed in the economic base case analysis, reflecting the duration of the MEAD studies. The true duration of treatment is unknown and likely to be variable by patient; therefore the average number of DEX700 injections required over three years of treatment is assumed to be equal to the average number of treatments received by patients in the MEAD studies over 3 years.
Average cost of a course of treatment	The total cost of a course of DEX700 (assuming an average of 4.47 treatments over 3 years as per the economic base-case) is expected to be £3,888.90 per treated eye.
Anticipated average interval between courses of treatments	It is anticipated that patients will receive treatment at intervals of approximately 6 months
Anticipated number of repeat courses of treatments	None
Dose adjustments	None

Key: DEX, dexamethasone
Note: average treatment based on cumulative analysis accounting for discontinuations during each 3-month cycle throughout the study period as used in the economic modelling.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Adult patients are eligible for DEX700 if they have visual impairment due to DMO and a pseudophakic lens, or if they have visual impairment due to DMO and are

considered insufficiently responsive to non-corticosteroid therapy, or if they have visual impairment due to DMO and are considered unsuitable for non-corticosteroid therapy.

There are no stipulated additional tests or investigations needed for selection. However, DEX700 is contraindicated in specific patient groups (Appendix 10.1) and its use should be avoided in patients for whom a potential IOP rise may be harmful.

DEX700 administration 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) by a qualified ophthalmologist experienced in intravitreal injections. Intravitreal injection is a common ocular procedure within the NHS, performed routinely as an outpatient procedure; therefore these conditions are already established. No special storage conditions are required for DEX700.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Patients should be monitored following the injection to permit early treatment if an infection or increased IOP occurs. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between 2 and 7 days following the injection. Such monitoring requirements during the week following injection are applicable to all intravitreal therapies.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

The patient should be instructed to self-administer broad spectrum antimicrobial drops daily for 3 days before and after each injection. Immediately prior to DEX700 injection, the periocular skin, eyelid and ocular surface should be disinfected (using for example drops of povidone iodine 5% solution on the conjunctiva and adequate local anaesthesia should be administered. Following the intravitreal injection patients should continue to be treated with a broad spectrum antimicrobial. These requirements are applicable to all intravitreal injection therapies.

If an IOP rise is detected post injection, topical IOP-lowering medicinal products may be prescribed.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

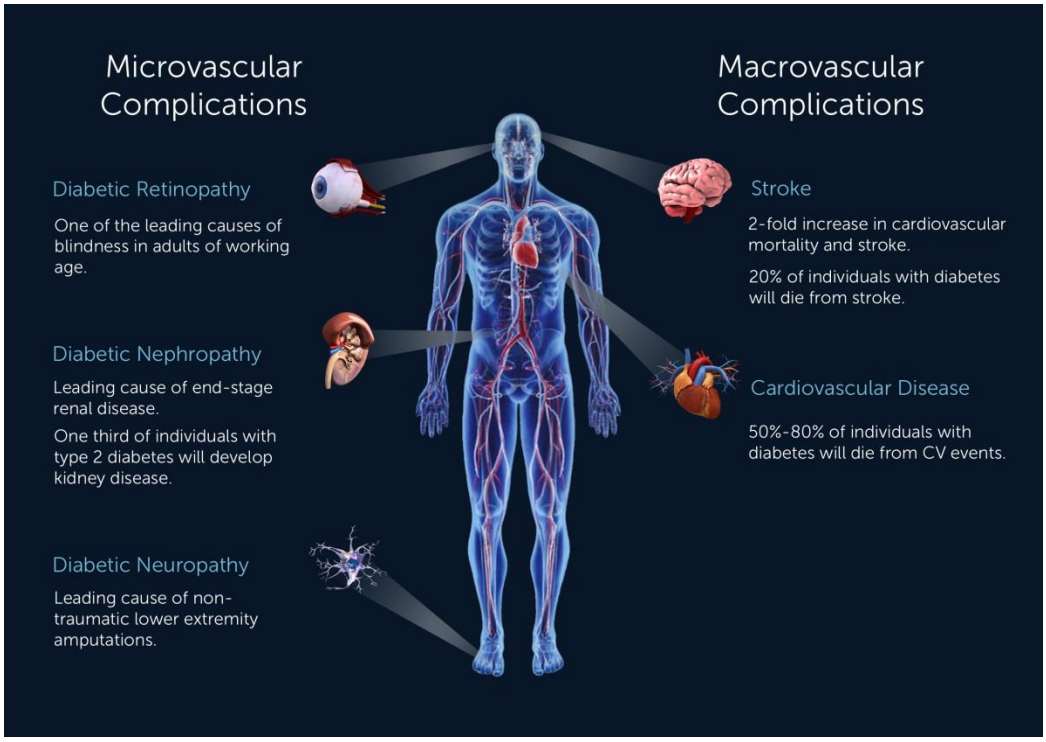
2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

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.[17-19] 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).[17] DM can be subdivided into a number of different types depending on its aetiology; the most predominant of which are Type 1 (5-15% of all diagnosed cases) and Type 2 (85-95% of all diagnosed cases).[18, 20-22] All types of DM are associated with a number of serious complications, presented in Figure 1, and subsequently high rates of morbidity and mortality.[18]

DM also raises the risk for visual impairment due to cataracts and glaucoma, both of which have been associated with as much as a five-fold prevalence increase in patients with DM compared with those without DM.[23-27] Cataract is one of the most common causes of blindness in older-onset patients with DM[28] and risk of its development appears to be greatest in non-insulin dependent DM, with a cataract rate of 13.5 per 1000 patient years reported in a large UK retrospective study for such patients.[29] In the population based Blue Mountains Eye Study, cataract formation resulted in a cumulative incidence of cataract surgery in DM patients of 20.9% over 10 years.[30]

Figure 1: Common vascular complications associated with DM



Key: CV, cardiovascular; DM, diabetes mellitus

Poor management of DM leads to exacerbations of these complications and the concomitant burden of disease.[18, 31] Patient's beliefs and behaviours regarding their condition are crucial to the successful control of DM, but high rates of non-compliance with recommended lifestyle changes and self-monitoring and medication are observed in practice.[31-36] Furthermore, recommended strategies for DM control within care structures are often not fully followed.[37] The resultant burden of DM on health systems is substantial with DM patients using health services many times per year as a consequence of their disease.[38] In the UK, it has been estimated that between~£10-13.75 billion is spent by the NHS on DM care per annum (based on 2010/2011 datasets).[39, 40] Further indirect costs attributed to DM in the UK are estimated at ~£14 billion.[39]

DMO is a common, debilitating complication of DM resulting from diabetic retinopathy (DR). DMO is estimated to affect approximately 7% of all DM patients and can reportedly double the burden of disease management in this population.[41-43]

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. It is estimated that the probability of losing two or more lines of visual acuity within 3 months is 4.5%[44] and nearly half of DM patients developing DMO will lose two or more lines of visual acuity within 2 years[45]; equivalent to 10 or more letters in the visual acuity score denoted according to vision impact presented in Appendix 19.[46] 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).[8, 47] 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, 47, 48]

Prompt identification and effective treatment of DR has been shown to significantly reduce the prevalence of sight loss attributed to this disease. As a result, the UK National Screening Committee (UK NSC) recommended a systematic population screening programme which was implemented across England between 2003 and early 2008.[49]

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. [4, 6-9, 47]

DMO development is strongly associated with the duration of DM, with incidence increasing with lengthening duration.[48] 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.[50, 51] and one in three people living with DM for 20 years or more develop DMO.[52] 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.[43] 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.[7, 53, 54] Such visual impairment negatively impacts both the physical and emotional functioning of the patient. 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;).[28, 55, 56] 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.[57, 58] 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.[59, 60]

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.[61] 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.[62] 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.[38, 63]

As a result, 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.[42] 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.[41] 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.[41] 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.[41]

As with all ophthalmological conditions, the magnitude of direct and indirect costs associated with DMO rise significantly with worsening of the condition as a result of insufficient treatment, challenging independent living and potentially resulting in irreversible vision loss.[64, 65]

Of important note, the landscape of DMO management has changed since the analysis reported by Minassian et al. (2012)[41] with the introduction of novel pharmaceutical therapies to the treatment algorithm (see section 2.5). These therapies provide improved clinical efficacy and costs of treatment related to worsening disease may be thought to have lessened since this analysis. However, their introduction has in reality put extreme pressure on the healthcare system, with capacity constraints and associated concerns on preventable sight loss incidence recently reported by the RNIB (see section 2.6). We may expect this to translate to substantial costs to the healthcare system. We can also expect all costs attributed to DMO to be steadily rising in correlation with the increasing prevalence of DM and associated conditions.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

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.[41, 66] Applying this prevalence rate to the DM population in England and Wales as of 2013 (2,876,343)[17] , 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, see section 2.7, given that laser monotherapy is rarely appropriate or beneficial and thus not commonly used in current clinical practice, see section 2.5), and would be considered for treatment with DEX700 (Table 4).

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 section 2.7 and detailed in the budget impact analysis presented in section 8 and Appendix 14) and would be considered for treatment with DEX700 (Table 4).

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 (Table 4).

Table 4: Patients covered by DEX700 therapeutic indication in the marketing authorisation

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 dialysis, prison population	20%	12%	28,000
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

Key: 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[67]

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. Bilateral DMO patients treated with anti-VEGF agents in both eyes may therefore need to attend separate administration appointments in clinical practice, though some ophthalmologists do treat bilaterally despite the recommendation against such practice. In clinics where this is not common practice, DEX700 may provide a preferable second eye treatment option to bilateral patients who cannot attend twice the number of injection appointments that bilateral anti-VEGF treatment would require.

It is important to note that these patient groups are not mutually exclusive and there will be cross-over between these estimates. For example, there will be some patients in the DMO population considered unsuitable for non-corticosteroid therapy that are also pseudophakic. Therefore, the true number of eyes eligible for DEX700 in the UK will be less than this estimate though this is likely to increase in line with increasing prevalence and earlier development of DM.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

DMO is not a fatal disease and thus is not directly related to increased mortality but there are a number of indirect factors that impact on mortality of people with the disease.

The majority of patients with DMO have lived with DM for many years and therefore have a number of additional diabetic co-morbidities (see section 2.1). The life expectancy of DMO patients is therefore reduced in comparison with their matched cohort from the general population.

In a cohort of 44,230 DM patients living in the UK, the hazard ratio for all-cause mortality in Type 2 DM compared with no DM was 1.93 (95% CI 1.89-1.97).[68] As Type 2 DM accounts for the majority of all diagnosed cases of DM (see section 2.2), the increased mortality in this population can be used as a good representation of

the increased mortality in all patients with DM in the UK compared to those without DM.

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.[69-71] This is likely due to commonalities between pathogenic mechanisms of retinal microvascular abnormalities and cerebral microvascular abnormalities that subsequently result in macrovascular complications.[69, 71, 72]

In an ongoing population-based cohort study initiated in the 1980s (The Wisconsin Epidemiologic Study of Diabetic Retinopathy, WESDR[73-75]), the hazard ratio for all-cause mortality in DM patients with clinically significant macular oedema compared with DM patients with no associated macular oedema was 1.27 (95% CI 1.01-1.61).[69]

Life expectancy appears to be further reduced when DMO results in vision loss. Indeed, a number of studies note a correlation between diabetic retinopathy severity and/or vision loss and mortality.[69-71, 76] In *post-hoc* analysis of patients enrolled in the Early Treatment Diabetic Retinopathy Study (ETDRS) of laser photocoagulation therapy in DMO (see section 2.5), poor visual acuity was significantly associated with mortality in DM patients after adjusting for other DM complications and baseline characteristics.[76] In patients with Type 1 DM, the hazard ratio for all-cause mortality in patients with visual acuity of between 20/20 and 20/40 compared with patients with visual acuity ≥20/20 was 1.74 (95% CI 1.10-2.75) using this model.[76] In patients with Type 2 DM, the hazard ratio for all-cause mortality in the same cohort was 1.24 (95% CI 0.99-1.56) and in patients with visual acuity of <20/40 compared with patients with visual acuity ≥20/20 was 1.36 (1.01-1.83).[76]

Vision loss has also been associated with reduced life expectancy in the general population with severe visual impairment associated with an all-cause mortality hazard ratio of 1.54 (95% CI 1.28-1.86) in a US sample of 135,581 adults.[77]

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE Guidelines

- *Type 1 diabetes: Diagnosis and management of Type 1 diabetes in children, young people and adults* [CG15][78]
- *Type 2 diabetes: The management of Type 2 diabetes* [CG87][79]

NICE Guidance

- *Preventing Type 2 diabetes: risk identification and interventions for individuals at high risk [PH38]*[80]
- *Preventing Type 2 diabetes: population and community-level interventions [PH35]*[81]
- *Diabetes on adults quality standard [QS6]*[82]

NICE Technology Appraisals

- *Ranibizumab for the treatment of diabetic macular oedema [TA237]*[83]
- *Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237) [TA274]*[84]
- *Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema after an inadequate response to prior therapy [TA271]*[85]
- *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]*[86]

Clinical Guidelines

- The Royal College of Ophthalmologists. *Diabetic Retinopathy Guidelines*. December 2012.[87]

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Laser photocoagulation was at the forefront of DMO therapeutics from the mid-1980s, when its efficacy in preventing further visual impairment in DMO patients was first shown in the landmark study: ETDRS.[88] Laser photocoagulation limits vascular leakage through a series of focal laser burns at leaking microaneurysms (blood vessel swellings) or grid laser burns at breakdown regions of the BRB. It therefore helps to stabilise vision but has not been shown to restore vision already lost to macular oedema in the long-term, perhaps as it does not target the pathophysiology of DMO. Laser is therefore not preferentially used to treat patients reporting loss of vision as a result of DMO. Laser photocoagulation can be associated with foveal burns, visual field defects, retinal fibrosis and laser scars, and therefore it is also not recommended for use in centre-involving oedema as the destructive nature of the treatment must be kept distant from the sensitive centre of the macular. It is estimated that 80% of patients with DMO present with centre-involving oedema (appendix 14, section 10.14). Practicing UK ophthalmologists confirm that since the introduction of pharmaceutical therapy options and the greater understanding of the limitations of its use, laser monotherapy is not commonly used to treat DMO.

More recently, confirmation of the role of pro-angiogenic factors in the pathophysiology of DMO has led to the use of anti-VEGF agents that specifically inhibit the actions of synthesised VEGF within the pathway. Anti-VEGF agents demonstrate superior clinical efficacy in comparison to laser photocoagulation therapy, potentially restoring vision loss due to DMO. Therefore, such agents are preferentially used to treat patients with centre-involving DMO and associated visual impairment. Ranibizumab (Lucentis®) is currently the only anti-VEGF agent licensed for use in DMO that is recommended for use by NICE. In England and Wales, ranibizumab is recommended for the treatment of visual impairment due to DMO in patients with baseline CRT of ≥400µm in England and Wales. Since the national screening programme initiation (see section 2.1), clinical opinion is that the majority of DMO patients presenting in clinical practice have CRT <400µm (~85%) though many of these will not have associated visual impairment and thus do not often receive pharmaceutical therapy (appendix 14; section 10.14). Bevacizumab is an alternative anti-VEGF that may be used off-licence to treat those patients with CRT <400µm that do experience visual impairment, but bevacizumab is only available in a restricted number of UK hospitals. Bevacizumab is not formulated for intraocular use

and therefore there are risks of adverse events associated with pharmacy-compounded formulations of this product. In addition, given its unlicensed status, there are no large-scale RCTs of bevacizumab in DMO that determine its long-term safety profile. Since the introduction of ranibizumab (a licensed alternative) to treat DMO, bevacizumab use has declined. According to feedback through consultation with practicing UK ophthalmologists, the use of bevacizumab is not established NHS practice in England and Wales: it is reportedly no longer available at all for use in DMO in the North East of England and its use is declining in the South of England with no London hospitals supporting its use. Both Liverpool and Broadgreen University Hospital and Moorfields Eye Hospital, through which bevacizumab was historically available for use in the eye, have discontinued the re-formulated manufacturing of bevacizumab (Avastin®) for intraocular use.

Of note, in 2014 (11 August), the anti-VEGF agent aflibercept (Eylea®) received marketing authorisation in Europe and the manufacturers have submitted for NICE recommendation. However, as this agent is not included in the current clinical pathway of care in England and Wales, it is not discussed further in this submission.

Whilst anti-VEGF agents inhibit the actions of VEGF within the inflammatory pathway, they still do not target the majority of inflammatory processes that drive the development and progression of DMO. This is reflected in the relatively high proportion of patients that fail to achieve sufficient or complete response when treated with anti-VEGF agents, estimated at 40-50% (see section 2.6).[89, 90] In order to fully address the multifactorial pathophysiology of DMO, there is a strong rationale to use an anti-inflammatory agent; the first of which to be licensed for the treatment of DMO is the non-biodegradeable fluocinolone acetonide implant (Iluvien®). The fluocinolone acetonide implant is licensed for use in chronic DMO (DMO ≥3 years) patients who are considered insufficiently responsive to available therapies. In England and Wales, the fluocinolone acetonide implant is recommended by NICE for the treatment of visual impairment associated with chronic DMO patients that is considered insufficiently responsive to available therapies only if the implant is to be used in an eye with an artificial (pseudophakic) lens. This restriction is based on concerns of cataract adverse event rates observed in the pivotal trial of the fluocinolone acetonide implant (FAME). There are additional safety concerns associated with the long-term, permanent nature of this implant (see section 6.9).

When these therapies are not eligible or are unsuitable for use (including when there are safety concerns), or when these therapies fail to elicit sufficient response, the only other treatment option currently available for DMO patients with associated visual impairment is vitrectomy. This surgical intervention involves the physical extraction of fluid and/or excess tissue from the eye through a small incision. Given its invasive nature, it is commonly only adopted in practice when the risk of vision loss is deemed severe.

Current UK clinical guidelines developed by the Royal College of Ophthalmologists (RCO) recommend the treatment algorithm presented in Table 5.[87]

Table 5: Maculopathy recommendations from the Royal College of Ophthalmologists (December 2012)

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**)

CSMO	Centre-involving	Visual acuity	Phakic /pseudophakic	OCT	Treatment options
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.

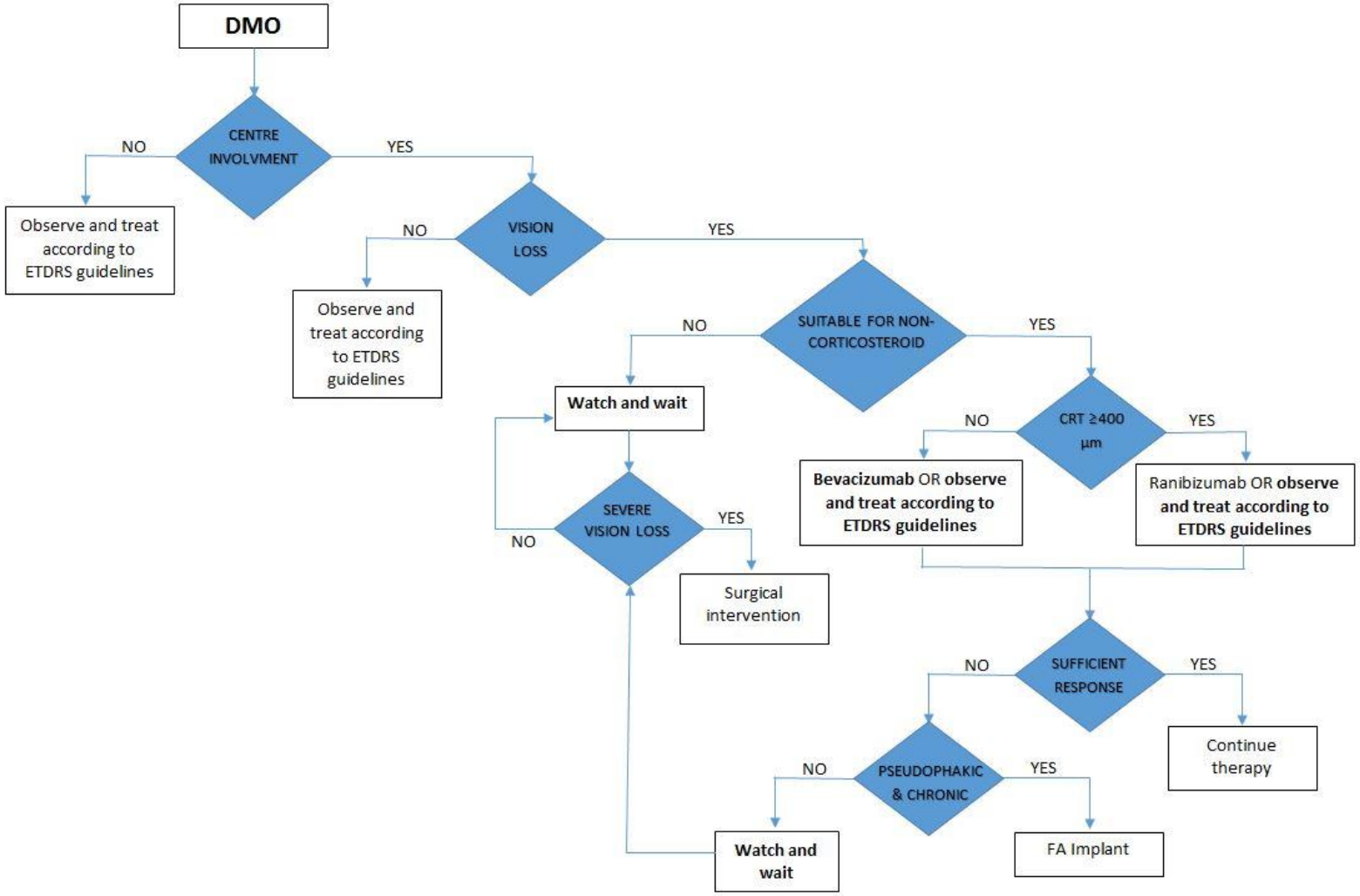
The RCO guidelines do, however, note that all potentially suitable treatment options for an individual patient should be discussed with the patient concerned, and treatment tailored to meet the individual patient need[87]; a concept endorsed by all UK ophthalmologists consulted to date as part of the submission development process. A more detailed overview of the current DMO treatment pathway in the UK of relevance to the decision problem has been developed in accordance with practicing UK ophthalmologists and is presented in Figure 2.

There are a number of scenarios in which there are currently no licensed treatment options, non-surgical treatment options or treatment options with proven long-term benefit for DMO patients in the UK (Figure 2; bold text). DEX700 can be used to treat these populations (Figure 3; bold text) as well as offering a less burdensome first-line therapeutic option compared with anti-VEGF agents to DMO patients with a pseudophakic lens and visual impairment (see section 2.6; section 4).

The potential treatment pathway in the UK with the addition of DEX700 in accordance with licence terms is represented by Figure 3.

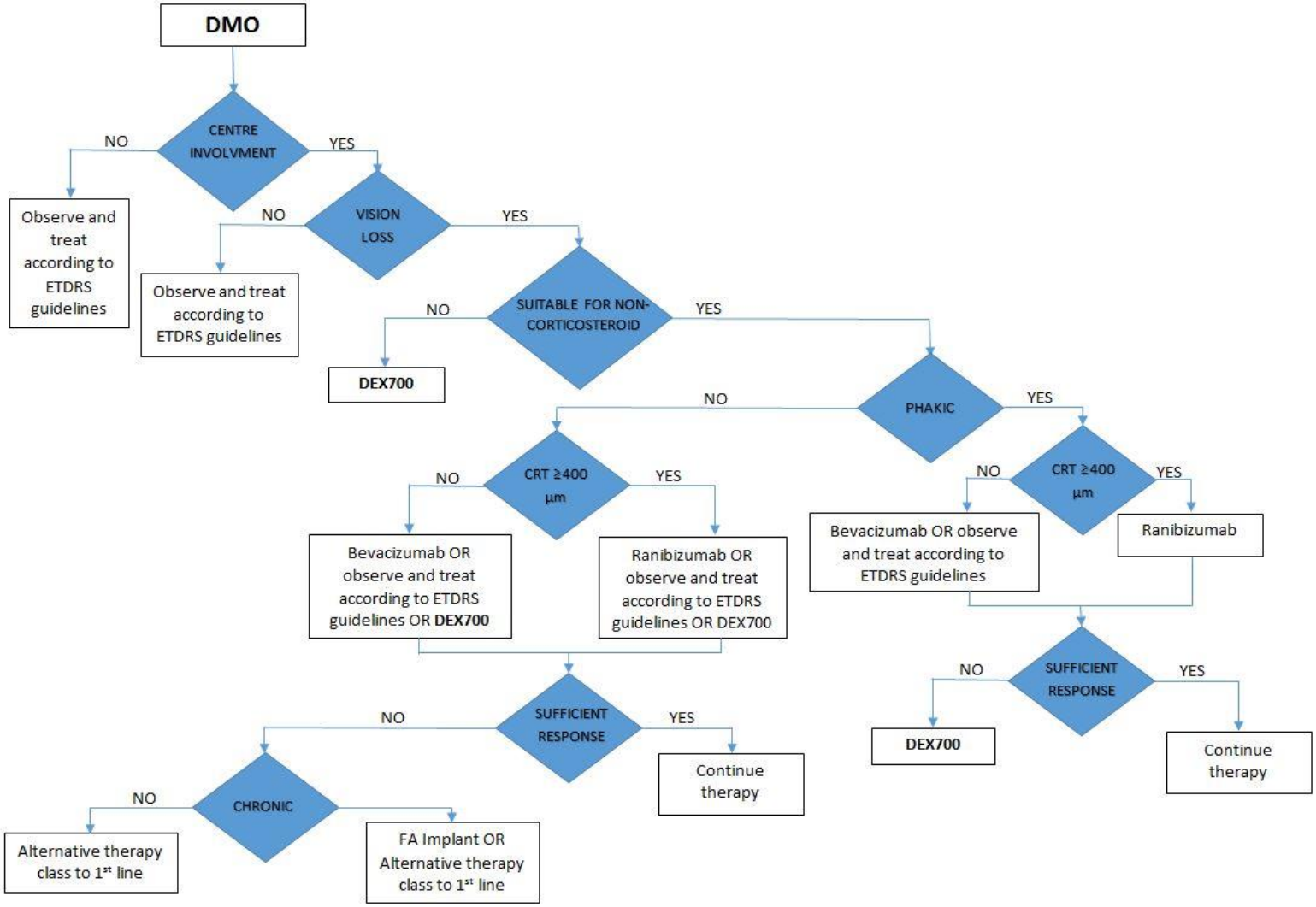
Within the clinical pathway of care, laser photocoagulation therapy may be administered alongside pharmaceutical treatments if oedema develops or progresses in a position or in a manner that physicians feel that patients would benefit from such therapy. This is the manner in which UK ophthalmologists confirm laser is commonly used in current practice rather than as a first-line monotherapy.

Figure 2: Current clinical pathway of care for DMO patients in the UK



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

Figure 3: Potential clinical pathway of care for DMO patients in the UK with recommendation of DEX700



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

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

One of the greatest challenges facing DMO patients and care providers in clinical practice is that current first-line pharmaceutical treatment options, anti-VEGF agents, only offer short-term duration of effect. Consequently, they need to be frequently administered for optimum efficacy. Considering the demanding disease management schedule patients experience to control their DM, (and potentially other co-morbidities), this critical and intense treatment regime of intravitreal injections may be challenging to comply with in practice. Appointment requirements over 6 months for the average DMO patient receiving anti-VEGF treatment based on UK market research ([redacted]) is depicted in Figure 4.[91]

Appointments for administration of anti-VEGF agents for the treatment of DMO, RVO or uveitis are reported to take up a total of [redacted] of patient's time in the UK on average with approximately [redacted] of this time demand spent travelling ([redacted]).[91] In some cases, anti-VEGF treatment is far more time consuming with some patients reportedly spending [redacted] attending administration appointments; for example, patients living in rural areas with hospital episodes statistics (HES) data reporting a DMO patient having to travel [redacted][92]; or patients receiving bevacizumab off-licence for whom ophthalmologists suggest approximately a [redacted] consultation pre-initial administration. In the working DMO population, this practical burden may also translate to financial burden with many days/year spent off work. Furthermore, some DMO patients will need assistance to attend appointments; in such circumstance, the time and financial demand associated with treatment regimens are burdensome to both patients and their helpers. An individual appointment calendar for such a patient living with multiple comorbidities in the UK and receiving bevacizumab therapy for DMO is presented in Figure 5.[93] This patient states that for each appointment a family member provides an hour of support and practical assistance as well as transportation to and from the hospital.[93]

[redacted] **Appointment calendar for the average DMO patient on anti-VEGF therapy in the UK**

[redacted]

K**ey:** DMO, diabetic macular oedema; GP, general practitioner; VEGF, vascular endothelial growth factor.
Source: UK Market Research[91]

[redacted] Appointment calendar for an individual DMO patient living with multiple comorbidities in the UK receiving bevacizumab therapy

[redacted]

Key: DMO, diabetic macular oedema; UK, United Kingdom.
Source: Individual Patient Calendars[93]

Alongside this practical burden, the intense yet optimally effective anti-VEGF treatment regimen can be associated with a physical and emotional burden. In a mixed patient cohort across Europe [redacted] more than [redacted] of the patients reported feeling anxious for at [redacted] days prior to receiving intravitreal injection therapies and nearly [redacted] reported that they suffered from side effects related to the injection.[94]

When asked to select the most desired improvement to the injection procedure from seven options, [redacted] of DMO and RVO patients receiving anti-VEGF therapy across Europe [redacted] chose having to have fewer injections (Figure 6).[94] In the UK cohort of DMO patients [redacted] selected this option including the patient for whom the individual appointment calendar is presented in Figure 5.[91]

An estimated 20% of appointments made for the treatment of DMO with anti-VEGF agents are missed in practice (appendix 14; section 10.14); the majority of which clinicians attribute to the impractical patient burden of frequent injection regimens.

[redacted] **Patient selection of the most desired improvement to the injection procedure**

[redacted]

Source: European Market Research[94]

In addition to this burden on patients, there are significant capacity constraints and funding limitations within the health service to consider. Such concerns in

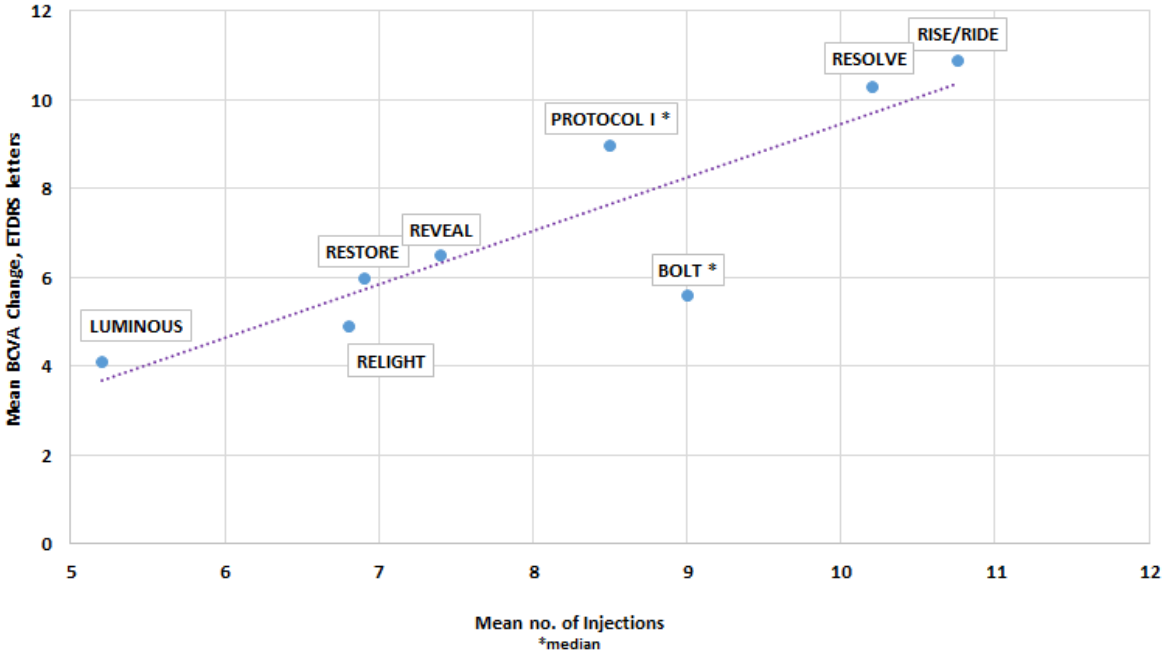
ophthalmology clinics have been explicitly highlighted by the Royal National Institute of Blind People (RNIB) for the UK.[95] In a survey of ophthalmology staff (n=172) across England, over 80% said their eye department has insufficient capacity to meet current demand with 94% reporting that future capacity will not meet rising demand within existing budgets. Worryingly, 37% of respondents felt patients were sometimes losing their sight unnecessarily due to delayed treatment and monitoring caused by capacity problems. The RNIB specifically note in their report that the introduction of anti-VEGF therapies has resulted in greater numbers of patients needing regular monitoring and treatment. Whilst the clinical benefit of such therapy is recognised, staff report being overwhelmed by anti-VEGF clinic appointments. Seventy percent of respondents stated their introduction has impacted other eye care services, and there were concerns that chronic eye conditions that cannot be treated with anti-VEGF therapies are being left untreated as a result.[95] Ophthalmologists practicing in some of the busier clinics in England recently reported frustration at not being able to assess and treat DMO in a single appointment due to such capacity constraints, termed a “one-stop service” (appendix 14, section 10.14). Instead, they have to make separate appointments for monitoring and treatment, termed a “two-stop service”, further exacerbating the practical burden on the patient associated with attending appointments for DMO therapy (appendix 14; section 10.14). This two-stop service is estimated to be the case in ~60-70% of all eye clinics in England and Wales (appendix 14; section 10.14).

Evidence of anti-VEGF use for the treatment of DMO in clinical practice supports the concern that dosing regimens in accordance with clinical trials and SPCs are not followed. Observational studies suggest the average number of anti-VEGF injections administered within the first 12 months of treatment for DMO is up to five.[96-98] Patients enrolled in the EU regulatory trial providing evidence for the use of ranibizumab in DMO (the RESTORE trial) received an average (mean) of seven injections within the first 12 months of treatment and patients enrolled in the largest RCT providing evidence for the use of bevacizumab in DMO (the BOLT trial) received an average (median) of 9 injections within the first 12 months of treatment.[99, 100] There is a strong correlation between the number of anti-VEGF injections received and visual gain (Figure 7) meaning that in practice, optimum treatment effect as reported in clinical trials is potentially not being achieved with

anti-VEGF therapy and the insufficiently treated oedema could progress to cause permanent retinal damage.[99-104]

In an ongoing observational study of ranibizumab first-line use in age-related macular degeneration (AMD), RVO and DMO in the US (LUMINOUS), BCVA improved by an average of 4.1 ETDRS letters at Month 12 compared with the 6.8 ETDRS letter gain reported with ranibizumab use in RESTORE.[96, 100] Similarly, in an open-label, single-arm study in the UK (RELIGHT), DMO patients treated with ranibizumab based on bi-monthly monitoring from Month 6 demonstrated an average mean change in BCVA at Month 12 of 4.9 letters with 13.8% of patients (n=100) achieving a 15-letter gain from baseline (compared with 22.6% of patients in RESTORE).[100, 105] The impact of real-world anti-VEGF treatment patterns on vision outcomes in patients with DMO was recently discussed at the 2014 annual meeting of the American Society of Retinal Specialists (ASRS) where Dr. Nancy Holekamp presented primary data of a retrospective analysis of electronic medical records from a US integrated health system. In patients with DMO, it was observed that only 2-3 anti-VEGF injections were being given in practice. The impact of this was investigated within a closed health system set-up and an average of 2.6 injections within a 12-month period was associated with an average BCVA gain of 4 letters.[98] Dr. Holekamp concluded that under-utilization of anti-VEGF agents in practice was putting patients' vision at risk.[98]

Figure 7: Correlation between number of anti-VEGF injections and mean ETDRS letter gain at 12 months



K**ey:** BCVA, best corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

The benefit of therapies that may help to alleviate the treatment burden associated with DMO management is recognised by the Royal College of Ophthalmologists in the UK who state "the longer acting steroid preparations are of particular interest due to the reduced frequency of treatment required, which may give a practical advantage compared to VEGF inhibitors".[87]

Further concerns in current clinical practice associated with current DMO therapeutics include limitations of use, lack of clinical efficacy in all patients and concerns of safety (see section 2.5 and section 6.9). Clinical guidelines only recommend use of laser photocoagulation in patients with non-centre involved DMO (estimated to be ~20% of the total DMO population) and/or DMO patients with no associated visual impairment due to concerns of safety and long-term clinical efficacy. UK ophthalmologists confirm laser monotherapy is not commonly used in current practice (appendix 14; section 10.14). In England and Wales, ranibizumab is not approved for use in DMO patients with associated visual impairment and CRT <400µm (estimated to be ~40% of the total DMO population based on DEX700 trial data). Bevacizumab, which is not licensed for use in DMO, is not available in most hospitals in England and Wales, therefore patients with centre-involved DMO of this

nature would be left untreated until their oedema progresses to worsening retinal thickness or severe visual impairment. In addition, there is some debate on the efficacy of intravitreal anti-VEGF injections in DMO patients with vitrectomised eyes, with some evidence suggesting diminished effect due to enhanced clearance with monkey models suggesting half-life of anti-VEGF is approximately halved in vitrectomised compared with non-vitrectomised eyes.[106, 107]

There are also a number of patients who are considered insufficiently responsive to anti-VEGF therapy in clinical practice, perhaps as a result of their single mechanism of action only targeting a single component of the inflammatory pathway of DMO. Trial data suggest approximately 40-50% of DMO patients treated with ranibizumab therapy fail to demonstrate complete oedema response, defined as the reduction of oedema to normal levels.[90] Post-hoc analysis of the Diabetic Retinopathy Clinical Research Network (DRCRN) PROTOCOL I study showed 38% of DMO patients treated with ranibizumab therapy failed to achieve a VA improvement of >10 letters and ≥20% reduction in CRT.[89] Across a series of advisory boards recently conducted, general consensus from practicing ophthalmologists is that if progressive oedema is observed after three or four injections or if fluid is still present after a maximum of six injections, alternative therapy should be sought.[108, 109] When independently questioned at an Allergan sponsored advisory board, practicing UK ophthalmologists estimated that approximately 25% of DMO patients insufficiently responsive to anti-VEGF therapy in practice would be considered for steroid therapy where insufficiently responsive is defined as despite recent repeated dosing there is visual impairment due to DMO that is >300 micron in any of the five central ETDRS zones or in the opinion of the treating clinician that there is potential for further visual improvement if oedema can be resolved further by alternative therapies (appendix 14; section 10.14).

The current unmet need of effective treatment for patients with persistent DMO despite anti-VEGF therapy is demonstrated by the recent initiation of a clinical trial investigating the clinical efficacy of combination corticosteroid + anti-VEGF treatment in such patients by the DRCRN(PROTOCOL U).[110]

Safety concerns associated with anti-VEGF therapies include systemic warnings related to their potential CV risk as noted in their SPCs[111, 112] and resulting in their exclusion from clinical trials. This is an important consideration when prescribing

treatment to the DM patient (particularly the elderly) who is already at higher CV risk than the general population (see section 2.1). As bevacizumab is not licensed for the treatment of DMO, an additional safety concern associated with this anti-VEGF agent is increased risk of endophthalmitis as a result of intravitreal injection preparation requirements.

Based on these issues relating to current clinical practice, there are a number of DMO patients that practicing UK ophthalmologists confirm may be considered unsuitable for non-corticosteroid therapy, outlined in Table 6 (appendix 14; section 10.14). In addition, there are some DMO patients that may refuse current therapeutic options due to anxiety associated with laser treatment or regular intravitreal injections. There are currently no alternative therapies available to treat patients considered unsuitable for non-corticosteroid therapy, which is clearly a significant unmet need.

Table 6: Patient populations considered unsuitable for non-corticosteroid therapy

Population	Rationale
Unsuitable for laser photocoagulation	
Centre-involving DMO	Clinical guideline recommendations due to safety concerns
DMO with associated visual impairment	Clinical guideline recommendations due to lack of evidence of vision restoration
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
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
High-risk co-morbidities e.g. CV morbidity	Systemic warnings of potential CV risk
Vitrectomised eyes	Diminished effect due to reduced half-life
Unsuitable for ranibizumab therapy	
CRT <400µm	NICE restriction in England and Wales

Key: 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, for patients who are considered insufficiently responsive to non-corticosteroid therapy, the only alternative pharmaceutical therapy available in

current clinical practice is the fluocinolone acetonide implant. However, this implant is only licensed for use in patients with chronic DMO who are insufficiently responsive to available therapies and is further restricted to use in patients with a pseudophakic lens in England and Wales. There are also some safety concerns associated with the fluocinolone acetonide implant in regard to the long-term, permanent nature of the implant with surgical removal required to treat serious, non-transient adverse events. Again, the fact that there are no alternative pharmaceutical therapies available to treat such patients is clearly an unmet need.

Practicing UK ophthalmologists confirm they would welcome an alternative therapy option to treat patients with visual impairment due to DMO who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy (appendix 14; section 10.14).

2.7 Please identify the main comparator(s) and justify their selection.

DEX700 is anticipated to be used as a second-line treatment in DMO patients with associated visual impairment who are considered insufficiently responsive to non-corticosteroid therapy, as a first-line or second-line treatment option in DMO patients with associated visual impairment who are considered unsuitable for non-corticosteroid therapy or as a first-line treatment option for DMO patients with associated visual impairment who are pseudophakic. As a result, there are a number of potential comparators to DEX700 as presented in Table 7 and

Table 8 and summarised below (see section 2.5).

For DMO patients with associated visual impairment who are considered unsuitable for non-corticosteroid therapy, there are no active treatment options available. In addition, for DMO patients with associated visual impairment who are considered insufficiently responsive to non-corticosteroid therapy and do not meet the eligibility criteria for fluocinolone acetonide implant use (see below), there are no active treatment options available. Such patients are currently monitored for disease progression (watch and wait) with severe vision loss potentially treated with surgical intervention.

Current pharmaceutical treatments licensed for us in DMO include the anti-VEGF agent, ranibizumab and the corticosteroid, fluocinolone acetonide implant:

- Ranibizumab is licensed for use in all patients with DMO but is restricted to use in patients with a CRT ≥400µm in England and Wales by NICE. Ranibizumab is the preferred first-line therapy option for DMO in the UK.
- The fluocinolone acetonide implant is licensed for use in patients with chronic DMO who are considered insufficiently responsive to available therapies. It is therefore viewed as a last line therapy option for DMO in the UK. NICE further restricted its use to pseudophakic patients in England and Wales. Coupled with the chronic DMO license restriction, it is therefore only available to a small group of patients.

In addition to licensed pharmaceutical treatment options, the anti-VEGF agent, bevacizumab has historically been used to treat DMO. Bevacizumab is not formulated for intraocular use and there are no large-scale RCTs providing long-term

clinical and safety evidence of its use in DMO. Since the availability of licensed pharmaceutical treatment options with large-scale RCT evidence, its use has therefore declined. It is still available in a handful of UK hospitals where it may be used to treat patients eligible for anti-VEGF therapy who do not meet the CRT restriction for ranibizumab use. Bevacizumab is not a preferred first-line therapy option for DMO in the UK (appendix 14; section 10.14).

Clinical guidelines do still recommend the use of laser photocoagulation therapy in DMO patients with non-centre involving DMO, though not in patients with associated visual impairment.[87] In clinical practice, the use of laser monotherapy for the treatment of DMO is rare since pharmaceutical treatment options became available as the destructive nature of the treatment must be kept distant from the sensitive centre of the macular and efficacy studies have generally shown that in appropriate patient's laser slows vision deterioration rather than improving vision. Laser monotherapy is not a preferred first-line option for DMO in the UK (appendix 14; section 10.14).

As noted in section 2.5, on 11 August 2014, aflibercept received market approval in Europe. Use of this agent is not established clinical practice in the NHS and therefore it is not considered a relevant comparator to DEX700 in line with NICE definitions.

Table 7: Primary comparators to DEX700

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.

Key: CRT, central retinal thickness; DEX, Dexamethasone; DMO, diabetic macular oedema; NHS, National Health Service; NICE, National Institute of Health and Care Excellence.

Table 8: Secondary comparators to DEX700

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.

Population	Comparator(s)	Licence restrictions	Clinical guideline restrictions	NICE restrictions	Justification
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.
Key: DEX, Dexamethasone; DMO, diabetic macular oedema; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; VEGF, vascular endothelial growth factor.					

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Broad spectrum antibiotics may be prescribed to manage any risk of eye infections. Elevations in IOP may be observed after intravitreal injection of a steroid, therefore effective topical IOP-lowering medicinal products may be prescribed where indicated.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

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. This may be conducted by an ophthalmologist within a hospital setting, but is often conducted by an optometrist or ophthalmology nurse, particularly if the patient has previously received DEX700 and not demonstrated a significant rise in IOP.

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 (see section 7.5.5).

All anticipated resource requirements are captured appropriately within the economic analysis presented in section 7.

2.10 Does the technology require additional infrastructure to be put in place?

No, infrastructure for the administration of intravitreal injections to treat DMO is already in place within the NHS.

The introduction of DEX700 should in fact help to alleviate some of the strain on current infrastructure caused by frequent intravitreal injection treatment regimens (see section 2.6). Efficiency may be improved with lower missed appointment rates predicted as a result of the reduced administration burden. It may also be the case that the introduction of DEX700 negates the need for additional clinics to be put in place to cope with rising demand in DMO management with anti-VEGF therapy.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

  Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

No equality issues are foreseen.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a ‘step-change’ in the management of the condition.

Successful disease management of DM poses a formidable challenge to patients, clinicians and payers with up to 40% of DM patients presenting with at least three co-morbidities in clinical practice.[113] The development of DMO further complicates disease management in this population and exacerbates the already extreme clinical and economic burden of DM. Effective, sustainable long-term management of DMO is therefore crucial to preserving and restoring vision in DM patients for whom self-monitoring and self-medication is the key to good disease management.[31, 36]

Corticosteroids provide a mechanism of action that targets the multifactorial pathophysiology of DMO; directly resolving macular oedema and stabilising the BRB. Such preservation of the integrity of the retinal structure is fundamental to achieving vision improvement in the long term.

Bolus intravitreal administration of dexamethasone is associated with suboptimal durability, due to a short half-life of approximately 3 hours.[11, 12] In order to overcome such barriers, DEX700 contains dexamethasone within a solid polymer drug delivery system. This innovative system is characterised by dual-phase pharmacokinetics; initially releasing a burst of dexamethasone to rapidly achieve a therapeutic concentration, then gradually releasing the remaining total dose (700µg) over several months. This allows for approximately 6 months of corticosteroid treatment through a single intravitreal application. In addition, DEX700 has a flexible retreatment criterion, allowing the optimisation of treatment frequency based on the individual patient need.

In the regulatory studies (the MEAD trial programme), patients treated with DEX700 demonstrated long-term vision restoration and improvement in macular oedema (in terms of magnitude and duration of effect). Clinical efficacy analyses showed statistically significant superiority of DEX700 over sham treatment (intended as a proxy for watch and wait in clinical practice). There are a number of DMO patient

groups considered unsuitable for non-corticosteroid therapy, for whom no active treatment options are currently available (see section 2.6). These patients are simply observed in clinical practice and there is a risk their oedema will progress to cause permanent retinal damage and irreversible vision loss.

DEX700 is associated with a low frequency of administration; a mean of 4-5 injections over a 3-year period in MEAD (see section 6.6).[67] This injection frequency is markedly reduced in comparison with the injection treatment schedules of anti-VEGF agents reported in clinical trials and clinical practice. In the RESTORE extension study, patients originally randomised to ranibizumab therapy and still enrolled in the study had received an average of 14.2 injections by Year 3.[114]

DMO patients' currently receiving anti-VEGF agents in UK clinical practice experience not only practical difficulties in relation to the requirements of frequent intravitreal injection regimens, but also report physical side effects and psychological difficulty.[91] This can have a significant impact on their well-being and the well-being of their family, friends and carers with many patients needing emotional support and/or practical assistance e.g. with transportation to and from treatment appointments (see section 2.6).[91] The NHS itself is also experiencing significant difficulties associated with anti-VEGF treatment demands with serious capacity concerns recently highlighted by the RNIB (see section 2.6).[95]

In light of the burden associated with optimum anti-VEGF treatment regimens, it is perhaps unsurprising that observational studies report lower injection frequencies in clinical practice.[96-98] Given the strong correlation between dosing and treatment effect, this may mean that in practice some DMO patients prescribed anti-VEGF therapy are not receiving adequate treatment and the insufficiently treated oedema could progress to cause permanent retinal damage and irreversible vision loss.

At present, laser photocoagulation is the only alternative therapy option for DMO patients who cannot comply with the anti-VEGF treatment regimen. In practice, laser monotherapy is not commonly used since the introduction of pharmaceutical therapy options due to greater understanding of the limitations of its use and the limited efficacy outcomes (appendix 14; section 10.14). Laser treatment is not recommended for use in patients where the centre of the macular is involved as the destructive nature of the treatment must be kept distant from the sensitive centre of

the macular.[87] With regards to efficacy, studies have generally shown that laser slows vision deterioration rather than improving vision.

DEX700 also offers a number of advantages over the corticosteroid implant, fluocinolone acetonide, which is currently available for the treatment of DMO patients who are considered insufficiently responsive to available therapies (non-corticosteroid therapy). Trial data suggest up to 50% of DMO patients fail to show sufficient response to anti-VEGF therapy (see section 2.6)[89, 90] and practicing UK ophthalmologists estimate ~25% of DMO patients considered insufficiently responsive to anti-VEGF therapy in practice would be considered for steroid therapy (see section 2.6) (appendix 14; section 10.14). Primarily, DEX700 offers a favourable safety profile compared with the fluocinolone acetonide implant (see section 6.9), due to a reduced affinity for the trabecular meshwork and lens: the catalyst for IOP elevation and lens opacification.[115] Furthermore, the DEX700 implant itself contains a material (copolymer, poly[lactic-co-glycolic] acid) similar to that used in dissolvable sutures, which dissolves and degrades into CO^2 and water over time (i.e. it is fully biodegradable), remaining in the vitreous for up to 270 days before completely dissolving. This biodegradable nature alleviates any concerns of the long-term safety associated with implant retention and eliminates the potential need for surgical implant extraction. In comparison, the fluocinolone acetonide implant is permanent and remains in the vitreous after all active treatment has been released.

There is clearly a significant unmet need in relation to the treatment of DMO patients with visual impairment who are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy that the introduction of DEX700 could negate. In addition, DEX700 offers a manageable injection regimen to pseudophakic patients with that could help alleviate the patient and healthcare system burden associated with anti-VEGF treatment regimens.

In conclusion, for adult patients with visual impairment due to DMO who are pseudophakic, or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy, DEX700 offers a clinically effective, sustainable treatment option with a medically manageable long-term safety profile. The introduction of DEX700 to the clinical pathway of care in the UK would therefore have a substantial and significant impact on health-related benefits in patients with DMO as summarised below:

- DEX700 has a mechanism of action that targets the multifactorial pathophysiology of DMO
  - Key to achieving oedema resolution and vision improvement in the long-term
- DEX700 administers active treatment for 6 months or more with a single intravitreal injection
  - Reducing the burden (emotional, physical and practical) in comparison with anti-VEGF treatment regimens to both patients and the NHS
  - Reducing the risk of permanent retinal damage as a result of insufficiently treated oedema
- DEX700 offers a favourable safety profile over the fluocinolone acetonide implant to patients who are considered insufficiently responsive to non-corticosteroid therapy and meet licence and HTA restrictions for use
  - Reducing both short-term and long-term safety concerns associated with corticosteroid therapy
- DEX700 offers the chance of vision restoration to a number of DMO patient groups for whom no treatment options are currently available i.e. patients considered unsuitable for non-corticosteroid therapy and patients considered insufficiently responsive to non-corticosteroid therapy and do not meet licence and HTA restrictions for use of the fluocinolone acetonide implant
  - Diminishing the risk of permanent retinal damage as a result of untreated oedema

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

One of the greatest challenges facing DMO patients and care providers in clinical practice relates to the injection regimen associated with optimum anti-VEGF therapy (see section 2.6). The reduced injection frequency of DEX700 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.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Whilst not quantifiable, the qualitative evidence used to make these judgments is presented in section 2.6.

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	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 • Bevacizumab (for people in whom ranibizumab and fluocinolone acetonide intravitreal implants are unsuitable)	• Laser photocoagulation alone (for people who are pseudophakic) The following technologies alone or in combination with laser photocoagulation: • Ranibizumab (for people who are pseudophakic) • Fluocinolone acetonide intravitreal implant (for people who are considered insufficiently responsive to non-corticosteroid	In accordance with EU licence terms for use of DEX700 in DMO

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
		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,	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	Not applicable

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	including the effects of changes in visual acuity	in visual acuity	
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. 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.	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. 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.	Not applicable

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
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: DEX, dexamethasone; DMO, diabetic macular oedema; EU, European Union; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

Key: HRQL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALY(s), quality-adjusted life year(s).

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic literature review designed to identify the clinical evidence base of RCTs able to assist in answering the decision problem was conducted in February 2014 and updated in July 2014.

Information retrieval methods were based upon the research question "what is the clinical efficacy and safety/tolerability of DEX700 and alternative therapeutic options for the treatment of DMO in patients with DM?"

Searches were performed in global electronic databases: Medline & Medline In-Process and other non-indexed citations; Embase; Cochrane database of systematic reviews (CDSR); Cochrane register of clinical trials (CENTRAL); Health Technology Assessment Database (HTA); Database of Abstracts of Review and Effects (DARE); and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

In addition, 2012-2013 or 2012-2014 annual conference proceedings of the American Academy of Ophthalmology (AAO), the Association of Research in Vision and Ophthalmology (ARVO), the European Association for Vision and Eye Research (EVER), Controversies in Ophthalmology (COPHY) and the European Society of Retina Specialists (EURETINA) were searched in order to identify any relevant, on-going research.

Reference lists of previous systematic reviews/meta-analyses and clinical guidelines identified were hand-searched to highlight any further relevant studies and unpublished data on file held by Allergan reviewed for relevance to the research question/decision problem.

Sections 6.1.1, 6.2.1 and 6.2.2 describe the methods and results of this systematic literature review of RCT evidence. Sections 6.2.3-6.5 describe the identified evidence base for DEX700, while the evidence base for relevant comparator trials are reported in Section 6.7, which reports the indirect comparative efficacy analyses.

A systematic literature review designed to identify the clinical evidence base of non-RCTs able to assist in answering the decision problem was also conducted in July 2014. This is described in section 6.8.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Full eligibility criteria applied to the systematic search results identifying the clinical evidence base of randomised controlled trials are outlined in Table 9.

As DEX700 is intended for use in various positions within the clinical pathway of care, no restrictions were placed upon the population in regard to treatment line or DMO cohorts (patient characteristics). All RCTs investigating DEX700 or any comparator therapies of relevance to all potential positioning's were included regardless of control arm as long as they were administered in accordance with UK licence terms or clinical practice in the case of bevacizumab, which is used off licence. 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: the current unmet need to be assessed within the decision problem.

Two levels of study screening were performed through use of the inclusion and exclusion criteria. Both levels of screening were conducted by two reviewers who

independently inspected each reference. Level 1 screening applied basic inclusion criteria (population, intervention, comparator, study design) to abstracts of each identified reference. All possibly relevant references accepted at the abstract level were retrieved in full text. Any discrepancies with regard to inclusion or exclusion of an article were resolved by a third reviewer. Articles were included if they satisfied all inclusion and none of the exclusion criteria.

Where multiple publications were identified for the same clinical trial; those reporting additional data that met the eligibility criteria of the review were included in the final list of included articles as secondary publications (kin papers). Papers reporting subgroup analyses of patient groups of relevance to the licence terms or HTA restricted use terms for each intervention were included along with papers reporting *post-hoc* analyses based on treatment exposure as both were deemed of relevance to the decision problem.

Table 9: Eligibility criteria applied to systematic search results identifying the clinical evidence base of RCTs

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)
Key: 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.	

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement

flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

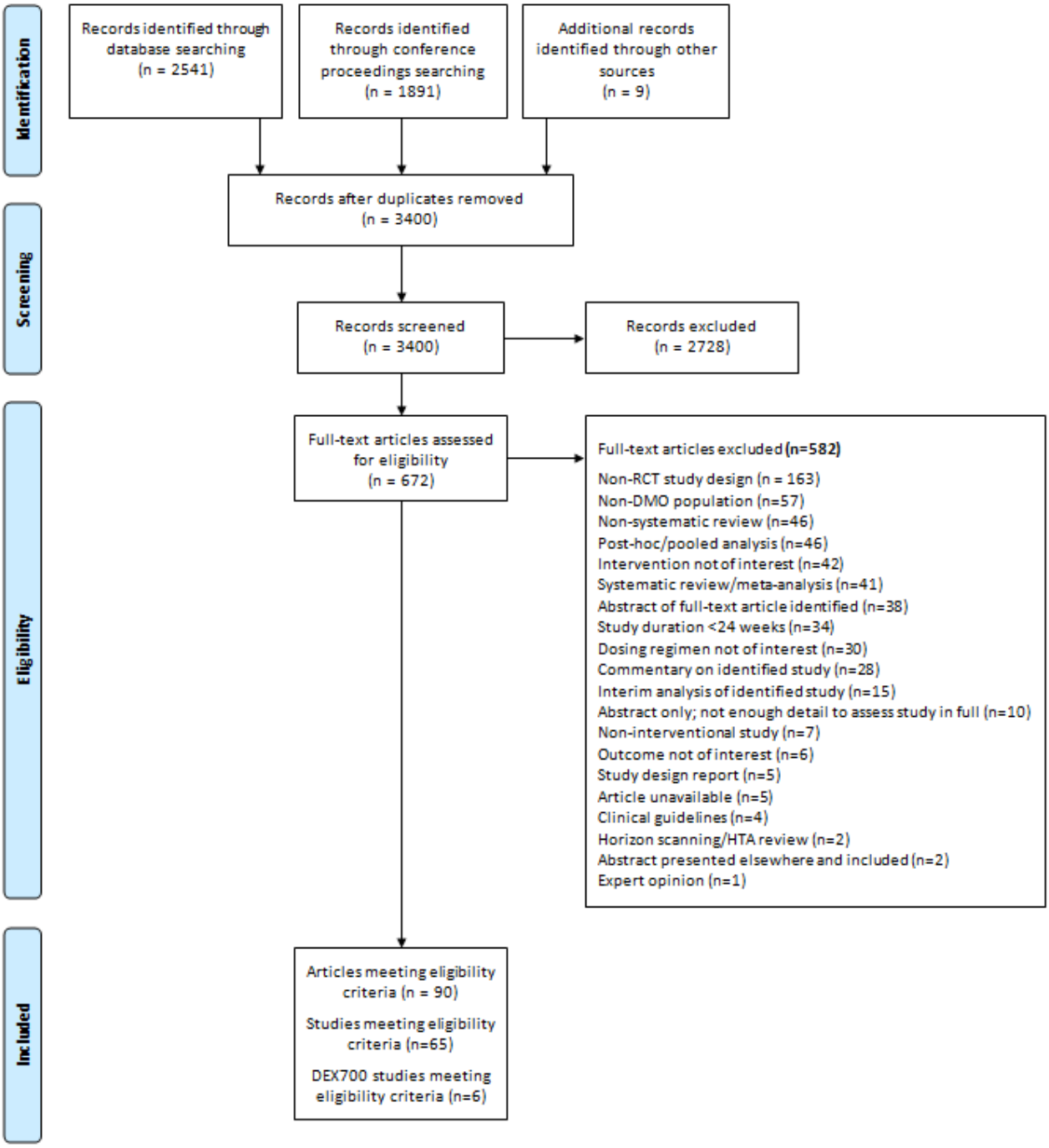
A flow diagram of the systematic review process is presented as a PRISMA diagram [116] in Figure 8.

Original searches of electronic databases, conducted in February 2014, identified a total of 2460 potentially relevant citations with some overlap between databases. After removal of duplicates, 1457 potentially relevant citations remained. Update searches of electronic databases, conducted in July 2014 with a data limit of 2014, identified a total of 81 potentially relevant citations with some overlap between databases. After removal of duplicates, 51 potentially relevant citations remained of which 8 had been identified in the original searches. Across both searches, 1503 unique potentially relevant citations were identified in the systematic searches of electronic databases and conference proceeding searches identified a total of 1891 potentially relevant citations.

An additional 9 citations were identified through other sources: 4 clinical study reports (MEAD-010, MEAD-011, PLACID, 024), the manuscript for the pooled MEAD data analysis [67], the protocol for BEVORDEX (Gillies et al. 2010[117]) and subgroup analysis of the ETDRS study to align patient with current practice[118] were accessed from confidential in house sources. A further citation (abstract presented at conference, 2011) was identified through reference review of an existing systematic review [119] and 1 final citation was identified through review of clinicaltrials.gov for additional information on trials reported only in abstract form.[120]

During abstract screening, 2728 citations were excluded as they were clearly not of relevance to the research question. Examples of reasons include non-DMO patient populations, non-RCT study designs or studies of interventions outside of scope. A total of 675 citations were accessed in full (where applicable and necessary) for further evaluation. Of these citations, 65 were original publications of trials meeting the eligibility criteria of the review and a further 25 were secondary publications, reporting additional information meeting the eligibility criteria of the review. Of the total trials meeting the eligibility criteria of the review, 6 investigated the clinical efficacy and safety of DEX700 (see section 6.2.3).

Figure 8: PRISMA flow diagram of the RCT systematic review process



Source: Moher 2009[116]

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The systematic literature review identified six RCTs investigating the clinical efficacy and safety/tolerability of DEX700 in patients with DMO. All relevant data sources for each of these trials are listed in Table 10.

Table 10: Sources of relevant data for DEX700 RCTs identified

Trial number	Primary reference	Secondary reference	Format	Summary of additional information
MEAD-010	CSR206207_010[121]	Boyer et al. 2014[67]	Journal article	Pooled data analysis
MEAD-011	CSR206207_011[123]	Hee Youn et al. 2014[122]	Conference abstract	Pseudophakic subgroup analyses
024	CSR206207_024[124]	-	-	-
PLACID	Callanan et al. 2013[125]	CSR206207-012[126]	Data on file	HRQL
NCT00035906	Kupperman et al. 2007[1]	Haller et al. 2010[5]	Journal article	DMO subgroup analyses
BEVORDEX	Gillies et al. 2014b[127]	Gillies et al. 2010[117]	Data on file	Study protocol
		Gillies et al. 2014a[128]	Conference abstract	Interim data analysis

Key: DEX, dexamethasone: DMO, diabetic macular oedema; HRQL, health-related quality of life; RCT, randomised controlled trial.

Interim results for one of the RCTs was identified in conference abstract form as part of the systematic literature review [128] but has since been published in full.[127] The full article was therefore accessed prior to data extraction but both sources were used to populate subsequent sections and therefore both references are included in Table 10.

Only data sources meeting the eligibility criteria were included in the final list of references of the review. *Post-hoc*/sub-group analyses that did not meet the eligibility criteria were excluded. Of the six RCTs investigating DEX700 for the

treatment of DMO, one data source related to study NCT00035906 was excluded on this basis. This was a *post-hoc* analysis publication of treatment effect based on pattern of DMO that only used 90 day data.[129] In addition, two abstracts of the MEAD pooled data analysis [130, 131] were excluded on the basis that the full publication containing reported data was identified.[67]

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Details of all RCTs that compare the intervention with other therapies are presented in Table 11.

Table 11: List of relevant RCTs identified by the systematic literature review

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[67]; CSR 206207_010[121]
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[67]; CSR 206207_011[123]
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[124]
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[125]; CSR 206207_012[126]
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	Haller et al. 2010[5]; Kupperman et al. 2007[1]

Trial number	Intervention	Comparator	Population	Study references
			67 letters due to clinically detectable macular 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[117]; Gillies et al. 2010b[127]

Key: BCVA, best corrected visual acuity; CRT, central retinal thickness; DM, Diabetes mellitus; DMO, diabetic macular oedema; OCT, Optical coherence tomography; RCT, Randomised controlled trials.

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

All of the RCTs identified directly compare DEX700 with a relevant comparator in adult patients with visual impairment due to DMO, though none compare the clinical efficacy of relevant therapies in the exact population(s) of interest to the decision problem in accordance with UK licence terms for DEX700:

- The MEAD trials along with NCT00035906 compare DEX700 with sham treatment (intended as a proxy for watch and wait) but not exclusively in people who are considered unsuitable for non-corticosteroid therapy and/or in people who are considered insufficiently responsive to non-corticosteroid therapy in whom the fluocinolone acetonide implant is unsuitable.
- Study 024 compares DEX700 with ranibizumab but not exclusively in people who are pseudophakic.
- BEVORDEX compares DEX700 with bevacizumab but not exclusively in people who are pseudophakic and in whom ranibizumab and fluocinolone acetonide implants are unsuitable.
- PLACID compares DEX700 + laser photocoagulation with laser photocoagulation monotherapy but not exclusively in people who are pseudophakic.

All RCTs do, however, include a proportion of people in which DEX700 is directly compared with the appropriate comparator with reference to the decision problem.

In the MEAD trial programme, patients had previously received prior medical or laser therapy or were considered unsuitable for laser photocoagulation therapy. When this study was initiated, no pharmaceutical therapies were approved for use in DMO. Therefore watch and wait was the appropriate comparator in this population as requested by regulatory agencies. Sham treatment was used as an intended proxy for watch and wait to maintain blinding. Though the clinical pathway of care has evolved since this time with the introduction of anti-VEGF therapies, patients in whom these agents are considered insufficiently responsive or are deemed unsuitable do not commonly present with disease characteristics that may impact

treatment effect with the exception of patients with vitrectomised eyes who were not eligible for enrolment. For example, a review of baseline factors and anatomic responses during the first year of ranibizumab therapy for association with vision outcome did not identify any features that would predict ranibizumab treatment effect.[89] Patients enrolled in the MEAD trials are therefore deemed representative of the patient profiles presenting in current clinical practice who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy i.e. laser or anti-VEGF therapies. Subgroup analyses based on treatment history of patients enrolled in the MEAD trial programme are presented in section 6.5 to support this assumption.

Patients enrolled in NCT00035906 were considered insufficiently responsive to medical or laser photocoagulation therapy and thus directly provide evidence for DEX700 in adult patients with visual impairment due to DMO who are considered insufficiently responsive to non-corticosteroid therapy. Some patients enrolled in the trial would have been eligible for treatment with the fluocinolone acetonide implant in current practice (see section 6.3.4), but the majority would not and therefore watch and wait, as represented by observation, is the relevant comparator in this population with reference to the decision problem.

In study 024, PLACID and BEVORDEX no restriction was placed on lens status at enrolment, but a proportion of patients presented with a pseudophakic lens. Potential acceleration of lens opacification and primary cataract formation in patients with DMO is associated with the corticosteroid mechanism of action and not the non-corticosteroid mechanism of action. Consequently, comparative efficacy data taken from mixed phakic/pseudophakic populations in studies comparing DEX700 with non-corticosteroid therapies provide a conservative estimate for DEX700 treatment effect in pseudophakic patients for whom such acceleration may negatively impact visual impairment. Subgroup analyses of people with a pseudophakic lens is available and thus presented for study 024, PLACID and BEVORDEX in section 6.5 as direct evidence of relevance to the decision problem. Subgroup analyses of people with a pseudophakic lens is also presented for the MEAD trial programme and is utilised in indirect comparative efficacy analyses presented in section 6.7 to formally align the clinical evidence base from all DEX700 studies to the decision problem for people with a pseudophakic lens.

Of note, some of the patient groups for whom non-corticosteroid therapy is considered unsuitable are unlikely to be enrolled in clinical trials. For example, patients who are unable to attend appointments for DMO at least once a month would therefore be unable to attend appointments in accordance with clinical trial protocols that are typically more demanding than normal practice. Therefore, whilst we would expect DEX700 treatment effect not to differ in such patients, it is difficult to accurately model this patient group as there is no relevant watch and wait data available in this population (see section 7).

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Not applicable.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Details of all DEX700 non-RCTs identified through systematic review of the non-RCT evidence base presented in section 6.8 are summarised in Table 12. Those considered relevant to the decision problem are highlighted in the final column with justification for their inclusion.

Table 12: List of all non-RCTs identified by the systematic literature review

	Study summary	Key endpoints	Results summary	Author conclusions	Justification for inclusion
Full publications identified in electronic database searches					
CHAMPLAIN (Boyer et al. 2011[132])	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[133]	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[134])	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 favourable safety profile. Patient follow-up must be adapted to	Evidence for patients considered insufficiently responsive to non-corticosteroid therapy

	Study summary	Key endpoints	Results summary	Author conclusions	Justification for inclusion
				half-life of the product with a control before M1 (intraocular pressure) and before M5 (DMO recurrence, BCVA)	
OCTOME (Mathew et al. 2014[135])	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[136]	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

	Study summary	Key endpoints	Results summary	Author conclusions	Justification for inclusion
Zucchiatti et al. 2012[137]	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[138]	Single-arm trial in patients with treatment-naïve DMO	Change from baseline in visual acuity and CRT up to 12 months	Significant BCVA and CRT improvement up to Month 12	Intravitreal dexamethasone implant was well tolerated and effective in the management of DMO in this study	
Giralt et al. 2014[139]	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

	Study summary	Key endpoints	Results summary	Author conclusions	Justification for inclusion
Gusson et al. 2013[140]	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[141]	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)

Key: BCVA, best corrected visual acuity; CRT, central retinal thickness; Dex- I, dexamethasone implant; DMO, diabetic macular oedema.; OCT, optical coherence tomography; RCT, randomised controlled trial; VA, visual acuity.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Details of the study design for all RCTs identified are presented in Table 13.

The MEAD studies are the pivotal regulatory studies for DEX700 use in DMO and therefore are the largest of the RCTs identified, run for the longest duration. The design of these studies was identical to allow pooling of patient data: both are Phase III, sham-controlled trials with a 36-39 month treatment period and primary efficacy outcome of mean best corrected visual acuity (BCVA) average change from baseline (discussed further in section 6.3.5).

Mean BCVA average change from baseline was also the primary efficacy outcome in the Phase IIIb RCT, study 024, though measurement methodology differed (see section 6.3.5). This study was of shorter duration at 12 months but has an active control arm in the form of ranibizumab, reflective of its more recent design. Due to differences in the administration regimens, patients were not blinded to treatment in study 024 as they were in MEAD; however, data collection and evaluation were conducted by masked individuals in both trial programmes.

All other RCTs identified were Phase II in design and share a primary efficacy outcome of the proportion of patients achieving at least a 10-letter gain from baseline with DEX700 therapy. PLACID is the largest of the Phase II trials and is the only one

to be double-masked; both NCT00035906 and BEVORDEX did not mask patients to treatment assignment (though patients in NCT00035906 were masked to dose assignment). BEVORDEX is planned for the longest duration of the Phase II trials (24 months), but at present only 12-month interim data are available. NCT00035906 is the shortest of all RCTs identified, conducting primary efficacy analysis at 6 months.

Both MEAD trials and study 024 had European study centres with MEAD-011 and study 024 having a UK patient cohort. None of the Phase II trials involved European study centres, with PLACID conducted across the US and Canada and BEVORDEX conducted exclusively in Australia.

The key differences across trials investigating the clinical efficacy of DEX700 are observed in the treatment regimens adopted. The MEAD and PLACID trial programmes adopted an as-needed treatment regimen in line with the EU licence terms. DEX700 was administered at baseline and subsequent administrations based upon retreatment criteria at no shorter than approximately 6 month intervals. The BEVORDEX trial also administered DEX700 on an as-needed basis but allowed a shorter minimum interval time between treatments of 4 months that has not been supported in a phase III trial as noted in the SPC. Study 024 adopted a regular treatment regimen, with DEX700 administered at 5- month intervals. This regular treatment regime is at a shorter interval than recommended in the EU licence and did not lead to demonstrably better outcomes (see section 6.5) and thus should not be adopted in clinical practice. As both BEVORDEX and 024 do however provide comparative efficacy analysis, they are considered of interest to the decision problem. Furthermore, the treatment regimen experienced by a proportion of patients within both trials represents the treatment regimen that may be applied to some patients in clinical practice. NCT00035906 is different again as this study investigates clinical efficacy of a single administration of DEX700.

In addition to the DEX700 treatment regimens, differences are observed in the concomitant therapeutics allowed within the study protocols (this is also the case across comparator trials, discussed in section 6.7). In the MEAD trial programme, no rescue or escape therapy was permitted, with any patients requiring additional treatment to DEX700 for DMO progression withdrawn from the studies. In study 024 and BEVORDEX, laser therapy was permitted alongside pharmaceutical treatment.

Whilst this may complicate interpretation of the efficacy outcomes reported in this trial, such a process is reflective of clinical practice where laser is administered if deemed appropriate alongside pharmaceutical treatment regimens. Again, NCT00035906 is different as additional DMO therapy, laser or pharmaceutical, was permitted and thus needs considering when interpreting trial data.

Table 13: Comparative summary of methodology of the RCTs

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, US)	72 study centres in 14 countries (Brazil, Canada, Colombia, France, Hungary, India, Italy, New Zealand, Poland, Singapore, South Korea, Taiwan, UK, US)	57 study centres in 11 countries (Denmark, France, Germany, Israel, Italy, Netherlands, Portugal, South Africa, Spain, UK, US)	48 sites in the US and Canada	29 retina practices in the US	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, 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 persistant 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.

Trial number	MEAD-010	MEAD-011	024	PLACID	NCT00035906	BEVORDEX
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.	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 patients in a 1:1 ratio. Randomisation was stratified by BCVA score at baseline (≥34 to ≤49 and ≥50 to ≤70).	The randomisation was stratified based on baseline BCVA in the study eye (≤49 or ≥50 letters). The randomisation schedule was computer generated and stored in a locked cabinet until the study ended. Patients were randomisation in a 1:1 ratio.	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 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	Patients were masked to the study treatments for the duration of the trial. Individuals collecting clinical	Individuals collecting primary efficacy (BCVA) data and evaluators at the reading center were masked to	Both the patients and the study personnel who collected BCVA, OCT and FA data were masked to the patient study	Patients in the dexamethasone treatment groups were masked regarding the dose they had received. Key efficacy	BCVA examiner masked. Investigators, study coordinator, photographer, surgeon

Trial number	MEAD-010	MEAD-011	024	PLACID	NCT00035906	BEVORDEX
	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.	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.	study treatment assignment for the duration of the trial. Patients and investigators were aware of the treatment assignment.	assignment.	variables were collected and evaluated by personnel who were masked to patient study treatment.	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) Sham (needleless) applicator system (Sham)	700µg dexamethasone posterior segment drug delivery system applicator system (DEX700) 350µg dexamethasone posterior segment drug delivery system applicator system (DEX350) Sham (needleless) applicator system (Sham)	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 + laser) Sham implant + modified ETDRS focal (direct/grid) laser photocoagulation	700µg dexamethasone posterior segment drug delivery system (DEX700) 350µg dexamethasone posterior segment drug delivery system (DEX350) Observation (no study treatment and no sham procedure)	700µg dexamethasone posterior segment drug delivery system (DEX700) 1.25mg bevacizumab (BEV)

Trial number	MEAD-010	MEAD-011	024	PLACID	NCT00035906	BEVORDEX
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	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	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	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

Trial number	MEAD-010	MEAD-011	024	PLACID	NCT00035906	BEVORDEX
	increased retinal thickening (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	increased retinal thickening (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		from retreatment and if the patient would benefit from 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).		evaluated for retreatment eligibility every 4 weeks. Patients were eligible for retreatment if CRT 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	None. Patients who required additional DMO therapy in the study eye were considered study treatment failures and were withdrawn from the study based on	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	None. Patients who required additional DMO in the study eye were withdrawn from the study based on when they last received study	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	Laser. Patients could receive laser treatment if the study eye developed an area of focal oedema with circinate exudates that may benefit from laser

Trial number	MEAD-010	MEAD-011	024	PLACID	NCT00035906	BEVORDEX
	on when they last received study treatment.	when they last received study treatment.	present and >12 weeks since previous laser session.	treatment.	triamcinolone) that the investigator deemed appropriate.	treatment in the opinion of the investigator.
Primary outcomes	Mean BCVA average change (area under the curve approach).	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	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	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	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

Trial number	MEAD-010	MEAD-011	024	PLACID	NCT00035906	BEVORDEX
	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	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	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			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.

Key: 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[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; Gillies et al. 2014b[127]; Haller et al. 2010[5]; Kuppermann et al. 2007[1]

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Full details of the eligibility criteria adopted in all RCTs are presented in Table 14. As the study design was identical for the MEAD trials, the inclusion and exclusion criteria adopted is only presented once in this table.

Key inclusion criteria were similar across clinical trials of DEX700. All trials enrolled patients with centre-involving macular oedema and associated visual impairment. With the exception of NCT00035906, only patients over the age of 18 qualified for trial inclusion. Eligible visual acuity ranges fell between 34 and 70 ETDRS letters in the majority of trials with the exception of BEVORDEX that allowed patients with severe vision loss (17 ETDRS letters) to also enrol. CRT had to be greater than 250µm for inclusion in any of the trials and greater than 300 µm for inclusion in the regulatory studies.

Key exclusion criteria were also similar across the DEX700 trial programme and primarily based upon safety concerns. Patients with uncontrolled systemic disease were not eligible for any of the trials. IOP could not be above 21mmHg for inclusion in any of the larger trials (MEAD, 024, PLACID) and patients with active glaucoma or a history of severe glaucoma were excluded from all trials.

Patients with bilateral DMO could be enrolled in all DEX700 trials, but the way in which they were handled differed across trials. Patients were not treated bilaterally in MEAD, 024, PLACID or NCT00035906: if both eyes were eligible for inclusion in MEAD, the eye with shorter duration of macular oedema was selected; if both eyes were eligible for inclusion in 024, [redacted] if both eyes were eligible for inclusion in PLACID, the eye with worse BCVA was selected. Patients were treated bilaterally in BEVORDEX but not with the same treatment: the right eye was randomised to treatment and the left eye received the reverse treatment.

Differences are also observed in the eligibility criteria relating to treatment history. In the MEAD trial programme, patients had to have had previous medical or laser photocoagulation therapy or have refused or in the opinion of the investigator would not benefit from laser photocoagulation therapy. In the 024 study, no restriction was placed against treatment history and both treatment naïve and treatment exposed patients were eligible for enrolment. To be eligible for PLACID or BEVORDEX, oedema had to be considered not amenable to laser photocoagulation therapy as stand-alone treatment. Finally, patients enrolled in NCT00035906 had to have failed to respond to medical or laser therapy within 90 days of receipt.

Table 14: Eligibility criteria in the RCTs

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 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.	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

Trial number	Inclusion criteria	Exclusion criteria
		within 3 months prior to baseline; periocular depot of steroids within 6 months prior to baseline; use of systemic 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
024	[redacted]	[redacted]

Trial number	Inclusion criteria	Exclusion criteria
		[redacted]

Trial number	Inclusion criteria	Exclusion criteria
		[redacted]
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

Trial number	Inclusion criteria	Exclusion criteria
		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%).
BEVORDEX	>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

Trial number	Inclusion criteria	Exclusion criteria
		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.

Key: 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[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]

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Key characteristics of patients enrolled in all RCTs investigating the clinical efficacy of DEX700 in DMO are presented in Table 15 and Table 16. Those analysed *post hoc* in line with licence terms/HTA restrictions of comparator therapies are highlighted.

Demographics and other baseline characteristics of participants were generally comparable and well balanced both within and across RCTs. The average age of patients was >60 in all trials with slightly more males enrolled than females and more Caucasians enrolled than any other race.

Average duration of DM was approximately 16 years and the average duration of DMO was approximately 2-3 years. Severity of diabetic retinopathy at baseline was only available for patients enrolled to MEAD and was classed as severe or worse in nearly half the total trial populations.

Patients presenting with a pseudophakic lens ranged from 24.5% to [redacted] of the total population enrolled in individual treatment arms across MEAD, 024 and PLACID. Such data is not reported for DMO patients enrolled in NCT00035906.

Baseline visual acuity was approximately 55 ETDRS letters in the majority of subjects across trials with DEX700 treated patients presenting with average visual acuity at baseline of between 54.7 to 56.1 ETDRS letters. Baseline visual acuity was [redacted] in patients enrolled to study 024 at [redacted] letters in all subjects; [redacted] letters in patients randomised to DEX700 treatment. Baseline CRT was approximately 457µm in the majority of subjects across trials with DEX700 treated patients presenting with average CRT at baseline of between 417.5µm and 465.1µm.

Some differences were observed in the treatment history of enrolled subjects in line with the differences in the eligibility criteria of the trials (see section 6.3.3). With the exception of study 024, between 50% and 70% of subjects enrolled in all trials had received prior laser photocoagulation therapy for DMO; thus less than half were treatment naïve at baseline (29.6% of DEX700 treated patients in the regulatory

trials). In study 024, [redacted] of all subjects enrolled were treatment naïve at baseline.

Trial populations of all studies investigating the clinical efficacy of DEX700 are deemed representative of the DMO population observed in clinical practice by practicing ophthalmologists in the UK aside from the treatment naïve subgroup of patients in MEAD. In current practice, most patients presenting with the disease characteristics of this trial population would have received at least one prior therapy. This is a reflection of the time at which the MEAD studies were initiated when only laser photocoagulation therapy was regularly used to treat DMO.

Furthermore, at least a subset of patients treated with DEX700 within each of the trials represents one or more of the populations of interest to the decision problem:

- Adult patients with visual impairment due to DMO who are considered insufficiently responsive to non-corticosteroid therapy (MEAD, 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, NCT00035906)

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Table 15: Characteristics of participants in the RCTs across randomised groups – MEAD trial programme

	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 DMO ≥3 years, n (%)*	37 (22.7)	-	43 (26.1)	38 (20.2)	-	44 (23.8)	75 (21.4)	-	87 (24.9)
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	56.2	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)

	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)**
letters (SD)	(10.05)								
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)

Key: BSE, best seeing eye; CRT, central retinal thickness; DEX, dexamethasone; 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[67]; CSR 206207-010[121]; CSR 206207-011[123]; Clinical Story MEAD Final[142]

Table 16: Characteristics of participants in the RCTs across randomised groups – 024, PLACID, BEVORDEX and NCT00035906

	024		PLACID		BEVORDEX		NCT00035906		
	DEX700 [redacted]	**RAN** [redacted]	**DEX + laser (n=126)**	**Laser (n=127)**	**DEX700 (n=46)**	**BEV (n=42)**	**DEX700 (n=57)**	**DEX350 (n=57)**	**Observation (n=57)**
Demographics									
Age, mean (years (SD)	[redacted]	[redacted]	61.8 (11.1)	61.3 (9.3)	61.4 (9.0)	62.2 (10.5)	63.8 (11.6)	63.8 (10.2)	62.9 (12.0)
Male, n (%)	[redacted]	[redacted]	62 (49.2)	66 (52.0)	30 (65.2)	26 (61.9)	29 (50.9)	30 (52.6)	31 (54.4)
Caucasian, n (%)	[redacted]	[redacted]	82 (65.1)	73 (57.5)	NR	NR	43 (75.4)	41 (71.9)	41 (71.9)
Disease Characteristics									
Duration of DM, mean years (SD)	[redacted]	[redacted]	8.7 (13.9)	17.0 (13.0)	16.7 (10.3)	16.7 (10.7)	NR	NR	NR
Type 2 DM, n (%)	[redacted]	[redacted]	98 (77.8)	107 (84.3)	NR	NR	NR	NR	NR
Baseline HbA1c, mean % (SD)	[redacted]	[redacted]	7.6 (1.4)	7.7 (1.2)	7.7 (2.5)	7.8 (2.1)	Median %: 7.6	Median %: 7.3	Median %: 7.3
IOP in study eye, mean mmHg (SD)	[redacted]	[redacted]	16.0 (3.1)	15.9 (2.7)	14.8 (3.0)	14.5 (2.4)	NR	NR	NR

	024		PLACID		BEVORDEX		NCT00035906		
	DEX700 [redacted]	**RAN** [redacted]	**DEX + laser (n=126)**	**Laser (n=127)**	**DEX700 (n=46)**	**BEV (n=42)**	**DEX700 (n=57)**	**DEX350 (n=57)**	**Observation (n=57)**
Duration of DMO, mean months (SD)	[redacted]	[redacted]	22.4 (29.7)	28.2 (33.7)	NR	NR	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 (%)*	[redacted]	[redacted]	26 (20.6)	37 (29.1)	NR	NR	NR	NR	NR
Pseudophakic lens, n (%)	[redacted]	[redacted]	35 (27.8)	32 (25.2)	16 (34.8)	10 (23.8)	NR	NR	NR
Baseline VA, mean letters (SD)	[redacted]	[redacted]	57.6 (9.4)	57.8 (9.7)	55.5 (12.5)	56.3 (11.9)	54.7 (11.0)	54.4 (9.96)	54.4 (11.88)
Baseline CRT, mean µm (SD)	[redacted]	[redacted]	438.4 (133.9)	430.3 (131.2)	474.3 (95.9)	503 (140.9)	428.3 (155.9)	446.5 (123.7)	417.5 (126.8)
CRT ≥400 µm, n (%)*	[redacted]	[redacted]	70 (55.6)	64 (50.4)	NR	NR	NR	NR	NR
Study eye was BSE, n (%)	[redacted]	[redacted]	22 (17.5)	20 (15.7)	NR	NR	NR	NR	NR

	024		PLACID		BEVORDEX		NCT00035906		
	DEX700 [redacted]	**RAN** [redacted]	**DEX + laser (n=126)**	**Laser (n=127)**	**DEX700 (n=46)**	**BEV (n=42)**	**DEX700 (n=57)**	**DEX350 (n=57)**	**Observation (n=57)**
Bilateral DMO, n (%)	[redacted]	[redacted]	74 (58.7)	83 (65.4)	NR	NR	NR	NR	NR
Treatment history for DMO in the study eye									
Treatment naïve, n (%)	[redacted]	[redacted]	48 (38.1)	42 (33.1)	NR	NR	NR	NR	NR
Prior laser, n (%)	[redacted]	[redacted]	78 (61.9)	84 (66.1)	NR	NR	35 (61)	34 (60)	29 (51)
Prior anti-VEGF, n (%)	[redacted]	[redacted]	2 (1.6)	7 (5.5)	NR	NR	NR	NR	NR
Prior steroid, n (%)	[redacted]	[redacted]	7 (5.6)	13 (10.2)	NR	NR	NR	NR	NR

Key: BEV, bevacizumab; BSE, best seeing eye; CRT, central retinal thickness; DEX, 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]

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Primary and secondary outcomes investigated across the DEX700 RCTs are presented in Table 17. As the study design was identical for the MEAD trials, the primary and secondary outcome measures adopted are only presented once in this table.

In all trials, the primary and key secondary outcomes were predominantly based around changes in BCVA and CRT: both clinically relevant endpoints used to guide treatment decisions in clinical practice.

As noted in section 6.3.2, the primary outcome measure of clinical efficacy for Europe was mean BCVA average change from baseline in the Phase III trials investigating DEX700 monotherapy (MEAD and 024).

For the MEAD trial programme, this primary efficacy outcome for Europe was amended from an original primary endpoint of the proportion of patients with a ≥15 letter gain at study end. Of note, the original primary endpoint remained as such for the US and is considered the key secondary outcome for Europe. This amendment in Europe was in line with changes in regulatory precedent and standard of care for DMO in the period over which the MEAD studies were conducted. Historically, the proportion of patients gaining at least 15 letters was considered a clinically significant endpoint in ophthalmology clinical trials and thought to reflect a true alteration in visual acuity. However, contemporary research using patient-reported outcomes and

visual acuity suggest that an improvement in 10 letters (or potentially as few as 5 letters) is clinically meaningful.[145] Furthermore, use of this endpoint measures clinical efficacy after a number of years of treatment at a single final time point.

In order to take into account the effect of multiple treatments and observation times during the entire 3-year study period, a primary outcome of mean BCVA average change from baseline (area under the curve (AUC) approach) was proposed. The regulatory precedent for use of this endpoint was the European pivotal trial of ranibizumab in DMO (RESTORE study), in which mean BCVA average change from baseline from Month 1 to Month 12 was recommended as the primary endpoint by the Committee for Medicine Products for Human Use.[100] AUC analysis is also a widely accepted method and has been used in many indications.[146-151] This endpoint amendment was accepted by the EMA (with note that the original primary endpoint was also clinically relevant and thus also of interest) and the rest of the world but was not accepted in the US.

In all other trials, the proportion of patients who had at least a 10-letter improvement in visual acuity was the primary outcome measure. As discussed, this is in line with traditional visual acuity measurement methodology in ophthalmology clinical trials but up to date with contemporary research. This endpoint was also named as a secondary outcome of interest in both MEAD and [redacted]

Common secondary outcome measures across two or more trials investigating the clinical efficacy and safety/tolerability of DEX700 in DMO include change in BCVA at specified post-baseline timepoints, proportion of patients with improved or worsened vision, change in CRT at specified post-baseline timepoints and change in total leakage area at specified post-baseline timepoints along with safety and HRQL measures.

Table 17: Primary and secondary outcomes of the RCTs

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
MEAD-010 MEAD-011	The EU primary outcome was mean BCVA average change (AUC approach) from baseline through Month 36/39 (final analysis). BCVA was measured using the ETDRS method. Average change was measured using an AUC approach.	BCVA is a clinically relevant endpoint used to guide treatment decisions and is directly referenced in the decision problem. 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. AUC analysis is a widely accepted method for average outcome measurement that has been used in many indications. AUC analysis takes into account the effect of multiple treatments and observation times. EU regulatory precedent for use of this endpoint was the pivotal EU trial of ranibizumab in DMO (RESTORE study).	Key secondary outcome in the EU was the proportion of patients with improvement of 15 or more letters from baseline. Othersecondary 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	BCVA is a clinically relevant endpoint used to guide treatment decisions and is directly referenced in the decision problem. CRT is a clinically relevant endpoint used to guide treatment decisions. Contrast sensitivity, health-related quality of life and safety are clinically relevant endpoints, directly referenced in the decision problem. The NEI VFQ 25 is a widely accepted method for assessing vision-related quality of life. All outcomes are consistent with other studies of therapeutic agents for DMO.

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
			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.	
024	[redacted]	[redacted]	[redacted]	[redacted]

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
		[redacted]	[redacted]	[redacted]
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. BCVA was measured using the ETDRS method.	BCVA is a clinically relevant endpoint used to guide treatment decisions and is directly referenced in the decision problem. 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.	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	BCVA is a clinically relevant endpoint used to guide treatment decisions and is directly referenced in the decision problem. CRT is a clinically relevant endpoint used to guide treatment decisions. Safety is a clinically relevant endpoint, directly referenced

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
			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.	in the decision problem. All outcomes are consistent with other studies of therapeutic agents for DMO.
NCT00035906	The primary outcome was proportion of eyes achieving at least a 10-letter improvement in BCVA at day 90. BCVA was measured using the ETDRS method.	BCVA is a clinically relevant endpoint used to guide treatment decisions and is directly referenced in the decision problem. 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.	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	BCVA is a clinically relevant endpoint used to guide treatment decisions and is directly referenced in the decision problem. CRT is a clinically relevant endpoint used to guide treatment decisions. Safety is a clinically relevant endpoint, directly referenced in the decision problem. All outcomes are consistent with other studies of therapeutic agents for DMO.

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
			reported, including seriousness, severity, action taken and relationship to study drug.	
BEVORDEX	The comparison of the proportion of eyes gaining 10 letters of visual acuity between the bevacizumab and dexamethasone implant arms. BCVA was measured using the ETDRS method.	BCVA is a clinically relevant endpoint used to guide treatment decisions and is directly referenced in the decision problem. 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.	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 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	BCVA is a clinically relevant endpoint used to guide treatment decisions and is directly referenced in the decision problem. 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.

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
			relationship to study drug.	

Key: AUC, area under the curve; BCVA, best corrected visual acuity; CRT, central retinal thickness; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study; DMO, diabetic macular oedema; OCT, ocular computed tomography; VA, visual acuity.

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; Gillies et al. 2014b[127]; Haller et al. 2010[5].

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

A summary of statistical analysis and study group definitions utilised in all DEX700 RCTs is presented in Table 18. As the study design was identical for the MEAD trials, statistical methodologies adopted are only presented once in this table.

Table 18: Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
MEAD-010 MEAD-011	The primary efficacy objective is to demonstrate that DEX700 and/or DEX350 is more effective than Sham in the improvement of BCVA. For the primary efficacy analyses, the null hypothesis is that there is no difference between DEX700µg and Sham in the BCVA average change. The alternative hypothesis is that there exists a difference between the 2 treatment groups.	The primary analysis of BCVA average change from baseline was performed using ANCOVA with treatment as a fixed effect and the baseline BCVA as a covariate in the ITT population. For a patient with no post baseline BCVA assessment, its average change from baseline will be 0. Primary comparisons between DEX700 and Sham, and between DEX350 and Sham were performed in a pairwise fashion using contrasts from the ANCOVA model. A gate-keeping procedure was used to control the overall type I error at 5% for the 2 between-group comparisons. The comparison of DEX700 versus Sham was considered significant if the p-value was ≤ 0.05. Only if the comparison of DEX700 versus Sham was significant	The sample size calculation was based on the primary efficacy analysis of the BCVA average change from baseline in the study eye comparing each DEX PS DDS dose and Sham. From 2 single-dose 6-month RVO studies (206207-008 and 206207-009); the observed BCVA average change from baseline during the study at Month 6 was 6.9 and 2.9 letters for the DEX700 and Sham groups, respectively. The observed standard deviation was 10 letters. For this DMO study, assuming a 4-letter mean difference (delta) in the BCVA average change from baseline during the study for DEX700 over Sham, and an increase of 20% in the standard deviation to 12.0 due to increased variation for multiple injections and longer study duration, the planned sample size of 170 patients	The primary analysis included all randomised eyes and followed the intent-to-treat principle with missing value imputed by last observation carried forward with the exception of AUC analysis that was conducted using observed data. Secondary analyses included all randomised eyes with missing value based on multiple imputation; and observed data in the per-protocol population (defined as randomised patients with no major protocol violations).

		at the 0.05 level was the comparison of DEX350 versus Sham to be performed, at a significance level of 0.05. If the comparison of DEX700 versus Sham was not statistically significant, the comparison of DEX350 versus Sham was not to be considered statistically significant regardless of its p-value. In addition, 2-sided 95% confidence intervals (CIs) were constructed for the 3 between-group differences based on the ANCOVA model.	per arm (510 patients total) would have a power of 86% (2-sided alpha of 0.05). The power calculation, using nQuery Advisor 6.01, was based on 2 sample t-tests with equal variances. The treatment difference and variance were estimated from 2 completed Allergan studies, 206207-008 and 206207-009, in RVO.	
MEAD pooled	To evaluate overall DEX700 and DEX350 treatment.	Integrated summary of effectiveness as per individual studies, data pooled prior to analysis. Treatment by study interaction for the primary analysis of BCVA average change from baseline was examined by ANCOVA with treatment, study, and treatment by study interaction as factors and baseline value as a covariate	Not applicable	Not applicable
024	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]

			[redacted]	
PLACID	The clinical objective was that combination therapy with the DEX implant and laser would have an acceptable safety profile, and more patients would have at least a 10-letter increase in BCVA after combination treatment than after laser treatment alone.	The between group difference in the primary objective was analysed based on an approximation to the Cochran-Mantel-Haenszel statistic using a linear model with the stratification factor of baseline BCVA category included in the model. Mean changes from baseline BCVA, the area under the curve of change from baseline BCVA, retinal thickness in the 1mm central subfield by OCT, and the area of fluorescein leakage were evaluated using an analysis of variance with treatment and baseline BCVA (34-49 letters or 50-70 letters) as main effects in the models. Within-group changes from baseline were evaluated with paired t tests.	The sample size was chosen based on an estimate that 30% and 14% of patients treated with combination therapy and laser alone respectively would achieve at least a 10-letter improvement in BCVA by Month 12. A sample size of 105 patients in each treatment group was required for 80% power. A study sample size of 124 patients in each treatment group was planned to allow for an anticipated dropout rate of 15%.	The primary analysis of efficacy parameters were performed for both the ITT population and the modified ITT population, defined as all randomised patients with diffuse macular capillary bed leakage at screening verified by the reading centre. Missing BCVA data were imputed with the method of last observation carried forward. Safety parameters were evaluated in the safety population of all randomised patients who received a DEX implant or sham treatment at baseline.

NCT00035906	The clinical objective was to evaluate the safety and effectiveness of an investigational medication to treat macular edema that persists despite current treatment methods.	Differences in the proportion of eyes achieving a given improvement from baseline BCVA between each of the dexamethasone DDS treatment groups and the observation group were analysed separately using the Pearson X^2 test. Categorical variables were analysed using the Pearson X^2 or Fisher exact test. Continuous variables were analysed using analysis of variance. All tests were 2-sided.	The study was not powered to detect statistically significant differences between treatment groups within various patients' subpopulations.	The data for all randomised patients with DMO (intent-to-treat population) were used for the analysis of primary and secondary efficacy parameters, with the last observation carried forward for any missing values. The data from all patients with DMO who received treatment (as-treated population) were used for the analysis of all safety parameters.
BEVORDEX	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	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.

	have a manageable and acceptable safety profile in eyes with DMO.			

Key: ANCOVA, analysis of covariance; ANOVA, analysis of variance; AUC, area under the curve; BCVA, best corrected visual acuity; CI, confidence interval; DEX, dexamethasone; 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]

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Pre-planned subgroup analyses in the MEAD trial programme included cohorts of patients defined by:

- 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

Post-hoc subgroup analyses in the MEAD trial programme included cohorts of patients defined by:

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

Pre-planned subgroup analyses in study 024 included cohorts of patients defined by:

[redacted]

In the PLACID study, the only pre-planned subgroup analyses defined patients by BCVA category at baseline (≥34 to ≤49 letters and ≥50 to ≤70 letters).

The BEVORDEX interim results publication references subgroup analysis of patients treated unilaterally, but the protocol does not outline pre-planned subgroup analyses.

Subgroup analyses based on cause of macular oedema was pre-planned for NCT00035906; the results of interest to the decision problem are those for the DMO subgroup of patients enrolled in this trial.

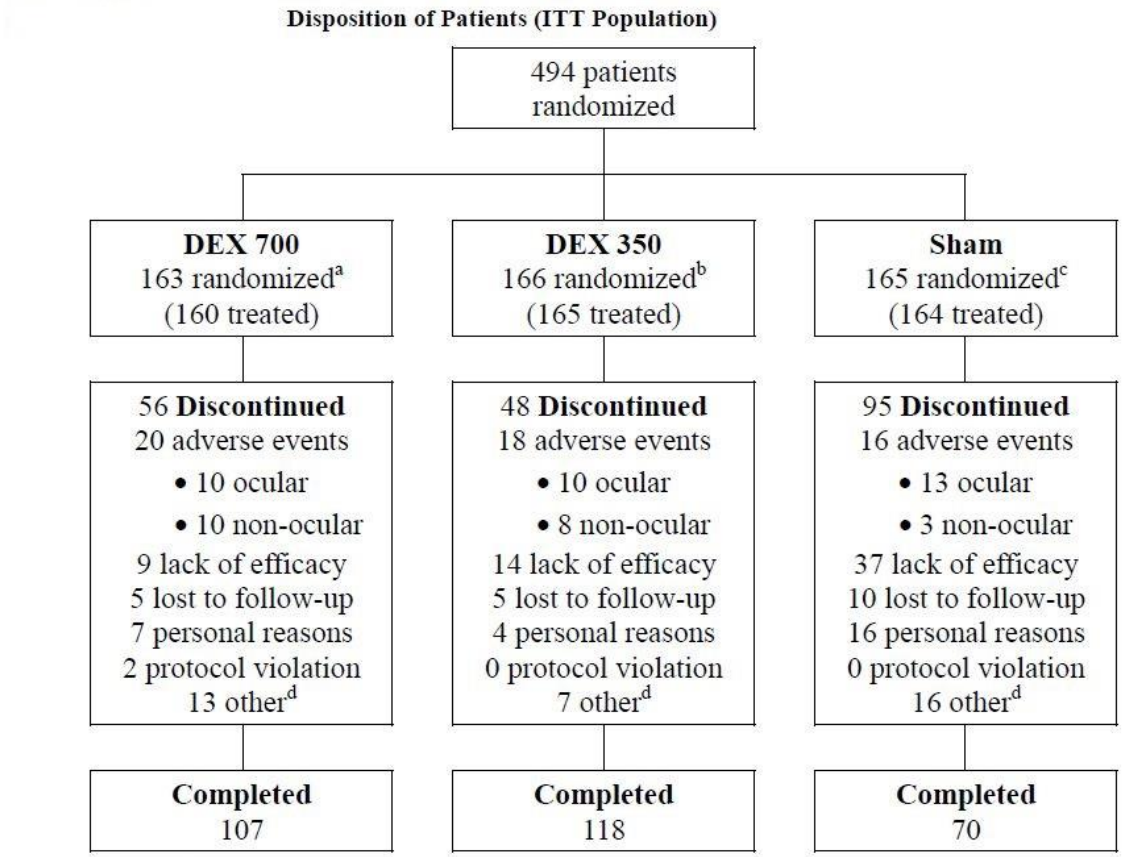
In consideration of the populations of relevance to the decision problem, only subgroup analyses relating to treatment history and lens status is presented in section 6.5.

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

CONSORT flow charts for completed RCTs identified that investigate the clinical efficacy of DEX700 are presented in Figure 9 to Figure 14. BEVRODEX is ongoing and therefore the CONSORT flow chart presented for this study is that for patient flow at 12 months. CONSORT flow charts for the individual MEAD studies are presented as well as that for the pooled MEAD trial programme.

Figure 9: MEAD-010 CONSORT flow chart



ITT = intent-to-treat

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

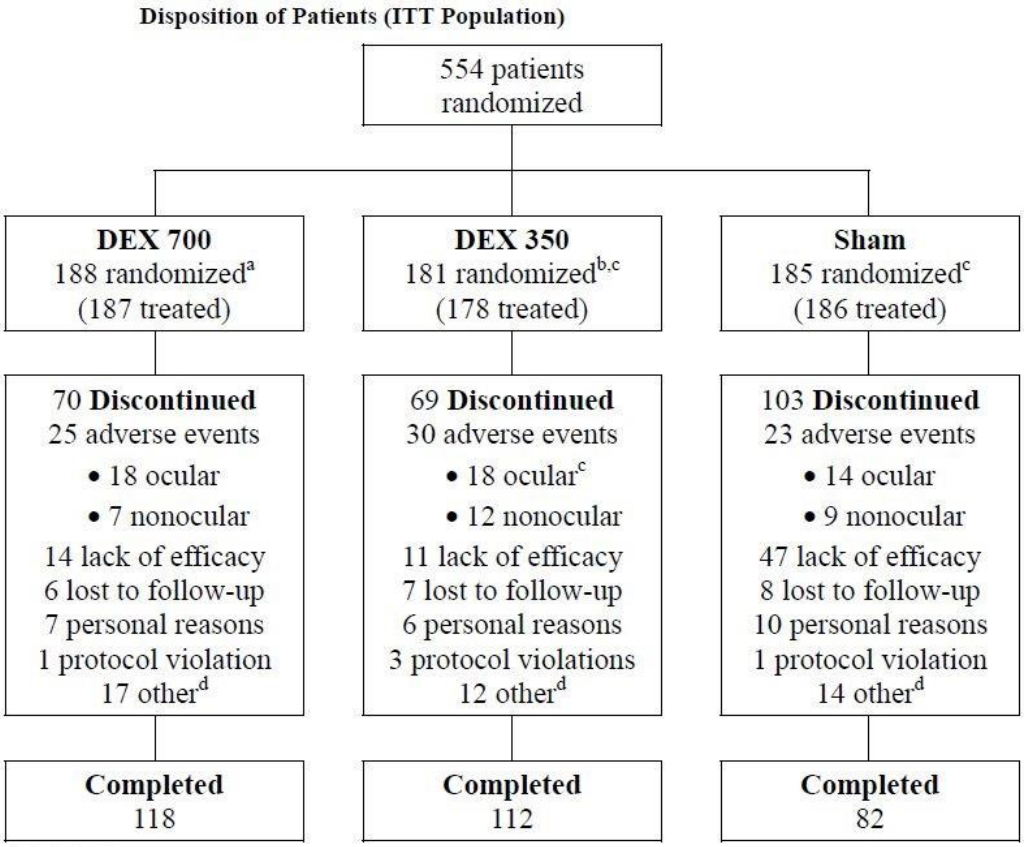
[b] One patient (4451-4278) was randomized to DEX 350 but never received treatment.

[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)[121]

Figure 10: MEAD-011 CONSORT flow chart



ITT = intent-to-treat

[a] One patient (4406-7060) was randomized to DEX 700 but never received any treatment.

[b] Two patients (0469-7856 and 5099-7160) were randomized to DEX 350 but never received any treatment.

[c] One patient (5941-8189) was randomized to DEX 350 but actually received Sham. This patient discontinued the study due to a serious adverse event of macular fibrosis in the study eye after Sham treatment. The patient is counted in the DEX 350 group for analyses based on the ITT population and in the Sham group for analyses based on the safety population.

[d] "Other" reasons for patient discontinuation included patient withdrawal of consent, patient relocation, site closure, etc

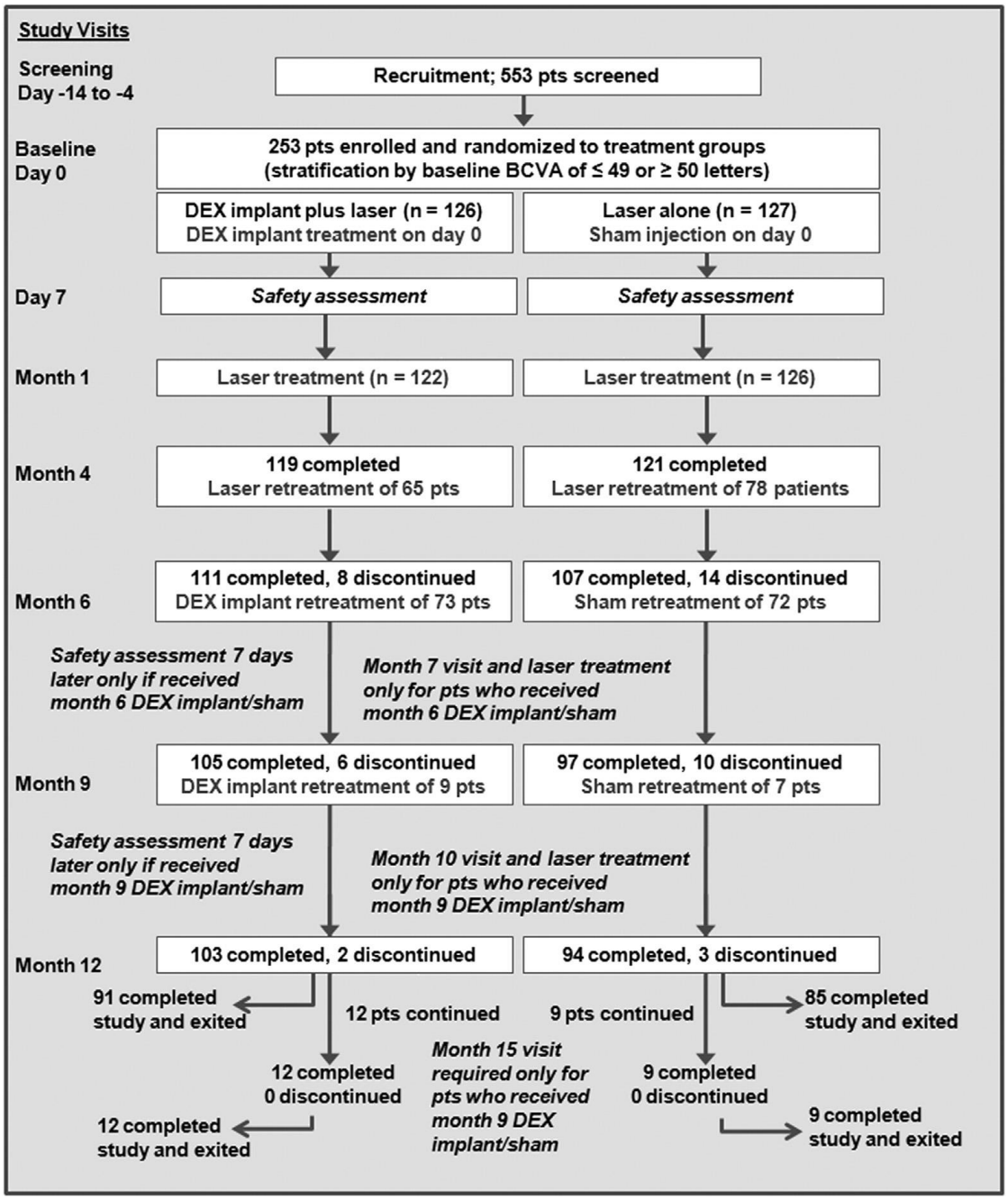
Source: CSR 206207-011[123]

[redacted] **024 CONSORT flow chart**

[redacted]

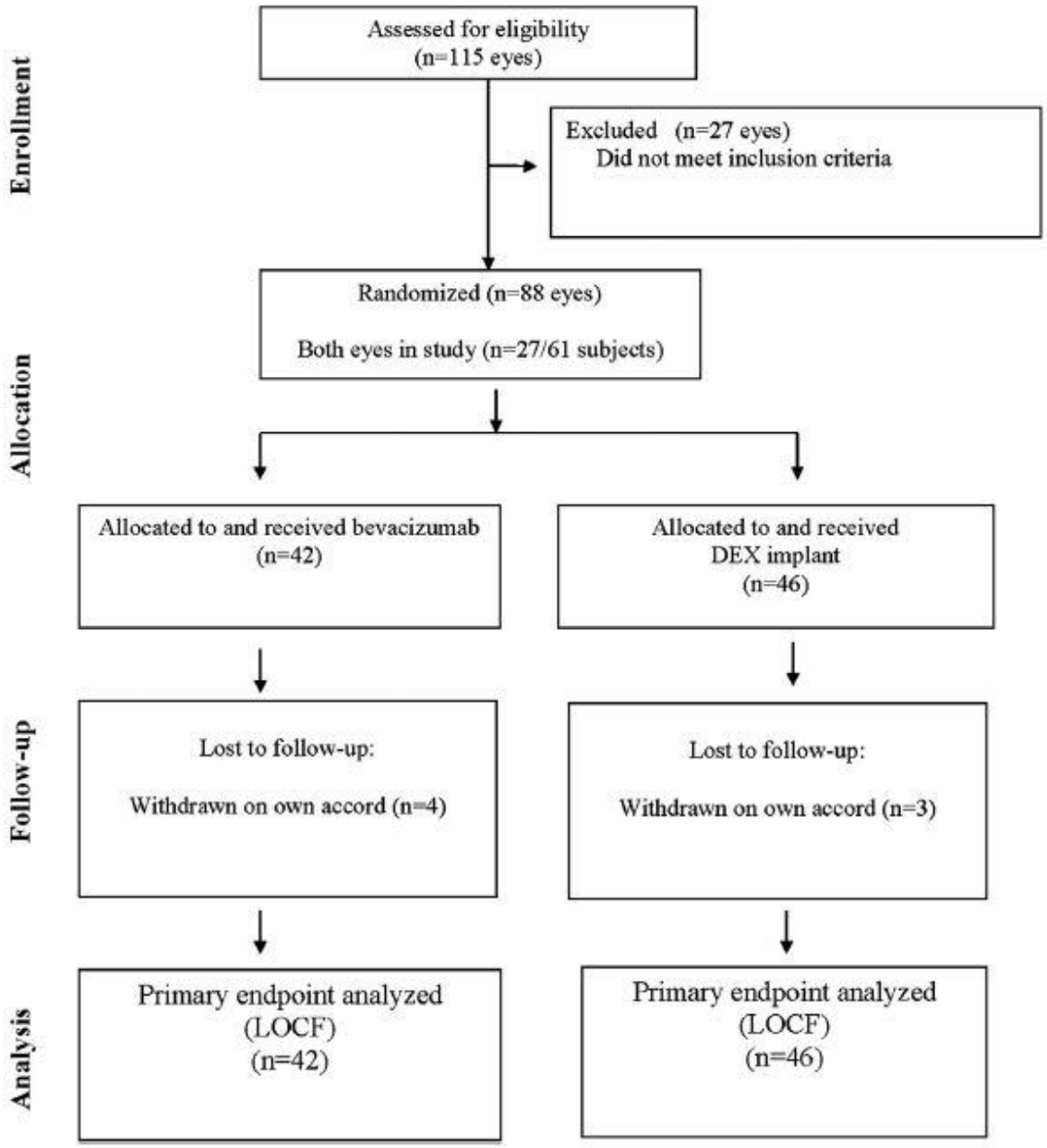
Source: CSR 206207-024[124]

Figure 12: PLACID CONSORT flow chart



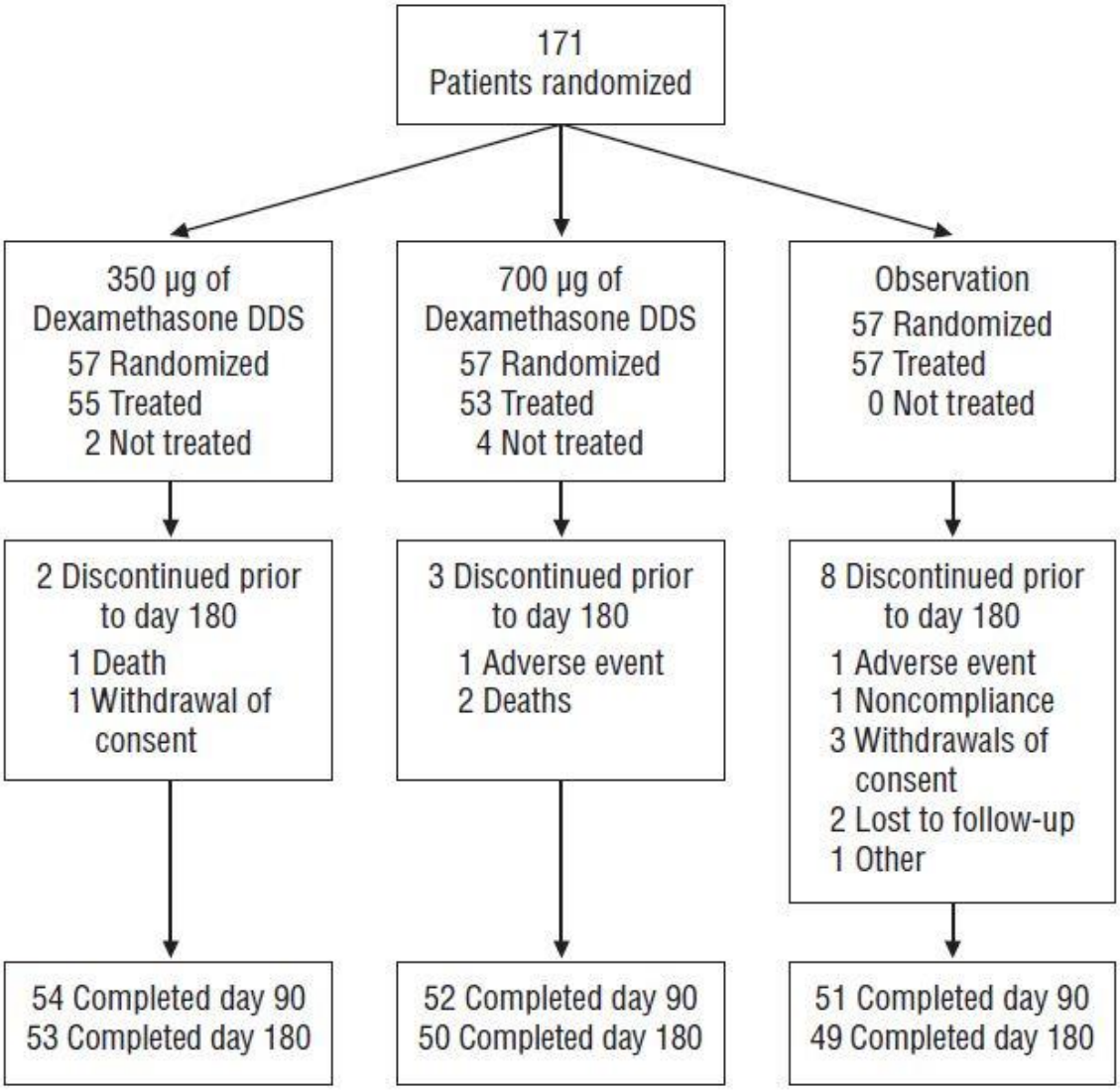
Source: Callanan et al. 2013[125]

Figure 13: BEVORDEX interim CONSORT flow chart



Source: Gillies et al. 2014b[127]

Figure 14: NCT00035906 CONSORT flow chart



Source: Haller et al. 2010[5]

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- 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)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Quality assessment results for all RCTs are summarised in Table 19.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

Complete quality assessment for each RCT is presented in Appendix 10.3

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Quality assessment results for all RCTs are summarised in Table 19.

Table 19: Quality assessment results for RCTs

	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 factors?	Yes	Yes	Yes	Yes	Yes	Yes
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.

	MEAD-010	MEAD-011	024	PLACID	NCT00035906	BEVORDEX
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[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]; Kupperman et al. 2007[1]						

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.

Results presented in section 6.5.3

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

Results presented in section 6.5.3

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

MEAD Trial Programme

BCVA Outcomes

In ITT analysis of the primary efficacy outcome using observed data, mean BCVA average change (AUC approach), DEX700 demonstrated superiority over sham treatment (Table 20). This superiority was statistically significant at the 95% level in MEAD-010 and the pooled MEAD analysis but failed to reach statistical significance in MEAD-011.[67, 121, 123] This has been fully investigated and accounted for in post-hoc analysis of severe vision loss attributed to cataract, discussed further on page 142.

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

	DEX700	DEX350	Sham	DEX700 vs. Sham p-value
MEAD-010	4.1 (8.3)	4.3 (8.5)	1.9 (7.7)	0.016
MEAD-011	2.9 (8.6)	2.9 (7.7)	2.0 (8.2)	0.366
MEAD Pooled	3.5 (8.4)	3.6 (8.1)	2.0 (8.0)	0.023

Key: AUC, area under the curve; BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study; SD, standard deviation.
Source: Boyer et al. 2014[67]; CSR 206207-010[121]; CSR 206207-011[123]

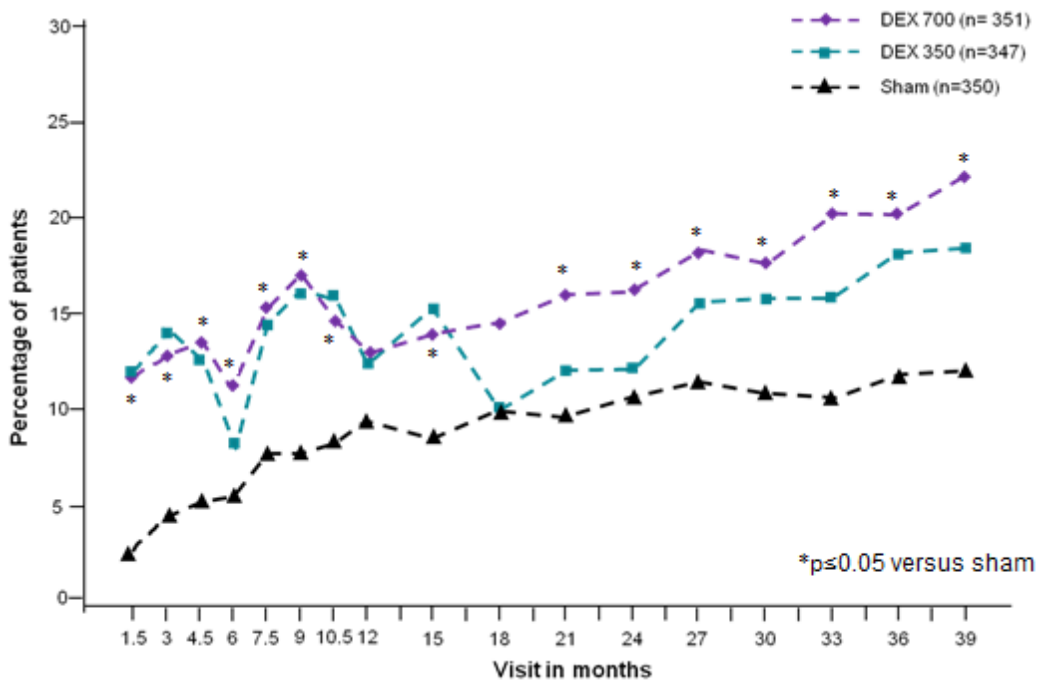
In ITT analyses of the original primary efficacy outcome, proportion of patients achieving ≥15 letter gain from baseline, DEX700 demonstrated superiority over sham treatment (Figure 20; Figure 15). This superiority was statistically significant at the 95% level in MEAD-010, MEAD-011 and the pooled MEAD analysis. [67, 121, 123, 152]

Table 21: Patients achieving a BCVA improvement of ≥15 letters from baseline at study end in the MEAD trial programme, n (%)

	DEX700	DEX350	Sham	DEX700 vs. Sham p-value
MEAD-010	36 (22.1)	31 (18.7)	22 (13.3)	0.038
MEAD-011	42 (22.3)	33 (18.2)	20 (10.8)	0.003
MEAD Pooled	78 (22.2)	64 (18.4)	42 (12.0)	<0.001

Key: BCVA, best corrected visual acuity; DEX, dexamethasone.
Source: Boyer et al. 2014[67]; CSR 206207-010[121]; CSR 206207-011[123]

Figure 15: Proportion of patients with ≥15-letter visual acuity improvement over time in the MEAD studies, % – pooled analysis



Key: DEX, dexamethasone.
Source: Summary of Clinical Efficacy[152]

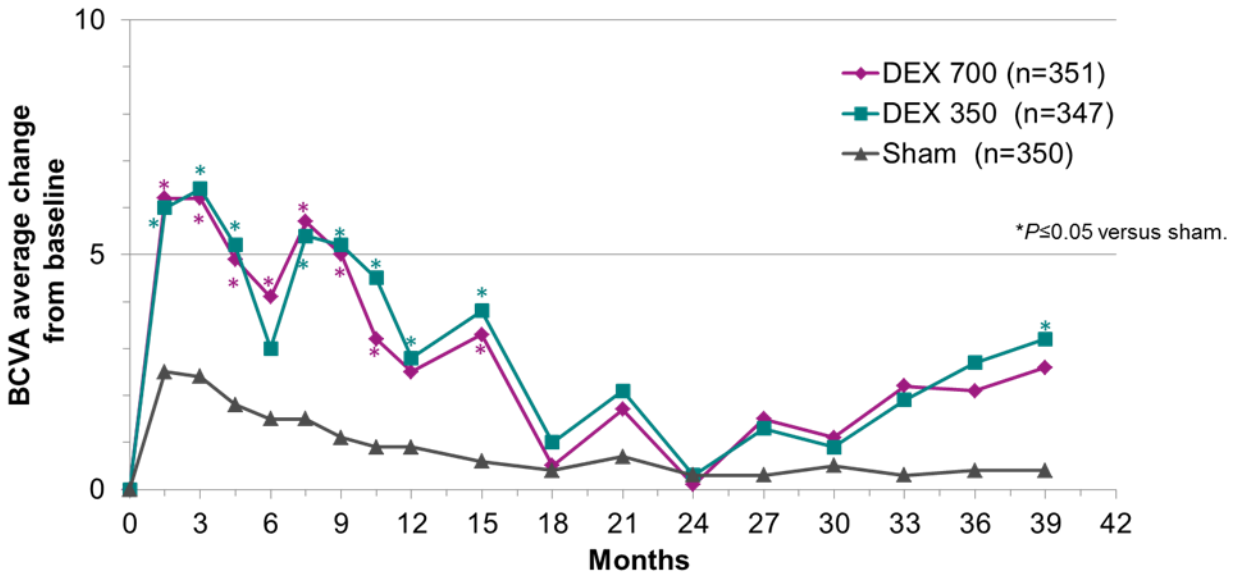
In ITT analyses of further BCVA outcomes at study end, DEX700 demonstrated numerical statistically significant superiority over sham treatment in mean BCVA change from baseline (Figure 16) and statistically significant superiority over sham treatment in the proportion of patients with clinically significant improvement in visual acuity (≥10 letters) from baseline (Table 22).[67, 121, 123, 152] At study end, 50.4% of patients treated with DEX700 across the MEAD trial programme had an improved BCVA of at least 5 letters which has been linked to a clinically meaningful change in HRQL among DMO patients.[153]

Table 22: Patients achieving a BCVA improvement of ≥10 letters from baseline at study end in the MEAD trial programme, n (%)

	DEX700	DEX350	Sham	DEX700 vs. Sham p-value
MEAD-010	63 (38.7)	57 (34.3)	38 (23.0)	0.002
MEAD-011	65 (34.6)	54 (29.8)	46 (24.9)	0.040
MEAD Pooled	128 (36.5)	111 (32.0)	84 (24.0)	<0.001

Key: BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study; SD, standard deviation.
Source: CSR 206207-010[121]; CSR 206207-011[123]; Summary of Clinical Efficacy[152]

Figure 16: Mean BCVA change from baseline in the MEAD trial programme, ETDRS letters – pooled analysis



Key: BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study.
Source: Boyer et al. 2014[67]

In BCVA outcomes analysis an unusually high response is observed in patients randomised to sham treatment. For example, in the only other DMO trial to include a pure sham treatment arm (RESOLVE), mean BCVA average change over the shorter study duration of12 months in patients randomised to sham was -0.1 ETDRS letters[103] which would be expected to worsen if monitored over an additional 24 months. This may be attributed, at least in part, to the discontinuation rules based on vision deterioration and rescue therapy requirements, where patients were removed from the study if they experienced vision loss of ≥15 letters from baseline or required additional DMO treatment i.e. rescue therapy. Across the MEAD trial programme,

56.6% of patients randomised to Sham discontinued from the study, 42.4% of these discontinuations (24% of the total Sham population) were due to lack of efficacy.[67] In the ITT analyses, discontinuations were accounted for using the LOCF method and thus the true deterioration of patients experiencing disease progression was not fully captured. Towards the end of the study period, the sham treatment arm consisted of what may be classed as 'super-responders'. This positive self-selection is represented by the proportion of patients randomised to sham treatment that experienced a 10-letter loss from baseline at study end that was markedly lower than that expected in accordance with natural history data (see section 7.3.1). There were no trends in the data that would enable these 'super-responders' to be predetermined.

Time to BCVA ≥10 and ≥15 letters improvement from baseline was significantly shorter in the DEX700 treatment arm compared with the sham treatment arm, demonstrating a rapid onset of treatment benefit (Data not shown).[121, 123, 152] This can also be observed in mean BCVA change from baseline analysis where peak DEX700 treatment effect is observed at approximately 3 months post implantation but sustained for up to 6 months in accordance with its drug delivery system (Figure 16).[67] Please note, from Month 6, patients' retreatment patterns could be staggered as assessments were conducted every 3 months, therefore trends post injection for the total population are only appropriate for up to Month 6.

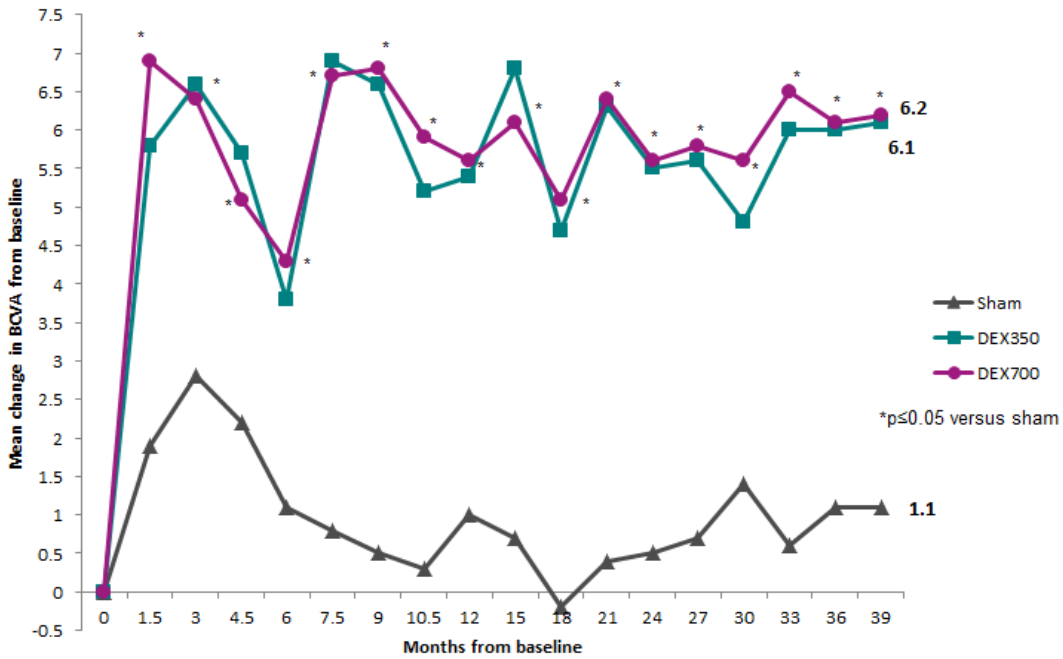
As expected *a priori*, the magnitude of treatment benefit associated with DEX700 in the early stages of the MEAD trial programme is not consistently observed throughout the 3-year study period. This appears primarily to be due to progression of lens opacification and primary cataract formation during the course of the study masking the treatment effect of DEX700. Cataract is a common complication of DM that may be accelerated with steroid use (see section 6.9). In the MEAD trial programme, the visual acuity of participants susceptible to cataract is being negatively impacted by progression of lens opacification and primary cataract formation.

This is clearly observed when comparing BCVA outcomes in the total population to those in subgroup analysis of patients with a pseudophakic lens at baseline, for whom primary cataract is not a possibility. In pseudophakic patients, the rapid onset of treatment benefit with DEX700 implantation is observed and is consistently

maintained throughout the 3-year study period (Figure 17); resulting in statistically significant superiority of DEX700 compared with sham treatment in primary efficacy outcome analysis of mean BCVA average change (Table 23).[67, 121, 123]

Aside from their lens status, other baseline characteristics of pseudophakic patients were similar to those of the total population (Appendix 20) and representative of pseudophakic patients presenting in clinical practice.

Figure 17: Mean BCVA change from baseline for pseudophakic patients in the MEAD trial programme, ETDRS letters – pooled analysis



Key: BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study.
Source: Boyer et al. 2014[67]

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

	DEX700	DEX350	Sham	DEX700 vs. Sham p-value
MEAD-010	8.1 (8.0)	6.3 (7.5)	2.1 (7.2)	<0.001
MEAD-011	4.9 (7.9)	5.5 (6.7)	1.3 (7.0)	0.018
MEAD Pooled	6.5 (8.1)	5.9 (7.1)	1.7 (7.1)	<0.001

Key: AUC, area under the curve; BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study; SD, standard deviation.
Source: Boyer et al. 2014[67]; CSR 206207-010[121]; CSR 206207-011[123]

In letter gain analysis, the proportion of DEX700 treated pseudophakic patients achieving ≥15 letter gain from baseline at study end was remarkably similar to that observed in ITT analysis of this endpoint: 23.3% and 22.2% respectively.[67]

The majority of cataract adverse events occurred between 12 and 24 months in the MEAD trial programme, as reflected in the loss of difference between DEX700 and sham treatment effect in mean BCVA change from baseline analysis of the ITT population in this time period (Figure 16).[67] As part of the MEAD protocol, cataract was managed by surgery as per standard clinical practice. The cumulative endpoint of mean BCVA average change (AUC approach) is therefore markedly 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 allows for the effect of this to be dispersed as patients experiencing visual impairment as a result of cataract had undergone cataract surgery by 36 months.

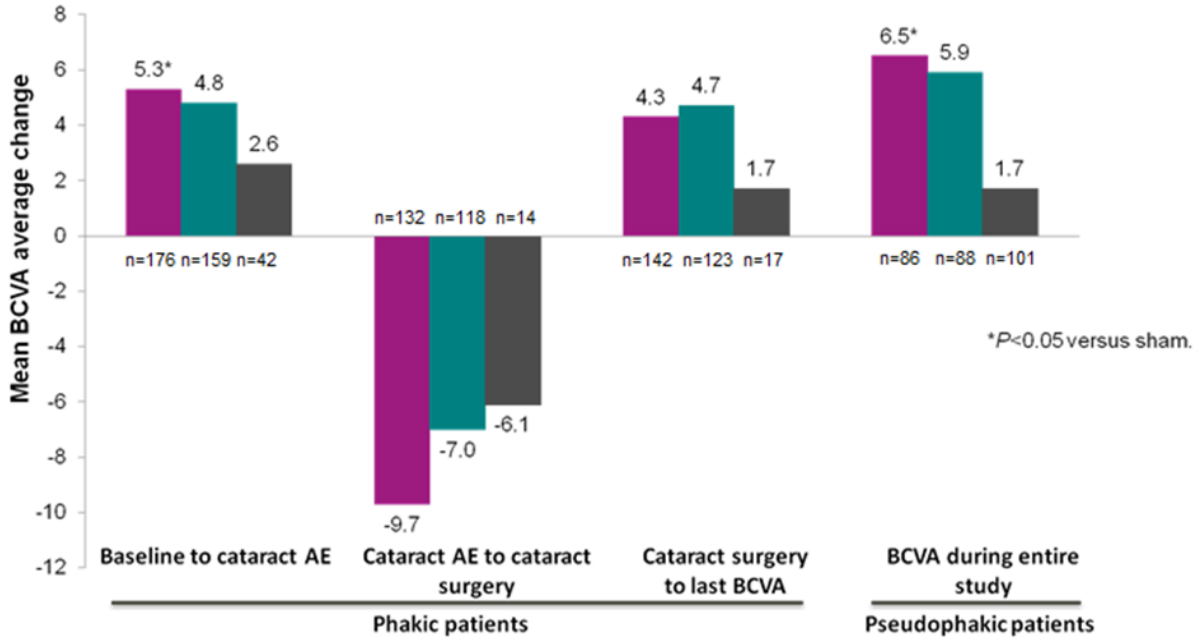
Progression of lens opacification and primary cataract formation also explains the observed difference in statistical significance of treatment effect across MEAD-010 and MEAD-011 in primary efficacy outcome analysis. The proportion of patients with worsening of ≥30 letters from baseline at any visit as the result of cataract was 4.9 times higher in the DEX700 treatment arm compared with sham in MEAD-011 while only 2.4 times higher in MEAD-010.[121, 123]

In retrospect, the non-cumulative original primary efficacy outcome analysis in the total trial population of MEAD actually better represents the true vision benefits that DEX700 therapy offers in clinical practice to patients with visual impairment due to DMO who are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy as it is less impacted by cataract events than the cumulative analysis of mean BCVA average change. In order to better understand the effect of primary cataract formation, mean BCVA average change relative to cataract event and treatment over time has been investigated using observed data.

This *post-hoc* analysis confirmed that during the period between the development of a cataract and cataract surgery, patients treated with DEX700 demonstrated severe vision loss in the MEAD trial programme; however, after cataract surgery, vision improvement returned close to precataract levels of treatment-improved vision (Figure 18).[67]

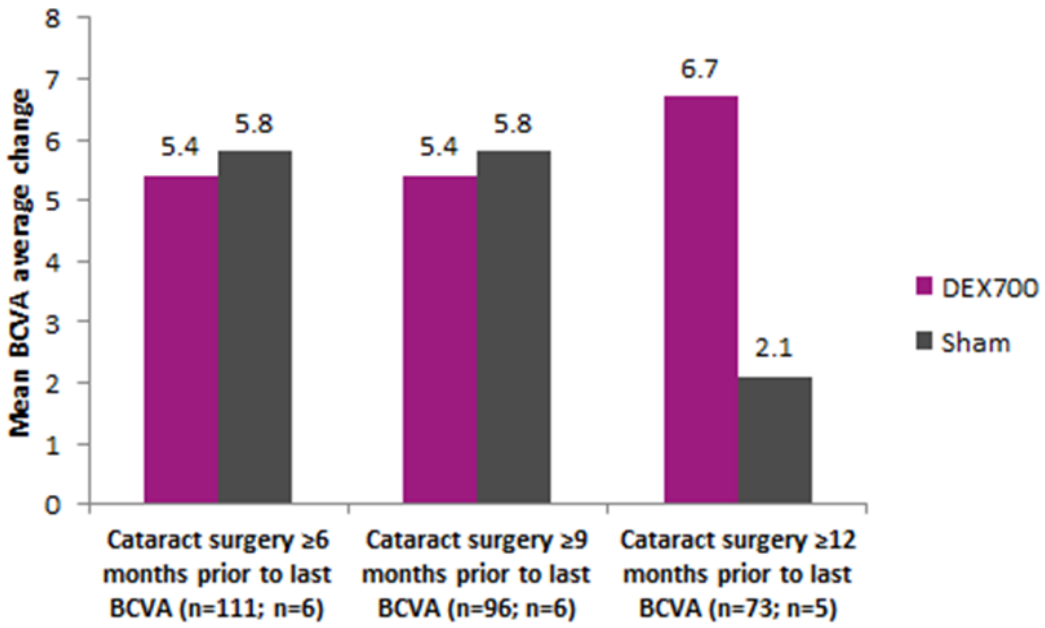
The magnitude of visual acuity improvement with DEX700 over sham treatment prior to cataract event or post cataract surgery was not quite as pronounced as that observed in the pseudophakic patient population. This (in part) appears to be attributed to insufficient follow-up time with DEX700 treated patients who remained in the study for at least twelve months post cataract extraction demonstrating comparable improvement in vision to DEX700 treated patients with a pseudophakic lens at baseline (Figure 19).[154]

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



Key: AE, adverse event; AUC, area under the curve; BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment of Diabetic Retinopathy Study.
Source: Boyer et al. 2014[67]

Figure 19: Mean BCVA average change (AUC approach) by timing of cataract surgery, ETDRS letters – pooled analysis



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[154]

In addition to patients with a pseudophakic lens at baseline, significant superiority of DEX700 over sham treatment was observed in primary efficacy analysis of mean BCVA average change (AUC approach) in subgroup analysis of patients with 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, numerical superiority of DEX700 over sham treatment was observed in primary efficacy analysis but this superiority failed to meet statistical significance.[152]

Subgroup analyses based on treatment history showed numerically higher mean improvement in vision over the course of the study with DEX700 compared with sham therapy regardless of treatment history (Table 24). In primary efficacy analysis of mean BCVA average change (AUC approach), this superiority was statistically significant for the treatment-exposed patients but fell just outside statistical significance in laser-naïve patients and patients who had received prior laser or anti-VEGF therapy (Table 24).[121, 123, 152, 155]

Table 24: Subgroup analyses based on prior treatment exposure: DEX700 vs. sham

	Mean BCVA average change, letters difference DEX700 minus Sham (p-value)			BCVA ≥15-letter improvement at study end, % difference DEX700 minus Sham (p-value)		
	MEAD-010	**MEAD-011**	**MEAD Pooled**	**MEAD-010**	**MEAD-011**	**MEAD Pooled**
Any prior treatment						
Yes						
N, DEX700/Sham	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean difference (p-value)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No						
N, DEX700/Sham	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean difference (p-value)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior laser therapy						
Yes						
N, DEX700/Sham	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean difference (p-value)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No						
N, DEX700/Sham	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean difference (p-value)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-VEGF therapy						
Yes	[redacted]	[redacted]		[redacted]	[redacted]	
N, DEX700/Sham			[redacted]			[redacted]
mean difference (p-value)			[redacted]			[redacted]

Key: BCVA, best corrected visual acuity; DEX, dexamethasone; VEGF, vascular endothelial growth factor.
Source: CSR 206207-010[121]; CSR 260207-011[123]; Summary of Clinical Efficacy[152]; Subgroup Analysis[155]

Further subgroup analyses based on treatment history requested by the CHMP as part of the licence application is presented in Appendix 21.

It should be noted that the MEAD trial programme was not powered to detect statistically significant differences in subgroups and some e.g. patients with prior anti-VEGF therapy included small patient numbers. With the exception of patients with a pseudophakic lens (for the reasons outlined previously), there is no clinical rationale to assume any other DMO patient subgroup would demonstrate significantly different treatment effect in clinical practice to that observed in total population data presented from the MEAD trial programme.

Contrast Sensitivity

No significant changes in contrast sensitivity from baseline to study end were observed in any treatment groups across the MEAD trial programme.[121, 123]

Anatomical Outcomes

Rapid and sustained anatomical improvements, as measured by OCT and fluorescein angiography were observed with DEX700 treatment in the MEAD trial program, with consistency achieved with time.

In ITT analyses of mean CRT average change (AUC approach), DEX700 demonstrated superiority over sham treatment (Table 25). This superiority was statistically significant at the 95% level in MEAD-010, MEAD-011 and pooled MEAD analysis.[67, 121, 123]

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

	DEX700	**DEX350**	**Sham**	**DEX700 vs. Sham p-value**
MEAD-010	-101.1 (119.2)	-103.9 (137.9)	-37.8 (104.0)	<0.001
MEAD-011	-120.7 (145.6)	-111.6 (134.1)	-45.8 (126.4)	<0.001
MEAD Pooled	-111.6 (134.1)	-107.9 (135.78)	-41.9 (116.0)	<0.001

Key: AUC, area under the curve; CRT, central retinal thickness; DEX, dexamethasone; SD, standard deviation.
Source: Boyer et al. 2014[67]; CSR 206207-010[121]; CSR 206207-011[123]

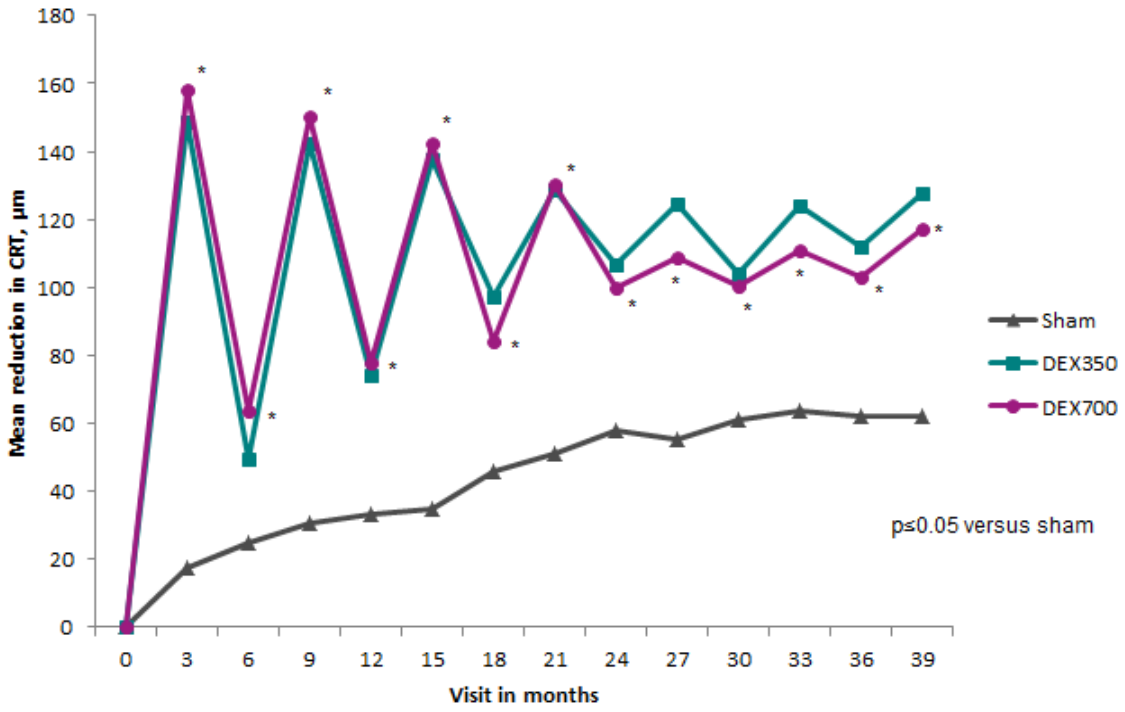
In ITT analyses of mean CRT change from baseline, DEX700 demonstrated superiority over sham treatment (Figure 20). This superiority was statistically

significant at the 95% level in MEAD-010, MEAD-011 and pooled MEAD analysis at all visits throughout the study and at study end.[152]

This significant reduction in macular oedema with DEX700 treatment was observed in all patients, regardless of baseline lens status (Figure 21)[67]; further supporting the theory that progression of lens opacification and primary cataract formation masks the treatment effect of DEX700 in BCVA outcome analyses.

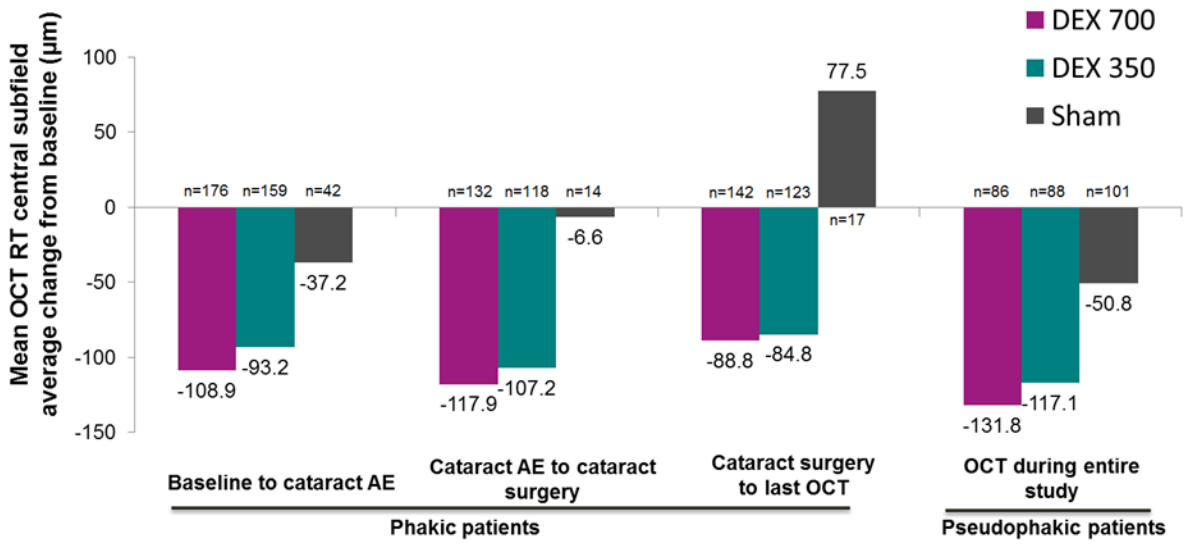
Of note, a high level of oedema was observed in sham treated patients following cataract surgery, probably as a consequence of the surgery. Such oedema is markedly reduced in the DEX700 treatment arm, suggesting a protective effect of DEX700 following cataract surgery, consistent with its anti-inflammatory action. The potential of a protective effect of dexamethasone following cataract surgery is currently under clinical investigation in an independent study.

Figure 20: Mean reduction in CRT from baseline in the MEAD trial programme, µm – pooled analysis



Key: CRT, central retinal thickness; DEX, dexamethasone.
Source: Summary of Clinical Efficacy[152]

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



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[67]

HRQL Outcomes

In the MEAD trial programme, HRQL and visual-functioning were assessed at baseline for each study arm using 2 generic HRQL instruments: the SF-36™ Health Survey version 1 (SF-36v1) and the EuroQol 5 Dimensions Health Questionnaire (EQ-5D); and 1 instrument specific to visual functioning and vision-related quality of life (the NEI-VFQ-25). The SF-36 and EQ-5D health surveys were not administered during follow-up because they do not contain vision-specific items and thus are not further discussed.

The NEI-VFQ-25 is a shortened version of the 51-item NEI VFQ field test version. The NEI-VFQ-25 consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and 1 general health item. Each item is assigned a coded value and the score for each subscale calculated as the average across the multiple items within each subscale. An overall composite score can then be calculated by averaging all 11 vision-targeted subscale scores, excluding the general health score. All scores are converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.[156] 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.

In ITT analyses of mean average NEI-VFQ-25 change (AUC approach) and NEI-VFQ-25 change of important difference at 36 months, where an important difference is defined as ≥10 point improvement[157], patients treated with DEX700 experienced some improvement in visual functioning but consistent, statistically significant differences between DEX700 and sham treatment arms were not observed (Table 26).[158]

Table 26: NEI-VFQ-25 change from baseline during the MEAD study period, pooled analysis

	[redacted]	[redacted]	[redacted]	[redacted]
Mean average change (AUC approach) from baseline during the MEAD study period, NEI-VFQ-25 score				
Overall composite score	[redacted]	[redacted]	[redacted]	[redacted]
General vision	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with near vision	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with distance vision	[redacted]	[redacted]	[redacted]	[redacted]
Mental health symptoms due to vision	[redacted]	[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]	[redacted]
General vision	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with near vision	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with distance vision	[redacted]	[redacted]	[redacted]	[redacted]
Mental health symptoms due to vision	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

As we may expect, it appears the vision-related quality of life of DEX700 treated patients is being negatively impacted by progression of lens opacification and primary cataract formation, as observed in visual acuity outcome analyses.

Post-hoc analysis confirmed that during the period between the development of a cataract and cataract surgery in the MEAD trial programme, patients experienced minimal improvement in vision-related quality of life; however, after cataract surgery, vision-related quality of life improvement exceeded precataract levels of treatment-improved vision-related quality of life and were similar to the improvement reported by pseudophakic patients (Figure 22).[158]

[redacted]

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

In addition to the negative impact of cataract on HRQL, visual functioning of patients in the MEAD trial programme appears to be disproportionately affected by the visual acuity in the BSE [redacted] Indeed, it has been previously reported that patient-reported vision change and impacts on vision-related function are

dependent on binocular vision, and are preferentially driven by changes in the BSE.[159] Only a minority of patients (21.9%) were treated with DEX700 in the BSE across the MEAD trial programme.[121, 123] The VFQ-25 results are therefore likely to be dependent on the nonstudy eye in the majority of patients.

In patients that experienced at least a 10-letter improvement or at least a 15-letter improvement in BCVA (both significantly larger populations in the DEX700 treatment arm compared with sham), significant improvements in NEI-VFQ-25 near vision activity and distance vision activity subscales were observed across multiple time-points for both the ITT and pseudophakic population (data not shown).[160, 161] In ITT analyses of DEX700 treated patients who had ≥15-letter visual acuity improvement from baseline at study end [redacted] also demonstrated an important difference (10 point improvement) in near vision and distance vision difficulty respectively.[160]

Mortality

There were 29 deaths in total across the MEAD trial programme; 9 in the DEX700 treatment group, 15 in the DEX350 treatment group and 5 in the sham treatment group.[67, 121, 123]

None of the deaths were due to ocular adverse events or considered by investigators to be related to treatment assignment.[67, 121, 123]

Study 024

BCVA Outcomes

In ITT analysis of the mean BCVA average change from baseline through Month 12 using observed data, DEX700 was shown to be [redacted] (Table 27). Secondary analyses of this outcome using the AUC approach for measuring the average change [redacted] (Table 27 [redacted]

Table 27: Mean BCVA average change from baseline during study 024, ETDRS letters (SD)

	DEX700 [redacted]	RAN [redacted]	DEX700 versus RAN		
			P-value	Difference	95% (CI)
Mean BCVA at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean BCVA average change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean BCVA average change (AUC approach)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AUC, area under the curve; BCVA, best corrected visual acuity; CI, confidence interval; DEX, dexamethasone; EDTRS, Early Treatment of Diabetic Retinopathy Study; RAN, ranibizumab.
Source: CSR 206207-024[124]

In pre-planned subgroup analyses, DEX700 was shown to be [redacted] In pseudophakic patients, mean BCVA average change from baseline was [redacted] in the DEX700 treatment arm compared with [redacted] in the ranibizumab treatment arm; CI [redacted].[124]

In ITT analysis of the mean BCVA change from baseline, [redacted] (Figure 23). [redacted] BCVA gain was observed post primary injection [redacted] BCVA gain was observed and at Month 12, the mean change from baseline in BCVA was [redacted] compared to the DEX700 group [redacted] (Figure 23). [redacted] lens opacification and primary cataract formation: for patients with a pseudophakic study eye at

baseline, the mean change from baseline BCVA at Month 12 was [redacted] letters in the DEX700 group compared to [redacted] letters in the ranibizumab group[redacted]

[redacted] **Mean BCVA change from baseline in study 024, ETDRS letters**

[redacted]

Key: BCVA, best corrected visual acuity; DEX, dexamethasone; ETDRS, Early Treatment Diabetic Retinopathy Study; RAN, ranibizumab
Source: CSR 206207-024[124]

In ITT analysis of BCVA category change from baseline (Table 28), the overall distribution at Month 12 was [redacted] of the DEX700 randomised patients had an improved BCVA of at least 5 letters at study end. Furthermore, for patients with a pseudophakic study eye at baseline, the proportion of patients with 15 or more letters improvement in BCVA from baseline at Month 12 [redacted]

Table 28: BCVA category change from baseline in study 024 at Month 12, n (%)

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

Key: BCVA, best corrected visual acuity; DEX, dexamethasone; RAN, ranibizumab.
Source: CSR 206207-024[124]

Anatomical Outcomes

[redacted] as measured by OCT and fluorescein angiography [redacted] the mean change from baseline in foveal thickness of the central subfield at Month 12 for the ITT population [redacted] as presented in Figure 24.[124]

[redacted] **Mean reduction in CRT from baseline in study 024, µm**

[redacted]

Key: CRT, central retinal thickness; DEX, dexamethasone; RAN, ranibizumab
Source: CSR 206207-024[124]

[redacted] CRT change was observed for patients [redacted] the mean change from baseline in foveal thickness of the central subfield was [redacted]

In ITT analyses, [redacted] seen in the mean change from baseline in total leakage area (mm^2) at Month 12 [redacted] At baseline, the mean total leakage area [redacted] At Month 12, the mean change from baseline in total leakage area was [redacted]

HRQL Outcomes

At baseline, [redacted]

In the ITT population, [redacted] (Table 29). In

average change from baseline through Month 12 analysis, [redacted] (Table 29).[124]

[redacted] (Table 30).[124]

Table 29: NEI-VFQ-25 analysis in study 024, ITT population

	NEI-VFQ-25 raw scores at Month 12			**Mean NEI-VFQ-25 average CFB through Month 12**		
	DEX700 [redacted]	**RAN** [redacted]	**P-value**	**DEX700** [redacted]	**RAN** [redacted]	**P-value**
Overall composite score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with near vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with distance vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mental health symptoms due to vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CFB, change from baseline; NEI-VFQ-25, National Eye Institute-Visual Functioning Questionnaire; DEX, dexamethasone; RAN, ranibizumab.
Source: CSR 206207-024[124]

Table 30: NEI-VFQ-25 analysis in study 024, pseudophakic population

	NEI-VFQ-25 raw scores at Month 12			Mean NEI-VFQ-25 average CFB through Month 12		
	DEX700 [redacted]	**RAN** [redacted]	**P-value**	**DEX700** [redacted]	**RAN** [redacted]	**P-value**
Overall composite score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with near vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with distance vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mental health symptoms due to vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CFB, change from baseline; NEI-VFQ-25, National Eye Institute-Visual Functioning Questionnaire; DEX, dexamethasone; RAN, ranibizumab.
Source: CSR 206207-024[124]

Mortality

There were four deaths in total during the study; one in the DEX700 group and three in the ranibizumab group. No deaths were due to ocular adverse events or considered by the investigator to be treatment-related.[124]

PLACID

BCVA Outcomes

In ITT analysis of the primary efficacy outcome, proportion of patients achieving at least a 10-letter improvement in visual acuity, DEX700 + laser demonstrated superiority over laser monotherapy (Table 31). This superiority was statistically significant at the 95% level at the Month 1, Month 7 and Month 9 timepoints but failed to reach statistical significance at study end (Month 12) (Table 31).[125]

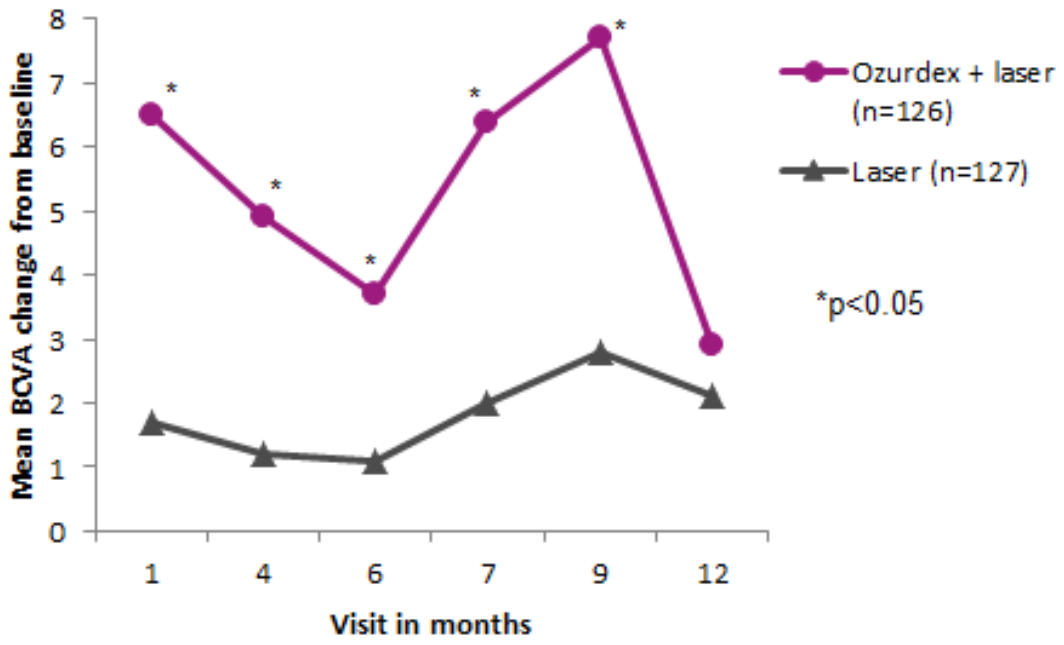
Table 31: Patients achieving a BCVA improvement of at least 10 letters from baseline at all timepoints in PLACID, n (%)

	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

Key: BCVA, best correct visual acuity; DEX, dexamethasone.
Source: Callanan et al. 2013[125]

Similar trends were observed in ITT analyses of secondary BCVA outcome endpoints with numerical superiority observed at all timepoints for the combination therapy in mean BCVA change from baseline analysis and statistically significant superiority observed at DEX700 peak treatment effect timepoints at 3-4 months post implantation (Figure 25). At month 4 (3 months after the first laser treatment), patients with verified diffuse oedema who were given DEX700 before laser treatment were approximately twice as likely to gain at least 10 letters in BCVA compared with patients who were given the sham injection (23.2% vs. 11.9%; p=0.035).[125]

Figure 25: Mean BCVA change from baseline in PLACID, ETDRS letters



Key: BCVA, best correct visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study.
Source: Callanan et al. 2013[125]

In addition, AUC analysis of the effect of treatment on the change from baseline BCVA over time demonstrated greater improvement in BCVA with DEX700 + laser combination therapy than with laser monotherapy over the intervals of 0 to 6 months and 0 to 12 months (P<0.001).[125]

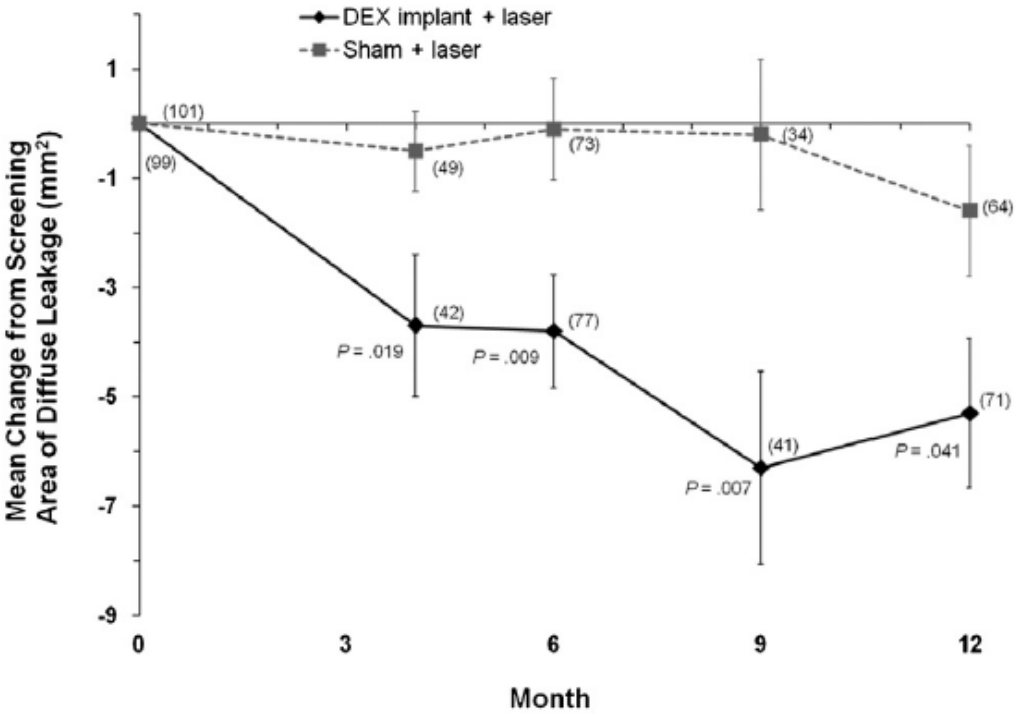
In *post-hoc* subgroup analysis based on analysis windows used in the MTC and economic modelling (see section 6.7), approximately [redacted] of pseudophakic patients achieved an improvement in BCVA from baseline of at least 5 letters in both treatment groups ([redacted]).[162]

<u>Anatomical Outcomes</u>

Statistically significant differences were shown in favour of DEX700 + laser combination therapy over laser monotherapy after 1-4 months of initial treatment and retreatment for the following anatomical measurements assessed as part of the PLACID trial: mean CRT; total macular volume; and average lesion thickness.[125, 126]

In patients with verified diffuse DMO, the decrease in the diffuse leakage area was significantly superior in patients treated with DEX700 in addition to laser therapy than in patients treated with laser alone at all timepoints (Figure 26).[125]

Figure 26: Mean reduction in the area of diffuse leakage from baseline in patients with verified diffuse DMO in placid, mm^2



Key: DEX, dexamethasone; DMO, diabetic macular oedema.
Source: Callanan et al. 2013[125]

HRQL Outcomes

As in the MEAD trial programme, HRQL and visual-functioning were assessed at baseline and throughout the study using the National Eye Institute VFQ-25 tool.

In patients treated with DEX700 + laser therapy, mean scores on several subscales increased during follow-up, reflecting improved vision-related quality of life (data not shown). Improvement in HRQL was not however significantly superior with DEX700 addition to laser therapy compared with laser monotherapy.[126]

Mortality

There were 6 deaths in total during the PLACID study period; 2 in the DEX700 + laser treatment group and 4 in the laser monotherapy group.[126]

None of the deaths were due to ocular adverse events or considered by investigators to be related to treatment assignment.[126]

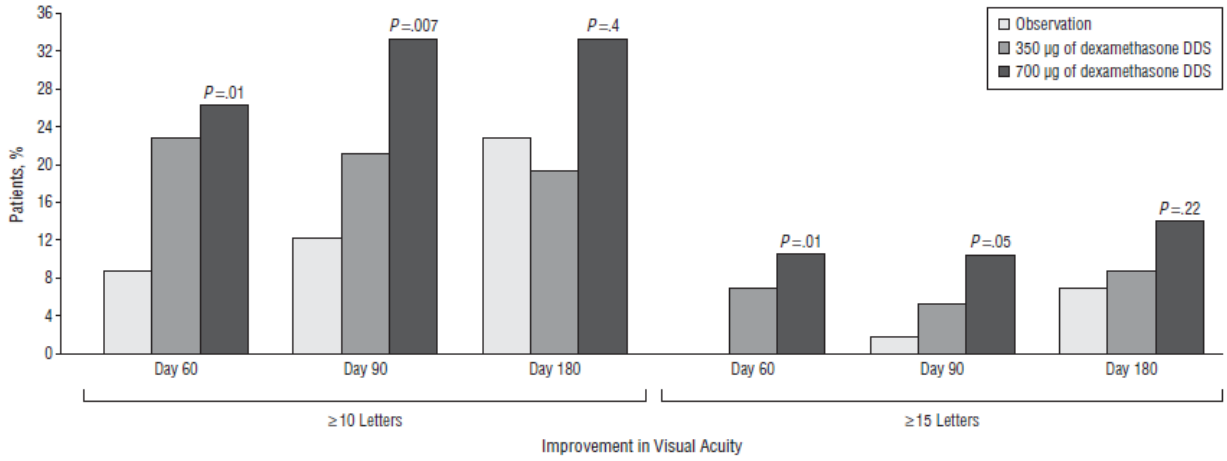
NCT00035906

BCVA Outcomes

In ITT analysis of the primary efficacy outcome, proportion of DMO patients achieving at least a 10-letter improvement in visual acuity, DEX700 demonstrated statistically significant superiority at the 95% level at days 60 and 90 over observation. This superiority persisted through day 180 but was no longer statistically significant at this timepoint (Figure 27).[5]

This trend was also observed in ITT analysis of the secondary efficacy outcome of patients achieving at least a 15-letter improvement in visual acuity (Figure 27).[5]

Figure 27: DMO patients achieving a BCVA improvement of at least 10 letters from baseline at all timepoints in NCT0035906, n (%)



Key: BCVA, best corrected visual acuity
Source: Haller et al. 2010[5]

Anatomical Outcomes

There was a statistically significant improvement in both central retinal thickness and fluorescein leakage in DMO eyes treated with DEX700 compared with eyes in the observation group.[5]

At Day 90, there was a mean decrease from baseline CRT of 132.3µm in the DEX700 treatment group (n=11) and an increase of 30.2µm in the observation group (n=19) (observed data; p<0.001). Unfortunately, Day 180 data for this outcome is not reported.[5]

Mortality

There were three deaths in total in the DMO subgroup of patients enrolled in trial NCT00035906; two in the DEX700 group and one in the DEX350 group. No further details are given on these deaths.[5]

BEVORDEX

BCVA Outcomes

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]

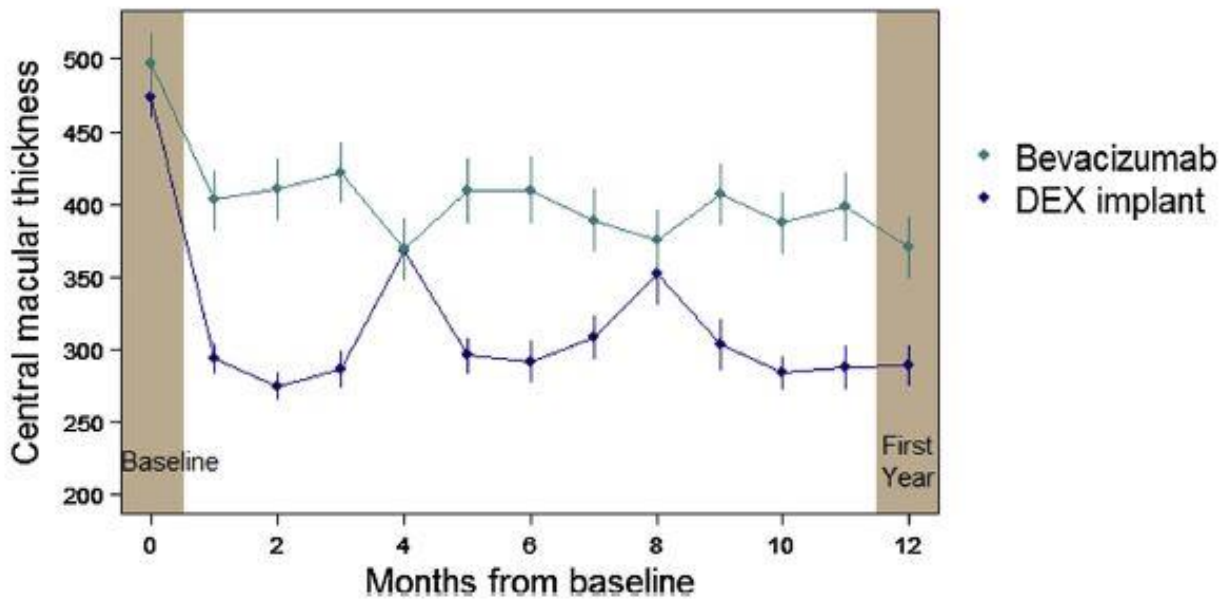
The mean improvement in BCVA in ITT analysis at 12 months was 8.9 letters (95% CI, 6.27-11.6) for eyes treated with bevacizumab and 5.6 letters (95% CI, 0.90-10.4) for eyes treated with DEX700. This difference did not reach statistical significance at the 95% level, p=0.24. Median gain in BCVA was 6.5 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]

Anatomical Outcomes

At 12 months, mean CRT in the ITT population was significantly lower in eyes treated with DEX700 compared with eyes treated with bevacizumab: 285.0µm versus 380.6µm; p=0.007.[128] This translates to a significant difference in the change observed in CRT from baseline in the two treatment groups with a mean change of -122µm for the bevacizumab group and -187µm for the DEX700 group; p=0.015 (Figure 28).[127]

Figure 28: Mean central macular thickness for each month of follow-up in BEVORDEX, µm



Source: Gillies et al. 2014b[127]

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]

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
    - Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Not applicable.

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Results of individual studies are presented in section 6.5 with the quality assessment of each RCT detailed in section 6.4.3.

Given the different dosing regimens adopted for DEX700 treatment across studies and varying primary efficacy timepoints, pooling of clinical efficacy outcomes in the form of a meta-analysis is not considered appropriate.

Indirect comparative efficacy analyses that allow varying DEX700 treatment regimens to retain independence are presented in section 6.7.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Not applicable.

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

The search strategy used to identify RCT evidence of relevant comparators is described in section 6.1.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

The identification and selection of trials meeting the eligibility criteria of the systematic review is described in section 6.2.

Prior to indirect comparison analyses, additional eligibility criteria outlined in Table 32 was applied to the 65 studies identified in order to confirm a final set of studies of relevance to the decision problem that could be used to populate the mixed treatment comparison (MTC) network. These additional eligibility criteria were applied to allow the network to be focused on the comparator set i.e. to remove

studies only providing noise to the network and to identify studies that reported data to be used in the MTC analysis. 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 (see section 7).

Table 32: Additional eligibility criteria applied to RCT systematic search results to identify the evidence base for MTC

Inclusion criteria	Exclusion criteria
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) • 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 • Placebo • Sham treatment • No treatment Outcomes (one or more of the following) • Proportion of patients achieving at least a 10 letter gain from baseline at 12 months • Proportion of patients achieving at least a 10 letter loss from baseline at 12 months	Comparators • Other active therapy
Key: BCVA, best corrected visual acuity; CRT, central retinal thickness; 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.	

In addition to MEAD-010, MEAD-011, study 024, PLACID and BEVORDEX, six trials met this eligibility criteria. These trials provided clinical evidence for all relevant comparators with the exception of the fluocinolone acetonide implant. The pivotal RCT providing evidence for this intervention did not meet the eligibility criteria for inclusion in the MTC as it did not report 10-letter analysis. Given that there is no direct evidence available for the comparative efficacy of DEX700 vs. the fluocinolone acetonide implant, indirect comparison of these interventions is essential. Therefore 15-letter analysis was used to estimate the 10-letter data used to populate the MTC in sensitivity analysis.

Key characteristics of the six comparator studies meeting eligibility and the fluocinolone acetonide study used in sensitivity analysis are presented in Table 33.

Table 33: Key characteristics of comparator trials meeting the eligibility criteria for inclusion in MTC analysis and the FAME trial used in sensitivity analysis

Trial number	Design summary	Patient population	Intervention (n)	Comparator (n)	Escape therapy	Primary outcome	Risk of bias
BOLT (Michaelides et al, 2010)[99]	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[118])	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)[163]	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)[164]	RCT	DMO (defined as having two or more disc areas of retinal thickening and involving the centre of the macular) with	Laser PRN (n=82)	No treatment (n=78)	None	BCVA change from baseline at 12 months	Unclear

Trial number	Design summary	Patient population	Intervention (n)	Comparator (n)	Escape therapy	Primary outcome	Risk of bias
		BCVA less than 20/32 and better than 20/200					
PROTOCOL I (DRCRN, 2010)[165]	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 laser (n=188)	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
RESTORE (Mitchell et al. 2011)[100]	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)[104]	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

As was observed within the DEX700 clinical evidence base, one of the main differences observed across the MTC evidence base is the rule on escape therapy applied within the trials. The ranibizumab monotherapy arm in the PROTOCOL I trial and the ETDRS no treatment arm allowed deferred laser as required and thus are viewed as allowing escape laser therapy as was the case in study 024 and BEVORDEX. As well as laser therapy, the FAME study protocol also allowed pharmaceutical therapy to be administered to patients at the investigators discretion. The clinical efficacy associated to such escape therapy cannot be disaggregated from the clinical efficacy associated to the fluocinolone acetonide implant in the reported outcomes.

Both the ETDRS study and the study reported by Olk that investigate laser photocoagulation therapy compared with no treatment were initiated in the 1980s. Since this time, management of DM has significantly improved and given the correlation between DM control and DMO, patients enrolled in these studies are unlikely to be representative of patients in current clinical practice. They are however essential for the connection of the network. In an attempt to reduce this heterogeneity in the ETDRS study, post-hoc analysis of the dataset has been conducted that identified a patient cohort more similar to DMO patients enrolled in more recent trials i.e. DMO patients with central macular thickening and baseline BCVA between 23-73 letters. This subgroup data is therefore used in the MTC analysis.

Baseline characteristics of patients in comparator trials are presented in Table 34. Differences are observed in a number of patient characteristics including duration of DMO and treatment history, both of which may be viewed as potential proxies of disease severity and baseline disease characteristics of BCVA and CRT that have historically been reported to potentially influence treatment effect. In addition, differences are observed in the lens status at baseline. In comparisons of trials investigating the clinical efficacy of corticosteroids, this is an important consideration given the impact of steroid-induced lens opacity progression and primary cataract formation on visual acuity outcomes. A subgroup analysis utilizing pseudophakic subgroup data to populate the MTC where available has therefore also been conducted. Of note, FAME did not report any letter gain/loss data for this subgroup

and therefore sensitivity analyses including this trial could not be conducted with this subgroup but a notably higher proportion of patients enrolled in the FAME trial presented with pseudophakic lens that needs to be considered when interpreting the indirect comparative efficacy estimates of DEX700 vs. the fluocinolone acetonide implant.

Table 34: Baseline patient characteristics of comparator trials meeting the eligibility criteria for inclusion in MTC analysis and the FAME trial used in sensitivity analysis

	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

	ETDRS (n=448)	BOLT (n=80)	FAME (n=560)	Olk (n=160)	PROTOCOL I (n=668)	RESTORE (n=345)	REVEAL (n=396)
Treatment history for DMO in the study eye							
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
Source: Campochiaro et al. 2011[163]; DRCRN, 2010[165]; Hornberger et al. 2006[118]; Michaelides et al. 2010[99]; Mitchell et al. 2011[100]; Ohji et al. 2012[104]; Olk et al. 1986[164]							

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

A summary of the trials used to conduct the MTC is presented in Table 40 and the total population and pseudophakic subgroup networks formed through connection of these trials are presented in Figure 29 and Figure 30.

Treatment arms from multi-arm trials that were not included in the comparator set were not included in the analyses as per the eligibility criteria presented in Table 30. Sham treatment and no treatment arms were assumed to be the same and thus are utilised as a pooled sham/no treatment arm in the final MTC evidence base.

Of note, pseudophakic subgroup data was not reported in some of the trials included in the MTC evidence base. These trials investigated the comparative efficacy of non-corticosteroid therapies and therefore visual acuity outcomes would not be influenced by steroid-induced lens opacity progression and primary cataract formation. Total population data is therefore utilised in the absence of pseudophakic subgroup data as a reasonable representation of the estimated treatment effect in such patients.

Table 35: Summary of the trials used to conduct the network-meta-analyses for the base case total population and pseudophakic subgroup

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

Figure 29: 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

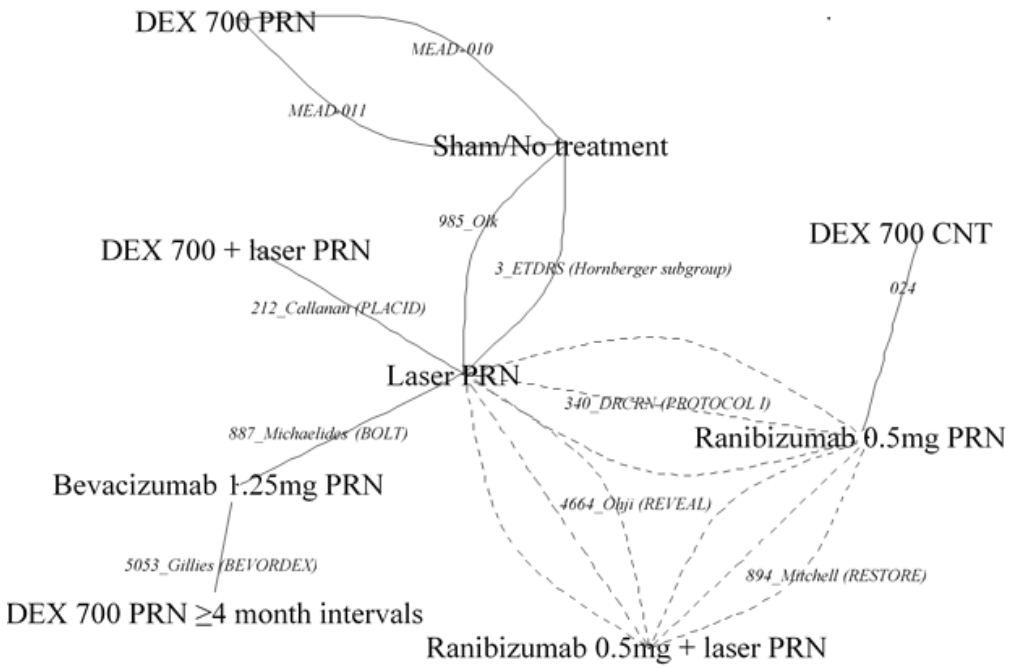
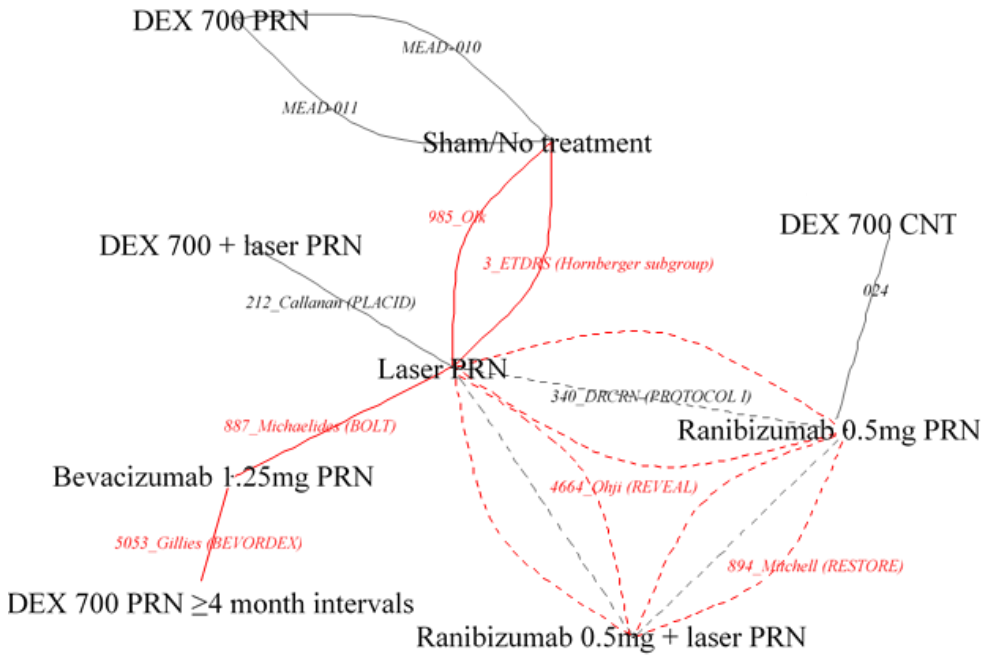


Figure 30: Network of evidence for trials included in the pseudophakic network meta-analysis of worsening of at least 10 letters, worsening/improvement of less than 10 letters and improvement of at least 10 letters at 12 months



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*

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

With the exception of BOLT, all trials included in the MTC evidence base reported data for both improvement and worsening of 10 letters at 12 months. The BOLT trial only reported data for the proportion of patients achieving a 10 letter improvement from baseline at 12 months. The model therefore uses the proportion of patients not achieving a 10 letter improvement from baseline at 12 months as a combined proportion of patients achieving 10 letter worsening from baseline at month 12 and proportion of patients demonstrating a change in vision within a 10-letter range.

A summary of the data used in both the total population and pseudophakic subgroup analysis is presented in Table 36.

Of note, the MEAD, 024 and PLACID data used in the MTC analysis is based on analysis windows adopted in the economic modelling. These are slightly different to those used in ITT analysis presented in section 6.5. In the MEAD trial programme,

BCVA was measured every 1.5 months during the 1st year followed by a 3-month interval during years 2 and 3. Other utility and efficacy measurements including VFQ-25 were measured by the same 3-month interval throughout the study duration. Since the cost-effectiveness analysis involves not only BCVA but also VFQ-UI variables, a consistent 3-month interval was pre-specified for the analysis windows but this results in different window intervals between the CE modelling and CSR analyses for visits during the 1st year. However, the overall conclusion should not be impacted regardless which set of analyses windows is used given the robustness of studies.

Table 36: Data used in MTC analysis

Trial number	Treatment arm	Total population analysis				Pseudophakic subgroup analysis			
		N	10 letter worsening, n	<10 letter change, n	10 letter improvement, n	N	10 letter worsening, n	<10 letter change, n	10 letter improvement, n
MEAD-010	DEX700 PRN	163	17	97	49	44	3	23	18
	Sham/No treatment	165	25	108	32	50	3	37	10
MEAD-011	DEX700 PRN	188	27	106	55	42	4	24	14
	Sham/No treatment	185	25	123	37	51	4	42	5
024	DEX 700 CNT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ranibizumab 0.5mg PRN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLACID	DEX 700 + laser PRN	126	15	76	35	35	5	24	6
	Laser PRN	127	12	85	30	32	2	18	12
BEVORDEX	DEX 700 PRN ≥4 month intervals	46	5	23	18	46	5	23	18
	Bevacizumab 1.25mg PRN	42	0	25	17	42	0	25	17

Trial number	Treatment arm	Total population analysis				Pseudophakic subgroup analysis			
		N	10 letter worsening, n	<10 letter change, n	10 letter improvement, n	N	10 letter worsening, n	<10 letter change, n	10 letter improvement, n
BOLT	Bevacizumab 1.25mg PRN	42	29[a]		13	42	29[a]		13
	Laser PRN	38	35[a]		3	38	35[a]		3
ETDRS	Laser PRN	144	22	94	28	144	22	94	28
	Sham/No treatment	293	75	189	29	293	75	189	29
Olk	Laser PRN	76	3	48	25	76	3	48	25
	Sham/No treatment	73	20	48	5	73	20	48	5
PROTOCOL I	Ranibizumab 0.5mg PRN	188	6	94	88	54	2	36	16
	Ranibizumab 0.5mg + laser PRN	187	6	86	95	56	3	29	24
	Laser PRN	293	39	173	81	101	10	61	30
RESTORE	Ranibizumab 0.5mg PRN	115	4	68	43	115	4	68	43
	Ranibizumab 0.5mg + laser PRN	118	5	62	51	118	5	62	51
	Laser PRN	110	14	179	17	110	14	179	17

Trial number	Treatment arm	Total population analysis				Pseudophakic subgroup analysis			
		N	10 letter worsening, n	<10 letter change, n	10 letter improvement, n	N	10 letter worsening, n	<10 letter change, n	10 letter improvement, n
REVEAL	Ranibizumab 0.5mg PRN	133	4	84	45	133	4	84	45
	Ranibizumab 0.5mg + laser PRN	129	7	74	48	129	7	74	48
	Laser PRN	128	8	103	17	128	8	103	17

Notes: [a] calculated within model

Source: MTC MEAD Final[166]; MTC 024 Final[167]; MTC PLACID Final[162]; Gillies et al. 2014b[127]; Hornberger et al. 2006[118]; Michaelides et al. 2010[99]; Mitchell et al. 2011[100]; Olk et al. 1986[164]; NCT00989989[120]

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Data were split into a series of three discrete, ordered and mutually exclusive groups: 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 deduced by the total number of patients minus the number of patients losing 10 or more letters and the number of patients gaining 10 or more letters. Of note, this is not a clinically representative definition of stable but simply that used in the MTC modelling.

By the nature of the data, a multinomial likelihood with a probit link function was used to estimate relative treatment effects, which are assumed to be constant regardless of the category of vision. Suppose r_{ikj} represents the number of patients in trial i, arm k and category of vision j, where j=1, 2,… ,J. The responses r_{ikj} belong to a multinomial distribution such that:

$$r_{ikj=1,\ldots,J} \sim \text{Multinomial}(p_{ikj=1,\ldots,J}, n_{ik}), \sum_{j=1}^{J} p_{ikj=1,\ldots,J} = 1,$$

where p_{ikj} is the probability that a patient in arm k of trial i has a response of category j.

The probit link function is the inverse of the normal cumulative distribution which maps the probabilities of being in each category of vision for each trial and treatment arm onto the real line such that:

$$\theta_{ikj} = \Phi^{-1}(p_{ikj}) = \mu_{ij} + \delta_{i,bk} I_{k\neq 1}$$

and

$$p_{ikj} = \Phi(\mu_{ij} + \delta_{i,bk} I_{k\neq 1})$$

The use of a multinomial model yields relative treatment effects which change the probit score of the control arm by $\delta_{i,bk}$ standard deviations where $\delta_{i,bk}$ are the study-specific treatment effects. These are assumed to come from a common population distribution with mean treatment effect relative to sham/no treatment, such that:

$$\delta_{i,1k} \sim N(d_{t_{i1},t_{ik}}, \tau^2)$$

As there were three categories of vision, there were be three cut-offs for each trial. The multinomial model was also able to account for trial data where only one of the categories of vision is reported (BOLT[99]) only reports data for 10 or more letter improvement). For this trial, the number of cut-offs would be two; a combined category of worsening of 10 or more letters and stable and then an improvement of 10 or more letters.

This multinomial relative treatment effect model is detailed further in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[168]

A baseline model was fitted to the sham/no treatment arm of the dataset for the first ordered category of vison (loss of 10 or more letters). This was a dichotomous outcome modelled using a binomial likelihood for the number of patients, r_{ik1} in each trial who had a loss of 10 or more letters when treated with sham/no treatment, such that:

$$r_{ik1} \sim \text{Binomial}(n_{ik}, p_{ik1})$$

A probit link function was used such that:

$$\Phi^{-1}(p_{ik1}) = \mu_i',$$

where Φ^{-1} is the inverse of the normal cumulative distribution

An estimated mean response (and its associated precision) in the sham/no treatment arm could then be combined with the relative treatment effects. By including the baseline effect for the sham/no treatment arm in the treatment effect model, this yielded absolute probabilities of being in each group of vision for each treatment, along with the relative risk (RR) of being in each group of vision for all pairwise treatment comparisons.

Bayesian network meta-analyses were undertaken using random-effects models. A Bayesian approach was used because of its ability to capture the uncertainty in model parameters and to be able to utilise the exact posterior distribution of relative treatments effects directly within the economic model. Random-effects models were fitted as there was no reason to believe à priori that the between-study heterogeneity would be zero.

All models were fitted in the freely available software, WinBUGS (version 14) (MRC Biostatistics Unit, Cambridge, UK), using R (version 3.1.1) as an interface to create relevant output. Parameters of interest (RR, probability of being in each group of vision etc.) were estimated using Markov Chain Monte Carlo (MCMC) methods. The initial 50,000 iterations were discarded as the 'burn-in' period, which was assessed by running two chains and checking convergence using the Brooks-Gelman-Rubin statistic. 10,000 samples were retained for the economic model. This was deemed an appropriate sample size by considering the Monte Carlo (MC) error, which was less than 5% of the standard deviation for each parameter in the model.[169] In this case, there was little to be gained by including more iterations in the sample. 10,000 was statistically a sufficient sample size but was also a feasible number to be incorporated into the economic model. Utilizing the CODA samples directly in the economic model preserved the correlation between treatment effects and avoiding the need to make assumptions about the shape of the posterior distribution.

Autocorrelation for each parameter was assessed and a thinning interval of 100 was applied to ensure the chain was mixing well and was representative of the posterior distribution. The goodness-of-fit of the model was assessed using the total residual deviance. Prior distributions were assigned to parameters which were non-informative so that the posterior distribution was primarily driven by the data. Prior distributions used were in-line with those given in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[168] Both the baseline and treatment effect model code (WinBUGS) is presented in Appendix 22.

6.7.6 Please present the results of the analysis.

From the baseline model fitted to the sham/no treatment arms only, the mean probability of losing at least 10 or more letters for sham/no treatment is [redacted] These values are used in the relative treatment effect model to estimate absolute probabilities of being in each category of vision.

Any relative risks 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 vs. reference treatment. For the outcome of losing at least 10 letters, a favourable point estimate is that which lies to the left of the dashed line (RR=1). For the outcome of gaining at least 10 letters, a favourable point estimate is that which

lies to the right of the dashed line (RR=1). Any 95% credible intervals which do not cross the dashed line (RR=1) indicates a statistically significant difference between any pair of treatments.

Considering Figure 31, all treatments have a RR of less than 1 vs. sham/no treatment for losing at least 10 letters, however, only six out of nine treatments (bevacizumab 1.25mg PRN, DEX 700 plus laser PRN, DEX 700 PRN ≥ 4 month intervals, laser PRN, ranibizumab 0.5mg + laser PRN and ranibizumab 0.5mg PRN) have a significantly reduced risk vs. sham/no treatment. Bevacizumab 1.25mg PRN and DEX 700 PRN ≥ 4 month intervals have the lowest point estimates [redacted] However, whilst statistically significant, there is much uncertainty around both of these values. This may be most likely attributed to the positioning of these treatments in the network (Figure 29), along with the nature of the data for the trials comparing bevacizumab 1.25mg PRN. The BOLT trial does not report data for worsening of 10 or more letters and the BEVORDEX trial report zero patients with a worsening of 10 or more letters for the bevacizumab 1.25mg arm. As a result, there is a great deal of uncertainty for many treatment comparisons with both bevacizumab 1.25mg PRN and DEX 700 PRN ≥ 4 month intervals (the latter treatment is only connected in the network though bevacizumab 1.25mg PRN). Where the uncertainty with this treatment comparisons is slightly smaller (e.g. ranibizumab 1.5mg PRN vs. bevacizumab 1.25mg PRN), this is due to both treatments having a low proportion of patients losing at least 10 letters. However, for DEX 700 CNT there is a higher proportion of patients losing at least 10 letters and so the relative risk of DEX 700 CNT vs. bevacizumab 1.25mg PRN may be extremely high (reflected in the 95% CrI) where extremely low probabilities are sampled for bevacizumab 1.25mg PRN (i.e. a denominator of almost zero will yield very large RRs).

Figure 32 shows the relative risks of gaining 10 or more letters. All interventions having ratios greater than 1 vs. sham/no treatment, indicating that all treatments show a trend of having a greater probability of gaining at least 10 letters compared with sham/no treatment. The same six treatments show a statistically significant relative risk as for losing at least 10 letters.

Figure 33 shows the absolute probabilities of being in each category of vision. Sham/no treatment has the greatest probability of all treatments at remaining stable

(0.65) and losing at least 10 or more letters (0.20). DEX 700 plus laser PRN, DEX 700 CNT, DEX 700 and laser PRN also have high probabilities of remaining stable (0.60, 0.63, 0.65 and 0.60 respectively). All interventions (excluding sham/no treatment) have less than 0.15 probability of losing 10 or more letters.

Figure 34 shows the probabilities of each treatment attaining each possible rank (1-9). These rankograms provide an indication of how each treatment ranks. DEX 700 - plus laser PRN, DEX 700 CNT and DEX 700 PRN show the highest probabilities of being ranked as the [redacted] best treatments (prob=0.45, 0.48 and 0.65 respectively).

[redacted]**All pairwise treatment comparisons of losing at least 10 letters at 12 months for base case total population**

[redacted]

[redacted] **All pairwise treatment comparisons of gaining at least 10 letters at 12 months for base case total population**

[redacted]

[redacted] **Absolute probabilities of being in each category of vision for all interventions in the base case total population analysis**

[redacted]

[redacted] **Ranking probabilities for all interventions in the base case total population analysis**

[redacted]

From the baseline model fitted to the sham/no treatment arms only for the pseudophakic subgroup, the mean probability of losing at least 10 or more letters for sham/no treatment is [redacted]. These values are used in the relative treatment effect model to estimate absolute probabilities of being in each category of vision.

In pseudophakic subgroup analysis, considering Figure 35, all treatments have a RR of less than 1 vs. sham/no treatment for losing at least 10 letters but only five out of nine treatments (bevacizumab 1.25mg PRN, DEX 700 PRN ≥ 4 month intervals, laser PRN, ranibizumab 0.5mg + laser PRN and ranibizumab 0.5mg PRN) have a significantly reduced risk vs. sham/no treatment. Bevacizumab 1.25mg PRN and DEX 700 PRN ≥ 4 month intervals have the lowest point estimates_[redacted]However, whilst statistically significant, there is much uncertainty around both of these values. This may be most likely attributed to the positioning of these treatments in the network (Figure 30), along with the nature of the data for the trials comparing bevacizumab 1.25mg PRN. The 887_Michaelides (BOLT) trial does not report data for worsening of 10 or more letters and the 5053_Gillies (BEVORDEX) trial report zero patients with a worsening of 10 or more letters for the bevacizumab 1.25mg arm. As a result, there is a great deal of uncertainty for many treatment comparisons with both bevacizumab 1.25mg PRN and DEX 700 PRN ≥ 4 month intervals (the latter treatment is only connected in the network though bevacizumab 1.25mg PRN). Where the uncertainty with this treatment comparisons is slightly smaller (e.g. ranibizumab 1.5mg PRN vs. bevacizumab 1.25mg PRN), this is due to both treatments having a low proportion of patients losing at least 10 letters. However, for DEX 700 CNT there is a higher proportion of patients losing at least 10 letters and so the relative risk of DEX 700 CNT vs. bevacizumab 1.25mg PRN may be extremely high (reflected in the 95% CrI) where extremely low probabilities are sampled for bevacizumab 1.25mg PRN (i.e. a denominator of almost zero will yield very large RRs).

Figure 36 shows the relative risks of gaining 10 or more letters. All interventions having ratios greater than 1 vs. sham/no treatment, indicating that all treatments show a trend of having a greater probability of gaining at least 10 letters compared with sham/no treatment. The same five treatments show a statistically significant relative risk as for losing at least 10 letters.

Figure 37 shows the absolute probabilities of being in each category of vision. Sham/no treatment has the greatest probability of all treatments at remaining stable [redacted] and losing at least 10 or more letters [redacted]DEX 700 plus laser PRN, DEX 700 CNT, DEX 700 and laser PRN also have high probabilities of remaining stable [redacted] respectively). All interventions (excluding sham/no treatment) have less than 0.15 probability of losing 10 or more letters.

Figure 38 shows the probabilities of each treatment attaining each possible rank (1-9). These rankograms provide an indication of how each treatment ranks. DEX 700 - plus laser PRN, DEX 700 CNT and DEX 700 PRN show high probabilities of being ranked as the [redacted]best treatments (prob=0.43, 0.31 and 0.44 respectively).

[redacted] **All pairwise treatment comparisons of losing at least 10 letters at 12 months for pseudophakic population (where applicable)**

[redacted]

[redacted]**All pairwise treatment comparisons of gaining at least 10 letters at 12 months for pseudophakic population (where applicable)**

[redacted]

[redacted] **Absolute probabilities of being in each category of vision for all interventions in the pseudophakic population (where applicable)**

[redacted]

[redacted] **Ranking probabilities for all interventions in the pseudophakic population (where applicable)**

[redacted]

The base case analysis of the total population and the pseudophakic subgroup yield similar results. For both analyses, all treatments' relative risks vs. sham/no treatment are all less than 1 for losing 10 or more letters and greater than 1 for gaining 10 or more letters.

However, the most noticeable difference is the relative risk of DEX 700 plus laser PRN losing 10 or more letters vs. sham/no treatment has increased from [redacted] for the total population to [redacted] for the pseudophakic subgroup and no longer has a statistically significant reduced risk of losing 10 or more letters vs. sham/no treatment.

The relative risks of DEX 700 CNT and DEX 700 PRN losing 10 or more letters vs. sham/no treatment are much lower for the pseudophakic subgroup [redacted] RR=0.47 respectively) than for the total population [redacted] RR=0.71 respectively), albeit remaining non-statistically significant results as the 95% credible intervals still include a relative risk of 1 and there is more uncertainty in these results due to a reduced sample size when looking at the pseudophakic subgroup of patients in trials which administer these two treatments.

When considering the outcome of gaining 10 or more letters, the relative risk is lower for the pseudophakic subgroup [redacted] than the total population [redacted] when comparing DEX 700 plus laser PRN vs. sham/no treatment and these relative risks are no longer showing a statistically significant result.

The relative risks of DEX 700 CNT and DEX 700 PRN gaining 10 or more letters vs. sham/no treatment are higher for the pseudophakic subgroup [redacted] RR=1.79 respectively) than for the total population [redacted] 1.40 respectively) but as for losing 10 or more letters, whilst showing a more favourable relative risk vs. sham/no treatment, they remain non-significant and there is more uncertainty in the results due to the reduced sample size. The pairwise relative risks are mostly quite similar between the total population and pseudophakic subgroup.

Both DEX 700 CNT and DEX 700 PRN have lower probabilities of losing 10 or more letters for the pseudophakic subgroup analysis [redacted] compared to the total population [redacted] and both treatments also have a greater probability of gaining 10 or more letters for the subgroup analysis [redacted] compared to the total population [redacted] DEX 700 plus laser PRN has a higher probability of losing 10 or more letters and a lower probability of gaining 10 or more letters in the pseudophakic subgroup [redacted] compared to the total population [redacted]

These differences affect the treatment rankings; DEX 700 plus laser PRN is much more likely to be ranked among the worst treatments for the pseudophakic subgroup, whilst DEX 700 CNT and DEX 700 PRN have increased probabilities of being amongst the top 6 treatments.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

The statistical measure of the between-study heterogeneity for each the base case and sensitivity analyses are given in Table 37. All models fitted to the total population result in mild to moderate heterogeneity present between the trials. The 95% credible intervals are quite wide suggesting some uncertainty around the true amount of heterogeneity.

The mean total residual deviance may be compared to the number of unique data points included within each of the models. For both models, the number of data points is lower than the corresponding total residual deviance. For the pseudophakic subgroup analysis, the number of data points is not significantly lower than the estimated total residual deviance using the critical value from the Chi-squared distribution.

Table 37: Between-study heterogeneity and model fit for base case total population and pseudophakic subgroup

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

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

There were two sensitivity analyses carried out and detailed as following:

SA1. Total population data with the inclusion of the FAME trial. Based on the proportion of patients achieving a 15 letter improvement from baseline at month 12 (digitised), data were estimated for 10 letter improvement and this was included in the network meta-analysis. To estimate this data, a relationship was established for

all trials reporting both ≥10 letter and ≥15 letter gain from baseline. The average (mean) multiplication factor was 1.989. Subsequently, the proportion of patients achieving a 10 letter improvement from baseline at month 12 was estimated using this factor multiplied by the reported 15 letter improvement data.

SA2. The second sensitivity analysis carried out was for a dichotomous outcome: gaining 15 or more letters at 12 months. Again, a random-effects model was fitted to the data, this time using a binomial likelihood with a logit link function. This analysis was included to see whether using the observed data for FAME instead of the estimated proportion of patients achieving a 10 letter improvement from baseline at month 12 data affected the results and yielded different conclusions or order of the treatment rankings. All but one of the trials[164] included within the base case analysis also reported the proportion of patients achieving a 15 letter improvement from baseline at month 12.

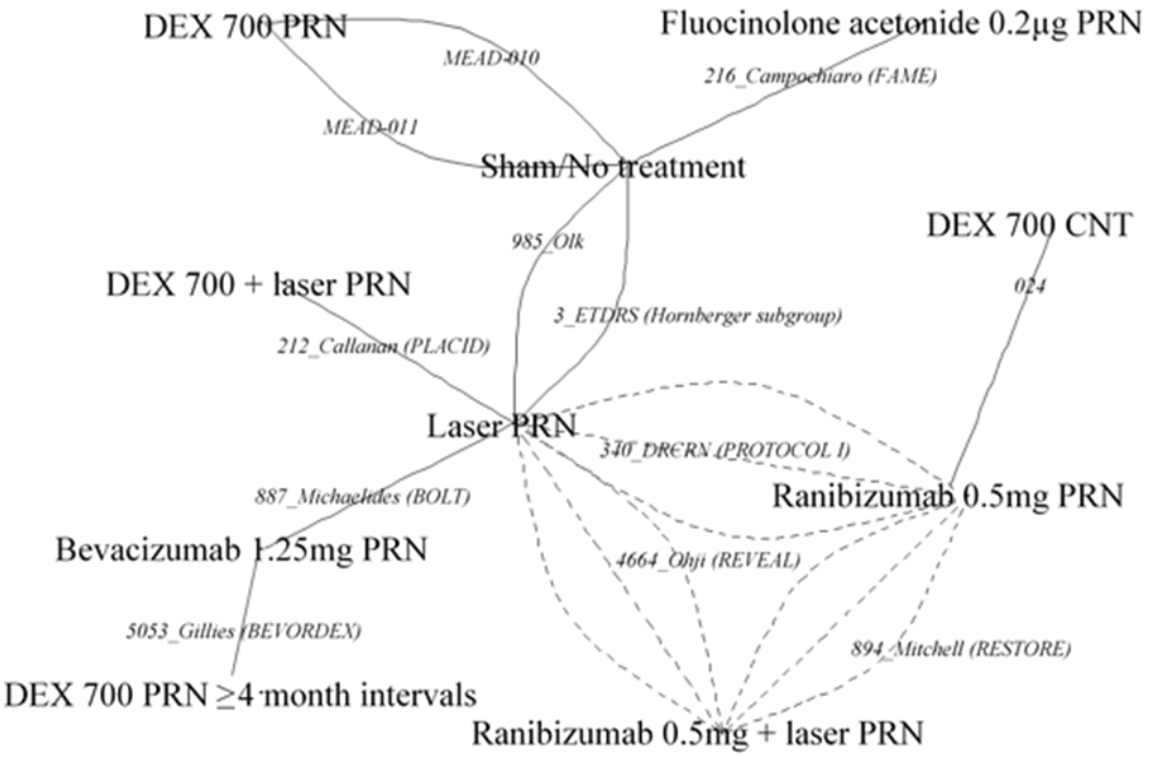
Results for both sensitivity analyses are presented in this subsection. The data used in SA1 is identical to that in the total population base case (presented in Table 36). The data for the additional trial is shown in Table 38 and a network diagram is presented in Figure 39.

Table 38: Additional data included in the network meta-analysis for total population analysis including FAME

Treatment arm	N	10 letter worsening, n	<10 letter change, n	10 letter improvement, n
Fluocinolone acetonide 0.2µg PRN	376	215[a]		161[b]
Sham/No treatment	185	139[a]		46[b]

Note: [a] calculated within model; [b] estimated from 15-letter data
Source: Campochiaro et al. 2011[163]

Figure 39: Network diagram for total population analysis including FAME



The results for all interventions included in the base case analysis remain largely unchanged when including FAME trial data. All relative risks and 95% credible intervals are very similar when comparing the two sets of forest plots (Figure 40 and Figure 41).

The RR of losing 10 or more letters for fluocinolone acetonide 0.2µg PRN vs. sham/no treatment is [redacted] with a statistically significant 95% credible interval [redacted] The RR for fluocinolone acetonide 0.2µg PRN vs. DEX 700 PRN is also lower than 1 [redacted] but the 95% credible interval includes 1 [redacted] This means that treatment with fluocinolone acetonide 0.2µg PRN has a lower risk associated with losing 10 or more letters, however this is a non-significant result vs. DEX 700 PRN.

The RR of gaining 10 or more letters is higher than 1 for fluocinolone acetonide 0.2µg PRN vs. sham/no treatment and this is also a statistically significant result [redacted] meaning there is a greater probability of fluocinolone acetonide 0.2µg PRN gaining 10 or more letters than sham/no treatment.

The RR of gaining 10 or more letters is also higher than 1 for fluocinolone acetonide 0.2µg PRN vs. DEX 700 PRN, however this is a non-statistically significant result, [redacted]

[redacted]All pairwise treatment comparisons of losing at least 10 letters at 12 months for total population sensitivity analysis 1 including 216_Campochiaro (FAME) trial

[redacted]

[redacted] **All pairwise treatment comparisons of gaining at least 10 letters at 12 months for total population analysis including FAME**

[redacted]

[redacted] **Absolute probabilities of being in each category of vision for all interventions in the total population analysis including FAME**

[redacted]

[redacted]**Ranking probabilities for all interventions in the total population sensitivity analysis 1 including 216_Campochiaro (FAME) trial**

[redacted]

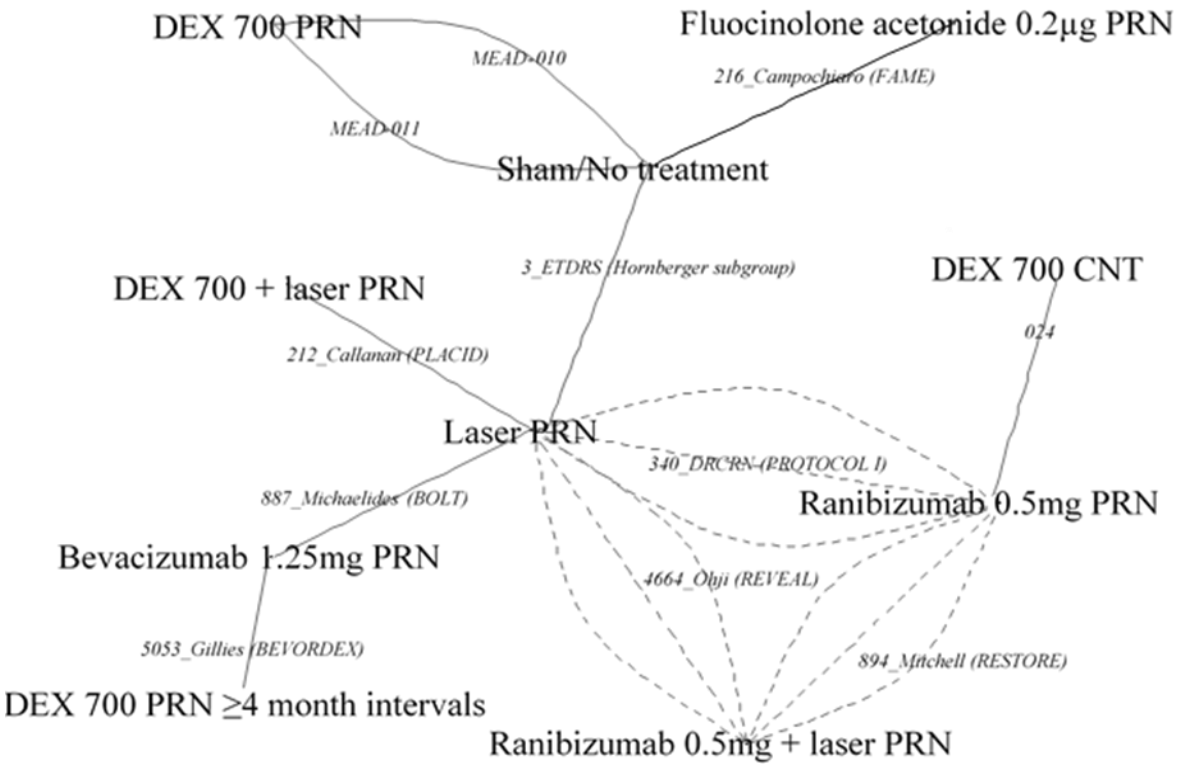
Data used to populate the second sensitivity analysis is presented in Table 39 with the associated network diagram presented in Figure 44.

Table 39: Data used in sensitivity analysis based on proportion of patients achieving at least a 15-letter improvement in BCVA from baseline at 12 months

Trial number	Treatment arm	N	15 letter improvement, n
MEAD-010	DEX700 PRN	163	22
	Sham/No treatment	165	16
MEAD-011	DEX700 PRN	188	23
	Sham/No treatment	185	19
024	DEX 700 CNT	[redacted]	[redacted]
	Ranibizumab 0.5mg PRN	[redacted]	[redacted]
PLACID	DEX 700 + laser PRN	126	21
	Laser PRN	127	14
BEVORDEX	DEX 700 PRN ≥4 month intervals	46	10
	Bevacizumab 1.25mg PRN	42	13
BOLT	Bevacizumab 1.25mg PRN	42	5
	Laser PRN	38	2
ETDRS	Laser PRN	144	12
	Sham/No treatment	293	8
FAME	Fluocinolone acetonide 0.2µg	376	81
	Sham/No treatment	185	23
PROTOCOL I	Ranibizumab 0.5mg PRN	188	52
	Ranibizumab 0.5mg + laser PRN	187	57
	Laser PRN	293	43
RESTORE	Ranibizumab 0.5mg PRN	115	26
	Ranibizumab 0.5mg + laser PRN	118	27
	Laser PRN	110	9

Trial number	Treatment arm	N	15 letter improvement, n
REVEAL	Ranibizumab 0.5mg PRN	133	25
	Ranibizumab 0.5mg + laser PRN	129	23
	Laser PRN	128	10

Figure 44: Network diagram for sensitivity analysis of proportion of patients achieving at least a 15-letter improvement in BCVA from baseline at 12 months



Whilst on a different scale, the ordering of the relative treatment effects vs. sham/no treatment remain almost identical in this sensitivity analysis [redacted] bevacizumab 1.25mg PRN has the greatest odds ratio (OR) of gaining 15 or more letters. DEX 700 PRN ≥4 month intervals and fluocinolone acetonide 0.2µg PRN have statistically significantly higher probabilities for gaining 15 or more letters vs. sham/no treatment [redacted] but non-statistically significantly higher odds of gaining 15 or more letters vs. sham/no treatment [redacted]

The rankogram for this dichotomous outcome (Figure 46) shows that whilst bevacizumab 1.25mg PRN remains the treatment with the highest probability of being the best treatment, this is not as high as before. DEX 700 plus laser, DEX 700 CNT and DEX 700 PRN all have slightly higher probabilities of being ranked amongst the top 5 treatments.

[redacted] **All pairwise treatment comparisons of gaining at least 15 letters at 12 months for total population analysis**

[redacted]

[redacted] Ranking probabilities for all interventions for gaining 15 or more letters at 12 months in total population analysis

[redacted]

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Consistency could not formally be checked as there were no feedback loops within the network and three-arm trials cannot be inconsistent.

A pairwise meta-analysis synthesising data from MEAD-010 and MEAD-011 was completed to estimate the direct estimate of DEX 700 PRN vs. sham/no treatment. This was then qualitatively compared with the estimated relative effect from the network meta-analysis. The direct RR from the pairwise meta-analysis of losing 10 or more letters was [redacted] Referring back to Figure 31, the network meta-analysis estimate was 0.71 (95% CrI [0.41, 1.08]). The direct RR from the pairwise meta-analysis is [redacted] Referring back to Figure 32, the network meta-analysis estimate is 1.40 (95% CrI [0.92, 2.14]). Whilst the point estimates are similar for the RR of losing 10 or more letters, the uncertainty around the estimated relative risk from the direct pairwise analysis is much larger. This is due to only two trials being included in the pairwise meta-analysis and the same non-

informative priors were used as in the network meta-analysis, resulting in much more uncertainty in the pairwise analyses. The RR of gaining 10 or more letters from the direct pairwise meta-analysis [redacted] is quite different to that from the network meta-analysis (1.40). This is likely due to a varying response in the sham/no treatment arms from each trial as the proportion gaining 10 or more letters ranged from 0.07 to 0.20 across the four trials which included a sham/no treatment arm. This varying response in the sham/no treatment arm support the qualitative suggestion that there are some differences between trials in terms of characteristics of patients and the positive response to sham treatment observed in the MEAD programme is clear: in alternative trials that administered no treatment to the control group, 25.6% and 27.4% of patients experienced worsening in visual acuity of at least 10 letters from baseline at month 12[118, 164] compared with only 15.2% and 13.5% of patients in MEAD-010 and MEAD-011.[166] These differences between trials and the reduced relative effect of DEX 700 PRN due to the unusually high sham result observed in MEAD likely contribute to the fact that outcomes from direct comparative efficacy analyses are not reflected in the [redacted] analyses in regard to [redacted] superiority of DEX700 vs. sham treatment.

Baseline BCVA has previously been shown to impact treatment effect with worse visual acuity at the time of treatment associated with an increased degree of improvement, attributed at least partially to “ceiling effects” on the degree of improvement possible for those with better visual acuity at the time of treatment.[89] Consideration was therefore given to the possible adjustment for baseline BCVA; however, there were no clear trends in the data set to suggest this was significantly impacting outcomes and the average baseline BCVA across trial populations were within the same health state (Figure 47) as per economic model definitions so no clear benefit of such an analysis could be foreseen.

[redacted] **Probability of losing or gaining 10 letters based on baseline BCVA**

[redacted]

Of note, the study reported by Olk et al. is not included in this analysis as mean baseline BCVA data was not reported. However, approximately 60% of patients enrolled in this trial had good visual acuity at baseline (≥20/63).[164] Reflective of the RCO guidelines[87] recommending such therapy when DMO is associated with mild vision loss, laser was shown to stabilise vision in the majority of patients in this trial with only 4% of laser treated patients presenting demonstrating a worsening of at least 10-letters from baseline.[164] Furthermore, 33% of laser treated patients achieved an improvement of at least 10-letters from baseline.[164] In clinical practice, of the DMO patients with visual impairment eligible for DEX700, a lesser proportion may be expected to demonstrate such a positive response.

Both the study reported by Olk et al.[164] and the ETDRS[88] study were initiated in the 1980s when DM management was not as advanced as current day. Subsequently, there are potential differences in the natural history of patients enrolled in these trials compared with those enrolled in the more recent clinical trials of pharmaceutical therapies, whose DM is likely to be better controlled. This is an unavoidable limitation of the network analysis, reflective of the evidence base available to connect DEX700 PRN to active comparator arms of interest to the decision problem.

Differences across the trials need to be considered when interpreting these analyses. This is particularly important in the case of the indirect comparative efficacy analysis of DEX700 vs. the fluocinolone acetonide implant as analyses of study characteristics shows a trend towards a higher proportion of patients gaining at least 10 letters from baseline when rescue therapy is allowed (Figure 48), as we may expect *a priori*. Furthermore, this comparison could only be made using total population data and a higher proportion of patients enrolled in the FAME trial compared to the MEAD trials presented with pseudophakic lens; a population in whom steroid-induced lens opacification progression and primary cataract formation does not impact visual acuity.

It should also be noted that the 12 month time point at which this indirect comparative efficacy analyses is conducted does not adequately capture the peak treatment effect of DEX700 therapy. In addition, the analyses are conducted using clinical trial data where the average anti-VEGF injection frequency is close to monthly within the 12 month analysis period. In clinical practice, capacity constraints and patient burden (often leading to missed appointments) result in a lesser injection

frequency of anti-VEGF agents. Given the correlation between anti-VEGF injection frequency and BCVA improvement, trial data may overestimate the benefit associated with anti-VEGF agents in clinical practice.

[redacted] Influence of rescue therapy on probability of patients gaining at least 10 letters in BCVA from baseline at 12 months

[redacted]

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

A systematic literature review designed to identify the clinical evidence base of non-RCTs able to assist in answering the decision problem was conducted in July 2014.

Information retrieval methods were based upon the research question “what is the clinical efficacy and safety/tolerability of DEX700 for the treatment of DMO in patients with DM?”

Searches were performed in global electronic databases: Medline & Medline In-Process and other non-indexed citations; Embase; Cochrane database of systematic reviews (CDSR); Cochrane register of clinical trials (CENTRAL); Health Technology Assessment Database (HTA); Database of Abstracts of Review and Effects (DARE); and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

In addition, 2013-2014 annual conference proceedings of the American Academy of Ophthalmology (AAO), the Association of Research in Vision and Ophthalmology (ARVO), the European Association for Vision and Eye Research (EVER), Controversies in Ophthalmology (COPHY) and the European Society of Retina Specialists (EURETINA) were searched in order to identify any relevant, on-going research.

Full eligibility criteria applied to the systematic search results identifying the clinical evidence base of non-randomised controlled trials are outlined in Table 40.

The primary difference to the systematic review identifying the clinical evidence base of RCTs aside from the study design is that the non-RCT systematic review was designed to exclusively identify the non-RCT evidence base for DEX700. As non-RCT data cannot be utilised in indirect comparative efficacy evidence, these were not identified for comparator therapies.

Two levels of study screening were performed through use of the inclusion and exclusion criteria. Both levels of screening were conducted by two reviewers who independently inspected each reference. Level 1 screening applied basic inclusion criteria (population, intervention, study design) to abstracts of each identified reference. All possibly relevant references accepted at the abstract level were retrieved in full text. Any discrepancies with regard to inclusion or exclusion of an article were resolved by a third reviewer. Articles were included if they satisfied all inclusion and none of the exclusion criteria.

Where multiple publications were identified for the same clinical trial; those reporting additional data that met the eligibility criteria of the review were included in the final list of included articles as secondary publications (kin papers). Papers reporting subgroup analyses of patient groups of relevance to the licence terms or HTA restricted use terms for each intervention were included along with papers reporting *post-hoc* analyses based on treatment exposure as both were deemed of relevance to the decision problem.

Table 40: Eligibility criteria applied to systematic search results identifying the clinical evidence base of non-RCTs

Inclusion criteria	Exclusion criteria
Population • Adult • Unilateral or bilateral DMO associated to DM • Pre-treated or treatment-naïve Intervention • Intravitreal dexamethasone 700ug • 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 • Prospective non-RCTs • Single arm trials • Observational studies Study duration • ≥6 months (24 weeks)	Population • Paediatric • Diabetic retinopathy patients without associated DMO • Macular oedema not associated to DM • DMO subgroup of <5 patients Interventions • Laser photocoagulation • Anti-VEGF therapy • Non-dexamethasone corticosteroids • Local corticosteroids Outcomes • Non-vision or anatomical related efficacy measures Study design • Randomised controlled trials • Case reports • Case series with <5 patients Study duration • <6 months (24 weeks)
Key: BCVA, best corrected visual acuity; CRT, central retinal thickness; 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.	

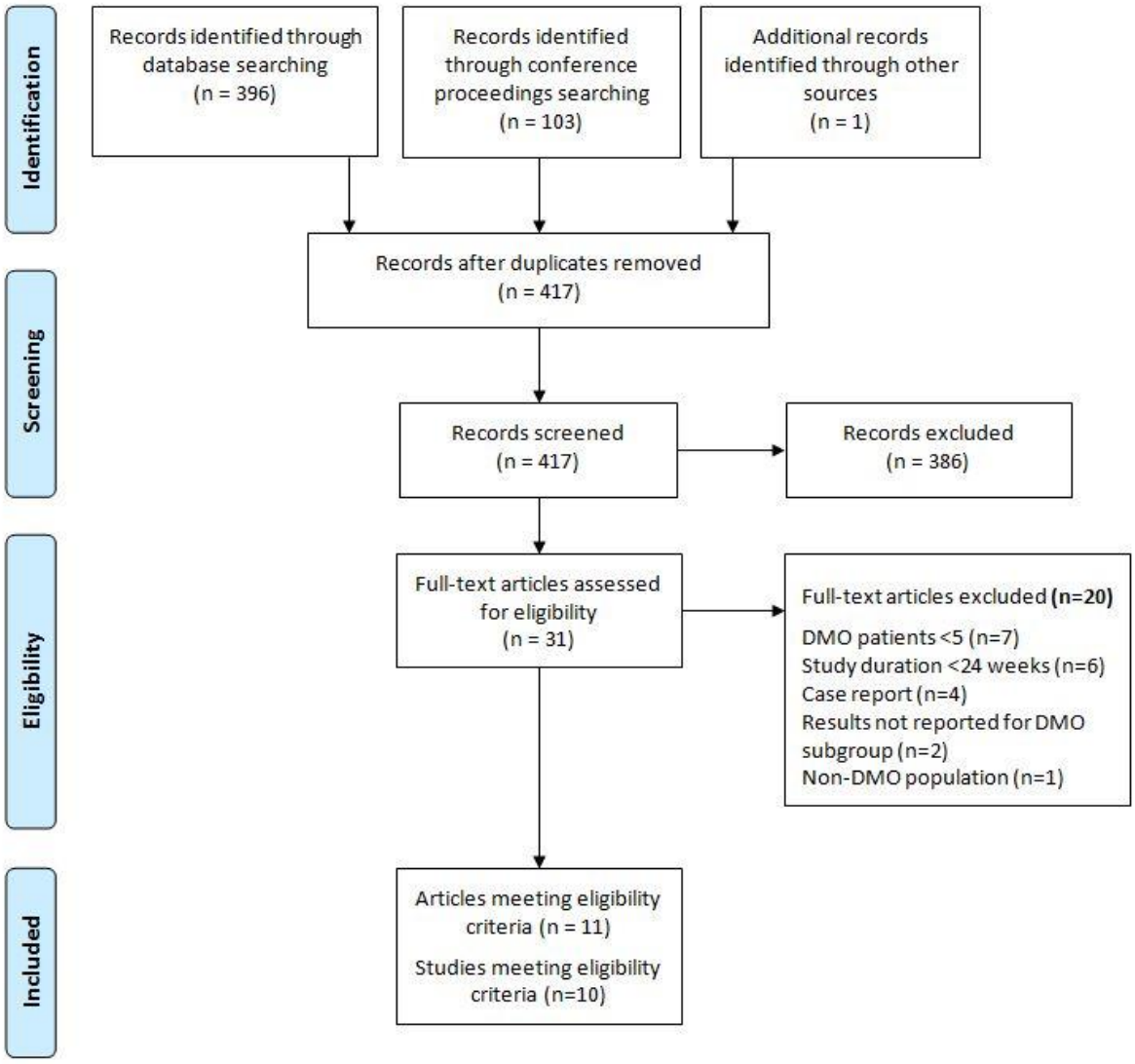
A flow diagram of the systematic review process is presented as a PRISMA diagram in Figure 49.

Searches of electronic databases identified a total of 396 potentially relevant citations with some overlap between databases. After removal of duplicates, 313 potentially relevant citations remained. These were combined with 103 potentially relevant citations identified through conference proceeding searches and an

additional citation (abstract presented at conference, 2010) accessed from in house archives.[170]

During abstract screening, 385 citations were excluded as they were clearly not of relevance to the research question. Examples of reasons include non-DMO patient populations, studies of interventions other than DEX700 or papers not reporting clinical trial/study results. A total of 31 citations were accessed in full (where applicable and necessary) for further evaluation. Of these citations, 10 were original publications of trials meeting the eligibility criteria of the review and one was a secondary publication, reporting additional information meeting the eligibility criteria of the review.

Figure 49: PRISMA flow diagram of the non-RCT systematic review process



The available evidence from non-randomised controlled studies take the form of single arm prospective studies and retrospective observational studies, in various patient populations. As outlined in Table 12, nine of the non-RCTs identified provide supportive evidence of relevance to the populations of interest to the decision problem.

These studies are highly variable in size (9-76 patients), duration (6-12 months), number of DEX700 treatments permitted (1-3) and retreatment intervals (no restriction, ≥6 months) as well as patient type. This has led to a wide variety of results from which no strong conclusions can be made. Data from non-RCT studies are therefore not utilised in comparative efficacy analyses or economic modelling exercises and thus are only summarised in this section.

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.

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

Safety measures including assessment of adverse effect of treatment were pre-specified as a key outcome of interest in all DEX700 trials identified. Details of all trials from which safety data are herein presented can be found in sections 6.1 to 6.5 and section 6.8.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

MEAD Trial Programme

Treatment Exposure

The mean number of DEX700 treatments per patient in the safety population was 4.1 across the MEAD trial programme with <10% of patients receiving therapy every 6 months (Table 41). Though discontinuations account for some reduced exposure, a number of patients were still experiencing treatment benefit 6 months after DEX700 administration and thus did not need retreating at all available timepoints. During the course of the 3-year study period, a total of 3037 study retreatments were administered. Of these, approximately 80% were administered between 5 to 7 months after the prior treatment: 39.9% were between 5 and 6 months, 41.7% were between 6 and 7 months, and 18.0% were after 7 months. This is reflected in exposure-adjusted analysis that demonstrates a mean injection rate over the 3-year study period of 5.1, equating to an injection rate of 1.7 per patient-year.[67, 121, 123]

Table 41: DEX700 treatment exposure across the MEAD trial programme

	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[67]; CSR 206207-010[121]; CSR 206207-011[123]			

Similar treatment exposure was reported for pseudophakic patients, for whom the mean number of DEX700 treatments per patient was 3.7 across the MEAD trial programme with an exposure-adjusted injection rate of 1.7 per patient-year.[142]

Safety Profile

Across the MEAD trial program, DEX700 was well tolerated with low discontinuation rates due to adverse events, low treatment-related serious AE (TRSAE) rates and no deaths attributed to treatment (Table 42). Both discontinuations and adverse event

rates were positively correlated with increased treatment exposure as anticipated *a priori* but did not exceed expected levels; the difference between the DEX700 group and the Sham group were at least in part due to the different study exposure between the treatment groups, as the longer a patient stayed in the study, the more likely the patient would have experienced one or more adverse events. The overall incidence of AEs adjusted for treatment exposure time was similar among treatment groups.[67, 121, 123, 171]

The most common discontinuation due to adverse event was for disease progression (macular oedema or visual deterioration; n=8).[67, 121, 123, 171]

Treatment-related adverse events were reported more frequently in patients treated with DEX700 compared with patients treated with sham as can be expected with any active therapy (Table 42). These were ocular in nature in the majority with systemic adverse events as expected in an older DM population and thus not related to treatment. Common treatment-related ocular adverse events are presented in Table 42. [67, 121, 123, 171]

Vitreous hemorrhage in the study eye was reported in 6.9% of patients randomised to DEX700 in total and was considered to be possibly related to treatment in 3.5% of patients (Table 42). In each case, the vitreous hemorrhage did not require vitrectomy, and most cleared spontaneously in a short period of time. Other ocular adverse events of interest, including retinal tear, retinal detachment, vitreous loss, endophthalmitis, hypotony, and complication of device insertion (implant misplacement), were reported in <2% of patients. [67, 121, 123, 171]

As with all ophthalmic steroid therapies, common ocular side effects associated with DEX700 treatment include IOP elevation and cataract formation (Table 43). Incidence of both was expected *a priori* in patients enrolled in all DEX700 trials.

The incidence of serious adverse events associated with intravitreal injection: retinal detachment and endophthalmitis were very low across the MEAD trial programme, each experienced in only a single patient. The most common TRSAE was cataract (n=10). Serious events of macular oedema, necrotising retinitis, lens dislocation and vitreous adhesion were also associated to treatment in single patients. There were two cases of implant misplacement; there was no decrease in vision in either case. [67, 121, 123, 171]

Table 42: Safety profile across the MEAD trial programme, n (%)

	MEAD-010			MEAD-011			MEAD Pooled		
	DEX700 (n=160)	**DEX350 (n=165)**	**Sham (n=164)**	**DEX700 (n=187)**	**DEX350 (n=178)**	**Sham (n=186)**	**DEX700 (n=347)**	**DEX350 (n=343)**	**Sham (n=350)**
All adverse events	153 (95.6)	162 (98.2)	124 (75.6)	180 (96.3)	172 (96.6)	157 (84.4)	333 (96.0)	334 (97.4)	281 (80.3)
Ocular	142 (88.8)	151 (91.5)	97 (59.1)	172 (92.0)	161 (90.4)	131 (70.4)	314 (90.5)	312 (91.0)	228 (65.1)
Study eye	139 (86.9)	147 (89.1)	85 (51.8)	157 (84.0)	156 (87.6)	118 (63.4)	296 (85.3)	303 (88.3)	203 (58.0)
Non-study eye	82 (51.3)	89 (53.9)	66 (40.2)	116 (62.0)	111 (62.4)	91 (48.9)	198 (57.1)	200 (58.3)	157 (44.9)
Non-ocular	106 (66.3)	111 (67.3)	90 (54.9)	135 (72.2)	126 (70.8)	117 (62.9)	241 (69.5)	237 (69.1)	207 (59.1)
Treatment related AE	115 (71.9)	115 (69.7)	31 (18.9)	129 (69.0)	112 (62.9)	59 (31.7)	244 (70.3)	227 (66.2)	90 (25.7)
Ocular	115 (71.9)	115 (69.7)	30 (18.3)	129 (69.0)	111 (62.4)	59 (31.7)	244 (70.3)	226 (65.9)	89 (25.4)
Study eye	115 (71.9)	115 (69.7)	30 (18.3)	129 (69.0)	111 (62.4)	59 (31.7)	244 (70.3)	226 (65.9)	89 (25.4)
Applicator	46 (28.8)	57 (34.5)	18 (11.0)	60 (32.1)	50 (28.1)	34 (18.3)	106 (30.5)	107 (31.2)	52 (14.9)
Treatment	102 (63.8)	97 (58.8)	13 (7.9)	110 (58.8)	89 (50.0)	30 (16.1)	212 (61.1)	186 (54.2)	43 (12.3)
Non-study eye	0	0	0	0	0	0	0	0	0
Non-ocular	2 (1.3)	0	1 (0.6)	1 (0.5)	1 (0.6)	0	3 (0.9)	1 (0.3)	1 (0.3)
Serious AE	52 (32.5)	52 (31.5)	34 (20.7)	63 (33.7)	68 (38.2)	49 (26.3)	115 (33.1)	120 (35.0)	83 (23.7)
Ocular	11 (6.9)	8 (4.8)	5 (3.0)	22 (11.8)	11 (6.2)	11 (5.9)	33 (9.5)	19 (5.5)	16 (4.6)
Study eye	9 (5.6)	7 (4.2)	2 (1.2)	15 (8.0)	7 (3.9)	2 (1.1)	24 (6.9)	14 (4.1)	4 (1.1)
Non-study eye	3 (1.9)	4 (2.4)	3 (1.8)	12 (6.4)	7 (3.9)	9 (4.8)	15 (4.3)	11 (3.2)	12 (3.4)
Non-ocular	45 (28.1)	48 (29.1)	30 (18.3)	49 (26.2)	60 (33.7)	40 (21.5)	94 (27.1)	108 (31.5)	70 (20.0)
Treatment related SAE	4 (2.5)	4 (2.4)	1 (0.6)	12 (6.4)	6 (3.4)	0	16 (4.6)	10 (2.9)	1 (0.3)
Discontinuations due to AE	20 (12.5)	18 (10.9)	16 (9.8)	25 (13.4)	29 (16.3)	24 (12.9)	45 (13.0)	47 (13.7)	40 (11.4)

	MEAD-010			MEAD-011			MEAD Pooled		
	DEX700 (n=160)	**DEX350 (n=165)**	**Sham (n=164)**	**DEX700 (n=187)**	**DEX350 (n=178)**	**Sham (n=186)**	**DEX700 (n=347)**	**DEX350 (n=343)**	**Sham (n=350)**
Deaths related to treatment	0	0	0	0	0	0	0	0	0

Key: AE, adverse event; DEX, dexamethasone; SAE, serious adverse event.
Source: Boyer et al. 2014[67]; CSR 206207-010[121]; CSR 206207-011[123]; Data on file – Summary of Safety[171]

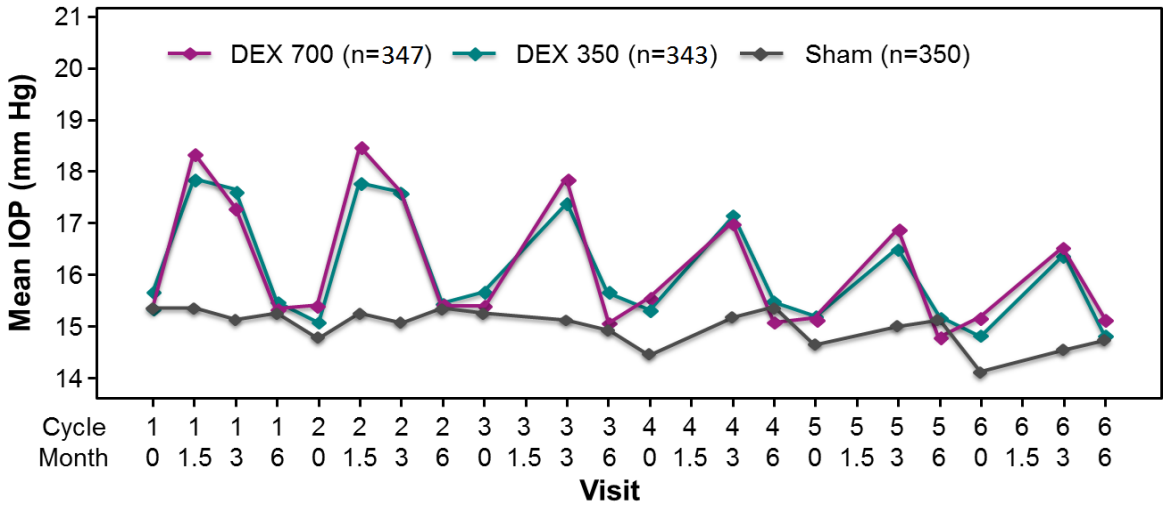
IOP Adverse Events

Across the MEAD trial programme, IOP elevation adverse events were reported in 36.0% of patients treated with DEX700 and were deemed related to treatment in 30.5% of patients (Table 43).[67, 121, 123, 171]

27.7% of DEX700 treated patients experienced an IOP rise ≥10mmHg at any visit during the MEAD study period; 32.0% of DEX700 treated patients experienced an IOP ≥ 25mmHg and 6.6% of DEX700 treated patients experienced an IOP ≥ 35 mmHg at any visit during the MEAD study period.[67]

The incidence or magnitude of IOP elevation did not increase over time with repeated DEX700 administration and resolved after each injection (Figure 50). By the sixth month after each injection, IOP elevations had dissipated considerably with <1% of patients having IOP ≥25mmHg.[67, 121, 123, 171]

Figure 50: Mean IOP by visit within the treatment cycle over the MEAD study period – pooled analysis



Key: DEX, dexamethasone; IOP, intraocular pressure.
Source: Boyer et al. 2014[67]; CSR 206207-010[121]; CSR 206207-011[123]; Summary of Safety[171]

IOP rises when they did occur were well managed with the use of topical IOP medications. 41.5% of patients treated with DEX700 required IOP-lowering medications in the study eye during the MEAD trial programme.[67] The maximum proportion of patients treated with DEX700 that were prescribed IOP-lowering

medication at any one time was 33%; this was within the first 12 months of the study so after the first or second treatment.[67, 121, 123, 171]

Table 43: Treatment-related ocular adverse events in the study eye that occurred in >2% of patients in any treatment group across the MEAD trial programme

	MEAD-010			MEAD-011			MEAD Pooled		
	DEX700 (n=160)	**DEX350 (n=165)**	**Sham (n=164)**	**DEX700 (n=187)**	**DEX350 (n=178)**	**Sham (n=186)**	**DEX700 (n=347)**	**DEX350 (n=343)**	**Sham (n=350)**
IOP elevation	56 (35.0)	50 (30.3)	3 (1.8)	40 (21.4)	36 (20.2)	5 (2.7)	106 (30.5)	86 (25.1)	8 (2.3)
Cataract	44 (27.5)	40 (24.2)	7 (4.3)	57 (30.5)	43 (24.2)	14 (7.5)	101 (29.1)	83 (34.2)	21 (6.0)
Conjunctival hemorrhage	29 (18.1)	48 (29.1)	15 (9.1)	28 (15.0)	29 (16.3)	19 (10.2)	57 (16.4)	77 (22.4)	34 (9.7)
Cataract subcapsular	18 (11.3)	16 (9.7)	6 (3.7)	16 (8.6)	14 (7.9)	5 (2.7)	34 (9.8)	30 (8.7)	11 (3.1)
Cataract nuclear	10 (6.3)	6 (3.6)	3 (1.8)	5 (2.7)	5 (2.8)	4 (2.2)	15 (4.3)	11 (3.2)	7 (2.0)
Conjunctival hyperemia	9 (5.6)	14 (8.5)	4 (2.4)	4 (2.1)	8 (4.5)	6 (3.2)	13 (3.7)	22 (6.4)	10 (2.9)
Eye pain	7 (4.4)	7 (4.2)	3 (1.8)	6 (3.2)	8 (4.5)	6 (3.2)	13 (3.7)	15 (4.4)	9 (2.6)
Conjunctival oedema	7 (4.4)	5 (3.0)	2 (1.2)	6 (3.2)	8 (4.5)	2 (1.1)	13 (3.7)	13 (3.8)	4 (1.1)
Vitreous hemorrhage	6 (3.8)	9 (5.5)	0	6 (3.2)	5 (2.8)	0	12 (3.5)	14 (4.1)	0
Vitreous floaters	6 (3.8)	2 (1.2)	0	4 (2.1)	1 (0.6)	1 (0.5)	10 (2.9)	3 (0.9)	1 (0.3)
Ocular hypertension	4 (2.5)	4 (2.4)	0	16 (8.6)	14 (7.9)	5 (2.7)	20 (5.8)	18 (5.2)	5 (1.4)
Lenticular opacities	3 (1.9)	5 (3.0)	0	5 (2.7)	2 (1.1)	0	8 (2.3)	7 (2.0)	0
Cataract cortical	1 (0.6)	4 (2.4)	2 (1.2)	5 (2.7)	6 (3.4)	5 (2.7)	6 (1.7)	10 (2.9)	7 (2.0)

Key: DEX, dexamethasone; IOP, intraocular pressure.
Source: Boyer et al. 2014[67]; CSR 206207-010[121]; CSR 206207-011[123]; Summary of Safety[171]

Of note, IOP elevation in DEX700 treated patients did not result in high rates of glaucoma formation or incisional surgery requirements: the clinically relevant outcomes of IOP adverse events. A total of 7 patients (2.0%) randomised to DEX700 developed glaucoma (open-angle glaucoma, glaucoma, angle-closure glaucoma) during the MEAD trial programme compared with 2 patients (0.6%) randomised to sham. None of these patients were under the age of 45 years. A total of 4 patients (1.1%) randomised to DEX700 required surgical intervention to treat IOP elevations: 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. No patient required removal of the DEX700 implant by vitrectomy to control IOP.[67, 121, 123, 171]

Cataract Adverse Events

At any time during the 3-year study period, 67.9% of phakic patients treated with DEX700 (n=262) experienced a cataract adverse event across the MEAD trial programme compared with 20.4% of phakic patients randomised to sham treatment (n=250) (Table 44). Of note, 85% of phakic patients presented with some degree of early lens opacification at baseline.[67, 121, 123, 171]

Table 44: Proportion of patients experiencing a cataract adverse event at any time during the MEAD study period, % - pooled analysis

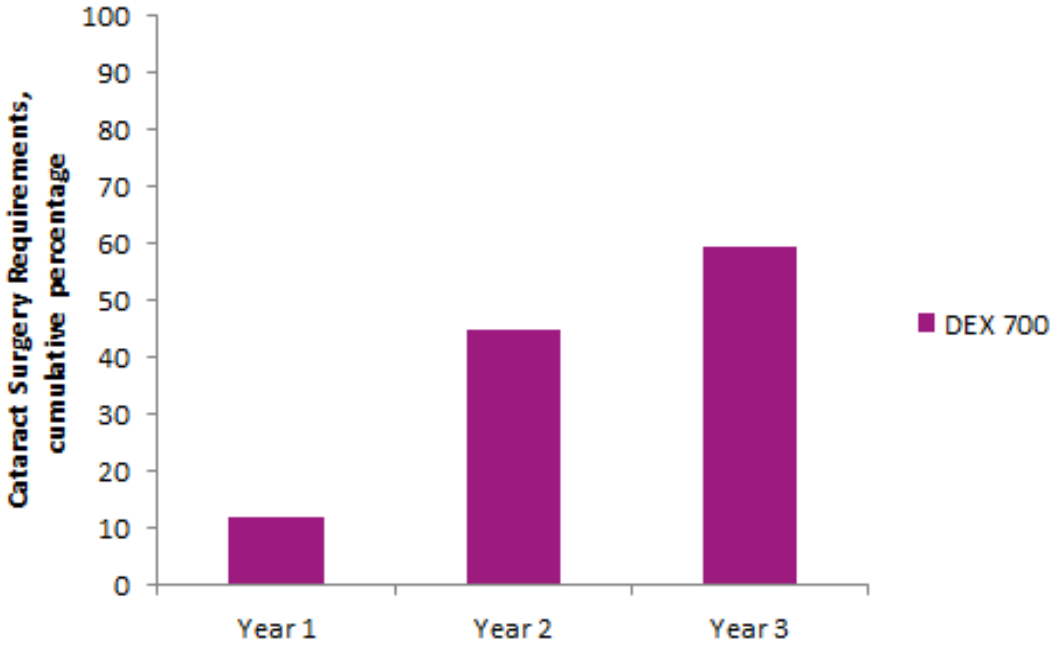
	DEX700	**DEX350**	**Sham**
MEAD-010	68.4	69.5	14.8
MEAD-011	67.6	59.4	25.2
MEAD Pooled	67.9	64.1	20.4

Key: DEX, dexamethasone.
Source: Boyer et al. 2014[67]; CSR 206207-010[121]; CSR 206207-011[123]; Summary of Safety[171]

Cataracts were managed by surgery as required, according to standard clinical practice and as defined in the MEAD protocol. At the end of the study period, cataract surgery had been performed in 59.2% of phakic patients treated with DEX700 across the MEAD trial programme compared with 7.2% of phakic patients randomised to sham treatment. The majority of cataract

extractions occurred within the second year of the study (Figure 51).[67, 121, 123, 171]

Figure 51: Proportion of patients requiring cataract extraction across the MEAD study period, % - pooled analysis



Key: DEX, dexamethasone.
Source: Boyer et al. 2014[67]; CSR 206207-010[121]; CSR 206207-011[123]; Summary of Safety[171]

Safety Profile in Pseudophakic Patients

As expected *a priori*, rates of ocular adverse events in the study eye were lower in patients with a pseudophakic lens at baseline randomised to active therapy due to the incidence of primary cataract reported in phakic patients in DEX treatment groups Table 45.[172]

Table 45: Safety profile across the MEAD trial programme, in pseudophakic subgroup, n (%)

	DEX700 (n=85)	Sham (n=100)
All adverse events Ocular – study eye Non-ocular	91 (95.3) 63 (74.1) 61 (71.8)	86 (86.0) 61 (61.0) 66 (66.0)
Serious AE Ocular – study eye Non-ocular	31 (36.5) 2 (2.4) 28 (32.9)	36 (36.0) 0 31 (31.0)
Treatment related SAE Ocular – study eye Non-ocular	2 (2.4) 2 (2.4) 0	0 0 0
Discontinuations due to AE	11 (12.9)	13 (13.0)
Deaths related to treatment	0	0
Source: Allergan EMEA Questions and Allergan Responses[172]		

In the pseudophakic subgroup, the incidence of serious adverse events was similar in the DEX700 group (36.5%) and the sham group (36.0%). Two pseudophakic patients treated with DEX700 experienced an ocular SAE: one of vitreous adhesion and the other of macular oedema. Discontinuations due to adverse events were reported in 13% of pseudophakic patients regardless of treatment assignment.[172]

The most common ocular AE reported was IOP increase (Table 46) but a lower proportion of DEX700 treated patients in the pseudophakic subgroup (24.7%) experienced such an AE compared with the total MEAD safety population (36.0%). Similar trends were observed in the timing of IOP AE incidences, indicating that there was no cumulative effect of DEX700 on IOP. IOP-lowering medication was prescribed to 32.9% of pseudophakic patients randomised to DEX700 during the MEAD study period; at the end of the study 22.0% of DEX700 treated patients were receiving IOP-lowering medication.[172]

Four pseudophakic patients demonstrated posterior capsule opacity across the MEAD trial programme, sometimes termed secondary cataract. This is a common complication post cataract surgery that is not related to corticosteroid therapy, managed with posterior capsulotomy in the MEAD studies as per clinical practice.[172]

Table 46: 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 (%)

	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 neovascularization	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)

Key: DEX, dexamethasone; IOP, intraocular pressure.
Note: * adverse events identified as 'cataract' were secondary cataract.
Source: Allergan EMEA Questions and Allergan Responses[172]

Safety Profile in Previously Treated Patients

The safety profile of DEX700 in the subgroup of patients with any prior treatment was similar to that seen in the overall safety population of the pooled studies (Table 47).[172]

There was a higher incidence of ocular adverse events in the DEX700 treatment group compared with the sham group, owing to the shorter time the patients in the sham group remained in the study and higher rates of cataracts and IOP elevation, as well as conjunctival haemorrhage (which is an expected event based on the intravitreal administration procedure) in the DEX700 group.[172]

Table 47: Safety profile of patients with any prior treatment, MEAD pooled, n (%)

	DEX700 (n=247)	**Sham (n=261)**
Ocular adverse events in the study eye Non-ocular adverse events	213 (86.2) 169 (68.4)	149 (57.1) 153 (58.6)
Serious adverse events Ocular study eye Non-ocular	84 (34.0) 17 (6.9) 72 (29.1)	66 (25.3) 2 (0.8) 59 (22.6)
Treatment-related serious adverse events Ocular Non-ocular	12 (4.9) 12 (4.9) 0	0 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)
Key: DEX, dexamethasone; IOP, intraocular pressure. **Source:** Allergan EMEA Questions and Allergan Responses[172]		

Study 024

Treatment Exposure

The mean number of treatment injections in the safety population was [redacted] in the DEX700 group, in accordance with the 5 monthly treatment regimen adopted in the protocol, and [redacted] in the ranibizumab group, administered in line with UK licence terms [redacted] of all patients randomised to ranibizumab

treatment needed monthly retreatment (Table 48). Similarly in the pseudophakic subgroup, the mean number of ranibizumab injections was [redacted] the mean number of DEX700 injections [redacted] pseudophakic patients randomised to ranibizumab treatment needing treatment each month (Table 48).[124, 144]

Table 48: Treatment exposure in study 024

	Safety population		**Pseudophakic population**	
	DEX700 [redacted]	**RAN** [redacted]	**DEX700** [redacted]	**RAN** [redacted]
Mean number of treatments	[redacted]	[redacted]	[redacted]	[redacted]
Median number of treatments	[redacted]	[redacted]	[redacted]	[redacted]
Total number of treatments, %				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]

Key: DEX, dexamethasone; IOP, intraocular pressure.
Source: CSR 206207-024[124]; Clinical Story 024 Final[144]

The mean number of concomitant laser treatments was [redacted] proportion of patients randomised to DEX700 received at least one laser treatment throughout the study period [redacted] This between group difference was

[redacted]

Safety Profile

[redacted] discontinuation rates due to adverse events, [redacted] TRSAE rates [redacted] attributed to treatment (Table 49). [redacted] discontinuation rates due to adverse events, [redacted] TRSAE rates and [redacted] attributed to treatment (Table 49). [124]

Table 49: Safety profile of treatments in study 024 , n (%)

	DEX700 [redacted]	**RAN** [redacted]
All adverse events	[redacted]	[redacted]
Ocular	[redacted]	[redacted]
Study eye	[redacted]	[redacted]
Non-study eye	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]
Treatment related AE	[redacted]	[redacted]
Ocular	[redacted]	[redacted]
Study eye	[redacted]	[redacted]
Study drug	[redacted]	[redacted]
Injection	[redacted]	[redacted]
Other	[redacted]	[redacted]
Non-study eye	[redacted]	[redacted]
Non-ocuar	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]
Ocular	[redacted]	[redacted]
Study eye	[redacted]	[redacted]
Non-study eye	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]
Treatment related SAE	[redacted]	[redacted]
Discontinuations due to AE	[redacted]	[redacted]
Deaths related to treatment	[redacted]	[redacted]

Key: AE, adverse event; DEX, dexamethasone; RAN, ranibizumab.
Source: CSR 206207-024[124]

Treatment-related adverse events were reported [redacted] (Table 50).

This was primarily due to higher rates of [redacted] in the [redacted] (Table 50). [redacted] discontinued the study due to treatment-related adverse events.[124]

Table 50: Treatment-related adverse events that occurred in >2% of patients in either treatment group in study 024, n (%)

	DEX700 [redacted]	RAN [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: DEX, dexamethasone; IOP, intraocular pressure; RAN, ranibizumab.
Source: CSR 206207-024[124]

Treatment-related serious adverse events were reported for [redacted] In the DEX700 group, [redacted] n the RAN group, [redacted]

Vitreous hemorrhage in the study eye was reported in [redacted] of patients randomised to DEX700 and [redacted] of patients randomised to RAN in total; vitreous heamorrhage was considered to be possibly related to treatment in [redacted] of patients randomised to DEX700 (Table 50). Other ocular adverse events of interest, including retinal tear, retinal detachment, vitreous loss, hypotony, and complication of device insertion (implant misplacement), were reported [redacted] There were [redacted] reports of complication of DEX700 device insertion or device dislocation to the anterior chamber.[124]

IOP Adverse Events

Adverse events related to IOP were reported in [redacted] of patients treated with DEX700 compared to [redacted] of patients treated with RAN. At Month 12, the mean (range) change from baseline in the study eye was [redacted] in the DEX700 group compared [redacted] in the RAN group [redacted]

[redacted] managed with the use of topical IOP medications. Overall, [redacted] of patients treated with DEX700 in study 024 received IOP-lowering medications in the study eye (compared to [redacted] in the RAN group) [redacted] procedure for elevated IOP was reported.[124]

Cataract Adverse Events

Adverse events related to cataract were reported in [redacted] of all patients treated with DEX700 compared to [redacted] of all patients treated with RAN and occurred from [redacted] of study 024. Cataract extractions were reported in the study eye for [redacted] patients in the DEX700 group and [redacted] in the RAN group.[124]

Safety Profile in Pseudophakic Patients

With the exception of [redacted] was demonstrated in the pseudophakic subgroup of patients treated with DEX700 (Table 51).[144]

Table 51: Safety profile in pseudophakic patients in study 024, n (%)

	DEX700 [redacted]	**RAN** [redacted]
All adverse events	[redacted]	[redacted]
Ocular adverse events in study eye	[redacted]	[redacted]
Ocular treatment-related adverse events in study eye	[redacted]	[redacted]

	DEX700 [redacted]	RAN [redacted]
Key: DEX, dexamethasone; RAN, ranibizumab. **Source:** Clinical Story 024 Final[144]		

The most common treatment-related ocular AE in the DEX700 group of the pseudophakic population was [redacted] and the most common treatment-related ocular AE in the RAN group of the pseudophakic population was [redacted], as was the case in the total study population (Table 52).[144]

Table 52: Treatment-related ocular adverse events that occurred in >2% of pseudophakic patients in either treatment group in study 024, n (%)

	DEX700 [redacted]	RAN [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Key: DEX, dexamethasone; IOP, intraocular pressure; RAN, ranibizumab. **Source:** Clinical Story 024 Final[144]		

Adverse events related to IOP were reported in [redacted] of pseudophakic patients treated with DEX700. There were [redacted] events of IOP elevation, [redacted] of which were deemed related to treatment; [redacted] patients experienced treatment-related ocular hypertension; and [redacted] developed treatment-related open angle glaucoma that required surgery.[144]

Adverse events related to cataract were reported in [redacted] of pseudophakic patients treated with DEX700 and there [redacted] conducted as a result of secondary cataract formation.[144]

PLACID

Treatment Exposure

Of the 126 patients randomised to the combination therapy arm, 73 patients (57.9%) received retreatment with the DEX700 implant at Month 6 and a

further nine patients (7.1%) received retreatment with the DEX700 implant at Month 9. The remaining patients (n=44, 34.9%) did not meet retreatment criteria at either of the reassessment appointments, demonstrating the potential long-term treatment effect of DEX700 (CSR 206207-012).

Of the 35 pseudophakic patients randomised to the combination therapy arm, 21 (60.0%) received retreatment with the DEX700 implant at either Month 6 or Month 9 with 40% of pseudophakic patients not meeting retreatment criteria at this visits, demonstrating the potential long-term treatment effect of DEX700 + laser therapy in this subgroup.[143]

Safety Profile

DEX700 administered in combination with laser therapy was also well tolerated with low discontinuation rates due to adverse events, no TRSAE rates and no deaths attributed to treatment (Table 53).[125, 126]

Table 53: Safety profile in PLACID, n (%)

	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

Key: AE, adverse event; DEX, dexamethasone; SAE, serious adverse event; TRAE, treatment-related adverse event.
Source: Callanan et al. 2013[125]; CSR 206207-012[126]

Events leading to the discontinuation of more than 1 patient across the treatment groups total were macular oedema, visual acuity reduced, vitreous haemorrhage, diabetic retinopathy, and malignant lung neoplasm. There were no statistically significant between-groups differences for any individual preferred term and none of the events were considered to be related to the study treatments.[125, 126]

Treatment-related adverse events were reported more frequently in patients treated with DEX700 in addition to laser compared with patients treated with laser monotherapy as can be expected with the addition of any active therapy (Table 53). These were all ocular in nature.[125, 126]

The most frequently reported ocular treatment-related adverse events (>2% in either treatment group) in the study eye were IOP increase, conjunctival haemorrhage, cataract, eye pain, vitreous haemorrhage, vitreous floaters, subcapsular cataract, ocular discomfort and conjunctival oedema. With the exception of IOP increase and cataract that are discussed further below, only treatment-related rates of vitreous haemorrhage showed a statistically significant between-group difference: 4.8% (n=6) with combination therapy compared with 0% in the laser monotherapy treatment group, p=0.014. All 6 reports were mild in severity, did not require treatment and all but one had resolved by the end of the study.[125, 126]

No serious adverse events associated with intravitreal injection were reported in patients treated with DEX700 with the only serious non-ocular AE reported being an incidence of vitreous haemorrhage not considered to be related to treatment.[125, 126]

IOP Adverse Events

IOP elevation adverse events, deemed related to treatment, were reported in 19.2% of patients treated with DEX700 alongside laser photocoagulation compared with none of the patients treated with laser monotherapy. By study end, only a single patient treated with DEX700 + laser therapy experienced an IOP rise ≥10mmHg in the study eye.[125, 126]

IOP rises when they did occur were well managed with the use of topical IOP medications. During the study, 15.9% of patients in the combination therapy arm received IOP-lowering medications compared with 1.6% of patients in the laser monotherapy arm. No patients required surgery for IOP elevation.[125, 126]

Cataract Adverse Events

During the PLACID study period, 22 patients (17.6%) treated with DEX700 + laser therapy experienced a cataract adverse event compared with 9 patients (7.1%) treated with laser therapy alone. Of note, 77.9% of patients had reported a history of cataracts in the study eye at baseline.[125, 126]

Treatment-related cataract in the study eye was reported in 8/91 phakic patients treated with DEX700 + laser combination therapy (8.8%) compared with none of the 95 phakic patients treated with laser monotherapy.[125, 126]

Cataracts were managed by surgery as required, according to standard clinical practice and as defined in the PLACID protocol. At the end of the study period, cataract surgery had been performed in similar numbers of patients in both treatment arms: 6 patients in the combination therapy arm and 5 patients in the laser monotherapy arm. Surgery was performed in both eyes in 5 patients, in the non-study eye for 2 patients and in the study eye for 4 patients. Nine of these 11 patients had a history of cataracts.[125, 126]

Safety Profile in Pseudophakic Patients

As observed in [redacted] was observed with DEX700 + laser treatment in pseudophakic patients with the exception of cataract adverse event rates that resulted in a slightly lower rate of ocular treatment-related adverse events (Table 54).[143]

Table 54: Safety profile in pseudophakic patients in PLACID, n (%)

	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)
Key: DEX, dexamethasone. **Source:** Clinical Story PLACID Final[143]		

The most frequently reported ocular treatment-related adverse events in the pseudophakic subgroup were IOP increase, conjunctival haemorrhage, eye pain, vitreous haemorrhage and ocular discomfort. No statistically significant between-group differences were observed in ocular treatment-related adverse event rates.[143]

Four pseudophakic patients experienced an IOP increase during the 12-month study period and two pseudophakic patients experienced a posterior capsule opacification.[143]

BEVORDEX

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.[127]

Safety Profile

Seven eyes (from six patients) discontinued the study, none of these were due to adverse events with the most common reason for discontinuation, cited by four patients, being difficulty meeting the rigor of attending monthly appointments. [127]

Most ocular adverse events reported in the study were anticipated with IOP elevation and cataract the most common AE associated with DEX700 treatment and intravitreal injection associated adverse events most commonly associated with bevacizumab treatment (Table 55). [127]

Table 55: Ocular adverse events across the BEVORDEX trial, n (%)

	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)

Key: BEV, bevacizumab; DEX, dexamethasone; IOP, intraocular pressure.
Source: Gillies et al. 2014b [127]

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.[127]

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.[127]

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.[127]

NCT0035906

Safety Profile

After a single treatment with DEX700, the most common ocular adverse events reported in DMO patients enrolled in NCT0035906 were anterior chamber cell, anterior chamber flare and vitreous haemorrhage (Table 56). There were no statistically significant between-group differences in the occurrence of any non-ocular adverse events.[5]

Table 56: Ocular adverse events reported in at least 10% of patients in any group at any time during NCT0035906, n (%)

	DEX700 (n=53)	DEX350 (n=55)	Observation (n=57)
Anterior chamber cell	14 (26.4)	16 (29.1)	1 (1.8)
Anterior chamber flare	11 (20.8)	15 (27.3)	5 (8.8)
Vitreous haemorrhage	12 (22.6)	11 (20.0)	3 (5.3)
Eye pain	5 (9.4)	10 (18.2)	2 (3.5)
VA reduced	9 (17.0)	9 (16.4)	6 (10.5)
Vitreous disorder	8 (15.1)	11 (20.0)	2 (3.5)
Increased IOP	5 (9.4)	8 (14.5)	0
Conjunctival haemorrhage	4 (7.5)	8 (14.5)	0
Maculopathy	4 (7.5)	7 (12.7)	1 (1.8)
Eye irritation	8 (15.1)	7 (12.7)	2 (3.5)
Vitreous floaters	9 (17.0)	4 (7.3)	0
Abnormal sensation in eye	8 (15.1)	4 (7.3)	2 (3.5)
Macular oedema	3 (5.7)	9 (16.4)	5 (8.8)
Eye pruritus	4 (7.5)	6 (10.9)	1 (1.8)
Retinal haemorrhage	6 (11.3)	6 (10.9)	12 (21.1)
Diabetic retinopathy	6 (11.3)	3 (5.5)	8 (14.0)

Key: AE, adverse event; DEX, dexamethasone; IOP, intraocular pressure; VA, visual acuity.
Source: Haller et al. 2010[5]

There were no incidences of TRSAEs associated with intravitreal injection: retinal detachment or endophthalmitis.[5]

IOP Adverse Events

IOP elevation to ≥25mmHg at any scheduled follow-up visit during the 180 day study period was reported in 13.2% of patients treated with DEX700 and included in the safety population (n=53) compared with no patients randomised to observation. The majority of these incidences (5/7) were single occurrences. Eight patients (15%) in the DEX700 safety population

experienced an IOP increase of ≥10mmHg compared with a single patient randomised to observation.[5]

All IOP rises were successfully managed with either observation or topical IOP lowering medication. No patients required laser or surgical intervention to control IOP.[5]

Cataract Adverse Events

There was no significant difference in the number of reports of cataract (as an adverse event) 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.[5]

Non-RCT safety analysis

Across all studies identified within the non-RCT review and presented in section 6.8, the safety profile was in line with that observed in the RCT evidence base with DEX700 generally well tolerated and common adverse events being ocular in nature and in line with the corticosteroid mechanism of action.[132-141]

Alternative Pharmaceutical Therapies

Treatment Exposure

The fluocinolone acetonide implant is designed to release 0.2µg/day fluocinolone acetonide in the eye for up to three years. In the pivotal EU regulatory trial programme of its use in DMO (FAME), subjects were eligible for retreatment after Month 12 if they experienced a loss of 5 or more letters in BCVA or an increase in foveal thickness of 50µm or more compared with the subjects best status during the previous 12 months. Of the 209 patients randomised to the fluocinolone acetonide implant in the FAME trial programme and still in the study at Month 36, 18.7% had received 2 study treatments and 5.3% had received ≥3 study treatments.[163, 173]

Anti-VEGF agents provide far shorter treatment effect duration and need administering much more frequently to achieve optimum clinical efficacy in DMO (see section 2.6). In the pivotal EU regulatory trial of ranibizumab use in DMO (RESTORE), subjects received 3 consecutive monthly injections and

were eligible for subsequent monthly retreatment if they had not reached stable VA (Mitchell et al. 2011). This treatment regimen has also been adopted in a number of additional trials of ranibizumab use in DMO, the largest of which are PROTOCOL I and REVEAL.[104, 165] Treatment exposure data from these three trials along with the largest trial of bevacizumab use in DMO (BOLT)[99], where subjects received 3 consecutive 6 weekly injections and were eligible for subsequent 6 weekly retreatment if they had not reached stable CRT, is presented in Table 57.

Table 57: Treatment exposure to anti-VEGF agents in key clinical studies of ranibizumab and bevacizumab use in DMO

	Number of injections, cumulative average		
Study	**Month 12**	**Month 24**	**Month 36**
RESTORE	Mean (SD) 7.5 (2.7) Median (range) 8.0 (3-12)	Mean (SD) 11.3 (5.6) Median (range) 10.0 (3-24)	Mean (SD) 14.2 (5.8) Median (range) 14 (3-23)
PROTOCOL I	Median (range) 9 (7-11)	Median (range) 12 (8-18)	Median (range) 14 (8-23)
REVEAL	Mean 7.8	-	-
BOLT	Median (range) 9 (8-9)	Median (range) 13 (11-15)	-

Key: DMO, diabetic macular oedema; SD, standard deviation; VEGF, vascular endothelial growth factor.
Source: DRCRN, 2010[165]; Michaelides et al. 2010[99]; Mitchell et al. 2011[100]; Ohji et al. 2012[104]

Safety Profile

In the FAME trial programme, the fluocinolone acetonide implant was associated with higher rates of steroid related adverse events compared with DEX700 in the MEAD trial programme.

At 36 months, the IOP elevation AE rate was 37.1% in patients treated with the fluocinolone acetonide implant (n=375) compared with 30.8% in patients treated with DEX700 (n=347).[173] In the MEAD trial programme, the majority of IOP elevations were managed with topical IOP-lowering medications. In the FAME trial programme, the proportion of patients treated with the fluocinolone acetonide implant that were initiated on IOP lowering medication over the 3-

year study period was 38.4%, slightly lower than the proportion of patients treated with DEX700 that needed IOP lowering medications in MEAD (41.5%).[67, 173] However, in the FAME trial, 4.8% of patients treated with the fluocinolone acetonide implant required incisional surgery to manage IOP elevation.[173] This is noteworthy as in incisional surgery can be associated with significant complications that can result in visual morbidity and permanent disability.[163, 174, 175] Whilst incidence of surgical implant removal to manage IOP is not formally reported in the FAME trial publication, vitrectomy is noted as a common undesirable effect in the summary of product characteristics for the fluocinolone acetonide implant.[176]

A considerably higher proportion of phakic patients needed cataract surgery within 36 months of therapy initiation with the fluocinolone acetonide implant compared with DEX700. Of the 235 phakic patients enrolled in the FAME study and treated with the fluocinolone acetonide implant, 74.9% had undergone cataract extraction by Month 24 post initial therapy, rising to 80.0% at Month 36 with a cataract adverse event rate of 81.7%.[163, 173] This resulted in a restricted recommendation of its use in pseudophakic patients only in England and Wales.

Across the pivotal trials of bevacizumab and ranibizumab in DMO, common ocular adverse events in the study eye were secondary to ocular surface disturbances related to intravitreal injections and included eye pain, conjunctival hyperemia, conjunctival haemorrhage and foreign body sensation.[99, 100, 165] In comparison with DEX700 treated patients, bevacizumab treated patients experienced higher rates of subconjunctival haemorrhage, eye pain and epiphora in the BEVORDEX trial.[127]

There have been reports of increased CV risk with anti-VEGF treatments across multiple disease areas but the evidence base in DMO is inconclusive and thus is an area of interest in ongoing research.[177-185] A recent meta-analysis of randomised trials of ranibizumab concluded it is considered safe when the patients are carefully selected based on systemic vascular conditions.[186] Indeed, systemic warnings related to their potential CV risk are included in the SPCs for both bevacizumab and ranibizumab.[111, 112]

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

DEX700 is associated with a stable and clearly characterised safety profile that is easily manageable in line with standard clinical practice and typical of intravitreal steroid therapies. DEX700 is already available in the UK and ophthalmologists are familiar with this safety profile that is consistent across ophthalmological conditions.

Across all trials investigating the use of DEX700 for the treatment of DMO, tolerability of the implant was consistently demonstrated with low rates of discontinuations due to adverse events, TRSAEs, serious adverse events related to intravitreal injections and no deaths attributed to DEX700 treatment.

The most common adverse events associated with DEX700 therapy were related to IOP elevation and cataract. Both were anticipated *a priori* and did not exceed expected levels in any of the DEX700 trials. Of note, primary cataract formation is not of concern to the pseudophakic DMO patients of interest to the decision problem.

IOP rises experienced by all but two patients treated with DEX700 in clinical trials were successfully managed with topical IOP lowering medications. There was no evidence of a cumulative effect of DEX700 on IOP and patients who did not experience IOP elevation after the initial DEX700 implant are unlikely to experience any rise in IOP with subsequent implantations. A single patient treated with DEX700 required trabeculectomy to manage steroid-induced IOP elevation in the MEAD trial programme and in study 024. No other surgical interventions were needed to treat DEX700 related IOP rises in any patients across all clinical trials.

Cataract event rates were highest in the regulatory trials (MEAD-010 and MEAD-011) at 67.9% of phakic patients after 3 years, reflecting the longer duration of these studies. Cataract event rates should however be considered in context of the DM patient who is predisposed to cataracts as a result of their DM. Indeed, cataract is one of the most common causes of blindness in older-onset patients with DM[28] and risk of its development appears to be greatest in non-insulin dependent DM with a cataract rate of 13.5 per 1000

patient years reported in a large UK retrospective study for such patients.[29] In the population based Blue Mountains Eye Study, cataract formation resulted in a cumulative incidence of cataract surgery in DM patients of 20.9% over 10 years.[30] This predisposition is reflected in the high proportion of patients presenting with lens opacity and/or history of cataracts in clinical trials of DMO therapies.

Due to their unique mechanisms of action (see section 4.1.1), DEX700 demonstrates a different safety profile to non-corticosteroid therapies available that may be preferential for some DMO patients presenting in clinical practice. In comparison with the alternative corticosteroid implant available in the UK, the fluocinolone acetonide implant, DEX700 demonstrates reduced rates of IOP elevation and cataract adverse events. Indeed, concerns over high cataract AE rates led to a restricted recommendation by NICE of the fluocinolone acetonide implant as a possible treatment for people with chronic DMO providing the implant is used in an eye with an artificial lens and their DMO has not got better with other treatments in England and Wales.

The average 6 month treatment effect of DEX700 compared to the average 3 year treatment effect of the fluocinolone implant allows individual patient safety to be assessed at more frequent intervals. In addition, due to its biodegradable nature, DEX700 holds no concerns associated with long-term retention of intraocular implants compared to the fluocinolone acetonide implant that is permanently located in the vitreous.

Anti-VEGF therapies are not commonly associated with IOP rises or cataract development or progression. They do, however, have systemic warnings in relation to their potential CV risk. This may be of concern to the DM patient presenting with DMO in practice that are likely to have a more severe CV morbidity than populations of clinical trials where patients at high CV risk are often excluded. This was the case in the pivotal trials of ranibizumab and bevacizumab, RESTORE and BOLT, but was not the case in [redacted] patients experienced serious treatment-related adverse events of a CV nature.

In adult patients with visual impairment due to DMO who are pseudophakic, the most common treatment-related adverse event associated with DEX700 treatment is IOP increase. In the majority, steroid-induced IOP elevations are manageable with topical IOP-lowering medications and do not result in the clinically relevant progression to glaucoma or requirement for surgery to manage IOP.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Effective management of diabetes and the associated complications of this chronic disease pose a significant challenge to the NHS. DMO is one such complication that can result in permanent retinal damage and irreversible vision loss if insufficiently treated. Therapeutic options currently available to treat DMO in the UK have limitations regarding long-term efficacy (and the administration regimens needed to achieve this in the case of anti-VEGF agents) or safety and restrictions on use (licence, guideline and/or HTA restrictions) and thus cannot be used to successfully manage all DMO patients with associated visual impairment that present in clinical practice. There is clearly still a continued unmet medical need for additional therapeutic options that allow clinicians to successfully treat more patients presenting with visual impairment due to DMO based on their individual requirements.

DEX700 is the first fully biodegradable corticosteroid implant to be licenced for use in DMO patients with associated visual impairment. Its novel drug delivery system allows approximately 6 months of active treatment to be administered to the vitreous of the eye through a single injection before the implant naturally dissolves. This active treatment (dexamethasone) targets the multifactorial inflammatory pathophysiology of DMO, directly stabilising the BRB which is key to effective long-term management of this condition.

Clinical Efficacy

In pooled analyses of the regulatory trials, MEAD-010 and MEAD-011, DEX700 PRN resulted in rapid and sustained anatomical and VA improvements in DMO patients with associated visual impairment. With a mean of only 4-5 injections over three years, DEX700 demonstrated statistically significant superiority over sham treatment in primary and key secondary efficacy outcomes: mean BCVA average CFB; proportion of patients with improved BCVA of ≥15 letters at study end; proportion of patients with improved BCVA of ≥10 letters at study end; mean CRT average

CFB. Statistically significant superiority was observed despite the unusually high results observed in the sham treatment arm that markedly reduced the relative effect between the treatment groups, particularly in cumulative BCVA analysis. In subgroup analyses of previously treated patients and pseudophakic patients, DEX700 continued to demonstrate statistically significant superiority over sham treatment in co-primary (EU and US) efficacy analyses with the magnitude of effect greater in pseudophakic patients for whom progression of lens opacification and primary cataract formation did not influence BCVA outcomes.

In direct comparison trials of DEX700 vs. anti-VEGF agents, [redacted] BCVA outcomes of mean BCVA average [redacted] and proportion of patients with improved BCVA of ≥10 letters at 12 months respectively. [redacted] was seen in the mean change from baseline in total leakage area (mm2) at month 12 [redacted] In pseudophakic subgroup analyses of both studies [redacted] effect associated with DEX700 therapy. In secondary efficacy analyses of patients with a pseudophakic study eye at baseline, [redacted] mean change from baseline BCVA at month 12, the proportion of patients with improved BCVA of ≥15 letters at study end, the mean change from baseline CRT at month 12, or the time to BCVA 15 letter improvement and [redacted] in the mean change from baseline BCVA at month 12. In study 024 and in the BEVORDEX trial, DEX700 was not administered directly in accordance with the confirmed EU marketing authorisation with more regular treatment schedules adopted. [redacted] demonstrated a reduction of treatment administration by approximately [redacted] injections over 12 months with [redacted]

[redacted] Furthermore, these more frequent treatment intervals did not lead to demonstrably better outcomes (see section 6.5) and thus should not be adopted in clinical practice.

Direct comparative efficacy analysis of DEX700 addition to laser photocoagulation therapy showed up to two DEX700 injections over a 12 month period results in reduced vascular leakage and retinal oedema and improved visual acuity compared to laser monotherapy. In pseudophakic patients, no between-group difference was observed in post-hoc analysis of proportion of patients with improved BCVA at study end based on various ETDRS letter categories.

Indirect comparative efficacy analysis based on proportion of patients with improved BCVA ≥10 letters at 12 months and proportion of patients with worsened BCVA ≥10 letters at 12 months demonstrated [redacted] No statistically significant differences in treatment effect were observed between DEX700 PRN and laser or fluocinolone acetonide therapy. Network analysis is modelled around the relative effect observed between treatment groups within individual trials. The modest relative effect observed in MEAD as a result of the unexpectedly positive treatment effect observed with sham is therefore carried over to all indirect comparisons made between DEX700 PRN and alternative therapies in the network. In alternative trials of no treatment, 12 month analysis shows approximately 26.5% of patients experienced at least a 10-letter loss in visual acuity from baseline. Natural history data suggests by 4 years, 36% of patients left untreated experience a 10-letter loss in visual acuity from baseline. Across the MEAD programme, 12 month and 36 month analysis shows a much lower proportion of patients experiencing a 10-letter visual impairment: 14.4% and 17% respectively. We may therefore expect direct comparative efficacy analysis to show more favourable differences between relative effects of DEX700 to alternative therapies, as observed in [redacted] In addition, superiority of DEX700 PRN to sham treatment /no treatment observed in

direct trial data was not demonstrated in the indirect comparative efficacy analysis. It appears the network is contributing uncertainty to this comparison. Such uncertainty may be attributed, in part at least, to heterogeneity across trials included in the network.

Safety

DEX700 is already available in the UK and ophthalmologists are familiar with its clearly characterised safety profile that is easily manageable in line with standard clinical practice and consistent across ophthalmological conditions. Across clinical trials, there were no unexpected adverse events and DEX700 demonstrated excellent systemic safety. The most common adverse events associated with DEX700 therapy were related to IOP elevation and cataract; both were anticipated a priori and did not exceed expected levels.

In the majority, incidences of IOP elevation were medically manageable and transient in nature with no cumulative effect of DEX700 on IOP observed across safety populations. The timing of IOP rises was predictable, and the incidence and magnitude of IOP elevations did not increase upon repeated injection or from year to year. Surgical intervention (trabeculectomy) for the management of steroid-induced IOP elevation was required in only two of the 752 (0.3%) DMO patients treated with DEX700 and included in the safety populations of the RCTs identified. In pseudophakic patients, the IOP elevation profile was comparable to that observed in all patients.

Cataract adverse events were highest in the three year regulatory studies with the majority of cataract formed between 12 and 24 months. The association between intravitreal corticosteroid therapy and progression of lens opacities and primary cataract formation is well documented and will be considered as part of the treatment decision process in clinical practice. In DMO, consideration of the cataract risk will be in context of the DM patient who is predisposed to cataracts as a result of their underlying disease i.e.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. Therefore, DEX700 would be viewed to accelerate rather than cause

primary cataract formation in elderly patients. For pseudophakic patients in whom primary cataract is not observed, incidence of cataract are effectively absent resulting in lower ocular adverse event rates overall in this population.

HRQL

Across the MEAD trial programme, patients treated with DEX700 experienced some improvement in visual functioning (measured using the NEI-VFQ25 tool) but consistent, statistically significant differences between DEX700 and sham treatment arms were not observed. In part at least this can be attributed to corticosteroid induced progression of lens opacification and primary cataract formation in DEX700 treated patients with greater improvement in visual functioning observed in the pseudophakic subgroup. In patients that experienced at least a 10-letter improvement in BCVA (a significantly larger population in the DEX700 treatment arm compared with sham), a significant improvement in NEI-VFQ-25 near vision activity and distance vision activity subscales were observed across multiple time-points for both the ITT and pseudophakic population.

Of note, in all RCTs identified, approximately 50% of patients treated with DEX700 achieved an improved BCVA from baseline of ≥5 letters at each assessment post treatment initiation. In post-hoc analyses, such an improvement has been associated with clinically meaningful changes in HRQL among DMO patients (assessed using NEI-VFQ-25 trial data from PLACID).[153]

In head-to-head trials of DEX700 vs. non-corticosteroid therapy, [redacted] in visual functioning was observed in pseudophakic patients [redacted] differences between the treatment groups. In bilateral DMO patients receiving both treatments in the BEVORDEX trial, approximately half specified a preference for DEX700 therapy compared with bevacizumab. This supports the conclusions of an independent retrospective analysis that showed despite the tunnel technique required for intravitreal injection of an implant compared with the non-tunnel technique required for intravitreal injection of a solution, DEX700 administration is not associated with increased pain compared with the anti-VEGF agent, bevacizumab.[187]

Clinical Benefit

DMO patients with associated visual impairment who are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy

DMO patients for whom the frequent anti-VEGF injection regimen is not possible to initiate or maintain may be considered unsuitable for such therapy. In addition, there are a number of other DMO cohort groups for whom non-corticosteroid therapy is considered unsuitable due to clinical rationale or HTA / clinical guideline restriction. In the current clinical pathway of care, there is no active treatment option for DMO patients with associated visual impairment who are considered unsuitable for non-corticosteroid therapy.

DEX700 offers a significantly superior efficacy profile to watch and wait, represented by sham treatment in clinical trials. In direct comparative efficacy analysis, DEX700 demonstrated statistically significant superiority over sham treatment in both BCVA and anatomical efficacy outcomes. Whilst DEX700 increases the risk of cataract in these patients, their cataract risk is already increased as a result of their underlying DM and artificial lens replacement surgery is routinely available to treat this condition, whereas oedema progression could lead to irreversible vision loss.

In addition to DMO patients considered unsuitable for non-corticosteroid therapy, approximately a quarter of patients are estimated to demonstrate insufficient response to non-corticosteroid therapy and would be considered for steroid therapy (based on clinical opinion of the proportion of patients that show insufficient response to anti-VEGF therapy given that laser photocoagulation is not commonly used as monotherapy in current clinical practice).

The only active therapy currently available for such patients is an alternative corticosteroid implant but this is only licensed for use in chronic DMO patients considered insufficiently responsive to available therapies and further restricted to use in pseudophakic patients in England and Wales. It is therefore viewed as a last-line therapy option available to only a small patient group in clinical practice and would continue to be viewed as such with the introduction of DEX700.

Indirect comparative efficacy analysis suggest there is no statistically significant difference in treatment effect between DEX700 and fluocinolone acetonide though marked heterogeneity between the MEAD and FAME trials (particularly in regard to the proportion of patients with pseudophakic lens at baseline and rescue therapy rules that may positively influence fluocinolone acetonide comparisons) warrant caution to be applied when interpreting these results.

DEX700 offers a favourable safety profile compared to the fluocinolone acetonide implant with reduced risk of long-term IOP elevation and associated events and reduced risk of lens opacification progression and associated events. This may be accounted for by differences in the pharmacologic and pharmacokinetic profiles of the active steroid treatments. There is also no long-term safety concern associated with implant retention of DEX700 given that it is biodegradable rather than permanent and the shorter-term treatment effect offers optimal monitoring intervals to physicians.

In DMO patients with associated visual impairment who are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy, DEX700 therefore provides an effective long-term treatment option that may help stop progression of insufficiently treated oedema to a point of permanent retinal damage and irreversible vision loss, with a medically manageable safety profile favourable to that of alternative corticosteroid therapy options available.

DMO patients with associated visual impairment who are pseudophakic

DM is associated with increased risk of cataract resulting in significant numbers of DM patients receiving artificial lens (pseudophakic) replacement surgery.

In DMO patients with associated visual impairment and pseudophakic lens, the preferred first-line treatment option in England and Wales is ranibizumab therapy. Due to the restricted recommendation of ranibizumab use to DMO patients with CRT ≥400µm in England and Wales, some pseudophakic patients may be offered the alternative anti-VEGF agent, bevacizumab, off-

license as a first-line treatment though this isn't an available option to the majority of eye clinics in the UK.

Laser photocoagulation may be administered alongside anti-VEGF therapy if physicians feel that patients are appropriate for and would benefit from such therapy but even in this manner its use is in decline and laser photocoagulation is not commonly used as a first-line monotherapy since the introduction of pharmaceutical treatment options and the greater understanding of the limitations of its use.

In comparison to the anti-VEGF agents that target a single component of the inflammatory pathway, DEX700 offers a multifactorial mechanism of action.

In direct comparative efficacy trials, DEX700 administered at fixed or intermittent intervals of 4-5 months [redacted] relative effect of DEX700 PRN vs. sham in MEAD being markedly reduced by the unexpectedly positive treatment effect observed with sham treatment in this trial programme. As a result of patients with significantly deteriorating vision being withdrawn from the study, only patients whose natural history was favourable remained. The average sham result is therefore considered to be superior to the outcomes expected with watch and wait therapy in true clinical practice.

This indirect comparative efficacy analyses utilises clinical trial data in which the average number of anti-VEGF injections administered over the 12 month analysis period was 8.0. In current clinical practice, one of the greatest challenges facing DMO patients and care providers is complying with such demanding treatment regimens with many eye clinics struggling to expand capacity to meet anti-VEGF injection needs of a DMO population of rising prevalence and patients in the UK stating reduced frequency is the most desired improvement to the DMO therapy injection procedure. Optimum efficacy of anti-VEGF therapy is directly correlated with injection frequency and observational studies suggest clinical trial efficacy of anti-VEGF therapies

is not therefore translated to clinical practice where reduced injection frequency is often observed. Furthermore, efficiency of eye clinics is reduced with high rates of missed appointments attributed to the impractical patient burden of frequent injection regimens observed in clinical practice. In comparison, whilst peak treatment effect is observed at between three to four months, DEX700 has proven clinical efficacy when administered at six monthly intervals or longer. In indirect comparative efficacy analysis, the average number of DEX700 injections administered over the 12 month analysis period was [redacted].

Due to the risk of primary cataract being absent in this population, the most common adverse event associated with corticosteroid therapy is IOP elevation. When this does occur, it is generally transient and medically manageable with topical IOP-lowering drops.

In DMO patients with associated visual impairment and pseudophakic lens, DEX700 therefore offers effective long-term management of DMO, with a low-burden treatment regimen and medically manageable safety profile.

In conclusion, DEX700 provides a favourable benefit/harm profile in the populations of relevance to the decision problem. With its low injection frequency, broad relevant mode of action and resulting significant efficacy, adoption of DEX700 into the clinical pathway of care for DMO should help to reduce the overall burden of this condition on the patient, the healthcare system and society. This is extremely important in the context of effective clinical management of the diabetic patient.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths

The primary strength of the clinical evidence base for the use of DEX700 in DMO is its extensive nature.

Six RCTs were identified that provide evidence of the clinical efficacy and safety of DEX700 treatment with an additional seven non-RCTs providing

supportive evidence for the populations of direct relevance to the decision problem.

Within this evidence base, DEX700 demonstrated proven benefit when administered as monotherapy or in combination with laser photocoagulation therapy. This is a direct reflection of how DEX700 would be utilized in clinical practice. Furthermore, head-to-head data is available for a number of relevant comparators: bevacizumab, ranibizumab, laser photocoagulation and sham treatment, intended as a proxy for watch and wait in clinical practice.

The three year study duration of the regulatory trials allows assessment of the long-term efficacy and safety profiles of DEX700 treatment in DMO; both of which were in line with the long-term efficacy and safety profiles of DEX700 treatment in other ocular conditions for which ophthalmologists have clinical experience.

In total, 761 DMO patients were randomised to DEX700 treatment in RCTs, providing a high quality evidence base against which its value to the NHS can be assessed.

Limitations

The primary limitation of the clinical evidence base is that none of the RCTs exclusively enrolled DMO populations of relevance to the decision problem and therefore were not statistically powered to detect significant differences in treatment effect in these populations.

No direct comparative efficacy evidence of DEX700 vs. the alternative intravitreal corticosteroid implant (fluocinolone acetonide) was identified and there are a number of limitations associated with the indirect comparative efficacy analysis for this comparison.

In addition, both trials providing direct comparative efficacy evidence for DEX700 vs. anti-VEGF therapy adopted treatment regimens that are not recommended in accordance with EU licence terms.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance

of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

In all trials contributing to the clinical evidence base for DEX700 use in DMO, at least a proportion of patients enrolled are directly relevant to the decision problem.

The regulatory trials (MEAD-010 and MEAD-011) along with the DMO cohort of patients enrolled in NCT00035906 also provide evidence of the clinical efficacy and safety associated with DEX700 treatment of DMO patients with associated visual impairment that may be considered unsuitable for or insufficiently responsive to non-corticosteroid therapy. Whilst both were initiated before the widespread adoption of anti-VEGF therapy for the treatment of DMO and thus eligibility criteria for insufficient response or unsuitable consideration was primarily based on laser therapy, post-hoc analysis of ranibizumab treated patients in clinical trials does not suggest patients that may be considered unsuitable for or insufficiently responsive to anti-VEGF therapy present with characteristics that would impact the treatment effect associated with DEX700.

Of the six RCTs identified, five provided evidence of the clinical efficacy and safety associated with DEX700 treatment of DMO patients with associated visual impairment who are pseudophakic. The treatment history of pseudophakic subgroups differed both within and across trials with both treatment naïve and treatment exposed patients included. This provides evidence of DEX700 use as both a first- and second-line treatment in pseudophakic patients with treatment history not shown to impact the treatment effect associated with DEX700.

Comparator arms across the RCT evidence base are also of direct relevance to the decision problem with all named comparators of interest to one of the DMO cohorts for which DEX700 treatment is licensed.

Primary efficacy outcomes across the clinical evidence base were based around improvement in visual acuity from baseline levels, directly reflecting the clinical benefits experienced by patients in practice. In addition, secondary

efficacy analyses of anatomical improvements directly reflect outcomes which guide treatment decisions in practice.

Consideration of the complete clinical evidence base thus allows a thorough assessment of the comparative efficacy and safety of DEX700 in DMO patients with associated visual impairment who are pseudophakic or are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

All study results presented are for the DEX700 implant currently recommended for use in RVO and Uveitis in England and Wales for which the EU marketing authorisation was recently extended to include DMO patients with associated visual impairment who are pseudophakic, or are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy.

The retreatment criteria within the SPC is based upon the regulatory trial evidence (MEAD) and states “retreatment may be performed after approximately six months if the patient experiences decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening DMO”. Similar retreatment criteria were adopted in PLACID.

In study 024, a constant treatment regimen of 5 month interval retreatment was adopted which is not in line with the DEX700 SPC. In clinical practice and in line with the SPC recommendations, retreatment will be administered if in the physician’s opinion, the patient may benefit from retreatment. Whilst this constant treatment regimen does not directly compare with how DEX700 would be used in clinical practice, clinical opinion is that the 5 month retreatment frequency is reflective of some patients need in practice.

In the BEVORDEX trial, retreatment eligibility could be performed after approximately 4 months if the patient experiences decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening DMO. DEX700 retreatment was therefore administered within a shorter interval than recommended in the SPC in some patients. Nonetheless, the average number of DEX700 injections administered/patient within the first 12 months of BEVORDEX was 2.4, suggesting at least a proportion of patients actually received DEX700 more in line with the SPC retreatment recommendations of approximately 6 months.

In clinical practice, peak treatment effect of DEX700 may be observed between three to four months but treatment effect is sustained for up to six months or longer. This efficacy profile allows for a flexible retreatment regimen and as per the SPC, physicians will make retreatment decisions at approximately six month intervals based on individual patient considerations.

Clinical trial populations are typically considered to be less severe that typical patients presenting in clinical practice. DEX700 trials adopted exclusive eligibility criteria in an attempt to reflect typical DM patients presenting with macular oedema in practice e.g. patients not excluded due to high CV risk. Baseline demographics and disease characteristics of the patient populations across trials are therefore thought to reasonably represent DMO patients presenting in clinical practice.

Only a small proportion of patients enrolled in the pivotal RCTs were based in the UK: MEAD, 0.6%; study 024: 8.0%. However, race has not been associated with significant differences in the natural disease pathway of DMO and country was not shown to impact efficacy outcomes in post-hoc analyses of DEX700 treated patients in MEAD.

Eligibility criteria for inclusion in clinical trials were not exclusively based around the approved EU licence terms for DEX700 use in DMO. In clinical practice however, patients would need to be assessed for eligibility against these terms. This does not represent a change to current clinical practice in which treatment decisions are already tailored to independent patient needs.

As standard, only DMO patients with associated visual impairment will be considered for pharmaceutical treatment. Patients who are pseudophakic will have their lens status recorded as standard and thus are easily identifiable in an objective manner. A more subjective assessment is needed to select patients who meet the licence criteria of adult patients with visual impairment due to DMO considered insufficiently responsive to or unsuitable for non-corticosteroid therapy. A number of practicing UK ophthalmologists have been consulted on this point with consensus reached for how such patients can be defined presented in Table 58.

Alongside these criteria, the safety profile of DEX700 will be considered when making treatment decisions. Again, this does not represent a change to current clinical practice.

Table 58: Criteria that would be used in clinical practice to select patients for whom DEX700 treatment would be suitable

Population	Measurement tool	Assessed as standard in current clinical practice
Unsuitable for laser photocoagulation		
Centre-involving DMO	Ophthalmoscopy Tomography	Yes
DMO with associated visual impairment	Visual acuity	Yes
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	Routine consultation "Did not attend" appointment rate	Yes
Pregnant women or women trying to conceive	Routine consultation Medical file	Yes
High-risk co-morbidities e.g. CV morbidity	Routine consultation Medical file	Yes
Vitrectomised eyes	Routine consultation Medical file	Yes
Unsuitable for ranibizumab therapy		
CRT <400µm	Tomography	Yes
Insufficiently responsive to anti-VEGF therapy		
Despite recent repeated dosing there is a visual impairment due to DMO that is >300 micron in any of the five central ETDRS zones or in the opinion of the treating clinician that there is potential for further visual improvement if oedema can be resolved further by alternative therapies.	Ophthalmoscopy Routine consultation Tomography Visual acuity	Yes

CRT, central retinal thickness; CV, cardiovascular; DMO, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A systematic literature review was conducted in February 2014, and updated in July 2014, to identify published cost-effectiveness studies of therapies used in the treatment of vision impairment due to DMO. The full search strategies for the literature review and the subsequent update are detailed in section 10.10, appendix 10 and described briefly here.

Searches were performed in Medline and moMedline 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. No date or language limits were applied. Filters for economic evaluation were applied based on SIGN recommendations.[188] Relevant NICE guidance was identified and included within the description of identified studies.

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.

The PRISMA diagram for the literature search of databases for cost-effectiveness studies conducted in February 2014 is provided in Figure 52. The PRISMA diagram for the updated searches conducted in July 2014 is provided in Figure 53. In the initial review seven relevant studies were identified through database searching. Two relevant NICE appraisals (each with a number of relevant publically available documents) were also identified through additional searches and were included in the description of identified studies, giving a total of nine identified studies of relevance. The updated searches conducted in July 2014 resulted in no additional studies being identified.

Figure 52: PRISMA diagram – cost-effectiveness studies literature review (February 2014)

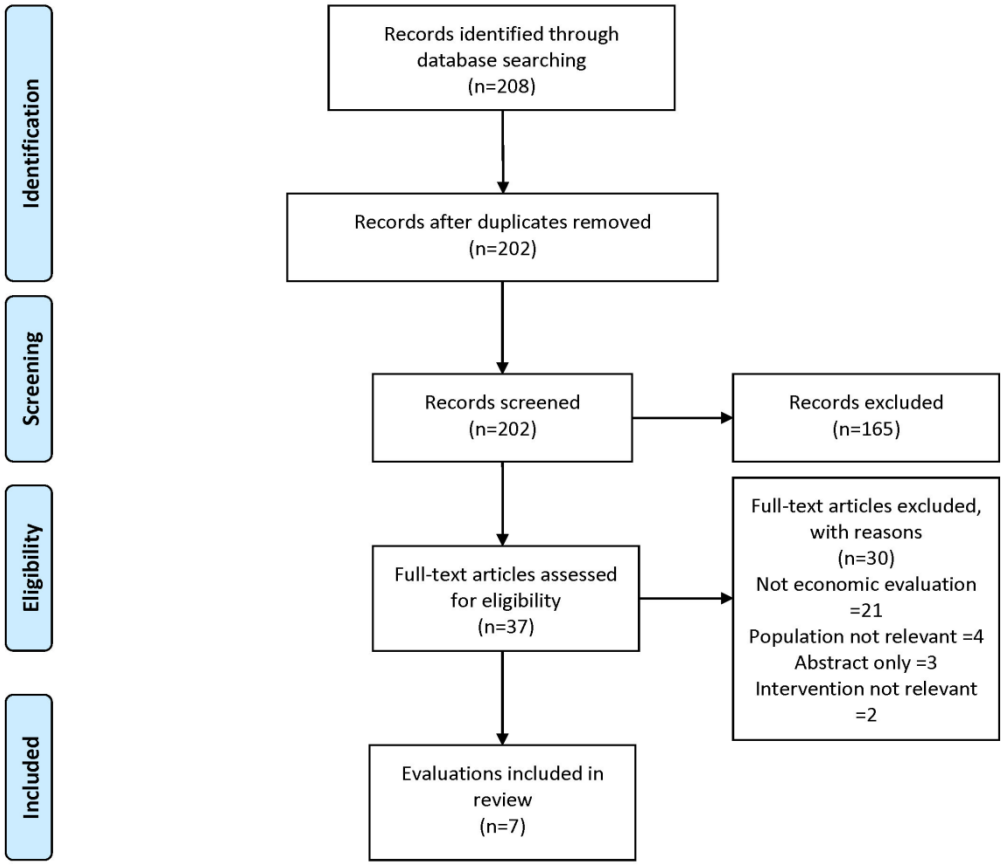
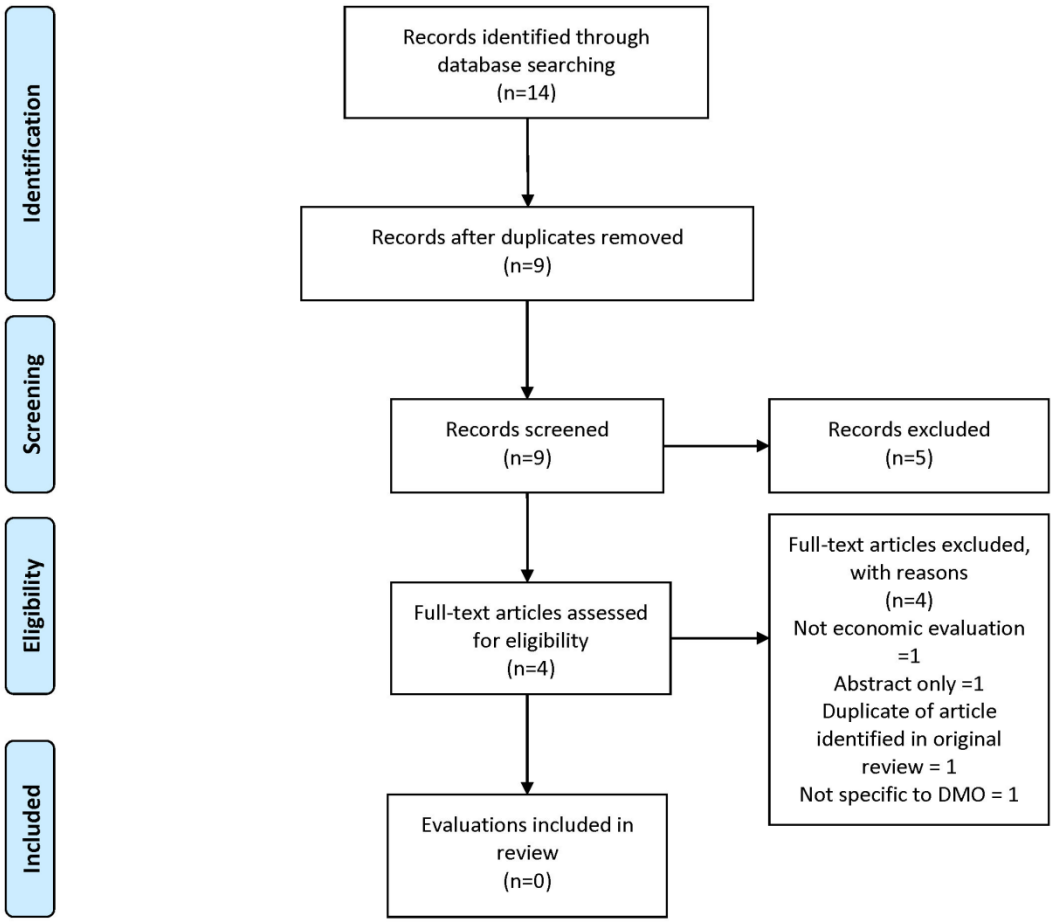


Figure 53: PRISMA diagram – cost-effectiveness studies literature review (update July 2014)



Key: DMO, diabetic macular oedema.

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Table 59: Summary list of other cost-effectiveness evaluations – methods

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)
Pershing *et al.* 2014	2010	USA	Markov cohort model of treatment and natural history of DMO. The model included mortality adjusted for DM or diabetic retinopathy, visual acuity, treatment acquisition costs, complications and societal costs including the costs of blindness (societal perspective) over a lifetime horizon. Costs and benefits were discounted annually at 3%. Strategies included were: no treatment (No Tx); ranibizumab 0.3mg monotherapy (RAN); triamcinolone 4mg monotherapy (TA); laser monotherapy (LAS); ranibizumab 0.3mg + laser (RAN+LAS); triamcinolone 4mg + laser (TA+LAS). Treatment was assumed in the better-seeing eye (BSE) for 1 year (or less if severe complications), then patients moved to receive no treatment in the base case. Lifetime treatment was also presented as a sensitivity analysis, with vision remaining stable during treatment. For lifetime treatment 3 RAN per year, 1 TA per year and 1 LAS every other year for monotherapy for life time, no LAS was assumed for combination. No information for the assumed duration of life time was provided. Visual acuity (VA) was categorised into 6 health states based on ETDRS letters (≤45, 46-50, 51-64, 65-69, 70-74, ≥75). VA in the BSE was translated to utility using a linear regression fit by the authors to time-trade-off utilities from the literature across a spectrum of eye diseases. Used clinical opinion and calibration to DRCR.net study cohort to estimate long-term transitions with no treatment (assuming constant visual decline, lower rate for laser strategies). On treatment data was taken from key trials: RESTORE, READ-2,	Patients with Type 1 or 2 DM, CSDMO and no previous cataract surgery. 50% were male and 50% were female. The average age at baseline was 63 years. Baseline visual acuity in the BSE was 20/63.

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)
			RISE, RIDE, RESOLVE, ETDRS. Treatment complications included were arterial thromboembolic events, glaucoma and cataracts. One-off costs and QALY decrements were applied for chronic complications.	
Stein *et al.* 2013	2011	USA	Markov model with a lifetime horizon. Mortality was included, adjusted for diabetic retinopathy. Costs included treatment acquisition and administration costs, the cost of monitoring and tests, costs of treatment of side effects caused by interventions and costs of blindness (when BCVA ≤20/200). Numbers of visits came from the DRCR.net trial. Costs and benefits were discounted at 3% per year. Strategies included were: laser (LAS), triamcinolone + laser (TA+LAS); ranibizumab + laser (RAN+LAS); ranibizumab + deferred laser (RAN+DLAS); Bevacizumab + laser (BEV+LAS) and bevacizumab + deferred laser (BEV+DLAS) were evaluated in sensitivity analysis (assuming equal efficacy with RAN regimens). VA was categorised into 6 health states based on Snellen VA (≥20/25, 20/32-20/40, 20/50-20/63, 20/80-20/100, 20/125-20/160, ≤20/200). In sensitivity analysis additional states were included for cerebrovascular accident and acute myocardial infarction with additional costs, lower HRQL and higher mortality for remaining lifetime. Visual acuity (VA) was translated to utility using values reported by Brown *et al*. (2003). QALYs lost from side effects were taken from various sources. On treatment efficacy data was taken from DRCR.net trial at Years 1 and 2. Beyond this vision was assumed constant.	Patients with newly diagnosed CSDMO. Average age at baseline 57 years. Baseline VA not reported.

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)
Dewan *et al*. 2012	2010	USA	Markov decision model using microsimulation based entirely on DRCR.net PROTOCOL I. A simulated cohort of 1,000 "subjects" was modelled 100 times, re-sampling each uncertain parameter from a specified distribution (total 100,000 simulated trials). Mean costs and letters gained were then calculated and used to perform an incremental analysis of cost per VA letter gained. The time horizon was 104 weeks. The perspective was that of the payer, using Medicare allowable charges. Costs included were treatment acquisition and administration costs, costs of selected adverse events (cataract, IOP increase, and endophthalmitis) and office visits. Strategies included were: sham injection + laser (LAS); ranibizumab + laser (RAN+LAS); ranibizumab + deferred laser (RAN+DLAS); triamcinolone + laser (TA+LAS). Patients received monthly updates of VA and macular thickness measured by OCT, based on PROTOCOL I. Costs and risks of treatment complications were also applied.	Patients in DRCR.net PROTOCOL I. Average age at baseline not reported. Baseline VA not reported
Mitchell *et al*. 2012	2009	UK	Markov model that calculated costs and changes in BCVA over a 15-year time horizon with a 3-month cycle length, Half cycle correction was applied. Costs and QALYs were discounted at 3.5% per year. Strategies included were: ranibizumab (RAN) monotherapy; ranibizumab + laser (RAN+LAS) and laser (LAS) monotherapy. BCVA was categorised into 8 health states based on ETDRS letters in the treated eye (86-100, 76-85, 66-75, 56-65, 46-55, 36-45, 26-35, 0-25). Each health state was assigned a cost and a quality of life index. Transitions between states were determined by transition probabilities for treatment effectiveness	Patients with DMO in the RESTORE trial. Average age at baseline 63 years. At baseline VA in the treated eye could fall into one of the following categories: 66-75, 56-65, 46-55, 36-45 letters.

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)
			and natural BCVA changes over time. Average BCVA achieved in Year 1 was assumed to be maintained in Year 2. In Year 3 onwards all arms were assumed to follow natural history based on the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Patients were assumed to receive RAN at frequency in RESTORE in Year 1 (7 injections) and at frequency in DRCR.net PROTOCOL I in Year 2 (2 injections for combination therapy, 3 for RAN monotherapy). After Year 2 no RAN was assumed, with LAS given as needed in all arms (2 sessions in Year 1, 1 session in Year 2 for both combination therapy and LAS monotherapy). Treatment discontinuation rates observed in RESTORE were applied in Year 1, with no further withdrawal in Year 2. Adverse events were assumed to have negligible impact on cost-effectiveness. Mortality was adjusted for DM and DMO. Utilities were calculated from EQ-5D data from RESTORE, using UK preference values. Mean utility was calculated for each health state, based on the treated eye (67.2% WSE patients). Costs included treatment acquisition and administration costs, cost of monitoring and costs (estimated from UK NHS reference costs) associated with blindness (as estimated by Meads & Hyde (2003), only applied to patients with treated eye <35 letters).	The distribution across these states was not reported.
Smiddy *et al* 2012	2011	USA	An index study (RCT with 6 month-1 year follow up) was chosen for each of the following strategies: natural history (No Tx); focal laser (LAS); triamcinolone (TA); bevacizumab (BEV); ranibizumab (RAN) and aflibercept (AFL). Where relevant, subgroups were also presented: poor VA (20/200-20/320) and pseudophakic.	Average age at baseline varied by strategy: LAS: 52 IVTA: 63

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)
			A resource utilisation profile was constructed and priced for 1 year of treatment, based on the index studies but "downsized" to reflect clinic setting. Lines of VA saved (assuming 1 line = 5 letters) were estimated based on 1 year of treatment and VA benefits were assumed to be maintained for lifetime. Natural history was used to adjust treatment benefits when internal natural history controls were not available for the index study. Costs were calculated using Medicare allowable amounts for hospital-based utilisation. The costs of complications of treatment were not included in the analysis. The mean age of each cohort was used to calculate a life expectancy (assumed equal to the general population), for the purpose of calculating the cost per line year saved. QALYs were calculated by assigning 0.03 marginal QALYs for each line gained, based on the BSE being treated (which was not the case for most index study cohorts).	BEV (PACORES): 60 BEV (BOLT): 65 RAN (DRCR): 63 RAN (READ): 62 AFL (2q4): 62 AFL (2q4 for 3 doses then q8): 63 **Poor VA subgroup:** LAS: 63 TA: 63 **Pseudophakic subgroup:** LAS: 63 TA: 62 RAN: 63 Baseline VA not reported.
Smiddy *et al*. 2011	2010	USA	An index study (RCT with 6 month-1 year follow up) was chosen for each of the following strategies: natural history (No Tx); focal laser (LAS); triamcinolone (TA); dexamethasone (DEX); pegaptanib (PEG); bevacizumab (BEV); ranibizumab (RAN) and vitrectomy (VIT). A resource utilisation profile was constructed and priced for 1 year of treatment, based on the index studies but "downsized" to reflect clinic setting. Lines of VA saved (assuming 1 line = 5 letters) were estimated based on 1 year of treatment and VA	Average age at baseline varied by strategy: LAS: 52 TA: 63 DEX: 63 PEG: 62

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)
			benefits were assumed to be maintained for lifetime. Natural history was used to adjust treatment benefits when internal natural history controls were not available for the index study. Costs were calculated using Medicare allowable amounts for hospital-based utilisation. The mean age of each cohort was used to calculate a life expectancy, for the purpose of calculating the cost per line year saved. QALYs were calculated by assigning 0.03 marginal QALYs for each line gained, based on the BSE being treated (which was not the case for most index study cohorts).	BEV (PACORES): 60 BEV (BOLT): 65 RAN (DRCR): 63 RAN (READ): 62 VIT: 66 Baseline VA not reported.
Sharma *et al*. 2000	2000	USA	Decision tree model constructed using TreeAge, for a population of patients with bilateral DMO who were treated with laser photocoagulation (LAS) in one eye or no therapy (No Tx). Patients entered the model in one of a number of possible initial visual acuity states (>20/20; 20/20-20/25; 20/30-20/40; 20/50-20/60 and <20/60) and were assigned a probability of doubling the visual angle (significant visual loss) or not by 3 years based on ETDRS study data. Outcomes at 3 years were extrapolated to a 40 year time horizon using net present value analysis and an annual discount rate of 5%. Utilities were obtained from a survey of 100 diabetic retinopathy patients using the time-trade-off technique. Mean utilities were assigned for each initial visual acuity state dependent on whether the visual angle had doubled or not. Disutilities were applied to the proportions of patients who incurred complications of laser treatment: rupture of Bruch's membrane, retinal vascular occlusion and foveal photocoagulation. These were based on discussions with a utility committee. Costs were obtained from Medicare reimbursement data. These	Patients with bilateral DMO Mean age at baseline was 47 years. Baseline VA not reported.

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)
			included all variable costs associated with laser treatment: initial outpatient consultation; photocoagulation destruction of localised lesion of choroid and fluorescein angiography with interpretation and report.	
NICE TA271[189]/TA301[86, 190]	2012	UK	Model comparing fluocinolone acetonide intravitreal implant (FA) with 'optimised standard of care' (OSC) based on the FAME trial and with laser photocoagulation (LAS) based on DRCR PROTOCOL B over a 15 year time horizon. The cycle length was 3 months. Costs and benefits were discounted at a rate of 3.5% per year. The model included 13 BCVA-defined health states (defined by 5-letter increments in the treated eye) and a state for death. Utilities were assigned to each BCVA-defined health state using data from Brown *et al*. (2000), extrapolated to fit the health states used by the manufacturer. A 25% QALY uplift was applied to bilateral patients. No utility decrement was applied for adverse events. No distinction was made between treatment in the BSE or the WSE; bilateral treatment was 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 the distribution of patients across BCVA-defined health states was taken directly from the FAME trials, beyond Year 3 a Markov structure was assumed using transition probabilities extrapolated from the last 4 quarters of the FAME trials. Patients receiving a 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	Patients with chronic DMO (original base case) and patients with chronic DMO and a pseudophakic lens (PAS submission scenario) Average age at baseline 62.9 years (OSC)/63.7 years (FA) Baseline VA not reported.

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)
			worsening by 5 letters in each cycle. One FA implant was assumed every 3 years. Re-treatment occurred at Month 36 if a patient had gained at least 5 letters. Withdrawal rates from the FAME trials were applied to calculate an adjusted re-treatment rate, applied equally across BCVA-defined states. Patients in both FA and OSC arms could receive LAS and other therapies (triamcinolone, ranibizumab, bevacizumab and dexamethasone) based on rates observed in FAME. Costs included treatment acquisition and administration costs, costs of treatment for adverse events and an annual cost of blindness for patients whose treated-eye BCVA fell below 35 letters. **Amendments based on ERG request for clarification:** Utility values were updated to a study by Heintz *et al*. (2012) and a number of other elements including amending the response rate based upon a 10-letter re-treatment criterion. **Patient access scheme submission:** Analyses were presented using utility values from Brown *et al*. (1999), Brown *et al*. (2000) and Czoski-Murray *et al*. (2009). It was assumed that changes in vision for patients treated in their WSE had 30% of the HRQL impact of the same change in vision from treating the BSE. 20% treated in BSE, 40% treated in WSE and 40% treated bilaterally.	
NICE TA237[191]/TA274[84,]	2009	UK	Markov model evaluating ranibizumab monotherapy (RAN), ranibizumab + laser (RAN+LAS) or laser monotherapy (LAS).	Patients with DMO.

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)
[192]			The model used a cycle length of 3 months and a time horizon of 15 years. Patients were assigned a starting BCVA between 75 and 36 letters. Health states were 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). Utilities were assigned to each health state based on EQ-5D data from RESTORE using a linear regression. No utility decrement was applied for adverse events. In line with RESTORE, 7 RAN injections were assumed in Year 1, with a stopping rule included where patients with BCVA >76 letters did not receive treatment costs. In Year 2, 3 additional injections were assumed for RAN and 2 additional injections were assumed for RAN+LAS in line with DRCR PROTOCOL I. Two and one laser treatments were assumed in Years 1 and 2, respectively. No treatment was assumed after Year 2. Transition probabilities were taken from RESTORE in Year 1. In Year 2 vision was assumed to remain constant based on DRCR.net PROTOCOL I. In Year 3 onwards a probability of improving or deteriorating was applied based on epidemiological data. Mortality data for the general population was adjusted using a relative risk for the death of people with clinically significant DMO compared with people with DM but without DMO. Adverse events included in the model were cataract, endophthalmitis, retinal detachment and vitreous haemorrhage. Costs included were the costs of treatment acquisition and administration, costs of treating adverse events, costs of monitoring and the costs of severe vision loss (applied to people whose treated eye was <35 letters).	Average age at baseline 63 years. Baseline VA not reported.

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)
			<u>Revised analysis based on appraisal consultation document (including first PAS):</u> The revised model considered treatment in the BSE only. A higher relative risk of mortality was applied to also account for the higher risk of mortality in a DM population relative to the general population. The stopping rule was 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 was assumed to remain stable in Years 2-4, with natural history applied from Year 5. A scenario analysis was provided whereby bilateral treatment was simulated for 35% of patients by doubling the costs of RAN and treatment administration costs. The cost of severe vision loss was decreased and a 25% uplift in QALYs was applied. Presented a subgroup analysis in patients with central foveal thickness >400µm. **<u>Revised patient access scheme submission:</u>** Approximated ICER for treatment of both eyes calculated by multiplying ICER from BSE model by 1.5. The revised model applied utility values from Czoski-Murray *et al*. (2009) in the base case. The number of RAN injections was amended to 7, 4 and 3 in Years 1-3, with no further injections. A reduced time horizon of 10 years was adopted.	

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)

Key: AFL, aflibercept; BCVA, best-corrected visual acuity; BEV, bevacizumab; BSE, better-seeing eye; CSDMO, clinically significant diabetic macular oedema; DLAS, deferred laser; DM, diabetes mellitus; DMO, diabetic macular oedema; DRCR.net, Diabetic Retinopathy Clinical Research Network; ETDRS, Early Treatment of Diabetic Retinopathy Study; EQ-5D, EuroQol-five dimensions questionnaire; ERG, evidence review group; FA, fluocinolone acetonide intravitreal implant; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IOP, Intraocular pressure; IVTA, Intravitreal triamcinolone acetonide; LAS, laser; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OCT, optical coherence tomography; OSC, optimised standard of care; PAS, Patient access scheme; PEG, pegaptanib; QALY(s), quality-adjusted life year(s); RAN, ranibizumab; RCT, randomised controlled trial; TA, triamcinolone; Tx, treatment; VA, visual acuity ; VIT, vitrectomy; UK, United Kingdom; USA, United States of America; WSE, worse seeing eye.

Table 60: Summary list of other cost-effectiveness evaluations – results

Study	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Pershing et al. 2014	**1 Year treatment** TA+LAS: 5.63 RAN+LAS: 6.19 RAN: 6.16 TA: 4.33 No Tx: 4.58 LAS: 4.66 **Lifetime treatment** TA+LAS: 5.16 RAN+LAS: 6.24 RAN: 6.23 TA: 3.73 LAS: 4.70 No Tx: 4.58	**1 Year treatment** TA+LAS: $97,998 RAN+LAS: $104,973 RAN: $106,213 TA: $167,162 No Tx: $169,469 LAS: $170,027 **Lifetime treatment** TA+LAS: $97,493 RAN+LAS: $126,082 RAN: $133,126 TA: $162,831 LAS: $167,341 No Tx: $169,469	**Incremental analysis, ICER relative to the next best treatment:** **1 Year treatment** TA+LAS: N/A RAN+LAS: $12,410 RAN: Dominated TA: Dominated No Tx: Dominated LAS: Dominated **Lifetime treatment** TA+LAS: N/A RAN+LAS: $26,477 RAN: Dominated TA: Dominated LAS: Dominated No Tx: Dominated
Stein et al. 2013	**Base model (incl. RAN):** Laser: 10.41 TA+LAS: 9.54 RAN+LAS: 10.83 RAN+DLAS: 10.99	**Base model (incl. RAN):** Laser: $20,013 TA+LAS: $23,877 RAN+LAS: $58,257 RAN+DLAS: $61,424	**Base model (incl. RAN):** Laser: N/A TA+LAS: Dominated RAN+LAS: $89,903 (extendedly dominated) RAN+DLAS: $71,271

Study	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
	Base model (incl. BEV): Laser: 10.41 TA+LAS: 9.54 BEV+LAS: 10.83 BEV+DLAS:10.99	**Base model (incl. BEV):** Laser: $20,013 TA+LAS: $23,877 BEV+LAS: $27,200 BEV+DLAS: $26,485	**Base model (incl. BEV):** Laser: N/A TA+LAS: Dominated BEV+LAS: Dominated BEV+DLAS: $11,138
Dewan *et al*. 2012	QALYs not calculated for comparison of treatments	**All patients** TA+LAS: $4,874 LAS: $5,250 RAN+LAS: $24,054 RAN+DLAS: $24,090 **Pseudophakic patients** TA+LAS: $4,508 LAS: $5,268 RAN+LAS: $24,229 RAN+DLAS: $24,560	QALYs not calculated for comparison of treatments
Mitchell *et al*. 2012	**Incremental QALYs:** RAN vs. LAS: 0.17 RAN+LAS vs. LAS: 0.13	**Incremental costs:** RAN vs. LAS: £4,191 RAN+LAS vs. LAS: £4,695	**ICER:** RAN vs. LAS: £24,028 RAN+LAS vs. LAS: £36,106
Smiddy *et al* 2012	QALYs not reported	LAS: $1,758 IVTA: $1,427 BEV (PACORES): $2,490 BEV (BOLT): $4,135 RAN (DRCR): $21,265	**Cost per QALY for each individual treatment (not incremental):** LAS: $7,600 IVTA: $6,267 BEV (PACORES): $1,800

Study	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		RAN (READ): $21,709 AFL (2q4): $25,913 AFL (2q4 for 3 doses then q8): $15,785 **Poor VA subgroup:** LAS: $2,333 TA: $1,907 **Pseudophakic subgroup:** LAS: $2,613 TA: $3,301 RAN: $21,289	BEV (BOLT): $3,533 RAN (DRCR): $18,300 RAN (READ): $18,700 AFL (2q4): $2,300 AFL (2q4 for 3 doses then q8): $1,870 **Poor VA subgroup:** LAS: $2,767 TA: $1,067 **Pseudophakic subgroup:** LAS: $5,267 TA: $3,333 RAN: $23,533
Smiddy *et al*. 2011	QALYs not reported	LAS: $1,326 TA: $1,574 DEX: $2,207 PEG: $10,500 BEV (PACORES): $2,684 BEV (BOLT): $4,718 RAN (DRCR): $21,265 RAN (READ): $21,709 VIT: $4,701	**Cost per QALY for each individual treatment (not incremental):** LAS: $5,862 TA: $6,246 DEX: $9,446 PEG: $16,667 BEV (PACORES): $2,013 BEV (BOLT): $4,160 RAN (DRCR): $23,119 RAN (READ): $19,251 VIT: $8,706

Study	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Sharma *et al*. 2000	**After 3 years:** LAS: 0.833 No Tx: 0.827 **Incremental QALYs after 3 years:** LAS vs. No Tx: 0.0059 **Incremental QALYs after 40 years:** LAS vs. No Tx: 0.236	**After 3 years:** LAS: $733 No Tx: $0 **Incremental costs after 3 years:** LAS vs. No Tx: $733	**After 3 years:** LAS vs. No Tx: $3,101 **Over 40 years:** LAS vs. No Tx: $3,655
NICE TA271[189]/TA301[86, 190]	**Base case incremental QALYs:** FA vs. OSC: 0.500 **Amendments based on ERG clarification request incremental QALYs:** FA vs. OSC: 0.619	**Base case incremental costs (no PAS):** FA vs. OSC: £11,300 **Amendments based on ERG clarification request incremental costs:** FA vs. OSC: £11,927	**Base case ICER (no PAS):** FA vs. OSC: £22,655 **Amendments based on ERG clarification request ICER:** FA vs. OSC: £19,268 **ICERs with PAS; chronic DMO:** FA vs. OSC (Brown 2000): £37,630 FA vs. OSC (Brown 1999): £63,472 FA vs. OSC (Czoski-Murray 2009): £42,663 **ICERs with PAS; chronic DMO and pseudophakic:** FA vs. OSC (Brown 2000): £17,639

Study	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			FA vs. OSC (Brown 1999): £30,296 FA vs. OSC (Czoski-Murray 2009): £19,884
NICE TA237[191]/TA274[84, 192]	QALYS not reported in guidance document	Costs not reported in guidance document	**Base case ICER (no PAS):** RAN vs. LAS: £19,075 RAN vs. RAN+LAS: RAN dominates **ICERs with PAS (no bilateral treatment):** RAN vs. LAS (All DMO): £30,277 RAN vs. LAS (CRT≥400µm): £21,418 **ICERs with PAS (including bilateral treatment):** RAN vs. LAS (All DMO): £44,355 RAN vs. LAS (CRT≥400µm): £35,719 **ICERs with revised PAS:** RAN vs. LAS(BSE): £14,137 RAN vs. LAS (Bilateral): £21,205 **ICERs with revised PAS (CRT ≥400 µm):**

Study	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			RAN vs. LAS (BSE): £8,881 RAN vs. LAS (Bilateral): £13,322 **ICERs with revised PAS (CRT <400 µm):** RAN vs. LAS (BSE): £28,861 RAN vs. LAS (Bilateral): £43,292

Key: AFL, aflibercept; BEV, bevacizumab; BSE, better-seeing eye; CRT, central retinal thickness; DLAS, deferred laser; DMO, diabetic macular oedema; DRCR.net, ERG, evidence review group; FA, fluocinolone acetonide intravitreal implant; ICER, incremental cost-effectiveness ratio; IVTA, Intravitreal triamcinolone acetonide; LAS, laser; N/A, not applicable; NICE, National Institute for Health and Care Excellence; OSC, optimised standard of care; PAS, Patient access scheme; PEG, pegaptanib; QALY(s), quality-adjusted life year(s); RAN, ranibizumab; TA, triamcinolone; Tx, treatment ; VIT, vitrectomy.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)a or Philips et al. (2004)b. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

The completed quality assessment for each study included in the review is presented in appendix 11 (section 10.11).

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The marketing authorisation for DEX700 states that DEX700 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."

The economic evaluation includes analyses that cover the anticipated licensed indication for DEX700 as follows:

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[a] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[b] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

Patients with DMO who are considered unsuitable for non-corticosteroid therapy

This analysis considers DEX700 as a first- or second-line treatment option and the comparator for this analysis is watch and wait as there are currently no available first-line treatment options for this patient population, hence there is a clear unmet need in this patient group as defined in Section 2.6.

This analysis is based on data for the whole DMO population. The population of DMO patients who are considered unsuitable for non-corticosteroid therapy (defined in Section 2.6) is a subset of the whole DMO population which is extremely difficult to quantify and is therefore a difficult population in which to perform an economic analysis. Given this, there is no available evidence for DEX700 in this population; therefore the assumption has been made that there is no differential efficacy of DEX700 in the population of DMO patients who are considered unsuitable for non-corticosteroid therapy compared with the whole DMO population.

Therefore, this analysis utilises data for the whole DMO population as a proxy for the population of patients with DMO who are considered unsuitable for non-corticosteroid therapy.

Patients with DMO who are considered insufficiently responsive to non-corticosteroid therapy

This analysis considers DEX700 as a second-line treatment option to non-corticosteroid therapy, including ranibizumab, bevacizumab and laser. The comparator for the base case analysis in this population is watch and wait as there is an unmet need for a treatment option in this patient population. A sensitivity analysis has been included that also incorporates fluocinolone acetonide as a comparator treatment. Fluocinolone acetonide has been excluded from the base case analysis as market share data indicates minimal use of fluocinolone acetonide in clinical practice. This is assumed to be due to the restrictions placed on its use in clinical practice both by its marketing authorisation[176] and by NICE guidance.[86]

The marketing authorisation for fluocinolone acetonide states that it is indicated “for the treatment of vision impairment associated with chronic

diabetic macular oedema, considered insufficiently responsive to available therapies".[176] NICE guidance for the use of fluocinolone acetonide places a further restriction on its use in England and Wales; that the implant is only to be used in an eye with a pseudophakic lens.[86] These restrictions position fluocinolone acetonide as a last-line treatment for a small and very specific patient population. Allergan therefore does not believe that this is an appropriate comparator population for DEX700.

Despite this, the final scope for this appraisal includes fluocinolone acetonide as a relevant comparator treatment and therefore an attempt has been made to include fluocinolone acetonide within the analysis. However, there are major limitations in the data that are available 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
  - 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.

Therefore this comparison has been provided as a sensitivity analysis only, as this treatment was included as a relevant comparator in the final scope for the appraisal.

Available evidence does not suggest that there is a differential efficacy of DEX700 treatment in patients who are considered insufficiently responsive to non-corticosteroid therapy compared with the whole population:

- There was a long period of study enrolment for the MEAD trial (February 2005 to June 2009).[67] At the start of this enrolment period no pharmacological treatment was licensed for the treatment of DMO. Ranibizumab received positive CHMP opinion in 2010 and therefore only patients who were recruited later would have had the opportunity to be exposed to anti-VEGF treatments such as ranibizumab.[193] This means that the modified intention-to-treat (mITT)[c] population in MEAD included only a very small proportion of DEX700 patients who had received previous anti-VEGF therapy (▇) from which it would be difficult to draw any meaningful conclusions.[194]
- A higher proportion of DEX700 patients in the mITT population of the MEAD studies had exposure to laser treatment (▇) and in these patients there was no significant difference in outcomes compared with the mITT population.[194]

Therefore, this analysis utilises data for the whole DMO population as a proxy for the population of patients with DMO who are considered insufficiently responsive to non-corticosteroid therapy.

Patients with DMO who are pseudophakic

This analysis considers DEX700 as a first- or second-line treatment option and the comparator for this analysis is ranibizumab in the base case, as this is the most common first-line treatment for DMO used in clinical practice. This is supported by market share data (see Section 8) which indicates that

[c] The mITT population is the subset of the ITT population with at least one follow-up visit.

ranibizumab accounts for approximately [redacted] of the pharmaceutical DMO market in 2014.

Bevacizumab and laser were also included in the scope for this appraisal. Allergan believe that laser is rarely appropriate or beneficial and is no longer routinely used as a monotherapy and there are very few centres in which bevacizumab is still available as a treatment option for DMO since the introduction of ranibizumab. Bevacizumab is not formulated for intraocular use and therefore there are risks of adverse events associated with pharmacy-compounded formulations of this product. Historically, bevacizumab was available for use in the eye under a “specials license” through Moorfields Eye Hospital or Liverpool and Broadgreen University Hospital but the re-formulated manufacturing at both sites has now ceased. According to feedback through consultation with practicing UK ophthalmologists, the use of bevacizumab is not established NHS practice in England and Wales: it is reportedly no longer available at all for use in DMO in the North East of England and its use is declining in the South of England with no London hospitals supporting its use. These treatments have therefore been included only as a scenario analysis to demonstrate the cost-effectiveness of DEX700 compared with all possible treatment options for DMO in patients who are pseudophakic. Watch and wait has also been included in this scenario analysis for completeness.

This analysis is based on the subgroup of pseudophakic patients in the pooled MEAD clinical studies. Where possible, data for other treatments in the network of evidence are also for the pseudophakic population. 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 network has been constructed using data for the whole DMO population in the absence of data for the pseudophakic population.

As discussed in section 6.7 the studies that did not report pseudophakic data included anti-VEGF or laser treatments. These treatments are not known to have an increased risk of cataract as observed with corticosteroid therapies; hence the assumption that there is no subgroup effect for pseudophakic

patients receiving these treatments is justified to enable a comparison against these treatments in this population.

Including evidence for the whole DMO population for some treatments and data for the pseudophakic population for other treatments is a limitation of this 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. This limitation is recognised, however, it is necessary to enable a full network to be constructed in this population. Therefore this is felt to be the best analysis possible given the evidence base available.

It is noted that ranibizumab, bevacizumab and fluocinolone acetonide are included in the scope as either monotherapy or in combination with laser. No evidence was identified for bevacizumab + laser or fluocinolone acetonide + laser. In the technology appraisal of ranibizumab for the treatment of DMO, ranibizumab + laser was dominated by ranibizumab monotherapy.[191] Furthermore, clinician advice indicated that in practice, laser is not likely to be used as a true combination therapy regimen; instead laser is likely to be used in combination with anti-VEGF or fluocinolone acetonide on an *ad-hoc* basis, which is more likely to be reflected by the use of “rescue” laser therapy in clinical trials (appendix 14, section 10.14). Therefore ranibizumab, bevacizumab and fluocinolone acetonide have been included in the cost-effectiveness analyses in this appraisal as monotherapies only.

In all analyses DEX700 is assumed to be a PRN regimen as per the MEAD study whereby DEX700 is given as needed with a minimum treatment interval of 6 months. This is the licensed dose of DEX700 and is therefore felt to most appropriately reflect the way in which DEX700 will be used in clinical practice.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

A cohort model with a Markov structure was chosen to model changes in BCVA resulting from the treatment of DMO over a 15-year time horizon. A

cycle length of 3 months was adopted, consistent with the visit schedule of the MEAD studies. The model allows BCVA changes in both eyes to be modelled independently; with the better-seeing eye (BSE) and worse-seeing eye (WSE) defined at baseline and fixed throughout the time horizon. Treatment may be modelled in both eyes (bilateral DMO) or in either the BSE or WSE (unilateral DMO).

Visual acuity states

Both eyes may transition between six visual acuity states of 10-letter increments shown in Figure 54 and defined in Table 61. Treatment for DMO influences the probability of transitioning between the visual acuity states. In each 3-month cycle the eye may move up (improved vision) or down (worsened vision) by a maximum of one visual acuity state, or the eye may remain in the same visual acuity state (stable vision). Restricting the movements to a maximum of one visual acuity state in each cycle is a limitation of the analysis; the reasons for making this simplifying assumption and the potential impact are described further in section 7.3.2. The probability of moving between visual acuity states in each cycle is modelled using transition probability matrices (TPMs).

Figure 54: Model structure – visual acuity states

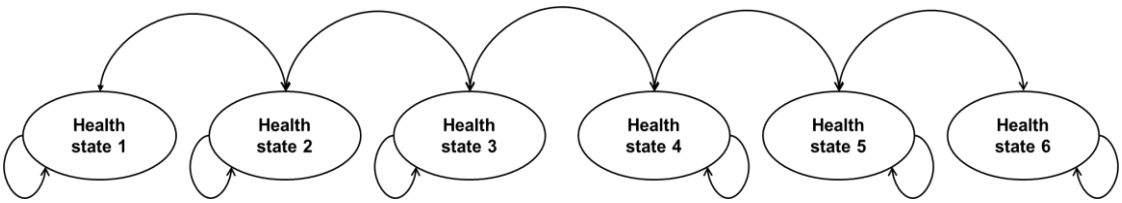


Table 61: Visual acuity health state definitions

	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	

Key: BSE, better-seeing eye; ETDRS, Early Treatment Diabetic Retinopathy Study.
Source: Gregori 2010[195]

Patient pathways

A cohort of patients entering the model is assumed to be receiving treatment for DMO, and may be affected with DMO in the BSE or the WSE (unilateral DMO) or in both eyes (bilateral DMO). The proportions of patients within the cohort who have unilateral DMO in the BSE or the WSE, or bilateral DMO at baseline are assumed to be as observed in the DEX700 treatment arm of the pooled MEAD studies. There were no differences in baseline demographic or study eye characteristics between the treatment groups in the MEAD studies.[67] These proportions are assumed to vary by population and are shown in Table 62.

Table 62: Baseline distribution of patients by DMO status

Population	Unilateral DMO in the		Bilateral DMO
	BSE	WSE	
All DMO	[redacted]	[redacted]	[redacted]
Pseudophakic	[redacted]	[redacted]	[redacted]

Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File 2014[194]

Patients within the cohort who are affected unilaterally at baseline may develop DMO in their second eye, termed fellow eye involvement and move to bilateral treatment. This is limited to occur only at the end of Year 1 or Year 2 and is described further in section 7.3.2.

Patients within the cohort who are affected bilaterally from baseline are assumed to receive the same treatment, at the same frequency and achieve the same level of efficacy in both eyes. This assumption is supported by Guillard *et al*. (2014)[196] who demonstrated that in 18 DMO patients treated bilaterally with ranibizumab a symmetrical functional response, defined as an

increase in BCVA of at least 5 letters on the ETDRS scale, was achieved in 72% of patients. This indicates that if both eyes are treated with ranibizumab the majority of patients will experience a symmetrical treatment response. It has been assumed that a similar response will be seen with any treatment for DMO.

The model assumes a maximum duration of treatment of 3 years in the base case, consistent with the maximum duration of key clinical trials (section 7.3.2). At any time during this period patients within the cohort may discontinue from treatment for one of two independent reasons (section 7.3.2):

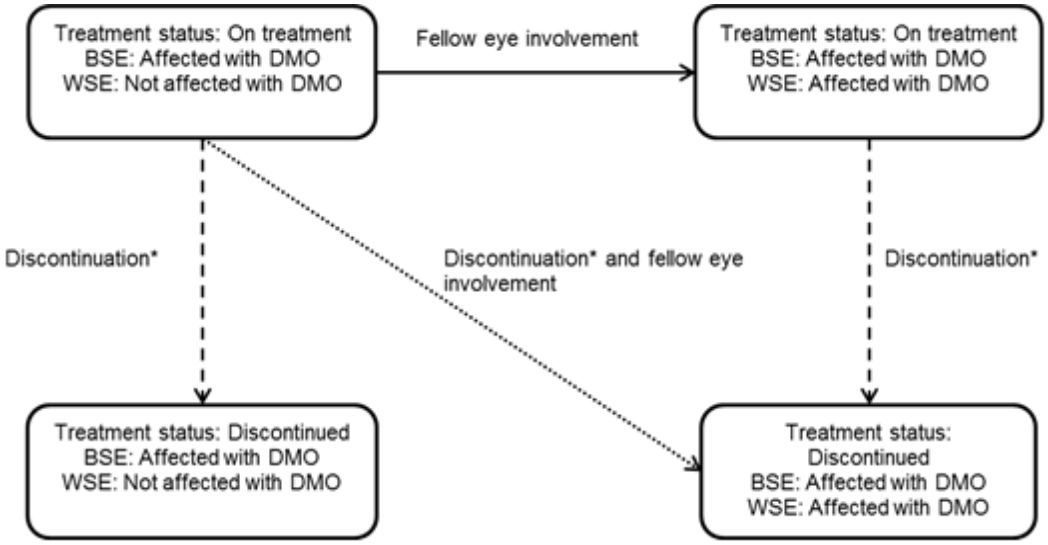
- Adverse events and other non-efficacy related reasons[d]
- Lack (or loss) of efficacy of treatment

All patients are at risk of death at all times. In the Markov model death is an absorbing state.

Figure 55, Figure 56 and Figure 57 show the patient pathways for patients within the cohort who have unilateral DMO in the BSE, unilateral DMO in the WSE or bilateral DMO at baseline. Figure 58 shows all possible movements for all patients within the cohort.

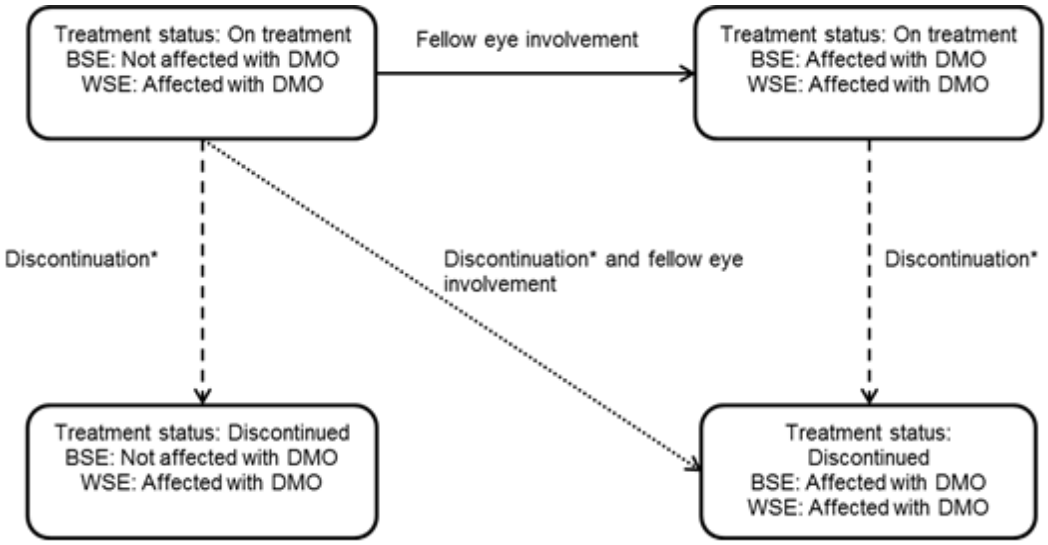
[d] Other non-efficacy-related reasons for discontinuation from initial treatment are assumed to include all reasons for discontinuation excluding adverse events, lack of efficacy, loss of efficacy, receipt of an off-protocol treatment (assumed to indicate lack of efficacy) or death. These may include withdrawal of consent, lost to follow-up, protocol violation, personal reasons, etc.

Figure 55: Patient pathway, patient with unilateral DMO in the BSE at baseline



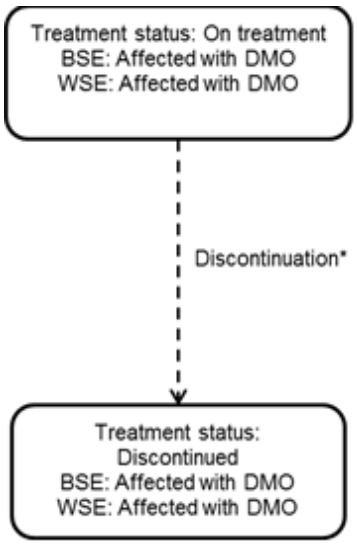
Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: *Discontinuation due to either adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment.

Figure 56: Patient pathway, patient with unilateral DMO in the WSE at baseline



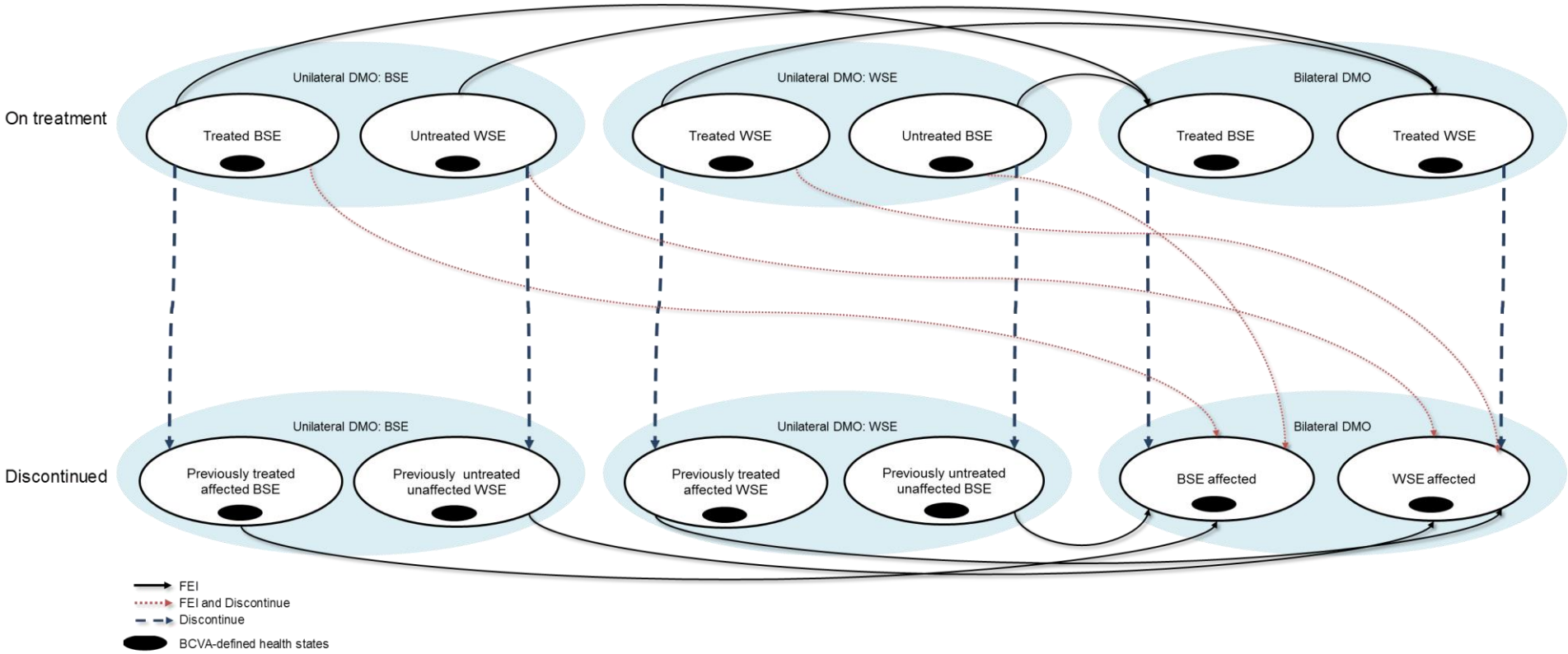
Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: *Discontinuation due to either adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment.

Figure 57: Patient pathway, patient with bilateral DMO



Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: *Discontinuation due to either adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment.

Figure 58: Model structure – Patient pathways*



Key: BCVA, best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; FEI, fellow eye involvement; WSE, worse-seeing eye.
Notes: *'Discontinued' states are repeated for the two reasons for discontinuation: adverse events and other non-efficacy related reasons; or a lack (or loss) of efficacy of treatment.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Visual acuity states

The visual acuity states are based on a 10-letter change in BCVA on the ETDRS eye chart, which is a standard method of measuring visual acuity in clinical trials. A gain (or loss) of 10 letters may be associated with a clinically significant change in HRQL, and therefore is considered relevant for the DMO population.[145]

Patient pathways

The patient pathways reflect the fact that patients may, in practice, be affected with DMO either unilaterally or bilaterally, and therefore may require treatment in one or both eyes. Patients who are affected unilaterally may be affected in either the BSE or WSE and in practice they may develop DMO in their fellow eye over time.

The explicit modelling of treatment in either or both eyes, and the subsequent possibility of development of DMO in the second eye, are adaptations of the *de novo* model submitted as part of this appraisal compared with previous economic modelling in DMO. These adaptations have been included to more accurately reflect the disease presentation and evolution compared with previous modelling.

The patient pathways additionally reflect that in practice patients may discontinue from treatment. Discontinuation has been modelled for two explicit reasons, 1) adverse events and other non-efficacy related reasons or 2) lack (or loss) of efficacy of treatment.

The explicit modelling of discontinuation from treatment for the two reasons stated is a further adaptation within the model presented here. This is intended to reflect the fact that, in practice within the clinical pathway, patients may be discontinued from a treatment for these reasons. The selection of these explicit and independent reasons for discontinuation is driven by the data from the MEAD studies for DEX700. Within the MEAD studies [redacted] DEX700 patients discontinued from the study due to adverse events

and other non-efficacy related reasons, [redacted] DEX700 patients discontinued from the study due to lack or loss of efficacy of treatment and [redacted] DEX700 patients were censored due to receipt of an off-protocol treatment as required by the study protocol.[194] These represent a non-trivial proportion of the MEAD clinical study population for DEX700 for whom there is no evidence of how their BCVA progressed following discontinuation or censoring and for whom it would be inappropriate to assume receive the costs and efficacy of treatment within the economic model.

7.2.4 Please define what the health states in the model are meant to capture.

Visual acuity states

The health states (Figure 54 and Table 61) are defined by visual acuity. DMO directly impacts visual acuity and hence the model captures the effect of treatment on the cohorts' vision and DMO.

Both eyes are modelled for all patients within the cohort, with different visual acuity TPMs applied for eyes with DMO which are on treatment or discontinued from treatment and for eyes without DMO.

Patient pathways

The patient pathways (Figure 55, Figure 56, Figure 57 and Figure 58) are intended to capture the treatment and disease status of the DMO cohort. The pathways capture the proportion of patients within the cohort who have unilateral DMO in the BSE or WSE, or bilateral DMO over time.

In addition, they capture whether the patients within the cohort remain on treatment or have discontinued from treatment due to either adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2

(Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

As described in section 2, DMO can affect either one or both eyes of the DM patient (unilateral or bilateral DMO); the model structure captures this by modelling vision in both eyes, for patients with bilateral or unilateral DMO. Patients with unilateral DMO are affected and therefore receive treatment in their BSE or their WSE and are at risk of developing fellow eye involvement thus becoming a bilateral patient at the end of Years 1 or 2 (see section 7.3.2).

Vision loss, potentially leading to blindness, is the main impact of disease progression for DMO for patients and is the outcome of interest for clinicians. This is captured through the modelling of transitions between visual acuity states as described in section 7.2.2, 7.2.3 and 7.2.4, and shown in Figure 54. Changes in visual acuity are associated with changes in HRQL.[197] Changes in visual acuity in the BSE are expected to have a larger impact on HRQL than changes in the WSE.[159] This is indicated by the accepted assumptions in previous NICE technology appraisals, whereby changes in visual acuity in the WSE were assigned 30% of the utility increment which would be assigned to the same change in visual acuity in the BSE.[86]

Severe vision loss (defined as BCVA ≤ 35 letters within the model) in both eyes is considered clinical blindness and is additionally associated with increased costs and mortality (section 7.5.6).[77]

In terms of transitions between visual acuity states, eyes that are affected with DMO are assumed to receive treatment for up to 3 years, and are assigned the efficacy associated with treatment, for as long as they remain on treatment. This is based on transition probabilities derived from relative efficacy from the mixed treatment comparison (section 6.7) applied to reference transition probabilities observed in the pooled MEAD clinical studies (see section 7.3.2).

During the initial 3-year treatment period patients are at risk of discontinuation from treatment either due to adverse events and other non-efficacy related reasons, or due to lack (or loss) of efficacy of treatment. Following discontinuation, it is assumed that patients receive no further treatment and as a result the vision in their affected eye(s) transitions through the visual acuity states at a rate consistent with the natural history of vision in patients with DMO, taken from Mitchell *et al*. (2012)[44] (see section 7.3.2, Table 81). This simplifying assumption has been made to reflect that the decision problem for this appraisal is to consider the cost-effectiveness of DEX700 for the treatment of DMO. Modelling an explicit next line of treatment following discontinuation could lead to a different decision problem being considered, i.e. to find the optimal sequence of treatments for DMO, particularly where multiple options for further treatment are available. The assumption is intended to reflect that vision may still be affected by DMO following discontinuation, hence the application of natural history of vision in DMO.

Following the initial treatment period, it is expected that eyes with DMO may still experience changes in vision as a result of the condition and hence visual acuity in these eyes is assumed to follow the natural history of vision in patients with DMO (see section 7.3.2).

Eyes without DMO are assumed to retain constant vision as the focus of this submission is the treatment of visual impairment due to DMO. It has been demonstrated that patients with DM are at a higher risk of ocular comorbidities such as diabetic retinopathy, a leading cause of visual loss in the developed world in those of working age.[8, 27, 50, 53, 54] DM may also raise the risk of visual impairment due to cataracts and glaucoma, both of which have been associated with as much as a five-fold prevalence increase in patients with DM compared with patients without DM.[24-27] As discussed in section 6.9.3, in the population based Blue Mountains Eye Study, cataract formation resulted in a cumulative incidence of cataract surgery in DM patients of 20.9% over 10 years.[30] Therefore in patients with DM, eyes that have not developed DMO may still be likely to experience a decline in vision and modelling stable vision in these eyes may under-estimate the true level of vision loss in DM patients. However, all patients within the cohort have the same probability of having

unilateral DMO and experience the same risk of ocular comorbidities in their fellow eye, regardless of the treatment received for DMO. Therefore, any vision loss resulting from ocular comorbidities as a result of DM would affect all cohorts equally and has not been considered within the economic model as a simplifying assumption.

The model assumes that the BSE and WSE are defined at baseline and fixed throughout the time as a simplifying assumption. 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). The exclusion of this functionality from the model is a limitation of the analyses presented here, as the true benefit of treatment (and equally the true detriment of a watch and wait strategy) may not be accurately captured. This assumption is, however, consistent with previous modelling in DMO.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 63: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	15 years	The baseline age of patients entering the model is [redacted] years (mITT) and [redacted] years (pseudophakic).[194] 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.	Section 5.1.15 to 5.1.17 of NICE Guide to methods of technology appraisal
Cycle length	3 months	The MEAD clinical trials that form the baseline transition probability matrices measured visual acuity in 6-weekly intervals in Year 1 and 3-monthly intervals in Years 2 and 3; hence a 3-month cycle length was chosen to enable the use of patient-level transition probability matrices from MEAD with a consistent cycle length.	MEAD studies
Half-cycle correction	Yes	Half-cycle correction is appropriate for a 3-month cycle length	N/A
Were health effects measured in QALYs; if not, what was used?	Yes	In line with the NICE reference case	Section 5.3.1 of NICE Guide to methods of technology appraisal
Discount of 3.5% for utilities and costs	Yes	In line with the NICE reference case	Section 5.6.1 of NICE Guide to methods of technology appraisal
Perspective	Yes	In line with the NICE	Section 5.5.1 of

(NHS/PSS)		reference case	NICE Guide to methods of technology appraisal
Key: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALYs, quality-adjusted life years.			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

DEX700 is implemented within the model as per its marketing authorisation, with two patient subgroups presented to represent the three populations covered by the marketing authorisation (Table 64).

Table 64: Patient subgroups presented

Patient subgroup	Comparator treatments	Population covered by marketing authorisation for DEX700
All DMO patients	Watch and wait	DMO patients who are considered unsuitable for non-corticosteroid therapy
	Watch and wait Fluocinolone acetonide*	DMO patients who are considered insufficiently responsive to non-corticosteroid therapy
Pseudophakic DMO patients	Ranibizumab Watch and wait* Bevacizumab* Laser*	DMO patients who are pseudophakic
Key: DEX, dexamethasone; DMO, Diabetic macular oedema. **Notes:** *Scenario analysis only. Fluocinolone acetonide is not considered a relevant comparator to DEX700 in this population due to the restrictions placed on its use in England by its marketing authorisation and NICE guidance (TA301)[86]. Bevacizumab is not indicated for use in the eye and therefore is not used very often. Laser is not widely used in clinical practice as a monotherapy.		

The marketing authorisation for DEX700 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 DEX700 PRN monotherapy is included, based on dosing and efficacy as observed in the MEAD clinical trials.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the ‘response’ criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Re-treatment and discontinuation

The marketing authorisation for DEX700 is based on as needed treatment, with a minimum between-injection interval of approximately 6 months. This is in line with the treatment decisions made by clinicians in the MEAD clinical trials, and hence in the economic model patients are assumed to receive DEX700 re-treatment at the rates observed in the pooled MEAD clinical trials.

Within the MEAD studies patients were censored upon receipt of non-study treatment (assumed due to lack, or loss, of efficacy) and some patients discontinued from DEX700 within the studies due to adverse events and other non-efficacy related reasons. Both of these groups of patients were non-trivial in size and the efficacy outcomes of these patients cannot be obtained from the trial data. Hence, discontinuation from DEX700 has been explicitly modelled, based on rates observed in the MEAD studies.

All comparator treatments are given on an as needed basis; therefore re-treatments and discontinuations are both applied at the rates observed in the key clinical trial for each comparator treatment.

Rescue therapy

The model allows the use of ‘rescue’ laser therapy according to the rates observed in the key clinical study for each modelled therapy, if this was allowed as part of the study protocol. This has been included as a number of key clinical trials allowed the use of rescue laser, and the additional efficacy gained from this use of rescue therapy cannot be disaggregated from the reported treatment effect. Therefore, as the efficacy values used to inform the network meta-analysis include the use of rescue laser, where applicable the costs of this therapy have also been included in the economic modelling. This use of laser therapy is consistent with clinical practice based on feedback from key opinion leaders (appendix 14, section 10.14).

Patients within the MEAD study who received rescue laser therapy were censored and hence efficacy estimates from the MEAD study do not include the effects of rescue laser therapy whereas for a number of other studies rescue laser therapy was permitted. This could be seen as a disadvantage to any treatment where rescue laser therapy was not permitted, including DEX700 and sham from MEAD, as the efficacy of other treatment regimens may be inflated due to the additional efficacy of rescue laser.

Average number of intravitreal injections and laser treatments per year

The average number of treatments with intravitreal injections per patient who remains on treatment in each month is calculated from monthly inputs for:

- The average number of intravitreal injections received from the last observation to the current observation
- The proportion of patients who received treatment from the last observation to the current observation

The average numbers of laser treatments in each month, for patients within the cohort who remain on their initial treatment, were entered into the model as a number per month.

Monthly inputs allow data to be entered accurately despite different clinical trials having different time periods between visits, and also despite the varied dosing schedules reported in study publications (where patient-level data were not available).

Where patient-level data were available these data were input at the time-point most closely reflecting the time of the observation.

Where patient-level data were not available the proportion of patients receiving intravitreal injections was fixed in line with the reported dosing schedule, to give the total number of treatments reported in the study publication(s). For example, if patients received an average of 3 injections in Year 1, and the protocol allowed injections at Months 0, 2, 4, 6, 8, and 10 then we would assume that 50% of patients received one injection at each of these time-points. The average number of treatments with laser was fixed at the average number reported in the study publication(s) and applied at the end of the time period reported. For example, if a publication indicated that patients received an average of 1 laser during Year 1 then we would assume that 1 laser is received at the end of Year 1.

The average numbers of intravitreal injection treatments assumed in Years 1-3 and the average number of laser treatments assumed for each treatment in Years 1-3 are shown below for each patient subgroup of interest. 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 (LOCF).

All DMO patients (DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy)

Table 65: Average numbers of intravitreal injection treatments per year; All DMO patients

Treatment	Average number of intravitreal injection treatments			Reference
	Year 1	Year 2	Year 3	
DEX700 PRN	[redacted]	[redacted]	[redacted]	MEAD[194]
Watch and wait	0.00	0.00	0.00	No treatment associated with watch and wait
Fluocinolone acetonide†	1.00	0.26	0.26	FAME[163, 173, 198]

Key: DEX, dexamethasone; DMO, Diabetic macular oedema; PRN, *pro re nata*.
Notes: *DMO patients who are insufficiently responsive to non-corticosteroid therapy only; †Scenario analysis only.

Table 66: Average numbers of laser treatments per year; All DMO patients

Treatment	Average number of laser treatments			Reference
	Year 1	Year 2	Year 3	
DEX700 PRN	0.00	0.00	0.00	No laser therapy permitted in MEAD, this resulted in censoring
Watch and wait	0.00	0.00	0.00	No treatment associated with watch and wait
Fluocinolone acetonide†	0.00	0.00	0.80	FAME[163, 173, 198] (average number of laser treatments reported over 3 years, no data reported for Year 1-2)

Key: DEX, dexamethasone; DMO, Diabetic macular oedema; PRN, *pro re nata*.
Notes: *DMO patients who are insufficiently responsive to non-corticosteroid therapy only; †Scenario analysis only.

DMO patients who are pseudophakic

Table 67 illustrates that there is a high treatment burden associated with anti-VEGF treatment regimens which could be significantly reduced with the introduction of DEX700 into the care pathway for DMO patients who are pseudophakic. This would have a positive impact for patients who would not require as many visits for treatment, and also for clinicians who would need to give injections less frequently thus increasing the capacity of the clinic.

Table 67: Average numbers of intravitreal injection treatments per year; DMO patients who are pseudophakic

Treatment	Average number of intravitreal injection treatments			Reference
	Year 1	Year 2	Year 3	
DEX700 PRN	[redacted]	[redacted]	[redacted]	MEAD[194]
Ranibizumab	7.00	3.90	2.90	RESTORE*[100, 114, 199]
Bevacizumab†	9.00	4.00	2.90	BOLT[99, 200] to Year 2 then assumed equal to ranibizumab based on clinical expert opinion about the use of bevacizumab in practice*
Laser†	0.00	0.00	0.00	No intravitreal injections associated with laser monotherapy
Watch and wait†	0.00	0.00	0.00	No treatment associated with watch and wait

Key: DEX, dexamethasone; DMO, Diabetic macular oedema; PRN, *pro re nata*.

Notes: *Based on the ITT population in the absence of published data for pseudophakic patients; †Scenario analysis only.

Table 68: Average numbers of laser treatments per year; DMO patients who are pseudophakic

Treatment	Average number of laser treatments			Reference
	Year 1	Year 2	Year 3	
DEX700 PRN	0.00	0.00	0.00	No laser therapy permitted in MEAD, this resulted in censoring
Ranibizumab	0.00	0.20	0.40	RESTORE*[100, 114, 199] (laser therapy allowed in Year 2+)
Bevacizumab†	0.00	0.00	0.00	BOLT*[99, 200] (no laser therapy allowed)
Laser†	[redacted]	[redacted]	[redacted]	Allergan analysis of PROTOCOL I[201] to Year 2, then LOCF**
Watch and wait†	0.00	0.00	0.00	No treatment associated with watch and wait

Key: DEX, dexamethasone; DMO, Diabetic macular oedema; PRN, *pro re nata*.

Notes: *Based on the ITT population in the absence of published data for pseudophakic patients; †Scenario analysis only; **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.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Treatment efficacy

Clinical data used to model treatment efficacy over the 3 year treatment period were incorporated as described in Table 69.

Table 69: Clinical data to model treatment efficacy

Treatments	Clinical data used to model treatment efficacy
DEX700 PRN	3-monthly probabilities of visual acuity in the treated eye(s) transitioning between visual acuity states generated from the DEX700 arm of the pooled MEAD studies
Watch and wait Ranibizumab Bevacizumab* Laser* Fluocinolone acetonide*	Relative effectiveness in terms of the probability 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) generated from a network meta-analysis of relevant clinical trials, applied to the transition probabilities for DEX700 PRN.
Key: DEX, dexamethasone; PRN, *pro re nata*. **Notes:** *Scenario analysis only.	

The MEAD clinical trials provide 3 years of evidence for the efficacy of DEX700 compared with sham injections, where BCVA in the study eye was measured every 3 months in patients who had not discontinued from the study or been censored following receipt of off-protocol therapy. Therefore 3-monthly transition probabilities between visual acuity states were generated from the MEAD data over the 3-year follow-up period. These transition probabilities were based on observed data in the study eye for a modified intention to treat (mITT) population, which included only patients who had at least one follow-up visit.

The efficacy of sham injections or ‘no treatment’ within the network of evidence have been used as a proxy for the efficacy of watch and wait.

It is felt that the MEAD sham treatment arm is likely to overestimate the true 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’.[194] 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.[173, 202]

Comparing the response to sham treatment in the MEAD trials with 4-year outcomes from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) illustrates the superior response observed in the sham arm of the MEAD trials compared with observed natural history data. The proportion of patients who gained at least 10 letters from baseline to study end in the sham arms of the MEAD trials is in line with observed natural history data from WESDR (Table 70). However, a much lower proportion of patients lost at least 10 letters from baseline to study end in the WESDR study compared with the MEAD studies (Table 70). 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 and is therefore not representative of a true “watch and wait” treatment arm.

Table 70: Comparison of sham result in MEAD with natural history data

	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%
Notes: *Reference for MEAD data is Table 03.1.6-1019, data from baseline to study end (Month 36 or Month 39); †Reference for WESDR data is Mitchell *et al*. (2012)[44], supplementary information Table 6.				

The positive self-selection in the sham arm of the MEAD studies is represented by the proportion of sham treated patients that had achieved a 15-letter gain from baseline at the year 3 final visit (12% in the pooled MEAD studies).[67] Given this, when looking at the relative efficacy between sham treatment and active treatment arms across trials using MEAD data for DEX700, differences may underestimate the true relative efficacy of DEX700 compared with sham and in turn underestimate the true relative efficacy of DEX700 compared with other therapies.

Given this, it is felt that the sham arm of the MEAD studies is not an ideal proxy for a “watch and wait” treatment arm as it is likely to over-estimate the true efficacy in these patients. Further, the base case network of evidence includes two additional studies[118, 164] which include a sham/no treatment arm (Table 35) for which only aggregate data are available and which are included in the network meta-analysis. The MEAD studies are, however, the only studies for DEX700 and therefore relative effects obtained from the network meta-analysis for all treatments compared with DEX700 are based on evidence for DEX700 from the MEAD studies only. Relative effects obtained from the network meta-analysis for all treatments compared with sham/no treatment are based on evidence for sham/no treatment from the four studies in the network.[67, 118, 164] Therefore 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 reference transition probabilities (based on MEAD studies only) and the estimates of relative effectiveness (based on the four studies for sham/no treatment). Hence, DEX700 has been chosen as the reference treatment for efficacy, with DEX700 transition probability matrices taken from the pooled MEAD studies, and the relative

effectiveness of all other treatments obtained from the network meta-analysis applied to these to ensure the best use of the available data.

Efficacy of watch and wait and other comparator treatments (ranibizumab, bevacizumab [scenario analysis only], laser [scenario analysis only] and fluocinolone acetonide [scenario analysis only]) have been incorporated by applying relative treatment effects generated from network meta-analysis to the DEX700 PRN transition probabilities. The relative treatment effects estimated were:

- The relative risk of improving by one health state, modelled as the proportion of patients gaining at least 10 letters BCVA from baseline at 12 months
- The relative risk of worsening by one health state, modelled as the proportion of patients losing at least 10 letters BCVA from baseline at 12 months
- The relative risk of maintaining stable vision, modelled as the proportion of patients gaining or losing less than 10 letters BCVA from baseline at 12 months

The relative risks of each treatment compared with DEX700 PRN were derived from the network meta-analysis described in section 6.7, using a Bayesian analysis and a random effects model. One model was used to estimate all three outcomes to ensure that correlation between the three outcomes would be accounted for. The main network meta-analysis was performed based on data for all DMO patients and excluding the FAME study which is subject to limitations described in section 6.7. Sensitivity analyses were performed for all DMO patients including those in the FAME study and for pseudophakic DMO patients as described in section 6.7.

Data sources

Allergan has access to patient-level data from the following studies which have been used as reference studies to inform the clinical parameters for the treatments listed within our *de novo* economic model:

- MEAD[194] (DEX700 PRN, sham or watch and wait)

- DRCR.net PROTOCOL I (laser; represented by ‘sham + laser’); scenario analysis only

Therefore for these studies and treatments all data were taken from Allergan statistical analyses rather than the study publications.

Data from the following reference studies for the treatments listed were taken from the study publications as patient-level data were not available:

- RESTORE[100, 114, 199] (ranibizumab)
- BOLT[99, 200] (bevacizumab); scenario analysis only
- FAME[163, 173, 198] (fluocinolone acetonide); scenario analysis only

It is of note that both the BOLT and FAME studies included a 100% prior treated population where the other studies in the network of evidence included a population which included some prior treated patients and some patients who had no prior treatment.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Within the *de novo* model it is assumed that no eye will receive treatment with any regimen for DMO for more than 3 years in the base case analysis. This treatment duration is consistent with the maximum duration of clinical trials in DMO, and hence limits the amount of extrapolation required. This assumption is tested in scenario analyses by extending the treatment duration to a maximum of 5 years. The assumptions made to enable this extrapolation are detailed in section 7.6.1. Whilst receiving treatment in either or both eyes patients are assumed to be at risk of discontinuation from treatment.

Patients within the cohort who are affected with DMO unilaterally at baseline may develop DMO in their fellow eye (fellow eye involvement) and become a bilateral patient. As a simplifying assumption this has been limited to occur at the end of Year 1 or Year 2 only (described in further detail below) and in the eye which has developed DMO treatment is assumed to be initiated at the end

of the year in which the eye developed DMO. For example, if a patient within the cohort is affected unilaterally at baseline in their BSE, and their WSE develops DMO during Year 1, it is assumed that the BSE will receive treatment during Years 1-3 and the WSE will receive treatment during Years 2-4, provided that the patient does not discontinue from treatment. This is illustrated in Figure 59 to Figure 62.

All patients within the cohort are at risk of death throughout the model time horizon.

Baseline visual acuity

The distribution of vision at baseline for a BSE or WSE affected with DMO was taken from the study eye data from the pooled MEAD clinical studies (DEX700 treatment arm). For a BSE or WSE without DMO the distribution of vision at baseline was taken from the non-study eye data from the pooled MEAD clinical studies (DEX700 treatment arm).

The baseline distribution of vision assumed for patients within the cohort with unilateral DMO in the BSE or WSE or with bilateral DMO is described in Table 71 and Table 72. Due to the study inclusion criteria no study eyes (i.e. no treated eyes) fell into Health State 6 at baseline.

Table 71: Baseline distribution of vision across visual acuity states; All DMO patients

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

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.

Notes: 1.Based on data for study eyes which were the BSE; 2. Based on data for non-study eyes which were the BSE; 3. Based on data for study eyes which were the WSE; 4. Based on data for non-study eyes which were the WSE.

References: Allergan MEAD Data on File[194]

Table 72: Baseline distribution of vision across visual acuity states; DMO patients who are pseudophakic

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

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: 1.Based on data for study eyes which were the BSE; 2. Based on data for non-study eyes which were the BSE; 3. Based on data for study eyes which were the WSE; 4. Based on data for non-study eyes which were the WSE.
References: Allergan MEAD Data on File[194]

Transition probabilities: Visual acuity states

Different transition probabilities between visual acuity states are applied to eyes with different characteristics for different time-periods as described in Table 73.

Table 73: Visual acuity state transition probabilities

DMO status	Treatment status	Time period (base case analysis)
Eye with DMO	On treatment	Years 1-3 following initiation of treatment
		Years 4+ following initiation of treatment
	Discontinued from treatment	From the point of discontinuation
Eye without DMO	N/A*	From baseline

Key: DMO, diabetic macular oedema.
Notes: *No treatment assumed for eyes without DMO.

As shown in Figure 54, movements were restricted to improving or worsening by a maximum of one visual acuity state. Therefore, any improvement or worsening of greater than one visual acuity state was restricted to a movement of only one state. This simplifying assumption was necessary to

enable a Markov health state structure to be informed by network meta-analysis given the level of reported information within study publications. To model movements of more than one visual acuity state would require evidence for the proportion of patients who gained or lost at least 20 letters which is not a widely reported outcome in study publications. In particular this outcome is not reported in the ETDRS study[88] which is a key component of the network of evidence, linking the MEAD study for DEX700 with studies for ranibizumab.

This is a limitation of the analysis as it will not capture the proportion of eyes which would gain or lose a high number of letters of visual acuity as a result of treatment and would therefore move up or down by more than one visual acuity state. This is likely to bias the analysis as both extreme positive and negative outcomes are under-estimated. This will affect treatments with better visual acuity outcomes negatively, and treatments with worse visual acuity outcomes positively. Extreme positive outcomes will not be captured, which under-estimates the treatment effect for treatments with better visual acuity outcomes. Conversely extreme negative outcomes will not be captured, which inflates the treatment effect for treatments with poorer visual acuity outcomes.

This is recognised as a limitation of the analysis; however it is believed to be the most robust approach to model outcomes from network meta-analysis within a Markov model structure. An alternative approach to modelling using the results of network meta-analysis would be a model based upon the mean change in BCVA from baseline. Modelling this outcome loses valuable information about the distribution of vision across the visual acuity states, which is particularly important when considering clinical blindness when visual acuity in the BSE falls below 35 letters. Therefore modelling within a Markov structure for visual acuity is preferred. Further, the estimation of the relative risk of improving, worsening and maintaining stable vision within network meta-analysis for use within the Markov model structure is an improvement upon previous work of this type.

The technology appraisal for aflibercept for the treatment of central retinal vein occlusion[203] included a model which applied the same limitations of a movement of a maximum of one visual acuity state in order to inform the

Markov model structure with network meta-analysis. This analysis used network meta-analysis 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 criticised by both the evidence review group and the appraisal committee.

Given this, the methodology used for this appraisal, whilst subject to limitations, could be considered the most robust analysis possible given the limited head-to-head data available.

Eyes with DMO, on treatment, Years 1-3 following initiation of treatment

Patients within the cohort may receive treatment in each eye for a maximum of 3 years from the initiation of treatment. During this period treatment efficacy is modelled through the probability of transitioning between visual acuity states (Figure 54). These transition probabilities are derived from patient-level data for a reference treatment (DEX700 PRN). Relative effects compared with the reference treatment obtained from network meta-analysis are applied to the reference transition probabilities to derive estimates of treatment efficacy for other treatments within the analysis.

Reference treatment (DEX700 PRN)

Changes in BCVA resulting from DEX700 PRN treatment during the 3-Year treatment period are modelled using 3-monthly transition probabilities derived from the DEX700 PRN arm of the pooled MEAD studies. Transition probabilities were calculated from the observed movements between visual acuity states in the study eye during each 3-month cycle of the studies.

The full set of transition probabilities for DEX700 PRN patients for Years 1-3 are presented in appendix 15 (section 10.15). An example of how transition probabilities were derived is presented using data from baseline to Month 3 for the all DMO patients (mITT) population in Table 74 and Table 75. This 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] (Table 74).[194] Therefore the probability of moving from Health State 3 to Health State 4 from baseline to Month 3 is calculated as [redacted]

Table 74: Patient-level study eye movements between visual acuity states: Baseline to Month 3 for DEX700 PRN patients; all DMO patients

		To						Total
		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6	
From	Health State 1	▮	▮	0	0	0	0	▮
	Health State 2	▮	▮	▮	0	0	0	▮
	Health State 3	0	▮	▮	▮	0	0	▮
	Health State 4	0	0	▮	▮	▮	0	▮
	Health State 5	0	0	0	▮	▮	▮	▮
	Health State 6	0	0	0	0	▮	▮	▮

Key: DMO, diabetic macular oedema.
Source: Allergan MEAD Data on File 2014[194]

Table 75: Transition probability matrix: Baseline to Month 3 for DEX700 PRN patients; all DMO patients

		To						Total
		Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6	
From	Health State 1	▮	▮	0.00	0.00	0.00	0.00	▮
	Health State 2	▮	▮	▮	0.00	0.00	0.00	▮
	Health State 3	0.00	▮	▮	▮	0.00	0.00	▮
	Health State 4	0.00	0.00	▮	▮	▮	0.00	▮
	Health State 5	0.00	0.00	0.00	▮	▮	▮	▮
	Health State 6	0.00	0.00	0.00	0.00	▮	▮	▮

Key: DMO, diabetic macular oedema.
Source: Allergan MEAD Data on File 2014[194]

The transition probability matrices for DEX700 PRN are used as the reference transition probabilities. Relative effects from the network meta-analysis are then applied to these reference transition probability matrices.

Other treatments (watch and wait, ranibizumab, bevacizumab, laser and fluocinolone acetonide)

The relative risk of improving, worsening or maintaining stable vision compared with DEX700 PRN were derived from network meta-analysis as described in section 6.7.

This analysis assumes that the outcomes in the network meta-analysis are equivalent to the BCVA outcomes being modelled. The relative risk of gaining ≥ 10 letters from baseline is assumed to be equivalent to the relative risk of moving up one 10-letter visual acuity state (improving vision), the relative risk of losing ≥ 10 letters from baseline is assumed to be equivalent to the relative risk of moving down one 10-letter visual acuity state (worsening vision) and the relative risk of gaining or losing <10 letters is assumed to be equivalent to remaining in the same 10-letter visual acuity state (stable vision). This is a key assumption within the economic model which is necessary to allow the use of the network meta-analysis to inform the Markov model structure, and builds upon previous modelling in the appraisal of aflibercept for central retinal vein occlusion.[203]

The relative effects are presented in Table 76 for the all DMO population base case analysis excluding FAME, Table 77 for the all DMO scenario analysis including FAME and in Table 78 for the pseudophakic population.

Table 76: Relative effectiveness of treatments; All DMO patients – base case (DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy)

Treatment	RR (95% CrI)		
	Improving vision	**Stable vision**	**Worsening vision**
DEX700 PRN (reference)	1 (1, 1)	1 (1, 1)	1 (1, 1)
Watch and wait	[redacted]	[redacted]	[redacted]
Key: CrI, credible interval; DEX, dexamethasone; DMO, diabetic macular oedema; PRN, *pro re nata*; RR, relative risk.			

Table 77: Relative effectiveness of treatments; All DMO patients - scenario analysis (DMO patients who are considered insufficiently responsive to non-corticosteroid therapy)

Treatment	RR (95% CrI)		
	Improving vision	Stable vision	Worsening vision
DEX700 PRN (reference)	1 (1, 1)	1 (1, 1)	1 (1, 1)
Watch and wait	[redacted]	[redacted]	[redacted]
Fluocinolone acetonide	[redacted]	[redacted]	[redacted]

Key: CrI, credible interval; DEX, dexamethasone; DMO, diabetic macular oedema; PRN, *pro re nata*; RR, relative risk.

Table 78: Relative effectiveness of treatments; DMO patients who are pseudophakic

Treatment	RR (95% CrI)		
	Improving vision	Stable vision	Worsening vision
DEX700 PRN (reference)	1 (1, 1)	1 (1, 1)	1 (1, 1)
Watch and wait	[redacted]	[redacted]	[redacted]
Ranibizumab	[redacted]	[redacted]	[redacted]
Bevacizumab*	[redacted]	[redacted]	[redacted]
Laser*	[redacted]	[redacted]	[redacted]

Key: CrI, credible interval; DEX, dexamethasone; DMO, diabetic macular oedema; PRN, *pro re nata*; RR, relative risk.
Notes: *Included in scenario analysis only.

The relative risks described in Table 78 and Table 76 are applied to the 3-monthly transition probabilities for DEX700 PRN patients (shown in appendix 15, section 10.15) to obtain independent transition probability matrices for each treatment, in each population as follows:

- The relative risk of improving vision was applied to all DEX700 PRN transition probabilities demonstrating an improvement of vision (i.e. all probabilities of moving up one visual acuity state), regardless of the starting state.
  - This assumes that the relative risk of moving from state 1 into state 2 is the same as the relative risk of moving from state 2 to state 3 and so on.

- The relative risk of worsening vision was applied to all DEX700 PRN transition probabilities demonstrating a worsening of vision (i.e. all probabilities of moving down one visual acuity state), regardless of the starting state.
  - This assumes that the relative risk of moving from state 6 into state 5 is the same as the relative risk of moving from state 5 to state 4 and so on.
- The relative risk of vision remaining stable was applied to all DEX700 PRN transition probabilities where vision remained stable (i.e. all probabilities of remaining in the same visual acuity state).
  - This assumes that the relative risk of remaining in state 1 is the same as the relative risk of remaining in state 2 and so on.

Each row of the transition probability matrix represents the probabilities of moving from a particular visual acuity state to all other visual acuity states during that cycle. The sum of probabilities in each row of the matrix must equal 1 to ensure that all patients who begin the cycle in each state are accounted for by the movements described by the probabilities in the corresponding row.

Applying the relative risks obtained from the network meta-analysis to the transition probabilities will not necessarily result in transition probabilities in each row of the matrix which sum to 1. Therefore the transition probabilities generated by applying the relative risks to the transition probabilities for DEX700 PRN were normalised to ensure the probabilities in each row of the resulting matrix sum to 1.

To illustrate this, an example is presented applying the relative risks for watch and wait for all DMO patients (Table 76) to the transition probabilities for DEX700 PRN shown in Table 75. Simply applying the relative risks to the transition probabilities gives the probabilities shown in Table 79, which do not sum to 1 across rows as required.

Table 79: Transition matrix: Baseline to end of Month 2 for watch and wait; All DMO patients

		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]

Key: DEX, dexamethasone; DMO, diabetic macular oedema; PRN, *pro re nata*.

Therefore normalised transition probabilities were calculated, where for each row of Table 79, the probability of each movement is 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 is equal to 1 (Table 80). For example, applying the relative risks gives probabilities of movements from health state 1 to state 1 of [redacted] and state 2 of [redacted] (Table 79). The sum of these probabilities is [redacted] Therefore the normalised probability of moving from state 1 to state 1 is calculated as ([redacted]) and the probability of moving from state 1 to state 2 is calculated as [redacted] as shown in Table 80, giving a total probability of moving from state 1 to any state of 1.00 (as the probability of moving from state 1 to state 3 or higher is zero).

Table 80: Transition probability matrix (normalised): Baseline to end of Month 2 for watch and wait; All DMO patients

		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]

Key: DEX, dexamethasone; DMO, diabetic macular oedema; PRN, *pro re nata*.

Applying the relative risks as described above assumes that the relative treatment effect versus DEX700 PRN is constant regardless of the level of vision. This assumption is recognised as a limitation of the analysis however it has been made so that one single network meta-analysis could be used to provide estimates of relative effectiveness for all outcomes of interest. Attempting to disaggregate the relative effects of treatments dependent on starting health state would lead to smaller sample sizes and hence less robust analyses, and this data is not likely to be available from key study publications for treatments within the network of evidence where only aggregate data are available.

The relative effects are also assumed to be constant over time; the relative risks shown in Table 78 and Table 76 are applied to the watch and wait transition probability matrices for each 3-month cycle in Years 1-3. The network meta-analysis uses Month 12 data which was the most commonly reported time-point in key clinical trials. The network includes studies which were of 12 month duration only; hence an analysis of further time-points would not be possible for all treatments within the network and the assumption is justified.

Eyes with DMO, Years 4+ following initiation of treatment

For all eyes with DMO, a single extrapolation is applied after the 3-year treatment period is over. This extrapolation assumes that vision declines at a rate that represents the natural history of vision in an eye with DMO.

Mitchell *et al*. (2012)[44] used data from the WESDR adjusted to account for the improvement in DM management since the study and demonstrated 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% or 4.5%. Applying these probabilities gives the 3-month transition probability matrix shown in Table 81. This transition probability matrix is applied to all eyes with DMO from Year 4 following the initiation of treatment, for the remainder of the model time horizon.

Table 81: Transition probability matrix: Natural history of vision in patients with DMO

		To					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
From	**Health State 1**	0.965	0.035	0.000	0.000	0.000	0.000
	Health State 2	0.045	0.920	0.035	0.000	0.000	0.000
	Health State 3	0.000	0.045	0.920	0.035	0.000	0.000
	Health State 4	0.000	0.000	0.045	0.920	0.035	0.000
	Health State 5	0.000	0.000	0.000	0.045	0.920	0.035
	Health State 6	0.000	0.000	0.000	0.000	0.045	0.955

Key: DMO, diabetic macular oedema.

Eyes with DMO, discontinued from treatment

Within the model patients can discontinue from their initially assigned treatment during the initial 3-year treatment period for two distinct reasons:

- Adverse events and other non-efficacy-related reasons

- Lack (or loss) of efficacy of treatment

Within the economic model these two reasons have been modelled as independent in accordance with the way the data is reported due to the non-trivial proportion of discontinuations for each reason within the DEX700 PRN treatment arm of the pooled MEAD studies. Considering these reasons for discontinuation independently within the model enables outcomes attributable to these patients to be disaggregated. However, despite discontinuation for two independent reasons being considered, visual acuity outcomes are assumed to be consistent regardless of the reason for discontinuation as there was no evidence available to suggest that outcomes would differ for the two populations.

No further treatment is assumed following discontinuation, with visual acuity assumed to follow the natural history of vision in eyes with DMO as described in Table 81 to reflect that vision may still be affected by DMO following discontinuation. This simplifying assumption has been made to reflect that the decision problem for this appraisal is to consider the cost-effectiveness of DEX700 for the treatment of DMO. Modelling an explicit next line of treatment following discontinuation could lead to a different decision problem being considered, to find the optimal sequence of treatments for DMO, particularly where multiple options for further treatment are available.

Eyes without DMO

Eyes without DMO are assumed to maintain constant vision as the focus of this submission is the treatment of visual impairment due to DMO. Therefore the identity matrix (Table 82), which forces vision to remain in the same visual acuity state is applied to eyes without DMO in each 3-month cycle of the model time horizon.

Table 82: Identity matrix

		To					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
From	**Health State 1**	1	0	0	0	0	0
	Health	0	1	0	0	0	0

	State 2						
	Health State 3	0	0	1	0	0	0
	Health State 4	0	0	0	1	0	0
	Health State 5	0	0	0	0	1	0
	Health State 6	0	0	0	0	0	1
Key: DMO, diabetic macular oedema							

Patient pathways: Event probabilities

Discontinuation from treatment

The proportion of patients who discontinue from treatment either due to adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment has been estimated from the patient-level data (where available) or from key study publication(s). The majority of study publications did not specify all of the reasons for discontinuation within the study, where this was the case all discontinuations were assumed to be due to adverse events and other non-efficacy related reasons. This does not impact the outcomes of the analysis as all patients receive the same assumptions following discontinuation for either reason.

Within the MEAD studies patients were censored upon receipt of non-study treatments. This accounts for a non-trivial proportion of the DEX700 PRN patient population ([redacted]) that was censored due to receipt of escape therapy. A further [redacted] discontinued from the study due to lack (or loss) of efficacy of treatment. The proportion of patients who discontinued due to adverse events or other non-efficacy reasons within the MEAD studies also accounts for a non-trivial proportion of the DEX700 PRN patient population [redacted].[194] These groups represent patients for whom no evidence is available regarding how their BCVA changes over time following censoring.

Given this, the decision was taken to explicitly model what happens to patients who discontinue from their initial treatment regimen in order to assume a pathway for these patients and thus include them within the

economic modeling. Despite all discontinuations being treated the same in terms of costs and outcomes, the two reasons have been modelled explicitly due to both reasons for discontinuation having a clear impact for DEX700 PRN in the MEAD studies and to retain flexibility to model different outcomes should evidence become available to support different assumptions.

The proportion of patients who discontinue from treatment due to either reason during each study cycle were taken from the key clinical studies for treatments and were entered into the model as a proportion per month. 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. For example in the MEAD study data were collected at Month 3, 6, 9, etc. and so within the model the data for the period between Month 3 and Month 6 are input at Month 6. Where patient-level data were not available, the rate reported in the study publications is applied at the end of the time-point at which the data are reported.

Beyond the study duration the discontinuation rates have been extrapolated using the average rate over the study duration applied in line with the relevant study cycle length. This method was chosen in preference to other methods (such as LOCF) as there was no clear pattern to the discontinuation rates over time.

A large proportion of sham patients in the MEAD studies were discontinued from the study due to lack or loss of efficacy, or were censored due to receipt of escape therapy. Therefore the BCVA of these patients following discontinuation or censoring is not known. Therefore to assume no discontinuation from watch and wait, while clinically plausible, would over-estimate the true efficacy of watch and wait as only patients who did not meet criteria for study discontinuation or receipt of escape therapy were followed up within the MEAD studies. Given this, discontinuation from watch and wait due to lack or loss of efficacy has been included within the model, with patients who discontinue assumed to receive the TPMs associated with natural history

in line with the assumptions made for patients who discontinue from active treatments.

It has been assumed in the base case that there is no discontinuation from watch and wait due to adverse events and other non-efficacy related reasons as these are not clinically feasible outcomes for a strategy of watch and wait. It is assumed that patients who discontinued from the sham treatment arm of the MEAD studies due to adverse events and other non-efficacy related reasons did so because of the sham procedure which was necessary to maintain blinding in the studies. It is believed that these patients would, in clinical practice, most likely receive the same efficacy as those who remained in the study as there is no procedure or treatment associated with a strategy of watch and wait.

The true BCVA evolution of these patients is however unknown and therefore a scenario analysis has been included in the populations of patients who are unsuitable for or insufficiently responsive to non-corticosteroid therapy whereby discontinuation from watch and wait due to adverse events and other non-efficacy related reasons is included based on observed discontinuation from the sham arm of the MEAD studies.

The proportions of patients who discontinue from each initial treatment during each of Years 1-3 for each reason are detailed in appendix 16, section 10.16, these are based on the proportions of patients who discontinued from the study. The proportions of patients who remain on treatment at the start of each year are presented in Table 83 and Table 84. This is calculated within the model in each month using the proportion of patients remaining on treatment from the previous month and the proportion of patients who discontinue in that month.

Table 83: Proportion of patients remaining on treatment; All DMO (DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy)

Treatment	Proportion remaining on treatment		
	Year 1	Year 2	Year 3
DEX700 PRN	[redacted]	[redacted]	[redacted]
Watch and wait	[redacted]	[redacted]	[redacted]
Fluocinolone acetonide*†	100.00%	100.00%	80.00%

Key: DEX, dexamethasone; DMO, diabetic macular oedema; PRN, pro re nata.
Notes: *DMO patients who are insufficiently responsive to non-corticosteroid therapy only; †scenario analysis only.

Table 84: Proportion of patients remaining on treatment; DMO patients who are pseudophakic

Treatment	Proportion remaining on treatment		
	Year 1	Year 2	Year 3
DEX700 PRN	[redacted]	[redacted]	[redacted]
Watch and wait*	[redacted]	[redacted]	[redacted]
Ranibizumab	100.00%	89.66%	84.25%
Bevacizumab*	100.00%	100.00%	85.71%
Laser*	[redacted]	[redacted]	[redacted]

Key: DEX, dexamethasone; DMO, diabetic macular oedema; PRN, pro re nata.
Notes: * Scenario analysis only.

Fellow eye involvement

The proportions of patients within the cohort who have unilateral DMO in the BSE or the WSE, or bilateral DMO are shown in Table 62. DMO patients who are affected unilaterally at baseline are at risk of developing DMO requiring treatment in their fellow eye, referred to as fellow eye involvement. It is assumed, based on clinician feedback (appendix 14, section 10.14), that upon development of DMO in the fellow eye, the same treatment as received in the first eye would be given for a period of up to 3 years starting from this point.

In order to reflect the more intensive treatment expected in the first year compared to subsequent years when considering as needed treatment regimens, it is assumed that patients are only at risk of fellow eye involvement by the end of Year 1 or Year 2. This simplifying assumption is essential given

the memory-less property of the model. In order to apply the cost of treatment, probability of discontinuation from treatment and efficacy of treatment relative to the time of initiation of treatment in the fellow eye it is necessary to track the time-point at which the fellow eye developed DMO. This therefore increases the complexity of an already complex model structure and thus it was assumed that this could occur at only two time-points, the end of Year 1 or the end of Year 2. This limits the number of additional health states required to track the time-point at which the fellow eye develops DMO and treatment begins.

This assumption has been validated against the MEAD clinical data, in which the majority of incidences of fellow eye involvement occurred during Years 1 and 2. Furthermore, this assumption has been validated with clinical experts who advised that this was a reasonable assumption and, if the second eye is going to develop DMO, it will likely do so within 2 years of the first eye doing so (appendix 14, section 10.14).

The proportion of fellow eyes that develop DMO in each year was estimated using data from the pooled MEAD studies, which indicated that approximately [redacted] of DEX700 patients developed fellow eye involvement over the 3-year study duration.[194] The economic model assumes that [redacted] of unilateral patients will develop fellow eye involvement during Year 1 or Year 2 of the model. This was converted into an annual rate of [redacted]of patients in each of Years 1 and 2 using the exponential cumulative distribution function and assuming that the risk is constant over time.

The rate presented above is based on the frequency of new incidences of “diabetic macular (o) edema”, “diabetic neuropathy”, “diabetic retinal (o) edema”, “diabetic retinopathy”, “macular degeneration”, “macular oedema”, “retinal degeneration” or “retinal neovascularisation”.

The protocol of the MEAD studies allowed the use of escape therapy and the efficacy data were censored for the subsequent visits by carrying forward the last BCVA observation collected prior to the use of escape therapy forward throughout the study exit. The use of escape therapy was recorded as treatment for either DMO or DMO-related diagnosis.

A scenario analysis has been presented whereby the rate of fellow eye involvement is based on the specific fellow-eye occurrence of “diabetic macular (o) edema” recorded in the non-study eye during the MEAD study.

This results in a lower rate of fellow eye involvement over the 3-year duration of the MEAD study of [redacted]% of DEX700 patients.[194] When this is converted to an annual rate over Years 1 and 2 of the model using the exponential cumulative distribution function, assuming that the risk is constant over time, this gives an annual rate of fellow eye involvement in Year 1 and Year 2 of the model of [redacted] per year.

A scenario has also been included assuming no fellow eye involvement to determine the impact this has on the cost-effectiveness of DEX700.

Patients who are on treatment (i.e. who have not discontinued) and who develop fellow eye involvement by the end of Year 1 (or 2) are assumed to continue to receive treatment in the initially affected eye at the rate expected in Year 2 (or 3), and to receive the efficacy of treatment associated with Year 2 (or 3). The newly affected eye is assumed to receive treatment at the rate expected in Year 1, and to receive the efficacy of treatment associated with Year 1. The model tracks whether the initially affected eye was the BSE or the WSE for the purposes of assigning utilities. Resource requirements are assumed to be the weighted average of the resource use associated with the year of treatment each eye is receiving.

Within the model it is assumed that the patient is at risk of discontinuation, rather than each eye being at risk, therefore, since the initially affected eye is at risk of discontinuation as observed in Year 2 (or 3) while the newly-affected eye is at risk of discontinuation as observed in Year 1, the patient risk of discontinuation is calculated using the formula for the probability of either eye discontinuing, assuming that the probabilities are independent:

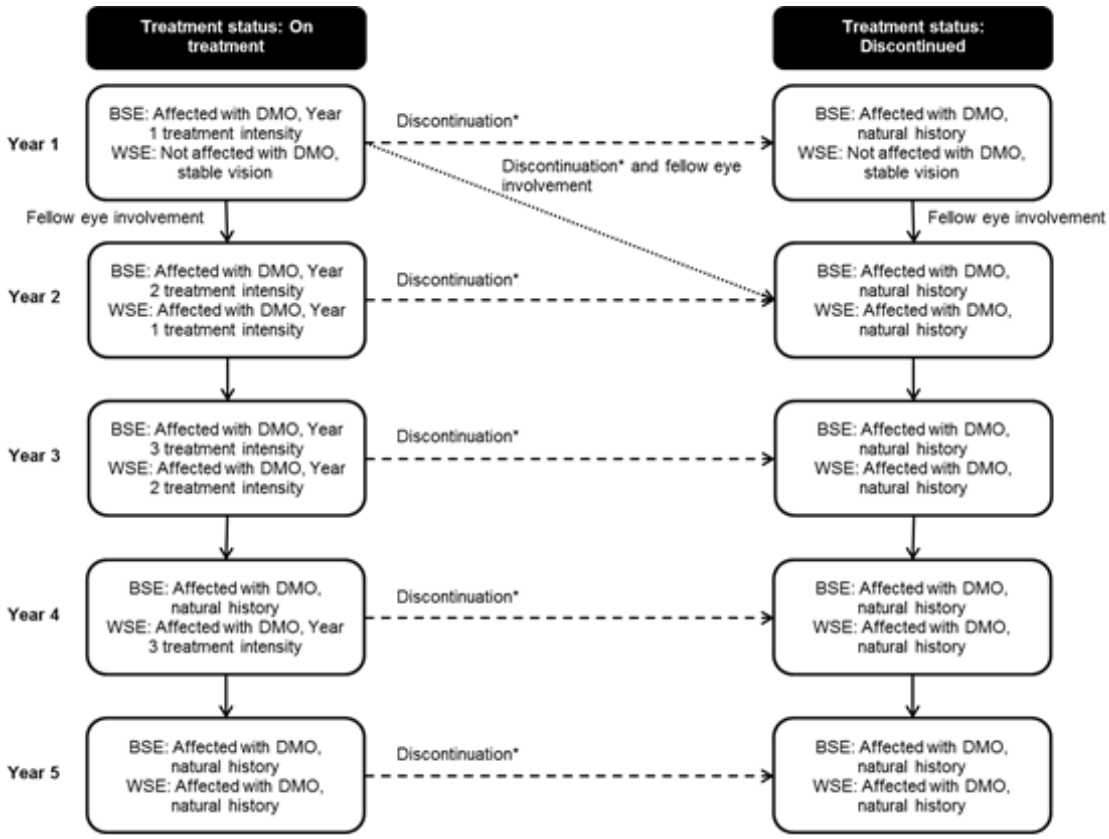
$$P(A \cup B) = P(A) + P(B) - (P(A) \times P(B))$$

Given this, if a patient has discontinued from treatment and then develops fellow eye involvement, it is assumed that both eyes will receive the transition probabilities associated with eyes with DMO which have discontinued from

treatment (as described above). This is a simplifying assumption within the model.

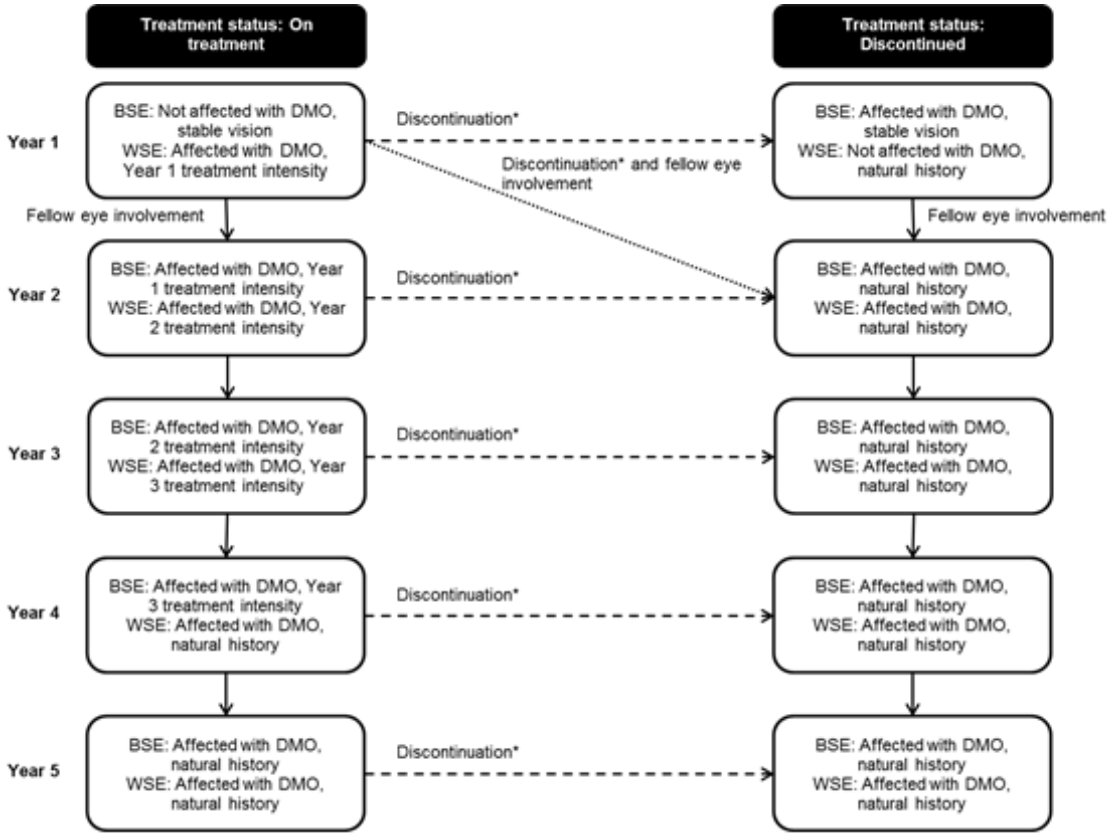
The patient pathways for patients who develop fellow eye involvement at the end of Year 1 are shown in Figure 59 and Figure 60 for patients who are initially affected in their BSE or their WSE, respectively. The patient pathways for patients who develop fellow eye involvement at the end of Year 2 are shown in Figure 61 and Figure 62 for patients who are initially affected in their BSE or their WSE, respectively.

Figure 59: Patient pathway, fellow eye involvement at the end of Year 1; initially affected BSE



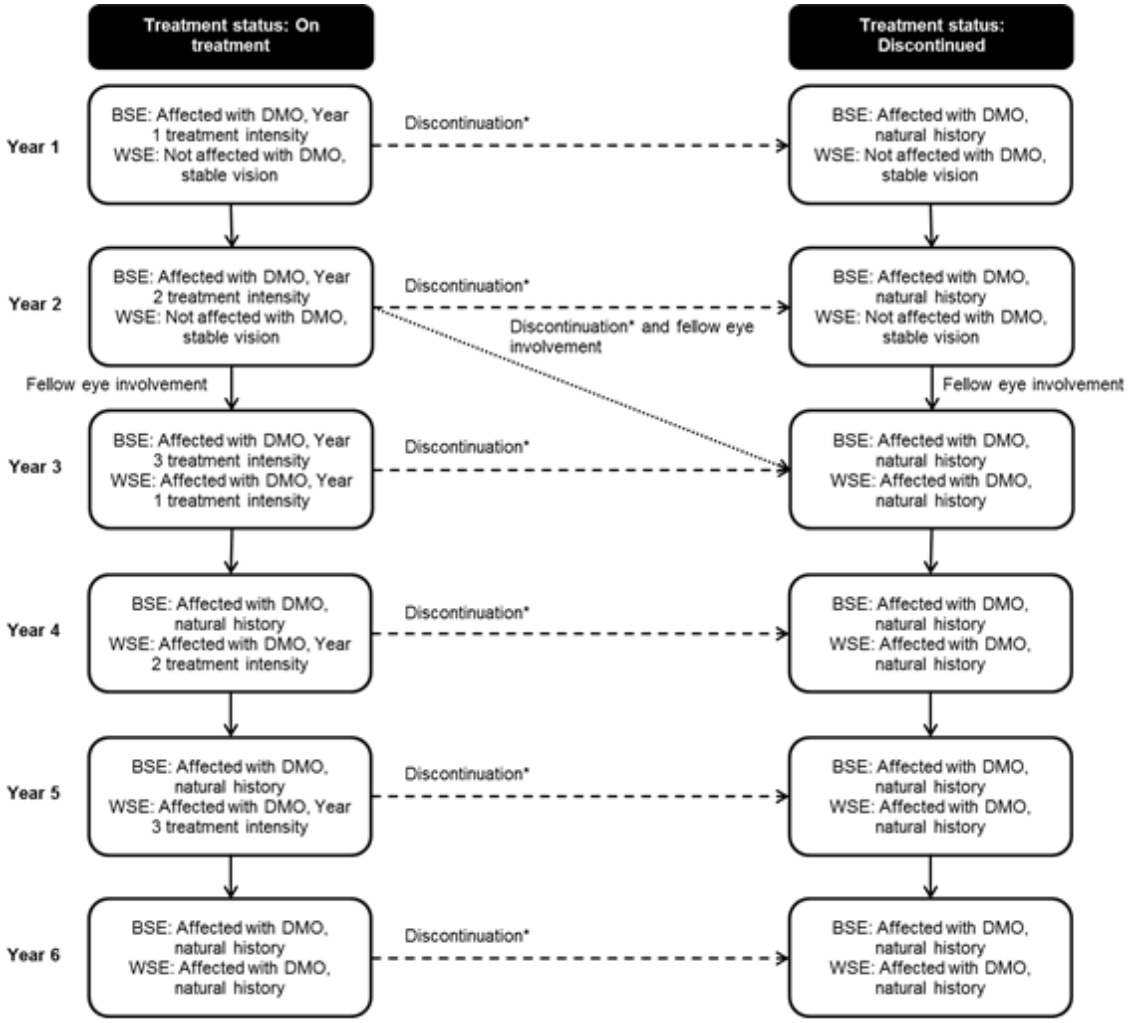
Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: *Discontinuation due to either adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment.

Figure 60: Patient pathway, fellow eye involvement at the end of Year 1; initially affected WSE



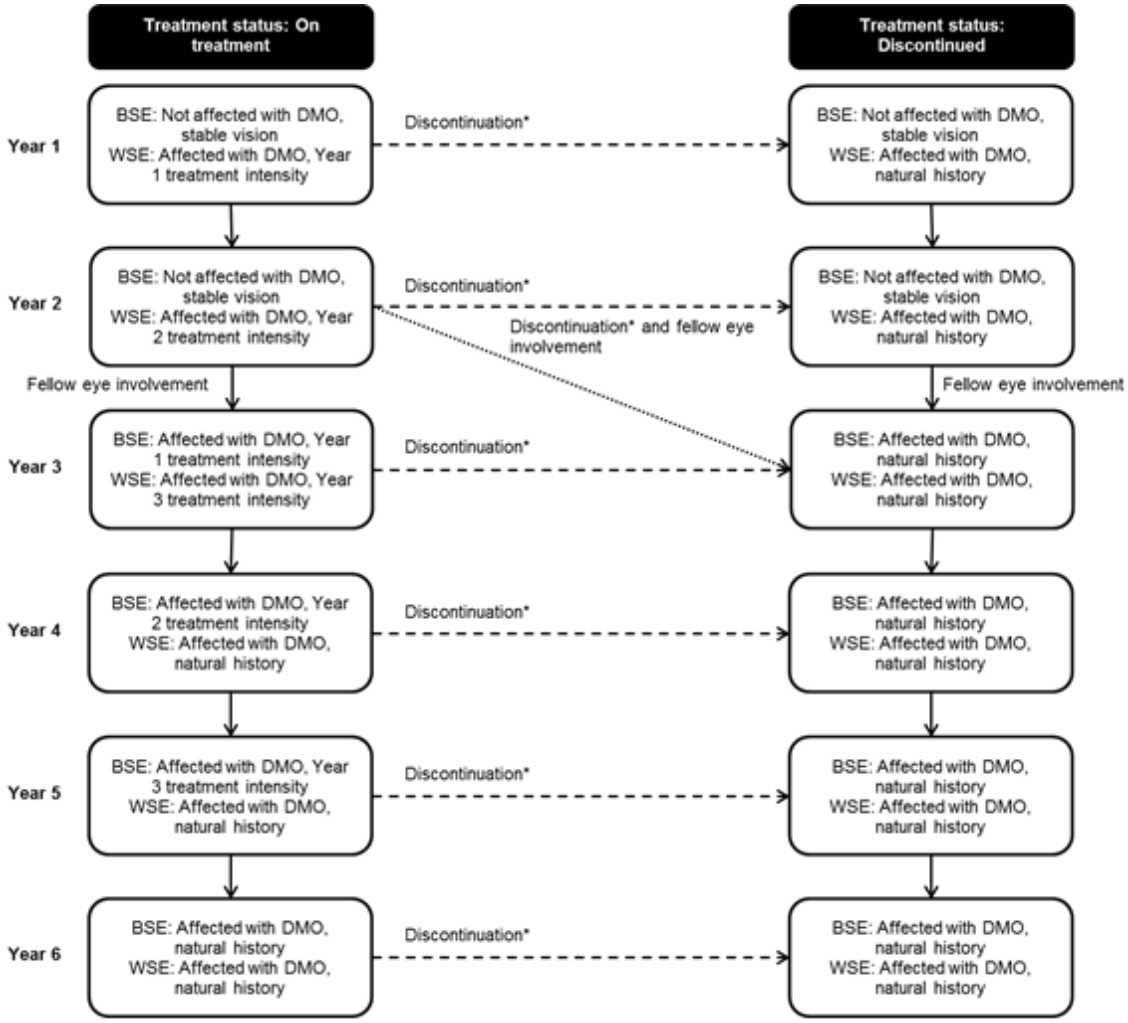
Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: *Discontinuation due to either adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment.

Figure 61: Patient pathway, fellow eye involvement at the end of Year 2; initially affected BSE



Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: *Discontinuation due to either adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment.

Figure 62: Patient pathway, fellow eye involvement at the end of Year 2; initially affected WSE



Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.

Notes: *Discontinuation due to either adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment.

In the base case it has been assumed that there is no effect on a patients' vision due to the development of DMO in the fellow eye. This is justified as it is assumed that development of DMO in the fellow eye will 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 is included whereby a decrement equal to one cycle of natural history of vision in an eye with DMO (Table 81) is applied on development of fellow eye involvement.

Mortality

All patients are at risk of death throughout the model. The risk of all-cause mortality is applied to all patients, adjusted for the additional mortality due to

DM (relative to the general population) and due to DMO (relative to the DM population) and assuming that mortality occurs equally across all visual acuity states in the base case. The model, however, includes the functionality to assume additional mortality for patients whose BSE has severe vision loss (i.e. clinical blindness, BCVA ≤ 35 letters) as there is evidence of increased mortality in blind patients.[77] In the base case no additional mortality is assumed to avoid double-counting of the risk as the hazard ratio for DMO is likely to include some patients who are clinically blind. This is also in line with previous economic evaluations in DMO, none of which have included this additional mortality. The additional mortality risk for patients whose BSE is categorised as having experienced severe vision loss is applied in a scenario analysis, and further information about this scenario is available in appendix 17 (section 10.17).

All-cause mortality is taken from interim life tables for England[204] and is based on the cohort's mean age. The mean age of the cohort at baseline is assumed to be consistent with the mean age of DEX700 PRN patients at baseline in the mITT (█ years of age) and pseudophakic (█ years of age) populations of the pooled MEAD studies.[194] The hazard ratio for the additional mortality due to DM relative to the general population is 1.93[68] and the hazard ratio for the additional mortality due to DMO relative to the DM population is 1.27.[69] These two hazard ratios are multiplied together to give a hazard ratio for the additional mortality relative to DM and DMO of 2.45.

There may 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 if this was the case, therefore in the base case these have been applied together as described above, consistent with previous technology appraisals for DMO.[189, 191] It is noted though that this may be over-estimating the additional mortality due to DM and DMO (although doing so equally for all treatment arms within the analyses), and so scenario analyses have been 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 is available for males and females. At baseline it is assumed that [redacted] of all DMO patients and [redacted] of pseudophakic DMO patients are male, consistent with the baseline characteristics of DEX700 patients in the mITT and pseudophakic populations of the MEAD clinical trials.[194] The proportion of male and female patients who remain is expected to change over time due to the differential mortality experienced by each gender. Therefore the model uses the annual risk of mortality for males and females, adjusted for DM and DMO to calculate the proportion of patients who remain alive and who are male and female in each year from the baseline age in the model. This increases the accuracy of general mortality applied within the model.

Adverse events

Treatments for DMO are associated with five key adverse events of interest that may require medical or surgical intervention. These are cataracts, raised IOP, retinal detachment, endophthalmitis and vitreous haemorrhage. These adverse events were selected to retain consistency with those included in previous economic models for DMO.[189, 191, 205]

The proportions of patients requiring treatment for each adverse event during each year of the 3-year treatment period are detailed here. Data were taken from key clinical trials and where necessary the data were extrapolated using last observation carried forward. The risk of adverse events is assumed to be equal irrespective of the patient population under consideration; with the exception that there is no risk of cataract in the pseudophakic population as those eyes already have an artificial lens.

Detail on the costs of treating adverse events is provided in section 7.5.7.

Cataract

As discussed in section 6.9.3, DMO patients are at a higher risk of requiring cataract extraction compared with the general population due to their DM. The Blue Mountain Eye Study demonstrated a cumulative incidence of cataract surgery in a DM population of 20.9% over 10 years.[30] Assuming that the risk is constant over time using the exponential cumulative distribution function this gives a risk of 2.34% per year. This is applied to phakic eyes which are

not receiving treatment within the model to reflect the underlying risk of cataract in the DM population. It is noted that the patient is assumed to be phakic or pseudophakic in both eyes where both eyes are affected with DMO. This is a further simplifying assumption of the economic model.

The proportions of phakic patients within the cohort receiving treatment who experience a cataract that requires extraction are shown in Table 85.

Table 85: Proportions of phakic patients with cataract requiring extraction

Treatment	Proportion phakic			Annual cataract extraction rate for phakic eyes			Reference
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	
DEX700 PRN	75.50%	69.16%	55.91%	8.40%	19.17%	2.94%	MEAD[194]
Watch and wait	75.50%	73.73%	72.01%	2.34%	2.34%	2.34%	Natural history assumed for watch and wait[30]
Fluocinolone acetonide†	75.50%	75.50%	26.02%	0.00%**	65.53%	41.98%	FAME[163, 173, 198] (note data reported at Year 2 and 3 only)

Key: DEX, dexamethasone; PRN, pro re nata.
Notes: *DMO patients who are insufficiently responsive to non-corticosteroid therapy only; †scenario analysis only; **FAME data reported at Year 2 and 3 only therefore there is no Year 1 estimate available.

Raised intraocular pressure

The proportions of patients within the cohort receiving treatment who experience raised IOP that requires treatment are shown in Table 86. These proportions have been assumed to be either the rate of raised IOP reported as an adverse event of treatment, or assuming that IOP ≥30mmHg would result in the initiation of treatment as indicated by clinical experts (appendix 14, section 10.14), dependent on the level of information reported in study publications.

Table 86: Proportions of patients with raised IOP

Treatment	Proportion with raised IOP			Reference
	Year 1	Year 2	Year 3	
DEX700 PRN	12.10%	4.61%	1.15%	MEAD[194] incidence of raised IOP ≥30mmHg
Watch and wait	0.00%	0.00%	0.00%	No treatment assumed for watch and wait
Ranibizumab	0.86%	0.00%	0.00%	RESTORE[100, 114, 199], no incidences of raised IOP SAEs (Table 9 Y1; Table 6 Y2; Table 7 Y3) and one incidence of "IOP increased" reported to be due to the study drug and/or procedure in Y1 only (Table 11 Y1; Table 10 Y2; Table 12 Y3)
Bevacizumab‡	9.52%	0.00%	0.00%	BOLT[99, 200], one patient had raised IOP ≥45 mmHg and 3 patients had raised IOP ≥30 mmHg
Laser‡	[redacted]	[redacted]	[redacted]	PROTOCOL I[201] incidence of raised IOP ≥30mmHg to Year 2, then LOCF†
Fluocinolone acetonide‡	0.00%**	4.80%	32.30%	FAME[163, 173, 198], data only reported in Years 2 and 3

Key: DEX, dexamethasone; IOP, intraocular pressure; PRN, *pro re nata*.

Notes: *DMO patients who are insufficiently responsive to non-corticosteroid therapy only ; †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; ‡scenario analysis only; **FAME data reported at Year 2 and 3 only therefore there is no Year 1 estimate available.

Raised IOP may be treated with either medication or surgery. The proportion of cases of raised IOP that are assumed to be treated with medication and with surgery are shown in Table 87. Clinical expert opinion indicated that patients with IOP ≥30mmHg would require treatment with medication, and patients with IOP ≥40mmHg would require surgical intervention rather than medication. This information has been used to determine the proportions in Table 87.

Table 87: Proportions of patients with raised IOP treated with medication vs. surgery

Treatment	Proportion with raised IOP that is		Reference
	Treated with medication	Treated with surgery	
DEX700 PRN	72.58%	27.42%	MEAD[194] incidence of raised IOP ≥40mmHg divided by incidence of raised IOP ≥30mmHg (i.e. number eligible for surgery divided by number eligible for any treatment); based on cumulative data over 3 years
Watch and wait	100.00%	0.00%	No treatment assumed for watch and wait
Ranibizumab	100.00%	0.00%	RESTORE[100, 114, 199] (no incidences of raised IOP SAEs reported)
Bevacizumab‡	100.00%	0.00%	BOLT[99, 200] (one patient had raised IOP ≥45 mmHg, but was subsequently diagnosed with ocular hypertension and was not reported to have required surgery)
Laser‡	[redacted]	[redacted]	PROTOCOL I[201] incidence of raised IOP ≥40mmHg divided by incidence of raised IOP ≥30mmHg (i.e. number eligible for surgery divided by number eligible for any treatment); based on cumulative data over 2 years†
Fluocinolone acetonide‡	11.11%	88.89%	FAME[163, 173, 198] (to Year 2: 16 reported cases of glaucoma surgery, out of 12 incidences of raised IOP + 6 incidences of glaucoma)

Key: DEX, dexamethasone; IOP, intraocular pressure; PRN, *pro re nata*.

**Notes: ***DMO patients who are insufficiently responsive to non-corticosteroid therapy only ; †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; ‡scenario analysis only.

Retinal detachment

The proportions of patients within the cohort receiving treatment who experience retinal detachment are shown in Table 88.

Table 88: Proportions of patients with retinal detachment

Treatment	Proportion with retinal detachment			Reference
	Year 1	Year 2	Year 3	
DEX700 PRN	0.00%	0.29%	0.29%	MEAD[194] (note no incidences in Year 1)
Watch and wait	0.00%	0.00%	0.00%	No treatment assumed for watch and wait
Ranibizumab	0.00%	0.00%	0.00%	RESTORE[100, 114, 199] (note no incidences reported)
Bevacizumab‡	0.00%	0.00%	0.00%	BOLT[99, 200] (note no incidences reported)
Laser‡	[redacted]	[redacted]	[redacted]	PROTOCOL I[201] to Year 2 then LOCF† (note no incidences in Year 1)
Fluocinolone acetonide‡	0.00%	0.00%	0.00%	FAME[163, 173, 198] (note no incidences reported)

Key: DEX, dexamethasone; PRN, *pro re nata*.

Notes: *DMO patients who are insufficiently responsive to non-corticosteroid therapy only ; †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; ‡scenario analysis only.

Endophthalmitis

The proportions of patients within the cohort receiving treatment who experience endophthalmitis are shown in Table 89.

Table 89: Proportions of patients with endophthalmitis

Treatment	Proportion with endophthalmitis			Reference
	Year 1	Year 2	Year 3	
DEX700 PRN	0.29%	0.29%	0.00%	MEAD[194] (note no incidences in Year 3)
Watch and wait	0.00%	0.00%	0.00%	No treatment assumed for watch and wait
Ranibizumab	0.00%	0.00%	0.00%	RESTORE[100, 114, 199] (note no incidences reported)
Bevacizumab‡	0.00%	0.00%	0.00%	BOLT[99, 200] (note no incidences reported)
Laser‡	[redacted]	[redacted]	[redacted]	PROTOCOL I[201] to Year

				2 then LOCF† (note no incidences in Year 2)
Fluocinolone acetonide‡	0.00%	0.00%	0.00%	FAME[163, 173, 198] (note no incidences reported)

Key: DEX, dexamethasone; PRN, *pro re nata*.

**Notes: ***DMO patients who are insufficiently responsive to non-corticosteroid therapy only ; †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; ‡scenario analysis only.

Vitreous haemorrhage

The proportions of patients within the cohort receiving treatment who experience vitreous haemorrhage are shown in Table 90.

Table 90: Proportions of patients with vitreous haemorrhage

Treatment	Proportion with vitreous haemorrhage			Reference
	Year 1	Year 2	Year 3	
DEX700 PRN	4.03%	1.15%	1.73%	MEAD[194]
Watch and wait	0.00%	0.00%	0.00%	No treatment assumed for watch and wait
Ranibizumab	0.00%	0.00%	0.00%	RESTORE[100, 114, 199] (note no incidences reported)
Bevacizumab‡	0.00%	0.00%	0.00%	BOLT[99, 200] (note no incidences reported)
Laser‡	[redacted]	[redacted]	[redacted]	PROTOCOL I[201] to Year 2 then LOCF†
Fluocinolone acetonide‡	0.00%	0.00%	0.00%	FAME[163, 173, 198] (note no incidences reported)

Key: DEX, dexamethasone; PRN, *pro re nata*.

**Notes: ***DMO patients who are insufficiently responsive to non-corticosteroid therapy only ; †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; ‡scenario analysis only.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

As described in section 7.3.2, transition probabilities between visual acuity states resulting from treatment were based on DEX700 PRN patients' transitions in the MEAD studies, which varied over the initial 3-year treatment period in 3-monthly cycles. Watch and wait and other comparator transition probabilities were calculated from these by applying relative risks of improving, worsening or maintaining stable vision calculated from the network meta-analysis. The relative effects were assumed constant over time while the baseline transition probabilities were allowed to vary over the 3-year treatment period.

Following this, the natural progression of vision in eyes with DMO was applied and assumed to remain constant over time due to a lack of evidence to inform an alternative assumption.

The rate of discontinuation from treatment was assumed to vary over time, based on the rates observed in key clinical trials as described in section 7.3.2.

Age-specific all-cause mortality was obtained from interim life tables[204] for England and 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[68] and due to DMO relative to the DM population[69] were assumed to remain constant over time given that the background mortality was already age-dependent to avoid double counting.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The main clinical outcome measure was changes in BCVA, which were estimated directly from trial data, and the network meta-analyses. These were directly informed by evidence for changes in BCVA taken from clinical trial data and key study publications. Changes in BCVA have been linked to changes in costs and HRQL.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[e]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts validated some key clinical assumptions described in section 7.3; however they did not directly provide any values. Details of clinician input are provided in appendix 14 (section 10.14).

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

[e] 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.

A table of variables included in the economic model for each population of interest is provided in PDF files which have been submitted separately. A PDF file has been supplied per model:

- "Parameters pseudophakic.pdf"
    - DMO patients who are pseudophakic
- "Parameters all DMO.pdf"
    - DMO patients who are insufficiently responsive to non-corticosteroid therapy (base case excluding FAME)
    - DMO patients who are unsuitable for non-corticosteroid therapy
- "Parameters all DMO_incl.FAME.pdf"
    - DMO patients who are insufficiently responsive to non-corticosteroid therapy (scenario analysis including FAME)

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

The majority of treatment-related clinical outcomes were not extrapolated beyond the trial results. The key clinical trials for each treatment regimen and the duration of follow-up are shown in Table 91.

Table 91: Key publications for each treatment

Treatment	Key publication for clinical inputs	Duration of follow-up
DEX700 PRN	MEAD	3 years
Watch and wait	MEAD	3 years
Ranibizumab	RESTORE	3 years
Bevacizumab*	BOLT	2 years
Laser*	PROTOCOL I	2 Years†

Fluocinolone acetonide*	FAME	3 years
Key: DEX, dexamethasone; PRN, *pro re nata*. **Notes:** *Scenario analysis only; 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.		

Treatment efficacy is modelled using 3-year data from the DEX700 treatment arm of the pooled MEAD studies, with constant relative treatment effects assumed as described in section 7.3.2. Following the 3-year treatment period the same natural history of vision is assumed for all patients in the absence of evidence to support an alternative assumption.

Clinical inputs for discontinuation from treatment and adverse events of treatment were applied only during the 3-year treatment period. 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), both applied in scenario analysis only] extrapolation beyond the trial follow-up was required, as described in section 7.3.2.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The key assumptions in the economic model are outlined in Table 92.

Table 92: Key assumptions in the *de novo* economic model

Assumption	Justification	Reference (section)
A maximum of 3 years of treatment has been assumed in the base case	This is consistent with the maximum duration of clinical trials in DMO, and hence limits the amount of extrapolation required in terms of numbers of treatments and treatment efficacy.	7.3.2
Relative treatment effects from the network meta-analysis are assumed to correspond to modelled efficacy outcomes. The relative risk of gaining ≥ 10 letters from baseline is 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 is assumed to be equivalent to the relative risk of moving down one 10-letter health state (worsening vision) and 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).	This assumption is necessary to allow the use of the network meta-analysis to inform the Markov model structure, and builds upon previous modelling in the appraisal of aflibercept for central retinal vein occlusion.[203]	7.3.2
Relative treatment effects are assumed to be constant regardless of starting health state and over time	One network meta-analysis was performed for each population of interest, using all available data for the probability of improving; worsening or maintaining stable vision at the most commonly reported time-point in key clinical trials. Attempting to disaggregate the relative effects of treatments dependent on starting health state would lead to smaller sample sizes and hence less robust analyses.	7.3.2
Following discontinuation from treatment patients are assumed to receive no further treatment and receive visual acuity outcomes consistent with the natural history of vision in patients with DMO	Discontinuation reflects a non-trivial proportion of the MEAD trial population for whom there is no evidence of how their BCVA progressed. The purpose of this economic model is to evaluate the cost-effectiveness of DEX700 for the treatment of DMO; it is not a treatment sequencing model.	7.3.2

Fellow eye involvement in Years 1 or 2 only	Simplifying assumption to prevent the need for further sets of health states; validated with clinicians and consistent with MEAD data.	7.3.2
No additional mortality due to blindness	Excluded to avoid double-counting as the hazard ratio for DMO is likely to include some blindness. However a scenario analysis is included where the additional mortality due to blindness is applied only to patients whose BSE falls below 35 letters	7.3.2
Natural progression of vision in eyes with DMO assumed constant over time	Lack of evidence to inform an alternative assumption	7.3.3
Eyes without DMO are assumed to have stable vision	The model only considers vision loss due to DMO.	7.3.2
BSE and WSE defined at baseline and assumed fixed throughout the model time horizon	Simplifying assumption consistent with previous economic modelling in DMO.	7.2.5
Key: DEX, dexamethasone; BCVA, Best-corrected visual acuity; DMO, diabetic macular oedema.		

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Adults experiencing sight loss incur an associated loss in HRQL.[197] As described in section 2.1. DMO is the leading cause of blindness in the DM population.[7, 53, 54] Visual impairment can negatively impact both the physical and emotional functioning of the DM patient. DMO can have a damaging effect on vision which can limit the patients' ability to perform everyday activities (see section 2.1 for examples). These factors are directly linked to the patients' quality of life.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Without treatment for DMO, the patient's vision is likely to deteriorate and in extreme cases the deterioration may progress to severe vision loss (defined as BCVA < 35 letters) in the affected eye, and even clinical blindness (defined as BCVA ≤ 35 letters in the BSE). Loss of vision is linked to loss of HRQL as described in section 7.4.1.

Treatment for DMO aims to improve, or at the very least stabilise vision, thus improving, or stabilising, HRQL.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

Health-related quality of life and visual-functioning were assessed at baseline for each study arm in the MEAD studies using 2 generic health-related quality of life (HRQL) instruments: the short form 36 question health survey version 1 (SF-36v1) and the EuroQol-5 Dimensions Health Questionnaire (EQ-5D); and 1 instrument specific to visual functioning and vision-related quality of life, the National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25).

The SF 36 and EQ-5D health surveys 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 than the VFQ-25. Moreover, research has shown that general preference instruments like the EQ-5D are relatively insensitive to visual functioning.[206]

EQ-5D

The EQ-5D is consistent with the NICE reference case but has been demonstrated not to be sensitive to changes in vision[207], and hence not to accurately capture the effect of changes in vision on HRQL. Espallargues *et al*.[206] (2005) demonstrated that, in a population with age-related macular degeneration, vision is one of the main factors which impacts HRQL as loss of vision reduces the ability to engage in many everyday activities such as reading, writing, driving and recognising people. Based on the age-related

macular degeneration population considered, they concluded that the EQ-5D appeared to fail to capture the impact on everyday activities resulting from loss of central vision.

The impact of vision loss in patients with DMO is likely to be worse than that for age-related macular degeneration as described by Espallargues *et al*.[206] (2005). 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 the EQ-5D is likely to also fail to capture the true impact of vision loss caused by DMO.

This is further supported by research by Kay and Ferreira[208] (2014) who mapped NEI 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 NEI 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 lack of correlation between NEI VFQ-25 and EQ-5D scores (based on EQ-5D visual analogue scale scores) has also been demonstrated by Lloyd *et al*.[157] (2013) who found only low to moderate correlation between the two measures in patients with DMO.

The mapping algorithm generated by Kay and Ferreira[208] (2014) consistently predicted EQ-5D utility scores which were above the population average given the age of the population. Scatter plots showing observed vs. predicted EQ-5D scores also demonstrated weak correlation. The predictive power of the preferred mapping equation was considered moderate (squared Spearman correlation coefficient 0.34).This further supports the conclusion of Espallargues *et al*.[206] (2005) that the EQ-5D may not reliably discriminate the impact of visual impairment in patients with DMO.

Fenwick *et al*.[209] (2012) have additionally demonstrated that the presence or severity of DMO and its associated vision loss are not associated with EQ-5D score. They concluded that EQ-5D is not sensitive to the impact of severity of

DMO, providing additional support for the conclusions made by Espallargues *et al*.[206] (2005).

As described in section 7.4.6 the committee for TA237 and TA274 considered the manufacturer's 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 Coski-Murray *et al*. (2009).[83, 84, 210] This study reported time trade-off utility values for members of the general population wearing lenses to simulate bilateral visual impairment resulting from age-related macular degeneration. The committee for TA271 and TA301 considered a range of utility sources, none of which were based on EQ-5D utility values (section 7.4.6).[85, 86] This further supports the exclusion of EQ-5D from the base case analysis.

In the MEAD studies, 946 patients receiving DEX700, DEX350 or sham had EQ-5D recorded at baseline (204 of these were treated in their BSE and 742 were treated in their WSE). A summary of the values observed in each health state at baseline are presented in Table 93. These demonstrate the inappropriateness of the EQ-5D for differentiating between changes in quality of life resulting from changes in vision. The overall mean score was 0.76 for patients treated in their BSE and 0.78 for patients treated in their WSE. These are similar to the UK population means for patients of the same age reported by Sullivan *et al*. (2011) who reported the mean EQ-5D score for adults in the UK aged 60-69 to be 0.774.[211] However, these are at odds with the mean EQ-5D score for patients with DM reported by Sullivan *et al*. (2011) of 0.644 without complications and 0.570 with complications.[211] This suggests that the EQ-5D may not be accurately capturing the impact of DM or DMO in the MEAD study population.

There is no clear pattern to the EQ-5D values as vision increases or decreases. We would expect that utility would increase as vision improves, and decrease as vision declines. However, this relationship is not demonstrated in Table 93. Further, each health state has a large amount of variability indicated by the standard deviations around the mean values in Table 93 and the wide variation between the minimum and maximum

observations, which span between negative utility and perfect health in the majority of visual acuity states.

Table 93: Distribution of EQ-5D scores at baseline in MEAD (pooled DEX700, DEX350 and sham patients)

	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]
	[redacted]						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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]

Key: BSE, better-seeing eye; DEX, dexamethasone; EQ-5D, EuroQol – 5 dimension; SD, standard deviation; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File 2014[194]

VFQ-UI

The NEI VFQ-25 is a non-preference based vision specific quality of life measure which has been validated in a DMO population.[157] The NEI VFQ-25 does not allow the direct estimation of utility weights.

Kowalski *et al*.[212] (2012) used 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 to produce a health-state classification system, the Visual Function Questionnaire Utility Index (VFQ-UI). Preference scores for the VFQ-UI have been elicited using time trade-off by 607 members of the general population in the UK, Canada, Australia and the USA.[213]

An algorithm (the VFQ-UI algorithm) was then produced using econometric modelling to allow the estimation of preference-based utility values from the VFQ-UI (using scores from the NEI VFQ-25). This research was conducted by an independent academic group including Professor John Brazier (University of Sheffield, UK) on behalf of Allergan.

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[214], which received a positive recommendation.

In the MEAD studies 932 patients receiving either DEX700, DEX350 or sham had NEI VFQ-25 scores recorded at baseline (200 of these were treated in their BSE and 732 were treated in their WSE). In a pooled sample across all time-points at which NEI VFQ-25 was measured, there were 9033 observations of NEI VFQ-25 that were converted to VFQ-UI scores. A summary of the values observed in each health state at baseline and across pooled visits are presented in Table 94 and Table 95. Whether the study eye was the BSE or WSE was defined at each visit to enable accurate classification of patients for utility calculations.

Table 94: Distribution of VFQ-UI scores at baseline in MEAD (pooled DEX700, DEX350 and sham patients)

	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]

Key: BSE, better-seeing eye; DEX, dexamethasone; SD, standard deviation; VFQ-UI, Visual Functioning Questionnaire Utility Index; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File 2014[194]

Table 95: Distribution of VFQ-UI scores across pooled visits in MEAD (pooled DEX700, DEX350 and sham patients)

	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]

Key: BSE, better-seeing eye; DEX, dexamethasone; SD, standard deviation; VFQ-UI, Visual Functioning Questionnaire Utility Index; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File 2014[194]

Scatter plots of VFQ-UI score against BCVA have been presented in appendix 18 (section 10.18) for information. These illustrate the 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 in Table 94 and Table 95. However, despite the wide variability in the VFQ-UI scores, the mean score in each visual acuity state appears to be reasonable and behave as expected, with better visual acuity being associated with higher utility. The data additionally illustrate 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 Health State 1 and Health State 6 being larger for patients treated in the BSE than the WSE.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping of HRQL data was undertaken for the *de novo* economic model.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

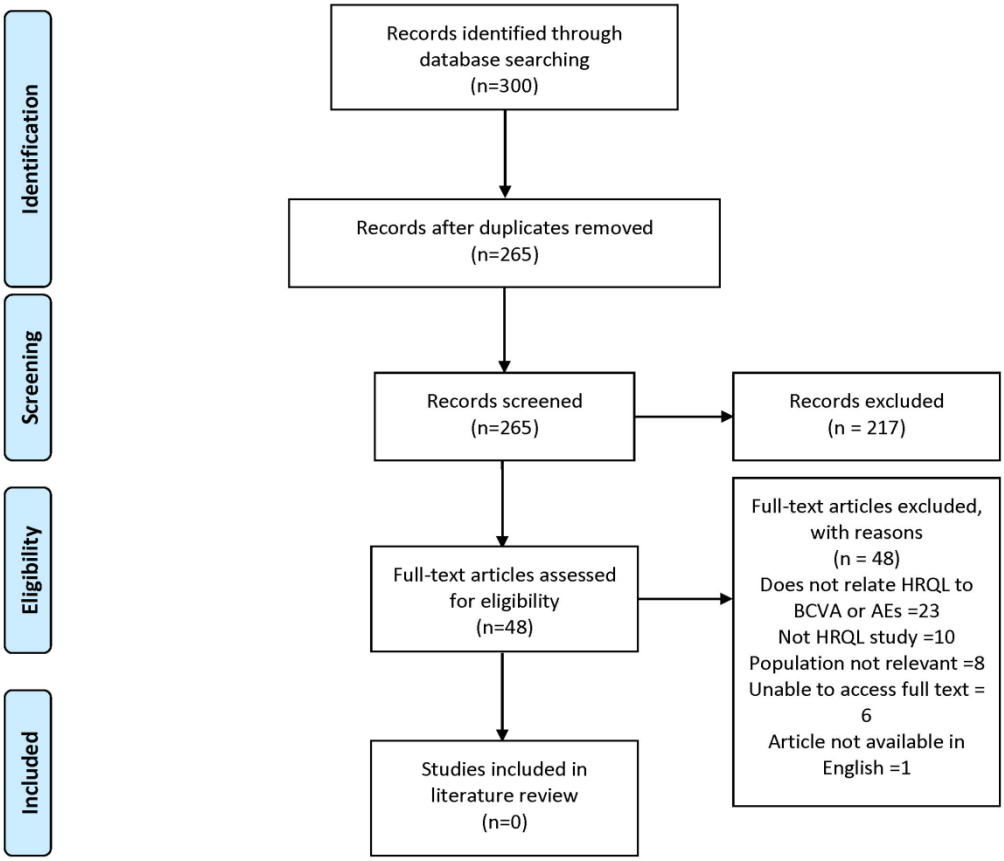
A systematic literature review was conducted in February 2014, and updated in July 2014, to identify published HRQL data for patients with DMO, including the effect of adverse events of treatments for DMO on HRQL. The full search strategy for the literature review and subsequent update are detailed in section 10.12 appendix 12 and described briefly here.

Searches were performed in Medline and Medline In-Process and other non-indexed citations, Embase, HTA, NHS EED, DARE, CINAHL and EconLit. No date or language limits were applied. Filters for quality of life were applied based on SIGN recommendations.[188] Relevant NICE guidance was identified and included within the detailed description of included studies.

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.

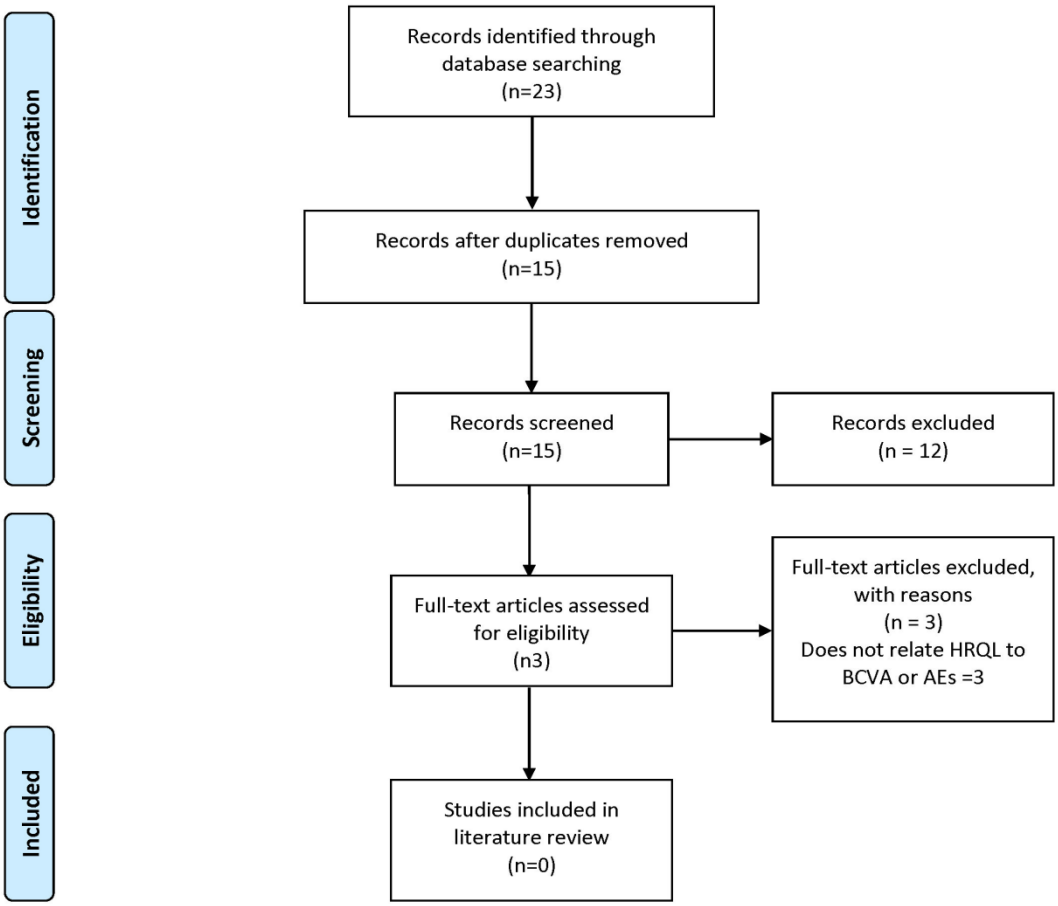
The PRISMA diagram for the literature search for HRQL data conducted in February 2014 is provided in Figure 63. The PRISMA diagram for the updated searches conducted in July 2014 is provided in Figure 64. In the initial review no relevant studies were identified through database searching. Two relevant NICE appraisals (each with a number of relevant publically available documents) were identified through additional searches and were included in the detailed description of included studies. The updated searches conducted in July 2014 resulted in no additional studies being identified.

Figure 63: PRISMA diagram – HRQL studies literature review (February 2014)



Key: AEs, adverse events; BCVA, best-corrected visual acuity; HRQL, health-related quality of life.

Figure 64: PRISMA diagram – HRQL studies literature review (update July 2014)



Key: AEs, adverse events; BCVA, best-corrected visual acuity; HRQL, health-related quality of life

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.

- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

No studies were identified that reported: utility or HRQL data related to either changes in BCVA or absolute BCVA in patients with DMO; or utility or HRQL data related to adverse events resulting from DMO treatment. Given this, identified relevant NICE guidance was reviewed to determine the HRQL data that were used in previous NICE technology appraisals for current DMO treatments.

For TA274, the original manufacturer's submission[191] used EQ-5D utilities from the RESTORE trial that were related to visual acuity health states using linear regression (without accounting for confounding variables). This analysis was based on the treated eye. No utility decrements were applied for adverse events associated with treatment of DMO. To address committee concerns, an extended regression was performed that contained additional covariates including age, sex, duration of DM, blood pressure control at baseline, baseline HbA_{1c} and eye status (BSE versus WSE). The only significant predictors of utility were found to be BCVA and sex. In addition to this, scenario analyses were included that used utility values from published sources: Lloyd *et al*.[215] (2008), Sharma *et al*.[216] (2003) and Czoski-Murray *et al*.[210] (2009). The study by Czoski-Murray *et al*.[210] (2009) was preferred by the committee.[84] These references were subsequently retrieved and reviewed.

Sharma *et al*.[216] reported time-trade-off utility values associated with visual loss secondary to diabetic retinopathy in the BSE in a sample of Canadian patients. Lloyd *et al*.[215] (2008) reported standard gamble, EQ-5D and HUI-3 utilities, and the VFQ-25 score for patients with diabetic retinopathy, based on their BSE. Czoski-Murray[210] reported time-trade-off 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 where the impact of treating the WSE was varied between having no improvement and having the same improvement as is associated with treating the BSE, using the Czoski-Murray 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 original manufacturer's submission used time-trade-off data from Brown *et al*.[217] (2000), 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*.[218] (2012); Heintz *et al*.[218] (2012) estimated time-trade-off, visual analogue scale, EQ-5D and HUI-3 utilities for Swedish diabetic retinopathy patients based on visual impairment in their BSE. However, this approach was not preferred by the committee as they felt that the "very slight differences" between vision loss in the BSE relative to the WSE lacked face validity.

The ERG for TA301 conducted a further sensitivity analysis using BSE utilities from Brown *et al*.[219] (1999), 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 where the impact of treating the WSE was varied between having no improvement and having the same improvement as is associated with treating the BSE, using different sources for the BSE utilities (Brown *et al*.[217] (2000), Brown *et al*.[219] (1999) and Czoski-Murray *et al*.[210] (2009)). The committee again preferred the analyses in 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 previous NICE technology appraisals for DMO are subject to a large number of limitations. There are no published utility values specific to the treatment of DMO; therefore values relating to visual impairment resulting from other causes have been applied. These values may

not be exactly representative of the utility experienced by a patient with DMO. Furthermore, the published values are, in the majority of cases based on vision in the BSE only, therefore requiring assumptions in order to address the impact of changes in vision resulting from treatment of the WSE or of bilateral treatment.

An additional limitation of published utility values is that the health states for which utility values have been published do not exactly match those used in any economic model for DMO. Consequently, adjustments or assumptions have had to be made to make the published data ‘fit’ within the model structures, which have all been based on one eye only. It is reasonable to believe that the level of vision in the fellow eye will impact the utility that can be achieved through changes in vision in either eye. This cannot be captured through the use of the published utility values, which are based, in general, on vision in the BSE only with no information reported on the level of vision assumed in the WSE.

Given these limitations, the values that have been used in previous NICE technology appraisals have not been considered further within this submission. Instead, the analyses that have been conducted on VFQ-UI data obtained from the MEAD clinical trials, which relate vision in both the BSE and WSE simultaneously to utility values for DMO patients, have been used within the cost-utility analysis that is presented here (section 7.4.3). These have been used in preference to the published values because they relate specifically to the DMO population, are measured using a vision-specific preference based measure (the VFQ-UI) and include vision in the BSE and vision in the WSE separately as explanatory variables.

The analysis conducted on EQ-5D values obtained from the MEAD clinical trials have been used in sensitivity analyses.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

As noted in section 7.4.6, no studies were identified that reported utility or HRQL data related to either changes in BCVA or absolute BCVA in patients with DMO. The published utility values used within previous economic evaluations for DMO were all based on populations that were not specific to DMO, and largely reported utility values relating to one eye only, in general the BSE. Furthermore, the utility equation used within our model considers vision in both the BSE and WSE, whereas the published values consider only vision in one eye, and do not provide information on the level of vision in the fellow eye.

It is therefore not appropriate to compare the values derived from the MEAD clinical trials and used within the economic model directly with these values.

The utility equations derived from the MEAD studies for our *de novo* economic model provide a more accurate assessment of the true patient utility and is therefore considered to be the best available evidence.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Adverse events associated with treatment for DMO are expected to have little effect on HRQL due to their nature. The main adverse events associated with DEX700 treatment in the MEAD trials were increases in IOP and a higher incidence of cataracts. Increases in IOP were predictable, transient and mainly required no treatment or were managed successfully with standard topical pressure-lowering medications. Cataracts are likely to have a detrimental effect on a patient's quality of life due to the effect on visual acuity; however, this is expected to be captured implicitly within the BCVA outcomes of the clinical trials. Any disutility associated with the cataract extraction procedure is experienced for a very short period of time and was therefore not considered.

Furthermore, regressions were estimated 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*. The estimated coefficients were small and were not found to be statistically significant at the 5% significance level, hence the adverse events of raised IOP and cataract were not found to be statistically significant predictors of VFQ-UI score. Further detail for these analyses is provided in appendix 18 (section 10.18).

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Linear regression analyses were performed using VFQ-UI and EQ-5D data from MEAD, giving the following algorithm 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 96 and Table 97. Both analyses use pooled data across treatments (DEX700, DEX350 and sham). The VFQ-UI analysis uses a mixed effects analysis, utilising pooled data across all time-points at which NEI VFQ-25 was collected within the MEAD studies. The EQ-5D was only collected at baseline within the MEAD studies and so this analysis utilises baseline measurements only.

Table 96: Regression analysis parameters – VFQ-UI (base case analysis)

Parameter	Number of observations	Mean	SE
Constant	[redacted]	[redacted]	[redacted]
$Coefficient_{BSE}$		[redacted]	[redacted]
$Coefficient_{WSE}$		[redacted]	[redacted]

Key: BSE, better-seeing eye; SE, standard error; WSE, worse-seeing eye; VFQ-UI, Visual Functioning Questionnaire Utility Index.
Notes: *p<0.05; †p<0.001; analysis is based on observed data without imputation for missing values. Patients, treatment arm, and study (010 vs. 011) were treated as random effects
Source: Allergan MEAD Data on File 2014[194]

Table 97: Regression analysis parameters – EQ-5D (scenario analysis)

Parameter	Number of observations	Mean	SE
Constant	[redacted]	[redacted]	[redacted]
$Coefficient_{BSE}$		[redacted]	[redacted]
$Coefficient_{WSE}$		[redacted]	[redacted]

Key: BSE, better-seeing eye; EQ-5D, EuroQol-five dimensions questionnaire; SE, standard error; WSE, worse-seeing eye.
Notes: *p<0.05; †p<0.001
Source: Allergan MEAD Data on File 2014[194]

The VFQ-UI analysis has been used in the base case as this is a vision-specific preference-based measure and the EQ-5D has been shown not to be sensitive to changes in vision.[206, 208, 209] Furthermore, the VFQ-UI was measured throughout the MEAD clinical studies, whereas the EQ-5D was only measured at baseline; hence the VFQ-UI analysis includes more data points than the EQ-5D analysis.

The EQ-5D analysis has been included as a sensitivity analysis to show the impact of the choice of measure of utility on the results of the economic model; however, the results of this analysis should be interpreted with caution. The EQ-5D regression equation implies that changes to the level of vision in the WSE do not impact utility, which is counter-intuitive and not consistent with published literature.

The VFQ-UI analysis demonstrates that changes in vision in the BSE have a larger impact on utility than the same change in the WSE, although changes

in both eyes will affect visual functioning. This is consistent with the findings of Bressler *et al*. (2010).[159]

The linear regression has been performed assuming normality: however, the relationship between BCVA and utility is unlikely to be normal, as illustrated by the clear ceiling and floor effects in Table 95, as well as Figure 94 and Figure 95 of appendix 18 (section 10.18). The mean utility in each health state appears to follow an approximately linear pattern which supports the use of a linear regression to approximate utility from BCVA in the BSE and the WSE. The selected analysis maximises the use of the data from the MEAD studies, using a vision-specific measure of utility. We believe that the equation presented appropriately captures the linearity and variability present in the data, while providing the best and a novel solution to modelling changes in utility resulting from changes in BCVA in both eyes.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6:]

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[6] 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.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical expert advice was sought regarding the utility values used in the *de novo* economic model.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

HRQL is expected to vary according to the visual acuity states into which patient's eyes fall. The higher the BCVA in each eye the better visual functioning and quality of life is expected to be, but changes in vision in the BSE are expected to have a greater effect on HRQL than the same changes in the WSE. This is demonstrated by the regression equation used in the model and described in section 7.4.9 whereby the coefficient for BCVA in the BSE is larger than the coefficient for BCVA in the WSE.

Within the economic model, the BSE and WSE are modelled independently for all patients within the cohort. For patients within the cohort with different characteristics (i.e. unilateral DMO in the BSE or WSE, or bilateral DMO and on treatment or discontinued from treatment), the distribution of vision in the BSE and in the WSE across the visual acuity states in each cycle is calculated by applying transition probabilities as described in section 7.3.2. This assumes that patients' BSE and WSE are independent.

Utility values for the patients within the cohort with different characteristics (as described above) in each cycle are calculated directly from the distributions of BCVA in the BSE and the WSE. This is achieved by applying the regression equation described in section 7.4.9 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 is consistent with Table 98 (all DMO patient population) and Table 99 (pseudophakic DMO patient population).

Table 98: Mean BCVA in each visual acuity state; All DMO patients

Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, Best-corrected visual acuity; DMO, diabetic macular oedema.
Source: Allergan MEAD Data on File 2014[194]

Table 99: Mean BCVA in each visual acuity state; DMO patients who are pseudophakic

Health State 1	Health State 2	Health State 3	Health State 4	Health State 5	Health State 6
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, Best-corrected visual acuity; DMO, diabetic macular oedema.
Source: Allergan MEAD Data on File 2014[194]

A summary of utility values based on the combinations of health states for the BSE and WSE are provided in Table 100 and Table 101, based on the mean BCVA in each health state given in Table 98 and Table 99. Health State 1 represents clinical blindness if the BSE falls into this state.

Table 100: Utility values for visual acuity states across two eyes – All DMO patients (DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy)

		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]

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; N/A, not applicable; WSE, worse-seeing eye.

Table 101: Utility values for visual acuity states across two eyes – DMO patients who are pseudophakic

		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]
Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; N/A, not applicable; WSE, worse-seeing eye.							

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

The effect of adverse events on HRQL was excluded from the analysis as described in section 7.4.8.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to vary over time as BCVA varies over time, using the relationship defined in section 7.4.9.

In the base case analysis utilities are not age-adjusted; however, a sensitivity analysis is included whereby utilities are adjusted due to the patients' age. This is done using a coefficient of -0.00029 per year reported by Sullivan *et al*.[211] (2011). This paper reports an analysis that provides a UK-based catalogue of EQ-5D index scores including a coefficient for age. The mean baseline age in the MEAD trials is 62 years and so the utility values obtained from the MEAD trial data are assumed to be relevant for patients of this age. The coefficient is 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.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

No amendments have been made to the values reported.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The HRG codes selected for the administration of laser and intravitreal injections are shown in Table 102.

Table 102: HRG codes used in economic model for treatment administration

Treatment procedure type	HRG code	HRG description
Laser	BZ23Z	Service code 130 Ophthalmology: Minor Vitreous Retinal Procedures
Intravitreal injection	BZ23Z	Service code 130 Ophthalmology: Minor Vitreous Retinal Procedures

Key: HRG, Healthcare Resource Groups.
Source: NHS reference costs 2012-2013[220]

These were selected to retain consistency with previous NICE technology appraisals of technologies for DMO[189, 191], which have based the choice of HRG code on Office of Population Censuses and Surveys (OPCS) codes from the NHS Information Centre PbR tariff.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Consistent with previous technology appraisals in retinal conditions NHS reference costs and the Monthly Index of Medical Specialities (MIMS) were used to cost resources associated with the treatment of DMO.

NHS Reference Costs were deemed more appropriate than the PbR tariff 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. These costs take into account staff time, event-based time and standard equipment time. Thus, they include opportunity costs, whereas the PbR Tariffs are prospective costs, which may not reflect the actual cost to the NHS. Thus at point of use in the model, costs based on the NHS reference costs will more accurately reflect opportunity costs of delivering care than the PbR tariff.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

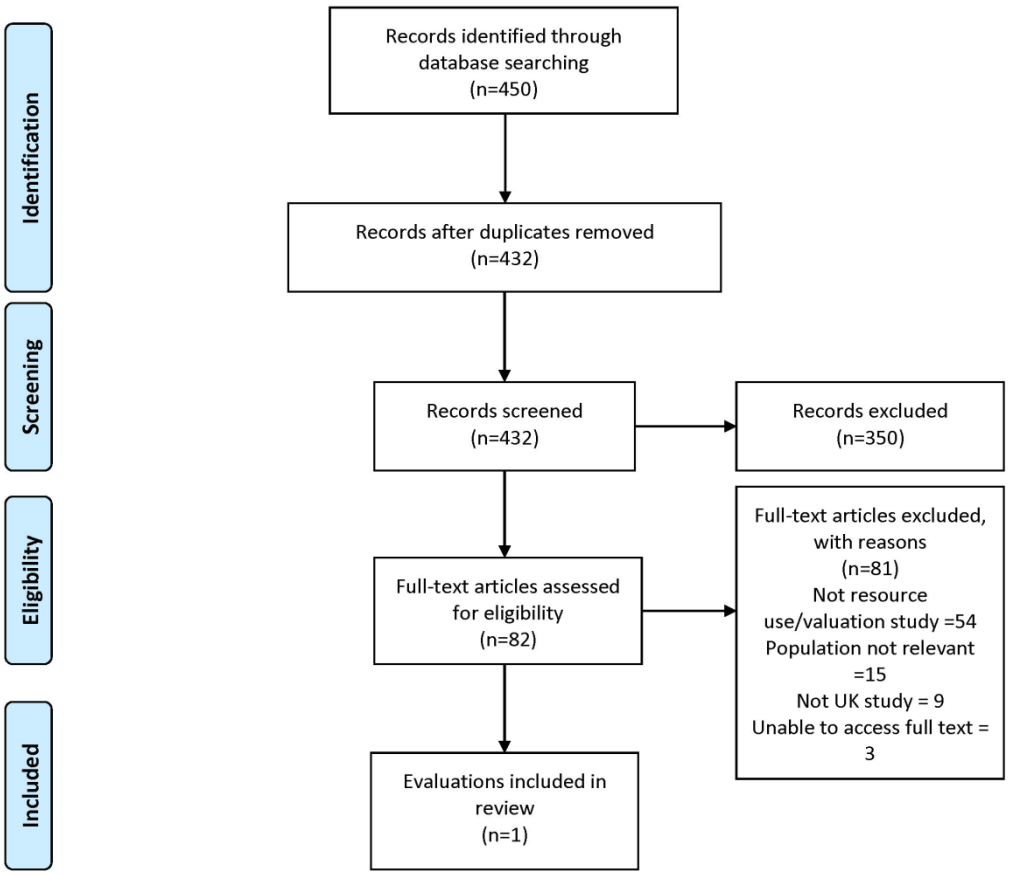
A systematic literature review was conducted in February 2014, and updated in July 2014, to identify published resource data for patients with DMO. The full search strategies for the literature review and subsequent update are detailed in section 10.13 appendix 13 and described briefly here.

Searches were performed in Medline and Medline In-Process and other non-indexed citations, Embase, HTA, NHS EED, DARE, CINAHL and EconLit. No date or language limits were applied. Filters for cost and resource were applied based on SIGN recommendations.[188] Relevant NICE guidance was identified and included within the detailed review of included studies.

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.

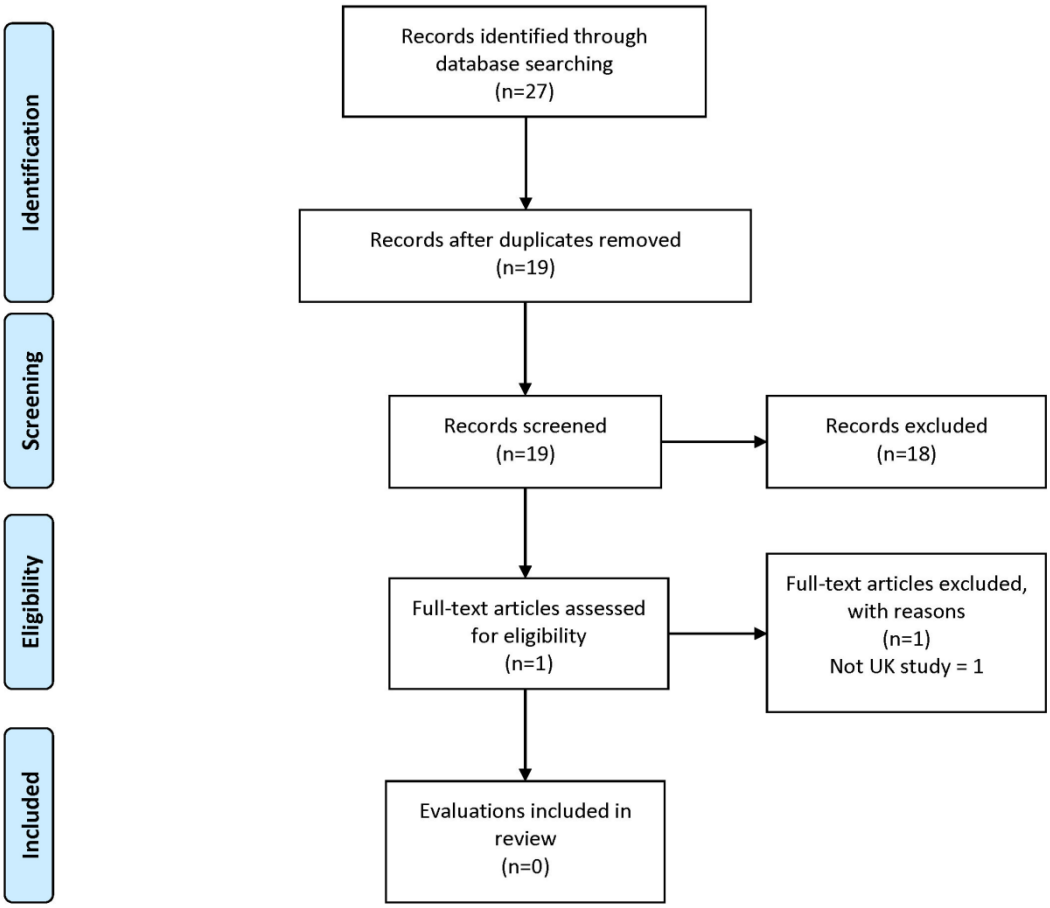
The PRISMA diagram for the literature search for resource data conducted in February 2014 is provided in Figure 65. The PRISMA diagram for the updated searches conducted in July 2014 is provided in Figure 66. In the initial review one relevant study was identified through database searching. Two relevant NICE appraisals (each with a number of relevant publically available documents) were also identified through additional searches and were included in the detailed description of included studies. The updated searches conducted in July 2014 resulted in no additional studies being identified.

Figure 65: PRISMA diagram – resource studies literature review (February 2014)



Key: UK, United Kingdom.

Figure 66: PRISMA diagram – resource studies literature review (update July 2014)



Key: UK, United Kingdom

The literature review identified one resource study of relevance to this appraisal by Minassian *et al*.[41] (2012). This study constructed a direct cost of illness study for DMO for the year 2010, from the perspective of the health and social care providers in the UK (specifically Wales). They derived most of their resource use and related costing data from government websites, noting the paucity of published literature in this area. General and disease-specific health costs were included, grouped into screening/detection (not relevant for this appraisal), outpatient diagnostic and treatment inputs and social care excess costs related to visual impairment from this disease.

Hospital diagnostic and treatment costs were based on resource inputs from the *National Screening Handbook*. They assumed that NHS estimates were

averaged across routine (70%) and complicated (30%) laser outcomes, adjusting the latter by a multiplier of 1.5 to reflect higher resource input. The NHS reference costs (2008-2009) were used for an outpatient appointment (£73) and an integrated diagnostic/monitoring cost, which was calculated as £206 per person. Laser treatment was the only treatment considered and was estimated to cost £844 per treatment without travel (four visits) and an outpatient appointment. The addition of travel and an outpatient appointment increased this to £966.60, assuming that travel and time for the patient and accompanying person were costed at £12.40 per visit on average (based on a cost for glaucoma treatment). Travel costs were included due to the age of the DMO population, bearing in mind government schemes for free travel.

Hospital-based and local authority low vision services were calculated per partially sighted or blind person. Hospital-based low vision services were estimated to be £134.40, including a hospital general ophthalmic appointment and a low vision consultation. Local authority services were estimated to cost £304.22, based on previous literature. Excess of routine health and social care service usage attributable to sight loss in general was also calculated per partially sighted or blind person. This was based on the UK Vision Strategy Report of 2009, which estimated specific usage estimates for the presence or absence of age-related macular disease (hence is not directly applicable to this appraisal). Direct non-ophthalmic medical-related costs were estimated to be £19.75 per year. The average cost of excess residential care for a partially sighted or blind person was £246 per year. The average cost of excess paid care per year was £9,711.56 per blind person and £1,981.95 per partially sighted person.

This study supports the use of NHS reference costs and the unit costs of health and social care for the valuation of the majority of resources associated with the management of DMO. The study does not provide sufficient information to directly inform this submission, but it confirms the paucity of literature in this area and the importance of the costs of blindness in the DMO population.

Given this paucity of published literature, identified relevant NICE guidance and the associated manufacturer’s submissions were reviewed to determine

the resource data that was used in previous NICE technology appraisals for treatments for DMO.

TA274:

In TA274 the manufacturer's original submission assumed 7 ranibizumab injections in the first year for both the ranibizumab monotherapy and ranibizumab + laser combination arms, and 3 (2) injections in Year 2 for ranibizumab monotherapy (combination). Both the ranibizumab + laser combination and laser monotherapy arms were assigned two laser treatments in Year 1 and one in Year 2. A revised model was later submitted assuming patients receiving ranibizumab would receive two injections in Year 3 and one injection in Year 4, while patients receiving laser would receive one treatment in Year 3 and in Year 4. A further revision to the model assumed ranibizumab patients would receive seven injections in Year 1, four in Year 2 and three in Year 3, based on a 2-year extension of the RESTORE study.

The cost of ranibizumab was £761.20 per injection (before the confidential PAS). Unit costs for a visit to an eye clinic for a check-up or treatment were based on NHS reference costs 2008/9, with both ranibizumab and laser assumed to be administered at an outpatient attendance costing £150. Combination therapy was assumed to be administered at the same visit costing £184. The cost of monitoring visits was £126. The manufacturer's submission indicated that this included a follow-up attendance (£73), OCT (£53) and VA assessment (£0).

Patients were assumed to receive 12 visits in the first year and 10 in the second year (ranibizumab monotherapy); 12 visits in the first year and 8 visits in the second year (combination therapy/laser monotherapy). All patients were assumed to receive four visits per year in Year 3 onwards. For treatment arms that included ranibizumab a treatment visit was assumed to include monitoring. Patients receiving laser monotherapy required separate visits for treatment and for monitoring. This difference in application was questioned by the ERG. A revised analysis was provided that assumed patients receiving ranibizumab received 12 visits in Year 1, eight visits in Year 2 and six visits in Year 3. Patients receiving laser were assumed to require four visits in each of

Years 1, 2 and 3. All patients were assumed to have two visits in Year 4 and all treatment visits were assumed to include monitoring.

Patients whose treated eye was associated with severe vision loss (BCVA < 35 letters) had an additional cost applied reflecting the additional resource use associated with those eligible to register as blind. These costs included low-vision aids, rehabilitation, residential care, district nursing, community care and the costs of treating complications such as depression and falls. This was largely based on a published costing study of blindness in the UK by Meads and Hyde[221] (2003), with costs updated for inflation as appropriate, giving a cost of £6,067 in the first year and £5,936 in subsequent years.

The manufacturer's submission indicated that the costs of treating adverse events of cataract, endophthalmitis, retinal detachment and vitreous haemorrhage were included, based on NHS reference cost tariffs for procedures and associated follow-up attendances.

TA301:

In TA301 the manufacturer's original submission assumed one fluocinolone acetonide intravitreal implant is needed every 3 years, with a further implant at 36 months assumed only for those 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 both fluocinolone acetonide and optimised standard of care (OSC) received laser, triamcinolone, ranibizumab, bevacizumab and DEX700 in line with the observed rates in the FAME trials. The manufacturer's submission indicated that the unit cost of fluocinolone acetonide was £5,500, bevacizumab was £105, ranibizumab was £742, triamcinolone was £7 and DEX700 was £870. All treatments were assumed to be administered in an outpatient procedure costing £150.

The manufacturer's submission indicated that monitoring costs were included in terms of follow-up attendances (£73), OCT (£53) and fluorescein angiography (laser only, £332). The costs of treating adverse events of cataract, endophthalmitis, retinal detachment, vitrectomy, glaucoma and elevated IOP were also included.

An annual cost of blindness of £6,298 was applied to patients whose treated eye BCVA fell below 35 letters based on Meads and Hyde (2003).[221]

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details7:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts provided advice about 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 included in the analysis. Full details of clinician input are provided in appendix 14 (section 10.14).

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example,

[7] 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.

drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Cost of treatment

The list prices of acquisition of each treatment included in the economic analyses for each population of interest are shown in Table 103. 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).[84, 86] The exact discount provided to the NHS is confidential; hence the list prices shown in Table 103 have been used in all base case analyses. Scenario analyses varying the discount to the price of these treatments in 10% increments from a 0% discount (list price) to a 50% discount (with all other inputs and assumptions as per the base case analysis) have been presented in section 7.7.9 to allow the committee to select the ICER that most closely represents the true cost to the NHS.

For all other scenario analyses, results are presented in section 7.7.9 at a 50% PAS discount for ranibizumab only, representing the most pessimistic results for DEX700, to avoid the need for reporting a large number of tables which may not be of interest. However, a discussion is provided which details at what point the decision would change as the level of discount applied is varied (if applicable). Further results tables have then been presented only if they are thought to be of interest in this context. The full sets of completed scenario analyses are provided within the submitted electronic economic models which will allow the committee to review the results of all scenarios at a selected level of discount if they require.

Table 103: List price costs of treatments

Treatment	List price	Reference[222]
DEX700	£870.00	MIMS (Accessed July 2014); 700 microgram intravitreal implant in applicator
Ranibizumab	£742.17	MIMS (Accessed July 2014); 10mg/ml solution for injection: 0.165ml prefilled syringe
Bevacizumab*	£50.00	Poku *et al*. (2012); lower price limit reported in NICE DSU report for the cost of a single pre-filled syringe of bevacizumab[223]
Laser*	£0.00	No acquisition cost is assumed for laser as all facilities are thought to have access to existing equipment to perform laser procedures
Fluocinolone Acetonide*	£5,500.00	MIMS (Accessed July 2014); 190 microgram intravitreal implant in applicator
Watch and wait	£0.00	No treatment cost is associated with watch and wait

Key: DEX, dexamethasone; DSU, NICE Decision Support Unit; MIMS, Monthly Index of Medical Specialities; NICE, National Institute for Health and Care Excellence.
Notes: *Scenario analysis only.

The cost of administration of laser is assumed to be £116.68 (NHS reference costs 2012/13 BZ23Z, service code 130 Ophthalmology, minor vitreous retinal procedures; outpatient procedure), consistent with previous technology appraisals for ranibizumab and fluocinolone acetonide for the treatment of DMO.[189, 191] In the base case all intravitreal injections are assumed to be performed in the outpatient setting at a cost of £116.68 (NHS reference costs 2012/13 BZ23Z, service code 130 Ophthalmology, minor vitreous retinal procedures; outpatient procedure). This is consistent with the assumptions made in TA271.[189]

Sensitivity analyses have been included varying the proportion of day case and outpatient procedures assumed, where a day case procedure is assumed to cost £356.35 (NHS reference costs 2012/13 BZ23Z, service code 130 Ophthalmology, minor vitreous retinal procedures; day case procedure). These scenario analyses have been included to reflect the variability of service provision.

The total costs per round of treatment (including acquisition and administration costs) are provided in Table 104 for unilateral and bilateral

DMO. For bilateral treatment the cost of treatment acquisition is doubled, as one unit is assumed to treat one eye.

Table 104: Total cost per round of treatment

Treatment	Unilateral DMO	Bilateral DMO	
	Total cost per round of treatment	Number of appointments for bilateral treatment*	Total cost per round of treatment
DEX700	£986.68	1.75	£1,944.19
Ranibizumab	£858.85	1.5	£1,659.36
Bevacizumab	£166.68	1.5	£275.02
Laser	£116.68	1	£116.68
Fluocinolone Acetonide	£5,616.68	1.75	£11,204.19

Key: DMO, diabetic macular oedema.
Notes: *Clinical expert opinion (appendix 14, section 10.14).

Based on clinical expert opinion (appendix 14, section 10.14) bilateral treatment with a steroid has been 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. In contrast, clinical experts believed that bilateral treatment with anti-VEGF may occur at the same visit more frequently, estimating that on 50% of occasions two separate administration visits would be required, with only one administration appointment on the remaining 50% of occasions, giving an average of 1.5 appointments for bilateral treatment with an anti-VEGF.

Anti-VEGF treatment was assumed to require two appointments for bilateral administration on fewer occasions than steroid treatment due to the less complex injection procedure associated with administration of an anti-VEGF compared with a steroid implant. These assumptions are tested in scenario analyses (section 7.6.1).

Bilateral treatment with laser has been assumed to be administered in the same visit on 100% of occasions, also based on clinical expert opinion (appendix 14, section 10.14).

Costs following discontinuation

No further treatment is assumed following discontinuation; therefore no further treatment costs are incurred.

Cost of monitoring and tests

Patients with DMO are assumed to require regular monitoring visits and tests. These may include routine monitoring visits, OCT, fluorescein angiography and IOP checks. The unit costs of each type of visit and test required by patients with DMO are shown in Table 105. These are in line with previous economic modelling in DMO.

Table 105: Unit costs of monitoring and tests

Resource	Unit cost	Reference[220]
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)
Intraocular pressure check	£80.04	NHS reference costs 2012/13 WF01A code 130 Ophthalmology; consultant led non-admitted, face to face attendance, follow-up
Key: NHS, National Health Service; OCT, optical coherence tomography.		

The numbers of each type of visit and test required by patients with DMO are expected to vary dependent on whether the patient is receiving treatment or not and if receiving treatment, the treatment that is being received. The amounts of each resource required in each of Years 1 to 3 onwards and the resulting total cost of resource use in each year for each treatment are shown in Table 106 to Table 111. All patients are assumed to receive a fluorescein angiography at baseline, with the exception of non-treated patients who are assumed to receive one per year. All patients are assumed to require routine monitoring visits including OCT, for DEX700 regimens this is in line with the

SPC and informed by clinician opinion, and for other therapy and non-treated patients this is in line with the assumptions made in previous economic evaluations (whose estimates were based on the SPC and/or relevant guidelines).

Table 106: Medical resource use; non-treated patient (including Watch and wait patients)*

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
Intraocular pressure check	0	0	0
Total cost per patient	**£509.08**	**£509.08**	**£509.08**

Key: NICE, National Institute of Health and Care Excellence; OCT, optical coherence tomography.
Notes: *Reference: Fluocinolone acetonide NICE submission (TA271)[189].

Table 107: Medical resource use; DEX700 treated patient (as per MEAD)*

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
Intraocular pressure check	2	2	2
Total cost per patient	**£669.16**	**£552.48**	**£552.48**

Key: DEX, dexamethasone; OCT, optical coherence tomography; SPC, summary of product characteristics.
Notes: *Based on the DEX700 SPC and clinical opinion; monitoring every 3-4 months including OCT, and intraocular pressure check at 8 weeks post injection.

Table 108: Medical resource use; ranibizumab treated patient*

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
Intraocular pressure check	0	0	0
Total cost per patient	**£1,293.88**	**£981.00**	**£392.40**

Key: NICE, National Institute of Health and Care Excellence; OCT, optical coherence tomography.
Notes: *Reference: Ranibizumab NICE submission (TA237)[191].

Table 109: Medical resource use; bevacizumab treated patient*

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
Intraocular pressure check	0	0	0
Total cost per patient	**£1,293.88**	**£981.00**	**£392.40**

Key: OCT, optical coherence tomography.
Notes: *Assumed equal to ranibizumab monitoring requirements.

Table 110: Medical resource use; laser treated patient*

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
Intraocular pressure check	0	0	0
Total cost per patient	**£509.08**	**£392.40**	**£392.40**

Key: OCT, optical coherence tomography.
Notes: *Reference: Fluocinolone acetonide NICE submission (TA271)[189].

Table 111: Medical resource use; fluocinolone acetonide treated patient*

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
Intraocular pressure check	0	0	0
Total cost per patient	**£509.08**	**£392.40**	**£392.40**

Key: OCT, optical coherence tomography.
Notes: *Reference: Fluocinolone acetonide NICE submission (TA271)[189].

These further highlight the burden associated with anti-VEGF treatment regimens, which could be significantly reduced with the introduction of DEX700 into the care pathway for DMO patients. Anti-VEGF regimens are associated with higher treatment and monitoring frequency compared with DEX700. Therefore the introduction of DEX700 would have a positive impact for patients who would not require as many visits, and also for clinicians who would need to see patients less frequently for both treatment and monitoring increasing the capacity of the clinic.

This is illustrated in Table 112 which compares the number of visits required for treatment with ranibizumab and with DEX700 in the pseudophakic population. This demonstrates that, particularly in the early stages of treatment, use of DEX700 can significantly reduce the visit burden for patients and for clinicians.

Table 112: Burden of treatment with ranibizumab vs. DEX700

Resource	Ranibizumab[100, 114, 191, 199]			DEX700[3, 194]		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Treatment visits	7.00	3.90	2.90	[redacted]	[redacted]	[redacted]
Monitoring visits	12	10	4	4	4	4
Total visits	**19.00**	**13.90**	**6.90**	**5.78**	**5.25**	**5.08**

Key: DEX, dexamethasone.

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

The costs accrued within the health states include the costs of treatment and monitoring, which are assumed equal across all health states.

If a patients' BCVA falls below 35 letters on the ETDRS chart they are classified as having severe vision loss. This definition is fixed within the model. Severe vision loss in the BSE (i.e. in both eyes) is associated with a number of additional costs including community care, residential care, hip replacement and depression, in line with Meads and Hyde[221] (2006) and Colquitt *et al*.[224] (2008) and consistent with previous economic evaluations in DMO.[189, 191, 221, 224] Meads and Hyde additionally reported one-off costs which are expected to be incurred when the patient first becomes blind of blind registration, low vision aids and low vision rehabilitation. These costs have been excluded in the base case analysis. However, they have been included in a sensitivity analysis and are not expected to have a large effect on the results. The costs of severe vision loss with and without the one-off costs are shown in Table 113.

Table 113: Severe vision loss costs

Resource	Unit cost	Cost type	% patients with severe vision loss requiring service (funded by NHS)*
Community care	£10,958.50†	Annual	6.00%
Residential care	£52,282.93¶	Annual	30.00%
Hip replacement	£4,222.42‡	Event	5.00%**
Depression	£517.24††	Annual	39.00%
Total cost per patient per year (base case)	**£16,755.23**		
Blind registration	£138.01††	One-off	95.00%
Low vision aids	£180.01††	One-off	33.00%
Low vision rehabilitation	£310.82††	One-off	11.00%
Total cost per patient per year (scenario analysis; first year only)	**£16,979.94**		

Key: NHS, National Health Service.

Notes: *Colquitt *et al*[224] (2008); Meads and Hyd[221]e (2003)

† Curtis (2013); based on weekly cost of community care package for the elderly (excluding accommodation costs) of £210.

¶Curtis[225] (2013); based on weekly cost of local authority residential care of £1002.

‡NHS reference costs 2012/13[220] 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).

††Colquitt *et al*[224] (2008), uplifted using Curtis[225] (2013) The hospital & community health services pay and prices index.

**annual incidence.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Treatments for DMO may be associated with five key adverse events of interest that may require medical or surgical intervention depending on the adverse event type. As described in section 7.3.2, these are cataracts, raised IOP, retinal detachment, endophthalmitis and vitreous haemorrhage.

This section details the cost of treating each adverse event with medication and/or surgical intervention. The proportions of patients who are assumed to experience these adverse events and incur these costs are described in section 7.3.2.

Cataracts

The unit cost of a cataract extraction procedure is assumed to be £865.56, taken from NHS reference costs (BZ02C, service code 130 Ophthalmology, Phacoemulsification cataract extraction and lens implant, with CC score 0-1 [day case]).[220]

Raised intraocular pressure

Raised IOP may be treated by either medication or by surgical intervention.

The unit costs of medications included within the model for the treatment of raised IOP are shown in Table 114. The average cost per patient of each medication is 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 will last. The total average cost per patient of IOP medication is calculated assuming equal use of all treatments.

Table 114: Cost of medications for the treatment of raised IOP

Resource	Unit cost	Mean number of days required*	Maximum number of days per bottle†	Average cost per patient	Reference[222]
Beta-blockers	£1.16	1096	28	£46.40	MIMS (Accessed July 2014); timolol 0.25%
Prostaglandins	£12.48	1096	28	£499.20	MIMS (Accessed July 2014); Xalatan
CA inhibitors	£6.92	1096	28	£276.80	MIMS (Accessed July 2014); Azopt
Combination	£10.05	1096	28	£402.00	MIMS (Accessed July 2014); Cosopt
Brimonidine	£2.19	1096	28	£87.60	MIMS (Accessed July 2014); Brimonidine tartrate
Total average cost per patient				**£92.85**	Assuming equal weighting for each treatment

Key: CA, carbonic anhydrase; IOP, intraocular pressure; MIMS, Monthly Index of Medical Specialties.

Notes: *Assumption; patients who have raised IOP will receive up to 3 years of treatment, consistent with the assumed duration of treatment for DMO.

†Based on the maximum shelf-life being 28 days from opening.

The unit costs of surgical procedures for the treatment of raised IOP are shown in Table 115. The total average cost per patient is calculated assuming equal use of all procedures.

Table 115: Cost of surgical procedures for the treatment of raised IOP

Resource	Unit cost	Reference[220]
Trabeculectomy	£1,421.92	NHS reference costs 2012/13 BZ17B, Service code 130 Ophthalmology, Major glaucoma procedures, with CC score 0 (day case)
Iridectomy	£1,123.44	NHS reference costs 2012/13 BZ18B, Service code 130 Ophthalmology, Intermediate glaucoma procedures, with CC score 0 (day case)
Iridotomy	£1,123.44	NHS reference costs 2012/13 BZ18B, Service code 130 Ophthalmology, Intermediate glaucoma procedures, with CC score 0 (day case)
Total average cost per patient	**£1,222.93**	Assuming equal weighting for each treatment
Key: CC, complication and comorbidity; IOP, intraocular pressure; NHS, National Health Service.		

Retinal detachment

The unit cost of a procedure for the re-attachment of the retina following retinal detachment is assumed to be £1,685.00, taken from NHS reference costs (BZ22B, Service code 130 Ophthalmology, Intermediate vitreous retinal procedure, with CC score 0 [day case]).[220]

Endophthalmitis

The unit cost of a vitreous biopsy procedure for endophthalmitis is assumed to be £1,393.00, taken from NHS reference costs (BZ23Z, Service code 130 Ophthalmology, Minor vitreous retinal procedure, non-elective inpatients [long stay]).[220]

Vitreous haemorrhage

The unit cost of a vitrectomy procedure for vitreous haemorrhage is assumed to be £1,685.00, taken from NHS reference costs (BZ22B, Service code 130 Ophthalmology, Intermediate vitreous retinal procedure, with CC score 0 [day case]).[220]

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No additional costs have been included within the *de novo* economic model. All costs included have been described above.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

There are a number of parameters and assumptions that have been varied in scenario analyses; these are outlined in Table 116.

Table 116: Scenario analyses performed (relevant to all populations under consideration unless stated)

Scenario number	Scenario	Base case assumption	Scenarios considered	Justification
1	***DMO patients who are pseudophakic*** Price of ranibizumab ***DMO patients who are insufficiently responsive to non-corticosteroid therapy*** Inclusion of fluocinolone acetonide and variation of price	List price for all treatments, fluocinolone acetonide not included in base case analyses for all DMO patients	Variable discount between 0% (list price) and 50%. Note the discount to ranibizumab will also be applied to all sensitivity analyses in the pseudophakic population.	A confidential PAS is available to the NHS for ranibizumab and fluocinolone acetonide. This analysis will allow the committee to select the most plausible ICER.
2	***DMO patients who are pseudophakic*** Inclusion of laser, bevacizumab and watch and wait	Ranibizumab is the only comparator	Comparators are ranibizumab, laser, bevacizumab and watch and wait	Ranibizumab 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 bevacizumab in practice so these have been included as a scenario analysis. Watch and wait has been included for completeness.

Scenario number	Scenario	Base case assumption	Scenarios considered	Justification
3	Alternative utility regression analysis	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	Age-adjusted utilities	No age-adjustment	Age-adjustment included using a coefficient of -0.00029 per year from Sullivan *et al.*[211] (2011)	The regression equation does not include a coefficient for age; therefore a sensitivity analysis including an age-adjustment has been included (section 7.4.14).
5	Extend treatment duration to 5 years, with LOCF efficacy	Maximum 3 years of treatment	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

Scenario number	Scenario	Base case assumption	Scenarios considered	Justification
6	Extend treatment duration to 5 years, assuming stable vision following this	Maximum 3 years of treatment	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.	assumptions for the efficacy beyond the MEAD study duration due to the uncertainty as to what these outcomes should be.
7	Vision decline upon development of DMO in fellow eye	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*.[44] 2012)	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	Stable vision following treatment cessation	Natural history of DMO applied following treatment cessation (Mitchell *et al*.[44] 2012)	Stable vision (identity matrix) applied following treatment cessation	Base case assumption is that DMO is a chronic condition and that 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.

Scenario number	Scenario	Base case assumption	Scenarios considered	Justification
9	Vary time horizon	15 years	1 year	To determine the impact of varying the time horizon on the results
10			5 years	
11			10 years	
12			20 years	
13	100% unilateral DMO in the BSE	Baseline distribution of patients across unilateral BSE, unilateral WSE and bilateral DMO obtained from the MEAD studies	100% unilateral DMO in the BSE; no fellow eye involvement	To assess the impact of treating only DMO in the BSE
14	100% unilateral DMO in the WSE	Baseline distribution of patients across unilateral BSE, unilateral WSE and bilateral DMO obtained from the MEAD studies	100% unilateral DMO in the WSE; no fellow eye involvement	To assess the impact of treating only DMO in the WSE
15	100% bilateral DMO	Baseline distribution of patients across unilateral BSE, unilateral WSE and bilateral DMO obtained from the MEAD studies	100% bilateral DMO	To assess the impact of treating only bilateral DMO
16	Alternative hazard ratio for additional mortality due to DMO	Hazard ratio of 2.45, applying both the risk of death due to DM (1.93, Mulnier *et al*,[68] 2006) and due to DMO (1.27, Hirai *et al*.[69] 2008)	Only hazard ratio due to DM (1.93, Mulnier *et al*.[68] 2006) 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.

Scenario number	Scenario	Base case assumption	Scenarios considered	Justification
17	Alternative hazard ratio for additional mortality due to DMO	Hazard ratio of 2.45, applying both the risk of death due to DM (1.93, Mulnier *et al*, 2006) and due to DMO (1.27, Hirai *et al*., 2008)	Only hazard ratio due to DMO (1.27, Hirai *et al*.[69] 2008) applied	
18	Include additional mortality due to severe vision loss	No additional mortality	Relative risk of 1.54 (Christ *et al*.[77] 2008) 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	Include one-off costs of severe vision loss in total cost	Not included in total cost of severe vision loss	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.

Scenario number	Scenario	Base case assumption	Scenarios considered	Justification
20	All intravitreal injection treatments administered as day case procedures 100% of the time	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	All intravitreal injection treatments administered as an outpatient procedure 100% of the time	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 intravitreal injection treatments administered as an outpatient procedure 100% of the time	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 100% of the time for anti-VEGF and 0% of the time for steroids	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.

Scenario number	Scenario	Base case assumption	Scenarios considered	Justification
24	Bilateral treatment on the same day 50% of the time for anti-VEGF and 0% of the time for steroids	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 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 and 50% of the time for steroids	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 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)	

Scenario number	Scenario	Base case assumption	Scenarios considered	Justification
26	Decreased risk of fellow eye involvement	Risk of fellow eye involvement 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.[194]	Risk of fellow eye involvement 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.[194]	The use of escape therapy in the MEAD studies was recorded as treatment for either DMO or DMO-related diagnosis and this definition has been 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 fellow eye involvement	Risk of fellow eye involvement based on analysis of incidences of DMO in the non-study eye in the MEAD clinical trials. Annual rate of [redacted] in Year 1 and Year 2.[194]	No risk of fellow eye involvement	To determine the impact of excluding fellow eye involvement.

Scenario number	Scenario	Base case assumption	Scenarios considered	Justification
28	***DMO patients who are insufficiently responsive to non-corticosteroid therapy and DMO patients who are unsuitable for non-corticosteroid therapy*** Inclusion of discontinuation from watch and wait due to adverse events and other non-efficacy related reasons	Discontinuation from watch and wait is 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 has been assumed that patients who discontinued from the sham arm of the MEAD studies would be likely to have the 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.
Key: BSE, better-seeing eye; DEX, dexamethasone; DM, diabetes mellitus; DMO, diabetic macular oedema;EQ-5D, EuroQol-five dimensions questionnaire; ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward ; NHS, National Health Service; PAS: Patient access scheme; VFQ-UI, Visual Functioning Questionnaire Utility Index; WSE, worse-seeing eye.				

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

A table of variables included in the model for each population and, where appropriate, lower and upper bounds for deterministic sensitivity analysis have been provided in PDF files submitted separately.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in

section 7.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

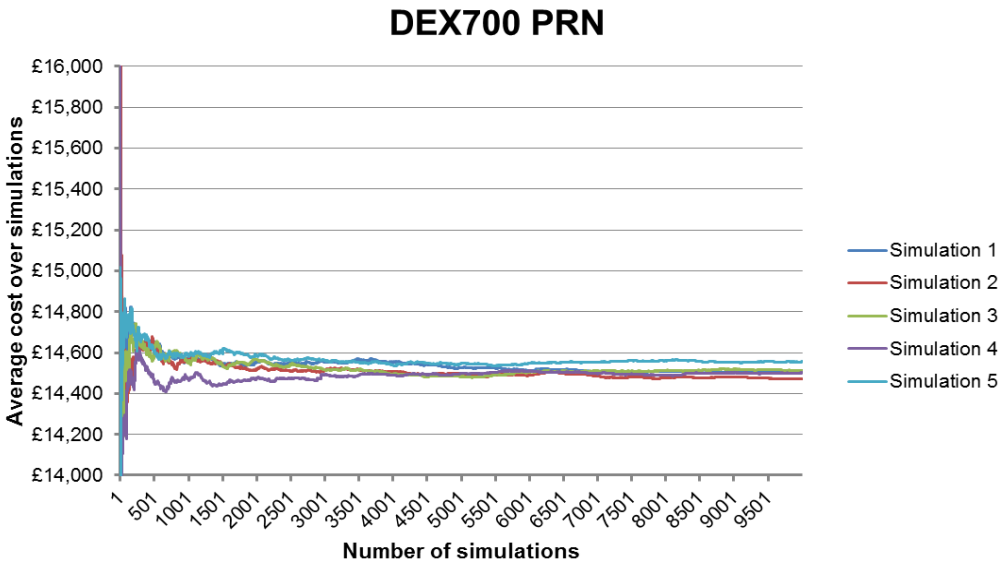
A table of variables included in the model for each population and, where appropriate, uncertainty distribution parameters for probabilistic analysis have been provided separately as PDF files. In general, costs were varied using a gamma distribution, probabilities using a beta-distribution and continuous variables using a normal distribution.

In addition to the parameters listed in these PDF files, transition probability matrices for the baseline treatment were also varied in PSA using the Dirichlet probability distribution.

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 network meta-analysis 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. As such, the relative risks for all treatments were sampled from the same network meta-analysis iteration, hence maintaining any correlation between parameters.

To determine the number of probabilistic simulations required to obtain approximately stable results from probabilistic analysis, 10,000 simulations were run. The total costs and QALYs for DEX700 PRN and watch and wait obtained from each simulation were recorded and averaged over an increasing number of simulations. This was repeated 5 times. The results were then plotted in Figure 67 to Figure 70 and based on these it was determined that approximately 5,000 iterations were required for probabilistic analysis to produce approximately stable results. Therefore all probabilistic analyses are based on the average results of 5,000 simulations.

Figure 67: Average cost over probabilistic simulations: DEX700 PRN



Key: DEX, dexamethasone; PRN, *pro re nata*.

Figure 68: Average cost over probabilistic simulations: watch and wait

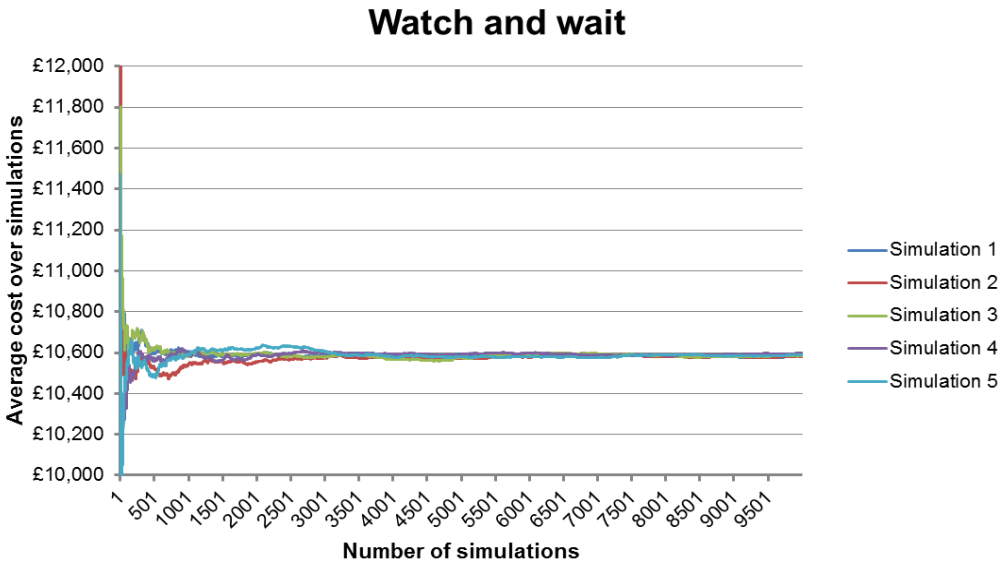
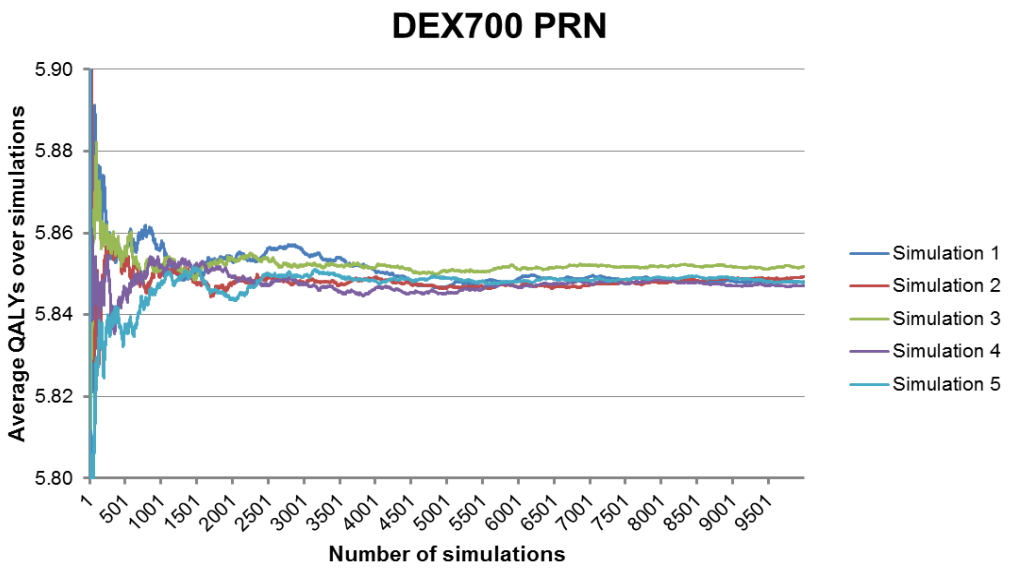
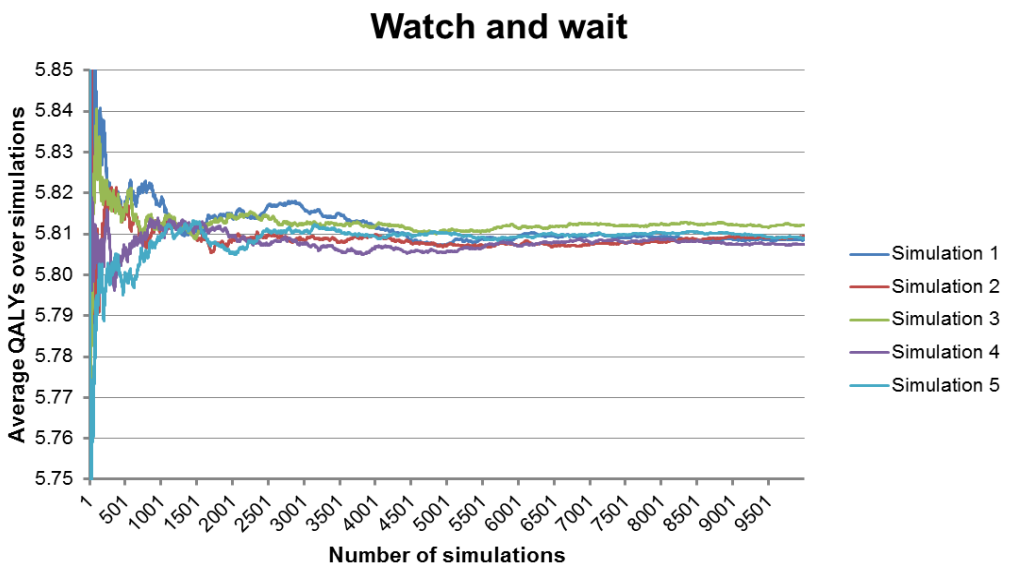


Figure 69: Average QALYs over probabilistic simulations: DEX700 PRN



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

Figure 70: Average QALYs over probabilistic simulations: watch and wait



Key: QALY, quality-adjusted life year.

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Given that the economic model considers bilateral treatment whereas the MEAD study only permitted treatment in either the BSE or the WSE, it is not appropriate to directly compare the output of the economic model with the trial data. This adapted model reflects a more pragmatic approach to modelling the true cost-effectiveness of treatment for DMO compared with previous models which have increased uncertainty due to the *ad-hoc* assumptions which are required to model treatment in the WSE and bilateral treatment, both of which occur in clinical practice.

All other clinical inputs including treatment frequency, discontinuation rates and adverse events were derived directly from the trial and so the model inputs are consistent with the clinical trial outcomes.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Given the large number of health states included in the model, it is not practical to report the Markov trace within this document. Therefore the Markov trace for each treatment has been exported in tabular form from the model to an Excel workbook, which has been submitted separately. A workbook has been supplied per model:

- “Markov traces_Pseudophakic.xlsb”
    - DMO patients who are pseudophakic
- “Markov traces_All DMO.xlsb”
    - DMO patients who are insufficiently responsive to non-corticosteroid therapy (base case excluding FAME)
    - DMO patients who are unsuitable for non-corticosteroid therapy
- “Markov traces_All DMO_incl.FAME.xlsb”
    - DMO patients who are insufficiently responsive to non-corticosteroid therapy (scenario analysis including FAME)

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs were calculated within the model by applying the utility equation (section 7.4.9) to the distribution of vision across the six visual acuity states in each type of patient’s BSE and WSE in each cycle (using the half-cycle corrected patient distributions). The coefficients for the BSE BCVA and the WSE BCVA were applied to the mean BCVA in the corresponding health state as described in Table 72. QALYs were discounted at a rate of 3.5% per year.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 119, Table 118 and Table 126 provide the LYs, QALYs and costs for each treatment, disaggregated by the status of DMO (unilateral DMO in the BSE or WSE, or bilateral DMO) for each population of interest. Given the two-eyed nature of the model this disaggregation by patient-level health states was felt more appropriate and informative than a disaggregation by BCVA-defined health states.

Table 117: Disaggregated LY and QALYs; DMO patients who are considered unsuitable for non-corticosteroid therapy

Outcome	LY	QALY	Cost (£)
DEX700 PRN			
Unilateral BSE	1.0704	0.5219	£2,194
Unilateral WSE	3.8169	1.9191	£3,521
Bilateral	6.9091	3.3010	£14,697
Total	11.7964	5.7420	£20,413
Watch and wait			
Unilateral BSE	1.1215	0.5405	£2,836
Unilateral WSE	3.9990	1.9959	£1,757
Bilateral	6.6760	3.1400	£17,288
Total	11.7964	5.6764	£21,882

Key: BSE, better-seeing eye; DEX, dexamethasone; DMO, diabetic macular oedema; LY, life years; QALY, quality-adjusted life year; WSE, worse-seeing eye.

Table 118: Disaggregated LY and QALYs; DMO patients who are considered insufficiently responsive to non-corticosteroid therapy

Outcome	LY	QALY	Cost (£)
DEX700 PRN			
Unilateral BSE	1.0704	0.5219	£2,194
Unilateral WSE	3.8169	1.9191	£3,521
Bilateral	6.9091	3.3010	£14,697
Total	11.7964	5.7420	£20,413
Watch and wait			
Unilateral BSE	1.1215	0.5405	£2,836
Unilateral WSE	3.9990	1.9959	£1,757
Bilateral	6.6760	3.1400	£17,288
Total	11.7964	5.6764	£21,882
Key: BSE, better-seeing eye; DEX, dexamethasone; DMO, diabetic macular oedema; LY, life years; QALY, quality-adjusted life year; WSE, worse-seeing eye.			

Table 119: Disaggregated LY and QALYs; DMO patients who are pseudophakic (list price for ranibizumab)

Outcome	LY	QALY	Cost (£)
DEX700 PRN			
Unilateral BSE	1.0222	0.5069	£1,905
Unilateral WSE	3.3221	1.7019	£3,025
Bilateral	5.8764	2.8798	£10,790
Total	10.2207	5.0886	£15,720
Ranibizumab			
Unilateral BSE	0.9915	0.5019	£2,114
Unilateral WSE	3.2223	1.6710	£6,313
Bilateral	6.0070	3.0336	£13,297
Total	10.2207	5.2066	£21,724
Key: BSE, better-seeing eye; DEX, dexamethasone; DMO, diabetic macular oedema; LY, life years; QALY, quality-adjusted life year; WSE, worse-seeing eye.			

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

The requested disaggregated results are presented below for each comparator and for each population of interest. As in section 7.7.4, given the two-eyed nature of the

model this disaggregation by patient-level health states was felt more appropriate and informative than a disaggregation by BCVA-defined health states.

DMO patients who are considered unsuitable for non-corticosteroid therapy

DEX700 PRN vs. watch and wait

Table 120: Summary of QALY gain by health state, DEX700 PRN vs. watch and wait

Health state	QALY intervention (DEX700)	QALY comparator (watch and wait)	Increment	Absolute increment	% absolute increment
Unilateral BSE	0.5219	0.5405	-0.0186	0.0186	28.36%
Unilateral WSE	1.9191	1.9959	-0.0768	0.0768	117.09%
Bilateral	3.3010	3.1400	0.1609	0.1609	245.45%
Total	5.7420	5.6764	0.0656	0.0656	100.00%

Key: BSE, better-seeing eye; DEX, dexamethasone; QALY, quality-adjusted life year; WSE, worse-seeing eye.

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.

Table 121: Summary of costs by health state, DEX700 PRN vs. watch and wait

Health state	Cost intervention (DEX700)	Cost comparator (watch and wait)	Increment	Absolute increment	% absolute increment
Unilateral BSE	£2,194	£2,836	-£642	£642	43.68%
Unilateral WSE	£3,521	£1,757	£1,764	£1,764	120.08%
Bilateral	£14,697	£17,288	-£2,591	£2,591	176.39%
Total	£20,413	£21,882	-£1,469	£1,469	100.00%

Key: BSE, better-seeing eye; DEX, dexamethasone; WSE, worse-seeing eye.

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.

Table 122: Summary of costs by component, DEX700 PRN vs. watch and wait

Item	Cost intervention (DEX700)	Cost comparator (watch and wait)	Increment	Absolute increment	% absolute increment
Treatment acquisition	£4,861	£0	£4,861	£4,861	330.88%
Treatment administration (including laser administrations)	£619	£0	£619	£619	42.15%
Severe vision loss	£8,971	£16,777	-£7,806	£7,806	531.39%
Adverse events	£863	£258	£605	£605	41.16%
Medical resource use	£5,100	£4,847	£253	£253	17.22%
Total	£20,413	£21,882	-£1,469	£1,469	100.00%

Key: DEX, dexamethasone.

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.

DMO patients who are considered insufficiently responsive to non-corticosteroid therapy

DEX700 PRN vs. watch and wait

Table 123: Summary of QALY gain by health state, DEX700 PRN vs. watch and wait

Health state	QALY intervention (DEX700)	QALY comparator (watch and wait)	Increment	Absolute increment	% absolute increment
Unilateral BSE	0.5219	0.5405	-0.0186	0.0186	28.36%
Unilateral WSE	1.9191	1.9959	-0.0768	0.0768	117.09%
Bilateral	3.3010	3.1400	0.1609	0.1609	245.45%
Total	5.7420	5.6764	0.0656	0.0656	100.00%

Key: BSE, better-seeing eye; DEX, dexamethasone; QALY, quality-adjusted life year; WSE, worse-seeing eye.

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.

Table 124: Summary of costs by health state, DEX700 PRN vs. watch and wait

Health state	Cost intervention (DEX700)	Cost comparator (watch and wait)	Increment	Absolute increment	% absolute increment
Unilateral BSE	£2,194	£2,836	-£642	£642	43.68%
Unilateral WSE	£3,521	£1,757	£1,764	£1,764	120.08%
Bilateral	£14,697	£17,288	-£2,591	£2,591	176.39%
Total	£20,413	£21,882	-£1,469	£1,469	100.00%

Key: BSE, better-seeing eye; DEX, dexamethasone; WSE, worse-seeing eye.

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.

Table 125: Summary of costs by component, DEX700 PRN vs. watch and wait

Item	Cost intervention (DEX700)	Cost comparator (watch and wait)	Increment	Absolute increment	% absolute increment
Treatment acquisition	£4,861	£0	£4,861	£4,861	330.88%
Treatment administration (including laser administrations)	£619	£0	£619	£619	42.15%
Severe vision loss	£8,971	£16,777	-£7,806	£7,806	531.39%
Adverse events	£863	£258	£605	£605	41.16%
Medical resource use	£5,100	£4,847	£253	£253	17.22%
Total	£20,413	£21,882	-£1,469	£1,469	100.00%

Key: DEX, dexamethasone.

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.

DMO patients who are pseudophakic

DEX700 PRN vs. ranibizumab

Table 126: Summary of QALY gain by health state, DEX700 PRN vs. ranibizumab (list price for ranibizumab)

Health state	QALY intervention (DEX700)	QALY comparator (ranibizumab)	Increment	Absolute increment	% absolute increment
Unilateral BSE	0.5069	0.5019	0.0050	0.0050	4.23%
Unilateral WSE	1.7019	1.6710	0.0308	0.0308	26.16%
Bilateral	2.8798	3.0336	-0.1538	0.1538	130.38%
Total	5.0886	5.2066	-0.1179	0.1179	100.00%

Key: BSE, better-seeing eye; DEX, dexamethasone; QALY, quality-adjusted life year; WSE, worse-seeing eye.

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.

Table 127: Summary of costs by health state, DEX700 PRN vs. ranibizumab (list price for ranibizumab)

Health state	Cost intervention (DEX700)	Cost comparator (ranibizumab)	Increment	Absolute increment	% absolute increment
Unilateral BSE	£1,905	£2,114	-£209	£209	3.49%
Unilateral WSE	£3,025	£6,313	-£3,287	£3,287	54.75%
Bilateral	£10,790	£13,297	-£2,507	£2,507	41.76%
Total	£15,720	£21,724	-£6,004	£6,004	100.00%

Key: BSE, better-seeing eye; DEX, dexamethasone; WSE, worse-seeing eye.

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.

Table 128: Summary of costs by component, DEX700 PRN vs. ranibizumab (list price for ranibizumab)

Item	Cost intervention (DEX700)	Cost comparator (ranibizumab)	Increment	Absolute increment	% absolute increment
Treatment acquisition	£4,337	£13,439	-£9,102	£9,102	151.60%
Treatment administration (including laser administrations)	£549	£1,884	-£1,336	£1,336	22.24%
Severe vision loss	£5,894	£850	£5,044	£5,044	84.01%
Adverse events	£424	£3	£420	£420	7.00%
Medical resource use	£4,516	£5,547	-£1,031	£1,031	17.17%
Total	£15,720	£21,724	-£6,004	£6,004	100.00%

Key: DEX, dexamethasone.

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.

Base-case analysis

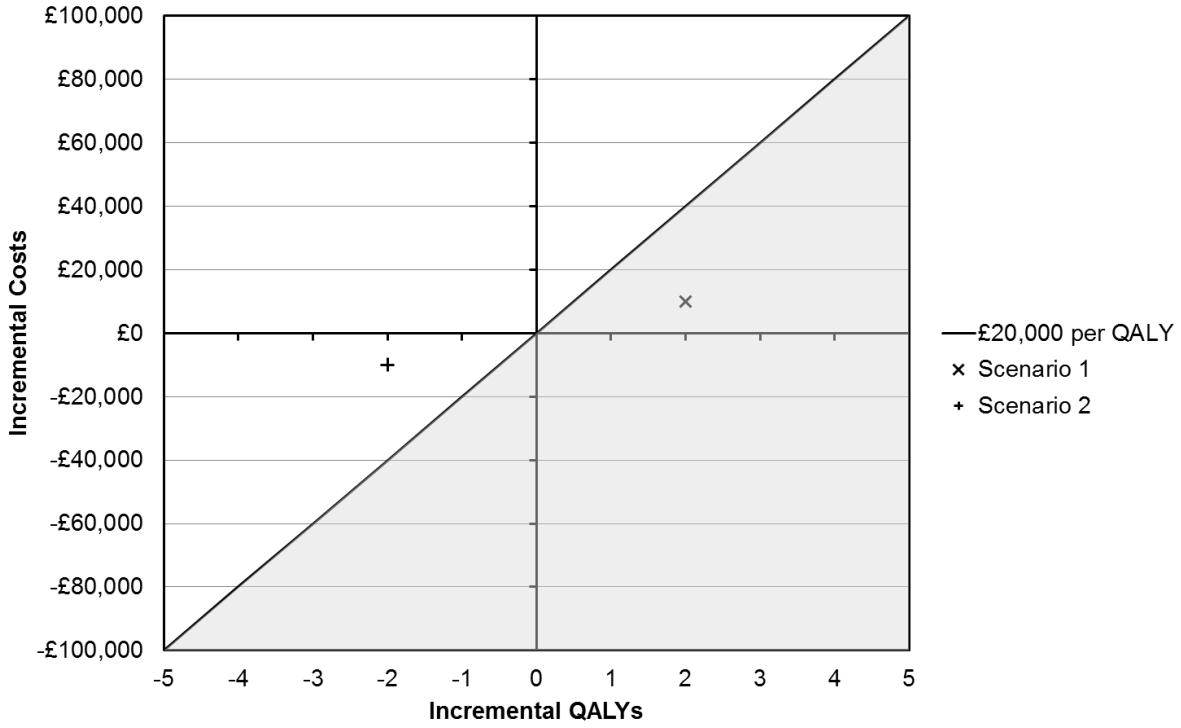
7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The base case results are shown below for each population of interest. Both deterministic and probabilistic results have been presented. Probabilistic results have been calculated from an analysis with 5,000 simulations using the mean costs and QALYs from the 5,000 simulations for each treatment. As there is no difference in mortality between treatments LYG are expected to be equal across treatment arms and so have only been included in the deterministic tables for interest.

In some comparisons the ICER falls into the South-West quadrant of the cost-effectiveness plane. In this case the ICER is difficult to interpret. Figure 71 shows some fictional scenarios to illustrate this point. Scenario 1 in Figure 71 shows positive incremental cost and QALYs, resulting in an ICER of £5,000 per QALY

which is considered cost-effective. Scenario 2 in Figure 71, shows negative incremental costs and QALYs of the same absolute magnitude, resulting in the same ICER of £5,000 per QALY, however this is not considered cost-effective at a willingness to pay threshold of £20,000 per QALY gained as this lies outside of the shaded cost-effective region.

Figure 71: Cost-effectiveness plane



Key: QALY, quality-adjusted life year.

In cases where the ICER falls into the South-West quadrant, the incremental net monetary benefit (NMB) may be used to determine cost-effectiveness. The NMB is the amount that the health care system is willing to pay for the QALYs gained minus the true cost of gaining these QALYs. A positive NMB indicates cost-effectiveness as this means we are willing to pay more than the total cost of gaining the QALYs.

This outcome has been presented where appropriate to aid interpretation.

DMO patients who are considered unsuitable for non-corticosteroid therapy

Table 129: Base case deterministic results; DMO patients who are considered unsuitable for non-corticosteroid therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
DEX700 PRN	£20,413	11.80	5.7420				
Watch and wait	£21,882	11.80	5.6764	£1,469	0.0000	-0.0656	DEX700 PRN dominates

Key: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PRN, *pro re nata*; QALYs, quality-adjusted life years.

Table 130: Base case probabilistic results; DMO patients who are considered unsuitable for non-corticosteroid therapy

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
DEX700 PRN	£20,827	5.7789			
Watch and wait	£22,536	5.7230	£1,708	-0.0559	DEX700 PRN dominates

Key: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PRN, *pro re nata*; QALYs, quality-adjusted life years.

DEX700 PRN dominates watch and wait in both the deterministic and probabilistic base case analyses as treatment with DEX700 PRN is associated with lower cost and higher incremental QALYs than watch and wait and therefore DEX700 is considered highly cost-effective compared with watch and wait in the population of DMO patients who are considered unsuitable for non-corticosteroid therapy.

DMO patients who are considered insufficiently responsive to non-corticosteroid therapy

Table 131: Base case deterministic results; DMO patients who are considered insufficiently responsive to non-corticosteroid therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
DEX700 PRN	£20,413	11.80	5.7420				
Watch and wait	£21,882	11.80	5.6764	£1,469	0.0000	-0.0656	DEX700 PRN dominates

Key: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PRN, *pro re nata*; QALYs, quality-adjusted life years.

Table 132: Base case probabilistic results; DMO patients who are considered insufficiently responsive to non-corticosteroid therapy

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
DEX700 PRN	£20,827	5.7789			
Watch and wait	£22,536	5.7230	£1,708	-0.0559	DEX700 PRN dominates

Key: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PRN, *pro re nata*; QALYs, quality-adjusted life years.

DEX700 PRN dominates watch and wait in both the deterministic and probabilistic base case analyses as treatment with DEX700 PRN is associated with lower cost and higher incremental QALYs than watch and wait and therefore DEX700 is considered highly cost-effective compared with watch and wait in the population of DMO patients who are considered insufficiently responsive to non-corticosteroid therapy.

DMO patients who are pseudophakic – list price for ranibizumab

Table 133: Base case deterministic results; DMO patients who are pseudophakic (list price for ranibizumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	Incremental NMB @ WTP = £20,000 per QALY
DEX700 PRN	£15,720	10.2207	5.0886					
Ranibizumab	£21,724	10.2207	5.2066	£6,004	0.0000	0.1179	£50,905*	-£3645*

Key: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PRN, *pro re nata*; QALYs, quality-adjusted life years; WTP, willingness to pay.
Notes: *Ranibizumab vs. DEX700 PRN.

Table 134: Base case probabilistic results; DMO patients who are pseudophakic (list price for ranibizumab)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Incremental NMB @ WTP = £20,000 per QALY
DEX700 PRN	£16,053	5.1422				
Ranibizumab	£22,762	5.2172	£6,710	0.0749	£89,531*	-£5,211*

Key: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PRN, *pro re nata*; QALYs, quality-adjusted life years; WTP, willingness to pay.
Notes: *Ranibizumab vs. DEX700 PRN.

When ranibizumab is assumed to be available at list price, ranibizumab is not considered cost-effective compared with DEX700 PRN at a willingness to pay threshold of £20,000 per QALY gained, therefore DEX700 PRN is cost-effective under this assumption at this threshold. DEX700 PRN remains cost-effective compared with ranibizumab at a willingness to pay threshold of £20,000 per QALY gained up to a discount of 27% to the list price of ranibizumab.

DMO patients who are pseudophakic – 50% PAS discount for ranibizumab

Table 135: Base case deterministic results; DMO patients who are pseudophakic (50% discount for ranibizumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	Incremental NMB @ WTP = £20,000 per QALY
Ranibizumab	£15,004	10.2207	5.2066					
DEX700 PRN	£15,720	10.2207	5.0886	£716	0.0000	-0.1179	Ranibizumab dominates	-£3,075*

Key: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PRN, *pro re nata*; QALYs, quality-adjusted life years; WTP, willingness to pay.
Notes: * DEX700 PRN vs. ranibizumab.

Table 136: Base case probabilistic results; DMO patients who are pseudophakic (50% discount for ranibizumab)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Incremental NMB @ WTP = £20,000 per QALY
Ranibizumab	£16,037	5.2172				
DEX700 PRN	£16,053	5.1422	£15	-0.0749	Ranibizumab dominates	-£1,514*

Key: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PRN, *pro re nata*; QALYs, quality-adjusted life years; WTP, willingness to pay.
Notes: * DEX700 PRN vs. ranibizumab.

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Tornado diagrams are presented for pair-wise comparisons of DEX700 PRN with watch and wait in the populations of DMO patients who are unsuitable for or insufficiently responsive non-corticosteroid therapy and with ranibizumab in the population of DMO patients who are pseudophakic.

The results for all populations are reported in terms of the incremental NMB at a willingness to pay threshold of £20,000 per QALY gained. A positive NMB indicates that DEX700 PRN is cost-effective and a negative NMB indicates that the comparator treatment is cost-effective.

DMO patients who are considered unsuitable for non-corticosteroid therapy

Figure 72 shows the tornado diagram for the comparison of DEX700 PRN vs. watch and wait in the population of DMO patients who are unsuitable for non-corticosteroid therapies.

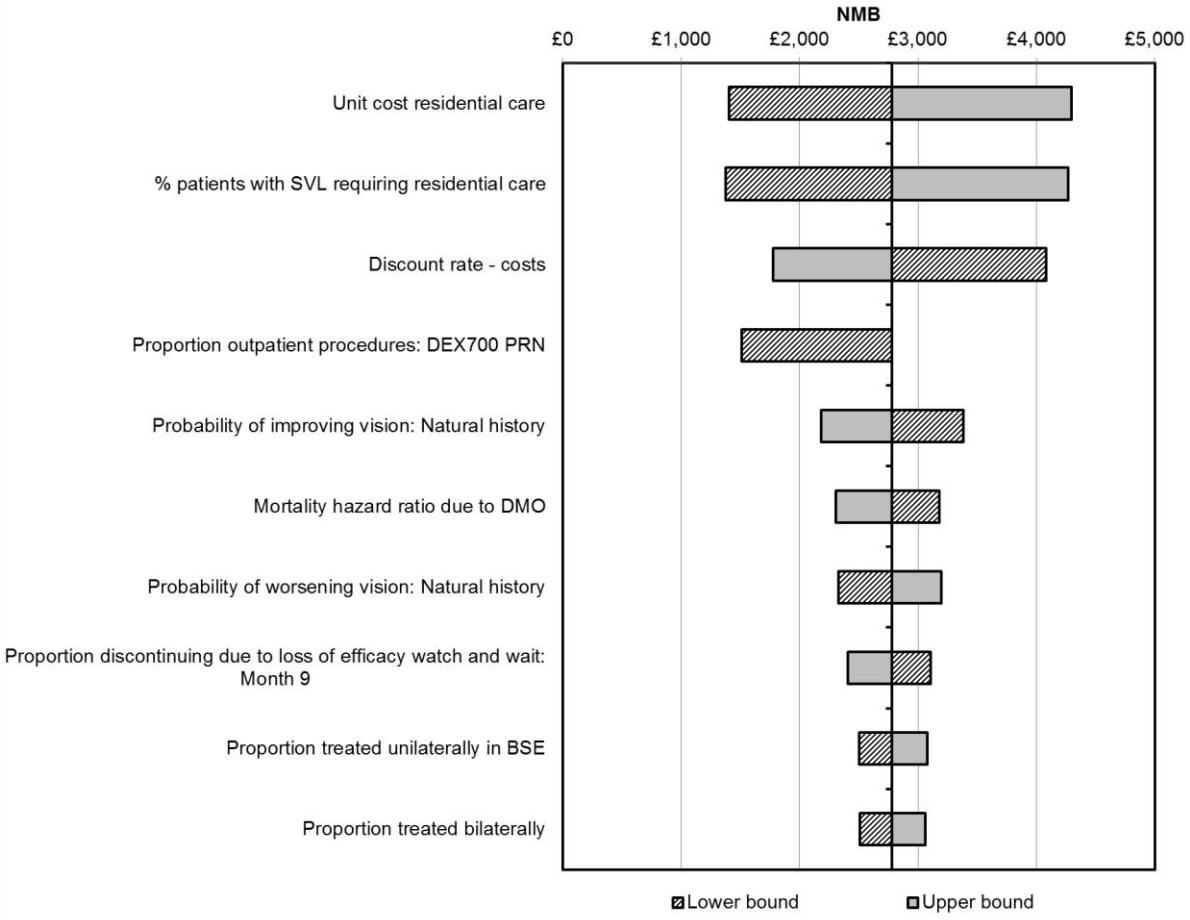
Under extreme values of all parameters DEX700 PRN remains cost-effective compared with watch and wait as the NMB remains positive under all extreme values.

The parameters with the largest influence on the results are the unit cost of, and proportion of patients requiring residential care to be funded by the NHS. This is expected as the cost of residential care is the largest component of the cost of severe vision loss.

The discount rate for costs, proportion of DEX700 administrations which are performed in the outpatient setting, the probability of improving and worsening vision associated with natural history and the mortality hazard ratio due to DMO also have some influence on the results of the analysis.

No other parameters, when set to their extreme upper or lower bounds, resulted in a change in the NMB of more than £1,000.

Figure 72: Tornado diagram; DEX700 PRN vs. watch and wait; results presented as incremental NMB



Key: BSE, better-seeing eye; DEX, dexamethasone; DMO, diabetic macular oedema; ratio; NMB, net monetary benefit; PRN, *pro re nata*; SVL, severe vision loss.

DMO patients who are considered insufficiently responsive to non-corticosteroid therapy

Figure 73 shows the tornado diagram for the comparison of DEX700 PRN vs. watch and wait in the population of DMO patients who are insufficiently responsive to non-corticosteroid therapies.

Under extreme values of all parameters DEX700 PRN remains cost-effective compared with watch and wait as the NMB remains positive under all extreme values.

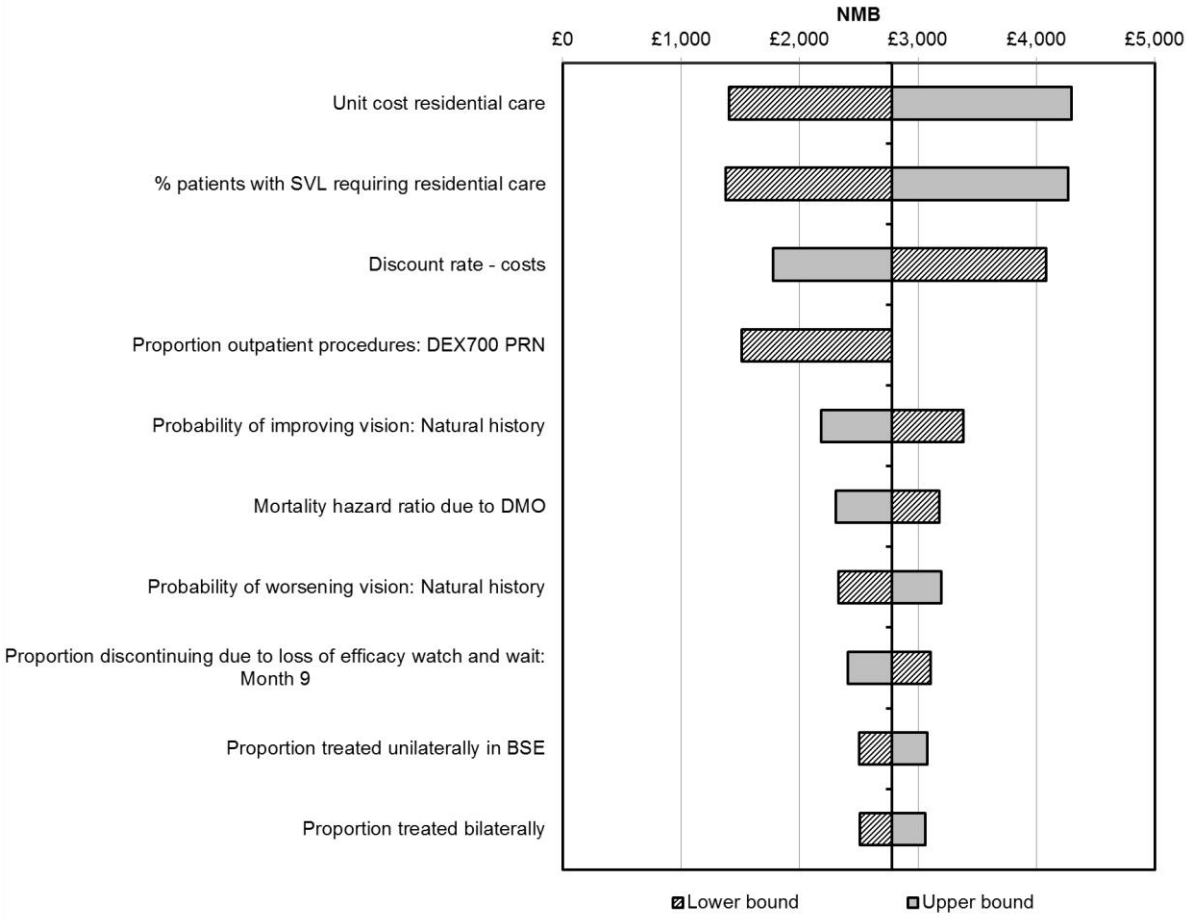
The parameters with the largest influence on the results are the unit cost of, and proportion of patients requiring residential care to be funded by the NHS. This is

expected as the cost of residential care is the largest component of the cost of severe vision loss.

The discount rate for costs, proportion of DEX700 administrations which are performed in the outpatient setting, the probability of improving and worsening vision associated with natural history and the mortality hazard ratio due to DMO also have some influence on the results of the analysis.

No other parameters, when set to their extreme upper or lower bounds, resulted in a change in the NMB of more than £1,000.

Figure 73: Tornado diagram; DEX700 PRN vs. watch and wait; results presented as incremental NMB



Key: BSE, better-seeing eye; DEX, dexamethasone; DMO, diabetic macular oedema; NMB, net monetary benefit; PRN, *pro re nata*; SVL, severe vision loss.

DMO patients who are pseudophakic

Figure 74 shows the tornado diagram for the comparison of DEX700 PRN vs. ranibizumab in the pseudophakic population when ranibizumab is provided at list price. DEX700 PRN is considered cost-effective compared with ranibizumab (at list

price) at a willingness to pay threshold of £20,000 per QALY gained in the pseudophakic population under extreme values of all parameters.

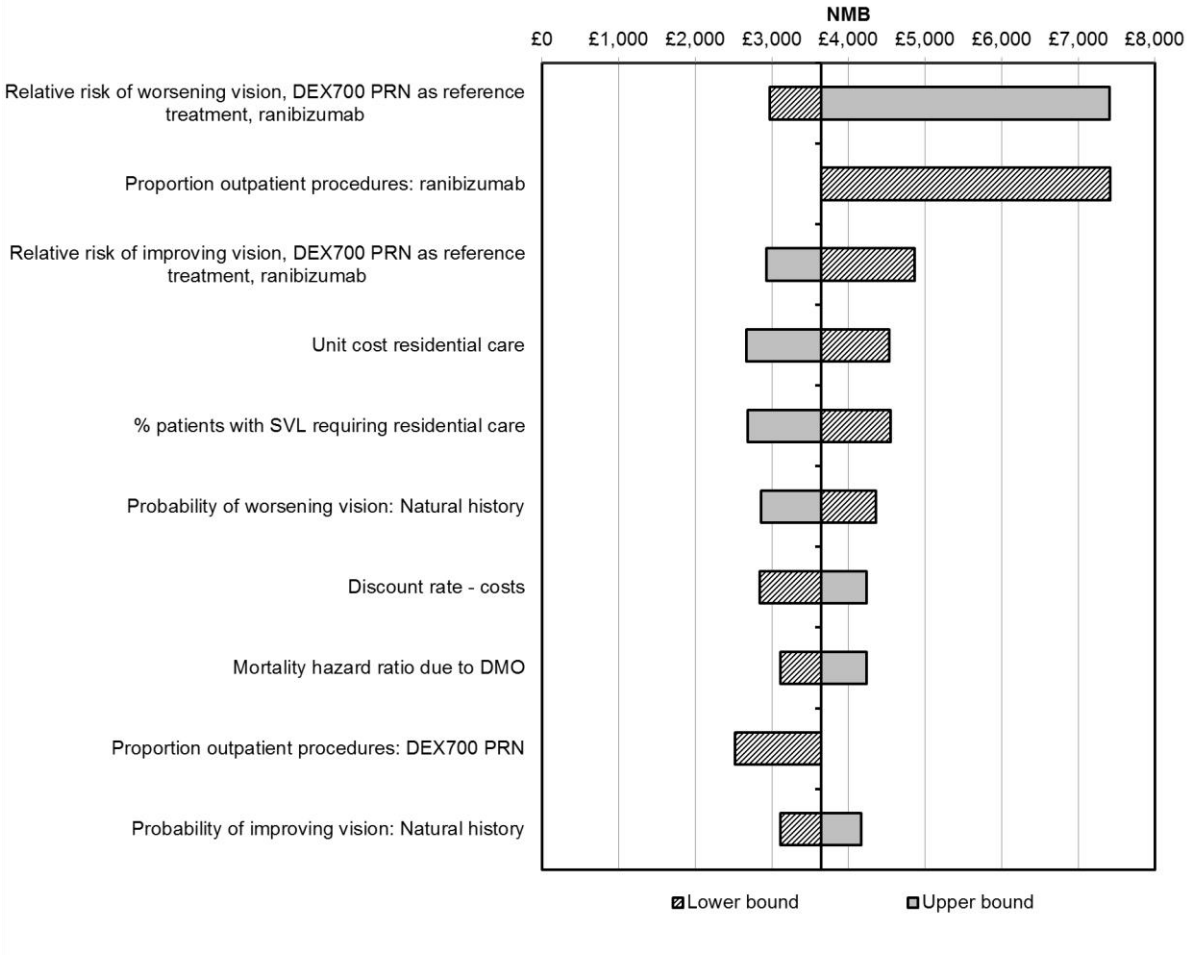
The relative risks of worsening or improving vision for ranibizumab vs. DEX700 PRN obtained from the network meta-analysis are highly influential to the results of the evaluation. This is expected as a high level of uncertainty was observed in the results of the network meta-analysis.

Decreasing the proportion of outpatient procedures for ranibizumab (and thus increasing the proportion of day case procedures) increased the cost-effectiveness of DEX700 PRN as variation in this parameter results in additional costs for ranibizumab. This was the second most influential parameter. Decreasing the proportion of outpatient procedures for DEX700 PRN (and thus increasing the proportion of day case procedures) was also influential, but to a lesser degree due to the lower treatment frequency with DEX700 PRN compared with ranibizumab. Decreasing this proportion reduced the cost-effectiveness of DEX700 as variation in this parameter results in additional costs for DEX700.

Other influential parameters included the unit cost of, and proportion of patients requiring residential care to be funded by the NHS. This is expected as the cost of residential care is the largest component of the cost of severe vision loss.

The discount rate for costs, the probability of improving and worsening vision associated with natural history and the mortality hazard ratio due to DMO also have some influence on the results of the analysis.

Figure 74: Tornado diagram; DEX700 PRN vs. ranibizumab (list price for ranibizumab); results presented as incremental NMB

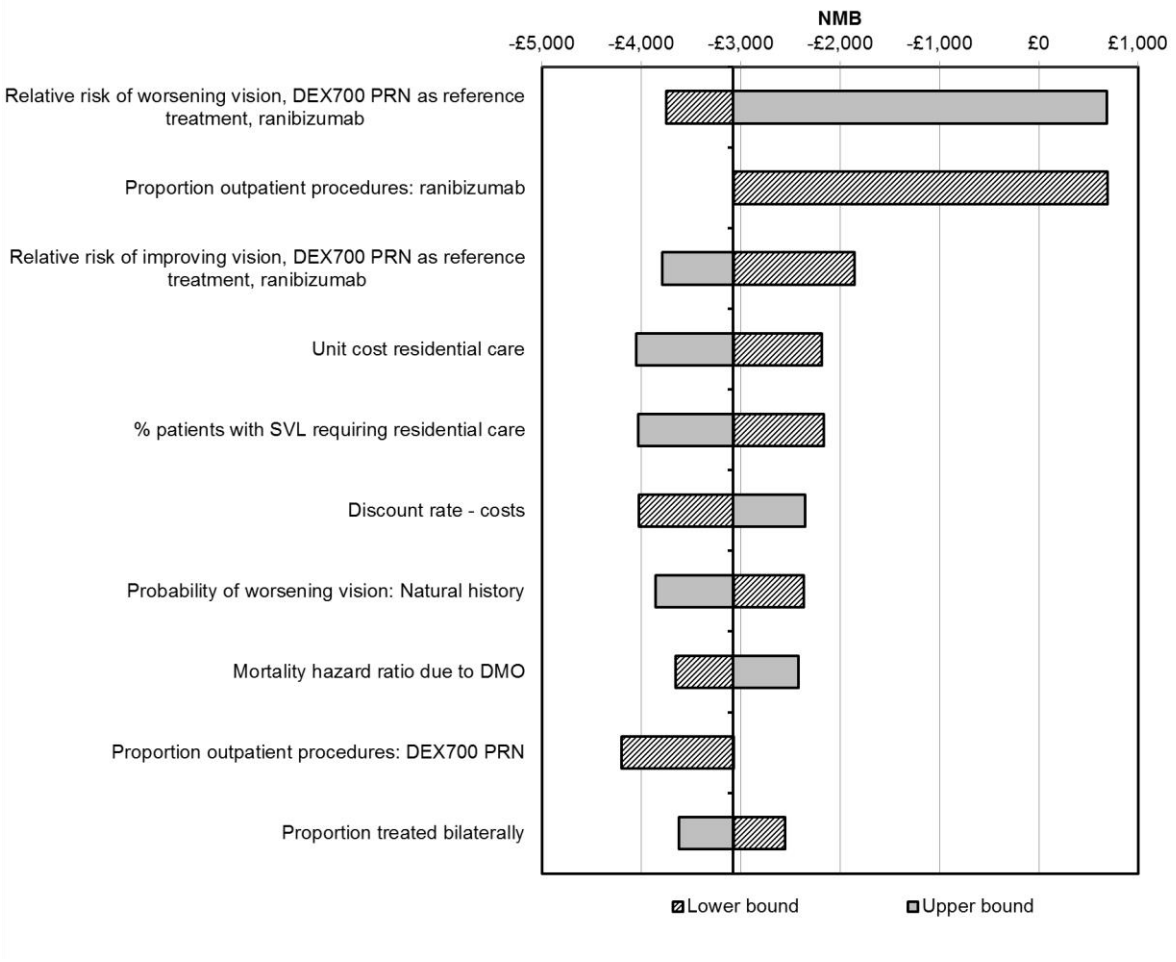


Key: DEX, dexamethasone; DMO, diabetic macular oedema; NMB, net monetary benefit; PRN, *pro re nata*; SVL, severe vision loss.

Figure 75 shows the tornado diagram for the comparison of DEX700 PRN vs. ranibizumab in the pseudophakic population when ranibizumab is provided at a 50% PAS discount.

The most influential parameters are broadly similar to those observed in the analysis with ranibizumab at list price.

Figure 75: Tornado diagram; DEX700 PRN vs. ranibizumab (50% discount for ranibizumab); results presented as incremental NMB



Key: DEX, dexamethasone; DMO, diabetic macular oedema; NMB, net monetary benefit; PRN, *pro re nata*; SVL, severe vision loss.

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

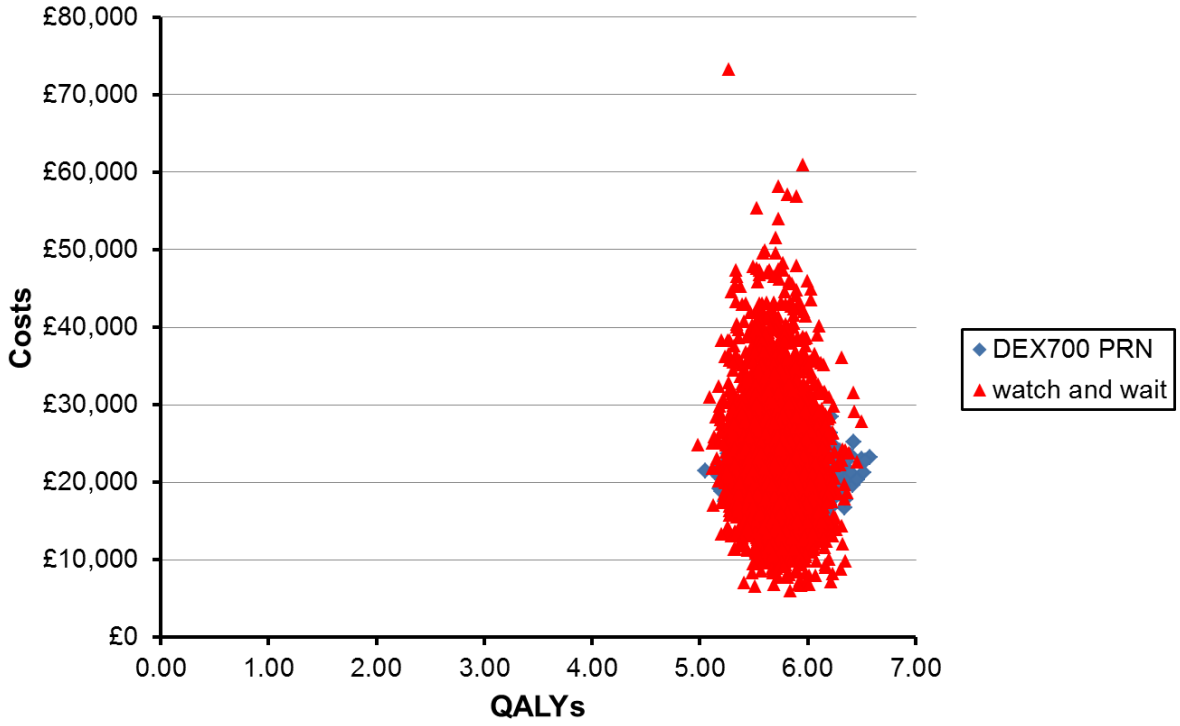
Total costs and QALYs and resulting incremental results from the probabilistic analyses have been presented in section 7.7.6. Scatter plots and 95% confidence ellipses of costs and QALYs are provided here along with cost-effectiveness acceptability curves for each population under consideration.

DMO patients who are considered unsuitable for non-corticosteroid therapy

Figure 76 shows the scatter plot of costs and QALYs for DEX700 PRN and watch and wait from 5,000 probabilistic simulations. Figure 77 shows the 95% confidence ellipses. These demonstrate that the costs and QALYs for DEX700 PRN and watch

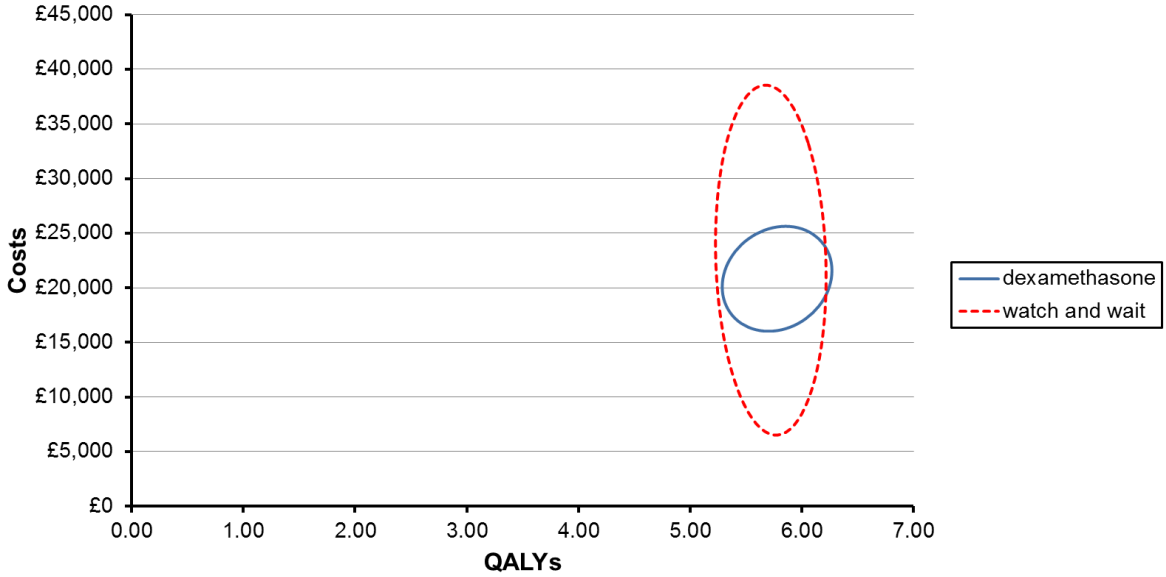
and wait overlap considerably, but that watch and wait is associated with a wider range of costs than DEX700 PRN.

Figure 76: Scatter plot of costs and QALYs for DEX700 PRN and watch and wait



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

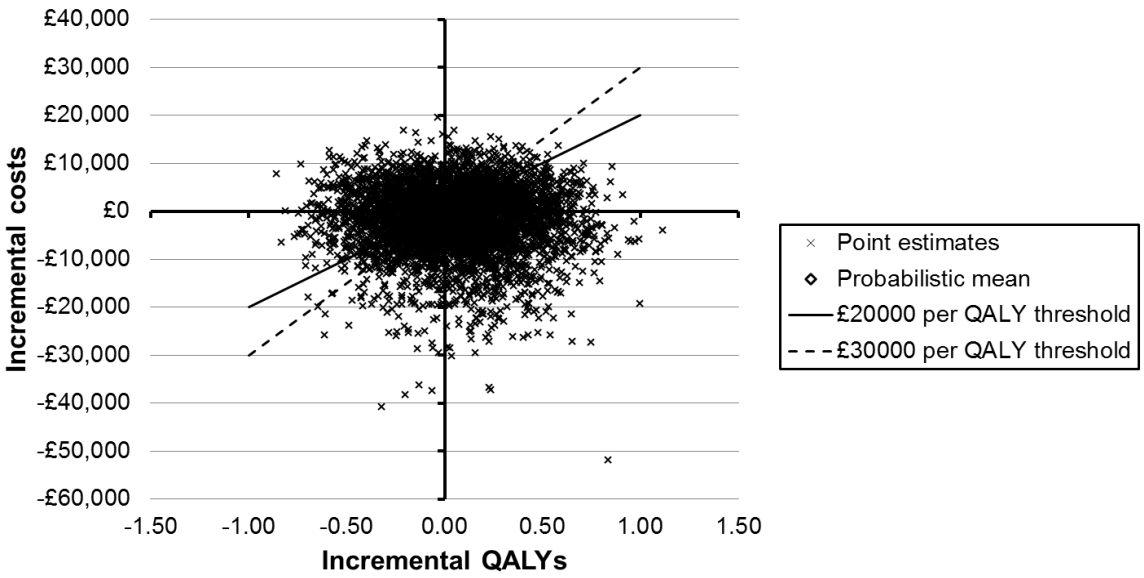
Figure 77: 95% confidence ellipses of costs and QALYs for DEX700 PRN and watch and wait



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

Figure 78 shows the scatter plot of incremental costs and QALYs for DEX700 PRN vs. watch and wait. The incremental costs and QALYs fall into all four quadrants of the cost-effectiveness plane.

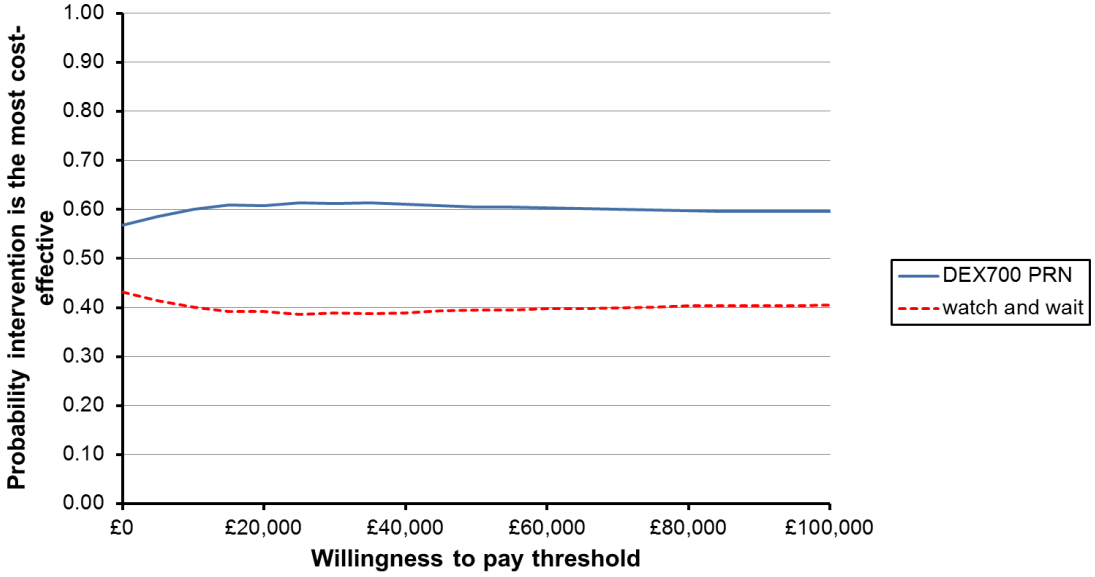
Figure 78: Scatter plot of incremental costs and QALYs for DEX700 PRN vs. watch and wait



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

Figure 79 shows the cost-effectiveness acceptability curve for DEX700 PRN and watch and wait based on the individual NMB at a range of willingness to pay thresholds to a maximum of £100,000 per QALY. This demonstrates that at a willingness to pay threshold of £20,000 per QALY gained DEX700 PRN is considered cost-effective compared with watch and wait on 60.8% of occasions.

Figure 79: Cost-effectiveness acceptability curve – individual NMB

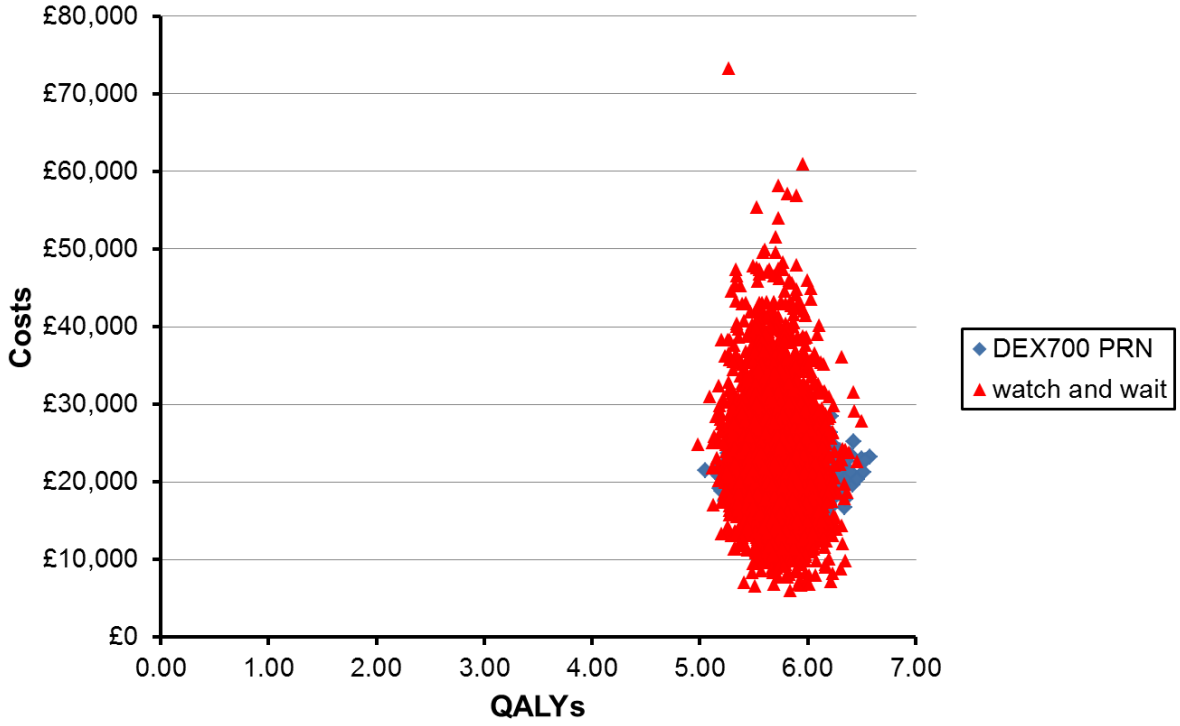


Key: DEX, dexamethasone; NMB, net monetary benefit; PRN, *pro re nata*.

DMO patients who are considered insufficiently responsive to non-corticosteroid therapy

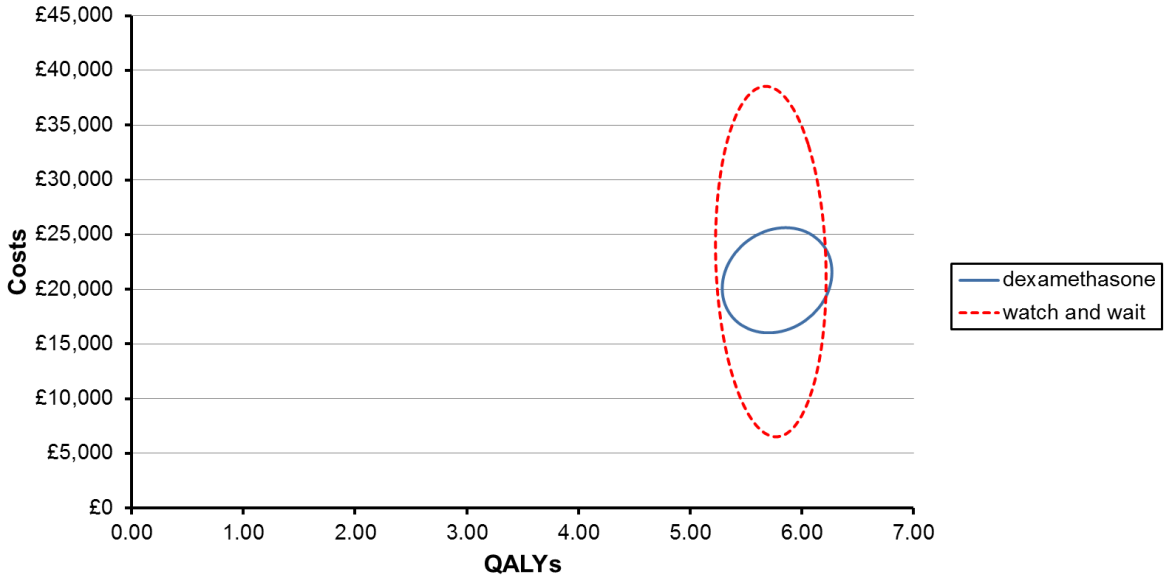
Figure 80 shows the scatter plot of costs and QALYs for DEX700 PRN and watch and wait from 5,000 probabilistic simulations. Figure 81 shows the 95% confidence ellipses. These demonstrate that the costs and QALYs for DEX700 PRN and watch and wait overlap considerably, but that watch and wait is associated with a wider range of costs than DEX700 PRN.

Figure 80: Scatter plot of costs and QALYs for DEX700 PRN and watch and wait



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

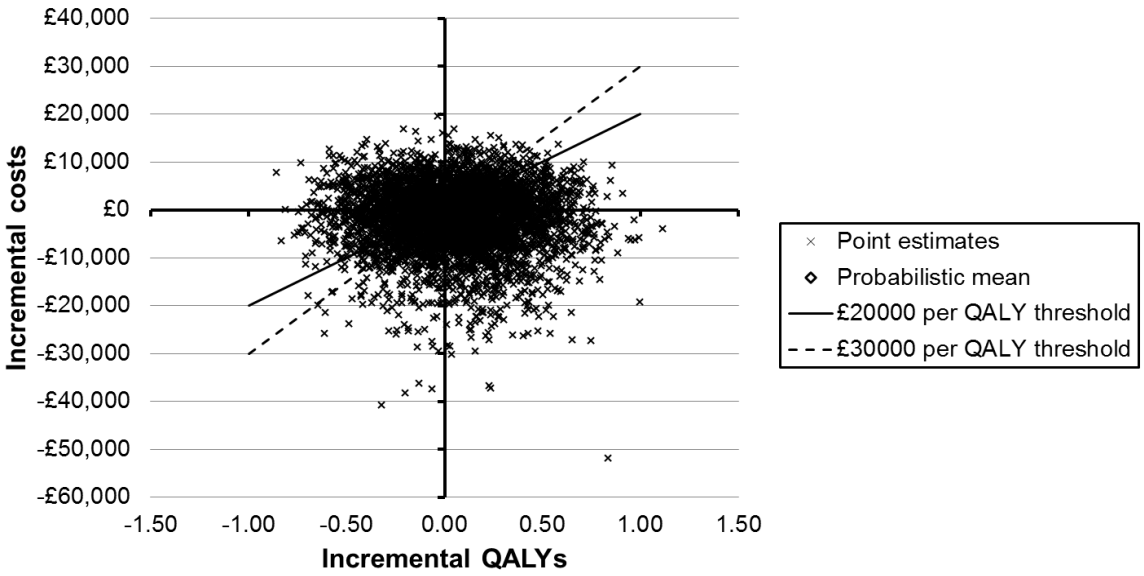
Figure 81: 95% confidence ellipses of costs and QALYs for DEX700 PRN and watch and wait



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

Figure 82 shows the scatter plot of incremental costs and QALYs for DEX700 PRN vs. watch and wait. The incremental costs and QALYs fall into all four quadrants of the cost-effectiveness plane.

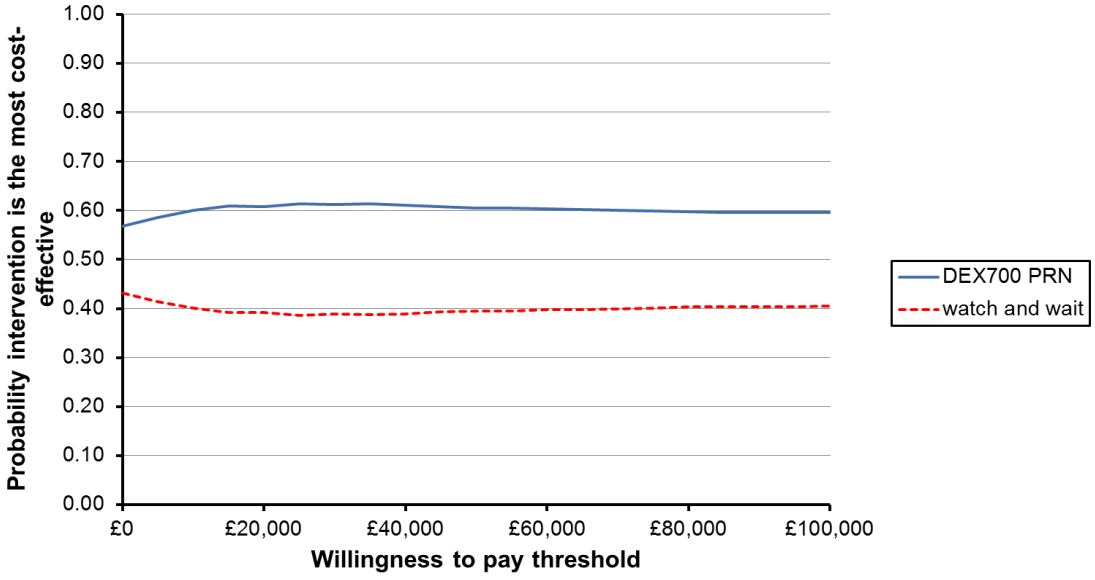
Figure 82: Scatter plot of incremental costs and QALYs for DEX700 PRN vs. watch and wait



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

Figure 83 shows the cost-effectiveness acceptability curve for DEX700 PRN and watch and wait based on the individual NMB at a range of willingness to pay thresholds to a maximum of £100,000 per QALY. This demonstrates that at a willingness to pay threshold of £20,000 per QALY gained DEX700 PRN is considered cost-effective compared with watch and wait on 60.8% of occasions.

Figure 83: Cost-effectiveness acceptability curve – individual NMB

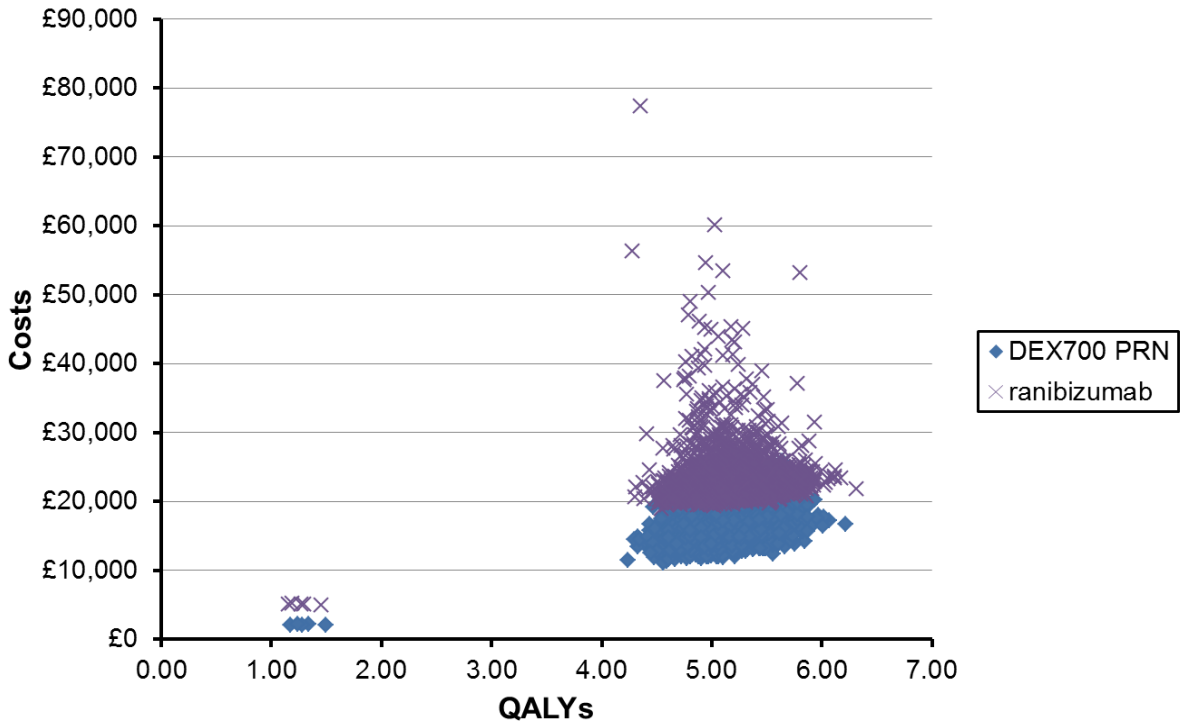


Key: DEX, dexamethasone; NMB, net monetary benefit; PRN, *pro re nata*.

DMO patients who are pseudophakic – list price for ranibizumab

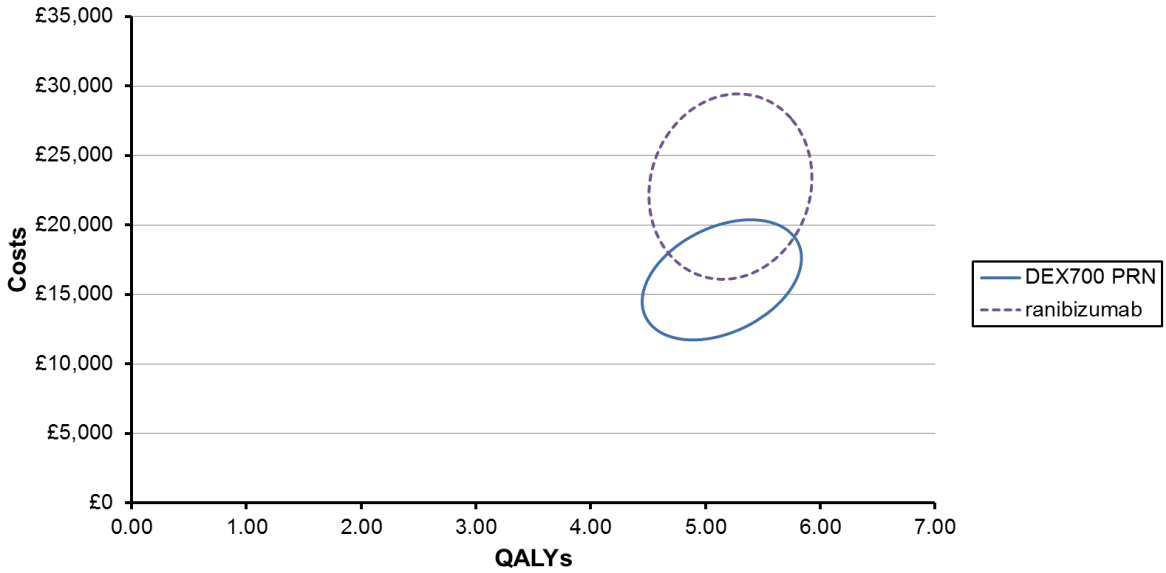
Figure 84 shows the scatter plot of costs and QALYs for DEX700 PRN and ranibizumab from 5,000 probabilistic simulations. These analyses have been performed at list price for ranibizumab. Figure 85 shows the 95% confidence ellipses. These demonstrate that ranibizumab is systematically higher in cost compared with DEX700 PRN, and that the range of QALYs obtained from probabilistic simulations are similar for both treatments.

Figure 84: Scatter plot of costs and QALYs for DEX700 PRN and ranibizumab (list price for ranibizumab)



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

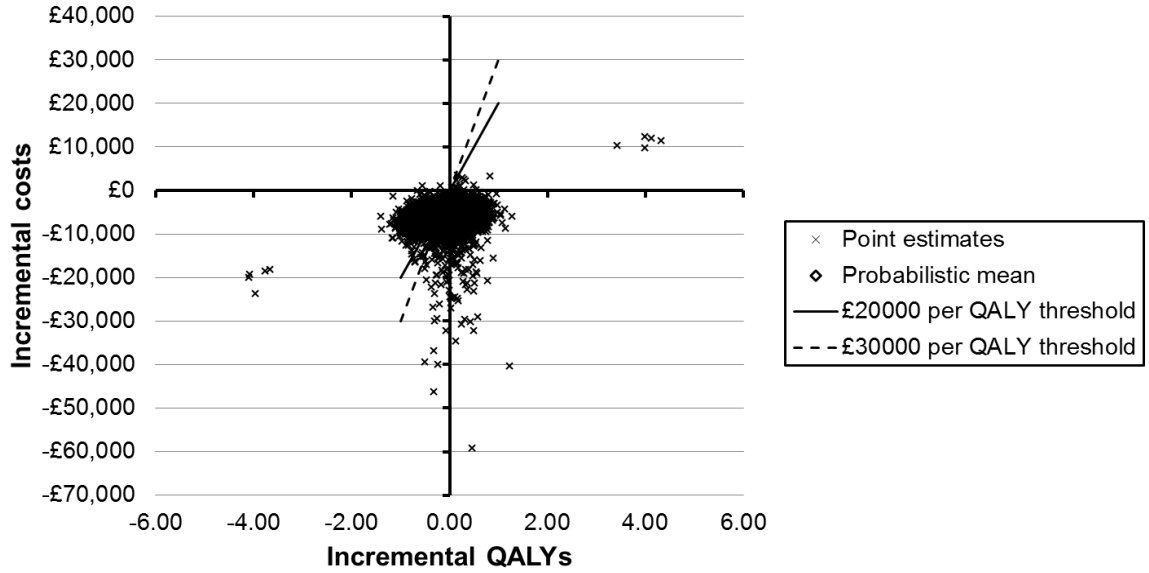
Figure 85: 95% confidence ellipses of costs and QALYs for DEX700 PRN and ranibizumab (list price for ranibizumab)



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

Figure 86 shows the scatter plot of incremental costs and QALYs for DEX700 PRN vs. ranibizumab. This indicates that in almost all probabilistic simulations DEX700 PRN was cheaper than ranibizumab, and that in a number of simulations DEX700 gains more QALYs than ranibizumab, therefore there are a high number of simulations where DEX700 PRN dominates ranibizumab. In contrast, there are very few simulations in which ranibizumab treatment dominates DEX700 PRN.

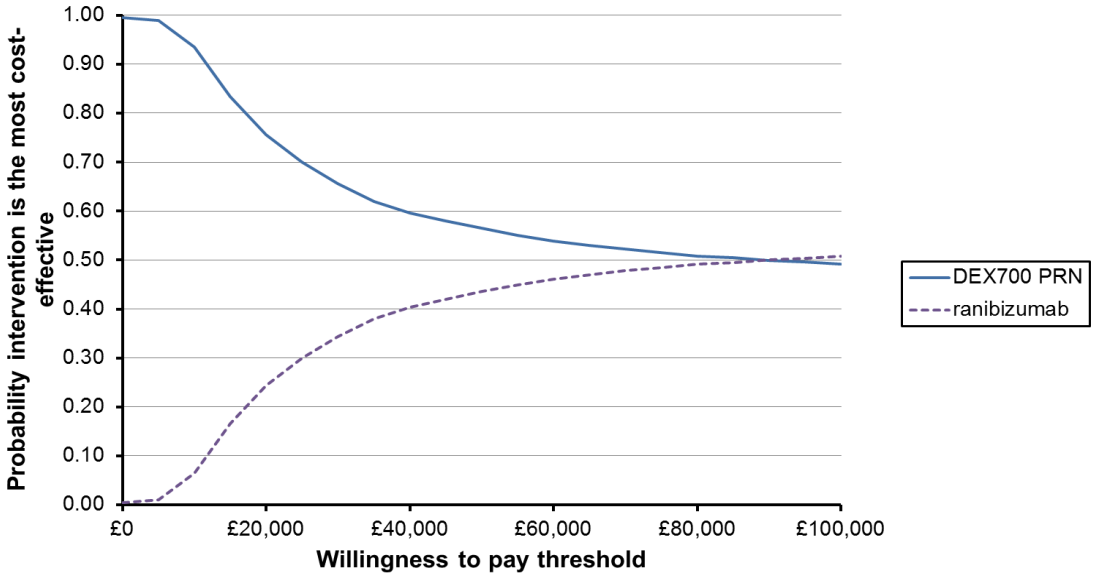
Figure 86: Scatter plot of incremental costs and QALYs for DEX700 PRN vs. ranibizumab (list price for ranibizumab)



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

Figure 87 shows the cost-effectiveness acceptability curve for DEX700 PRN and ranibizumab based on the individual NMB at a range of willingness to pay thresholds to a maximum of £100,000 per QALY. This demonstrates that at a willingness to pay threshold of £20,000 per QALY gained DEX700 PRN is considered cost-effective compared with ranibizumab on 75.6% of occasions.

Figure 87: Cost-effectiveness acceptability curve – individual NMB (list price for ranibizumab)

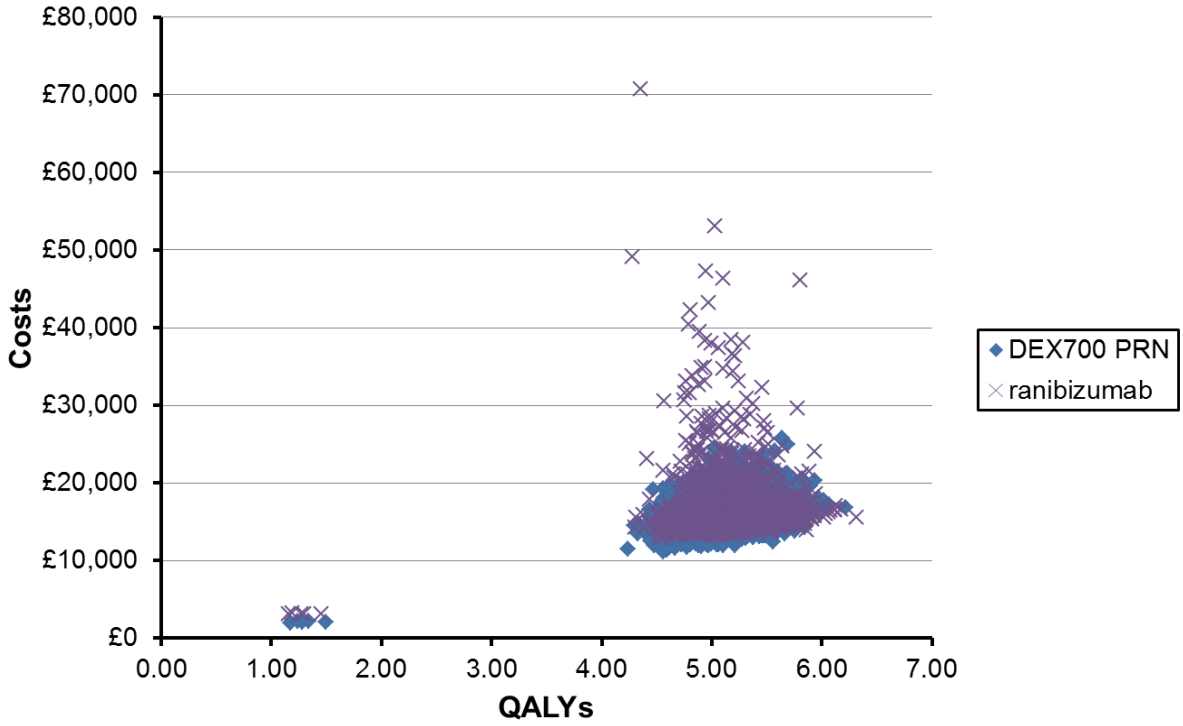


Key: DEX, dexamethasone; NMB, net monetary benefit; PRN, *pro re nata*.

DMO patients who are pseudophakic – 50% PAS discount for ranibizumab

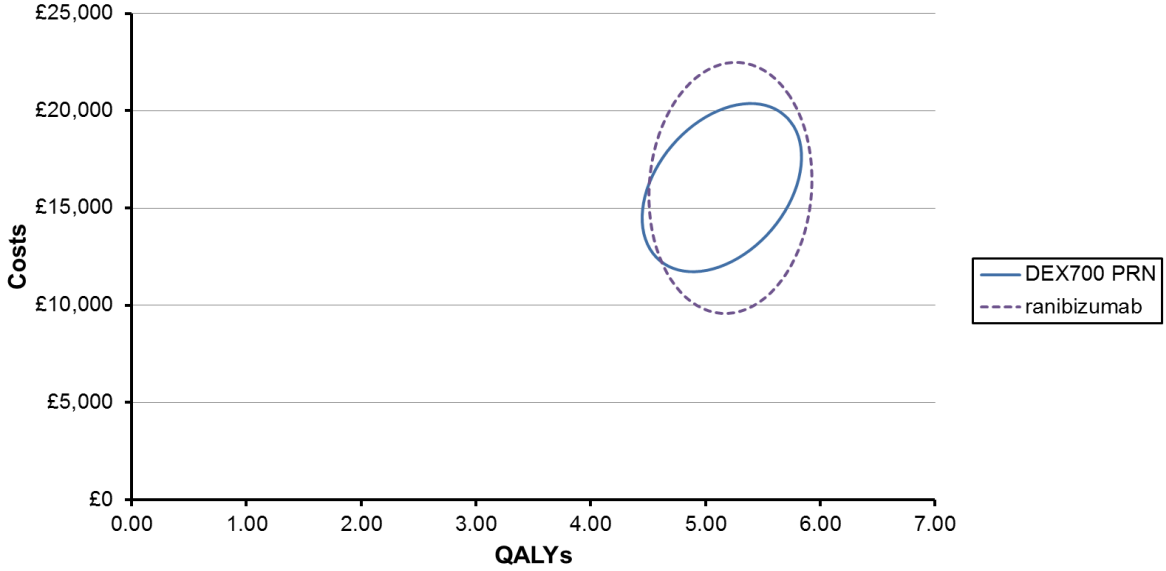
Figure 88 shows the scatter plot of costs and QALYs for DEX700 PRN and ranibizumab from 5,000 probabilistic simulations. These analyses have been performed at a 50% discount for ranibizumab. Figure 89 shows the 95% confidence ellipses. These demonstrate that the range of costs and QALYs obtained from probabilistic simulations are similar for both treatments.

Figure 88: Scatter plot of costs and QALYs for DEX700 PRN and ranibizumab (50% discount for ranibizumab)



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

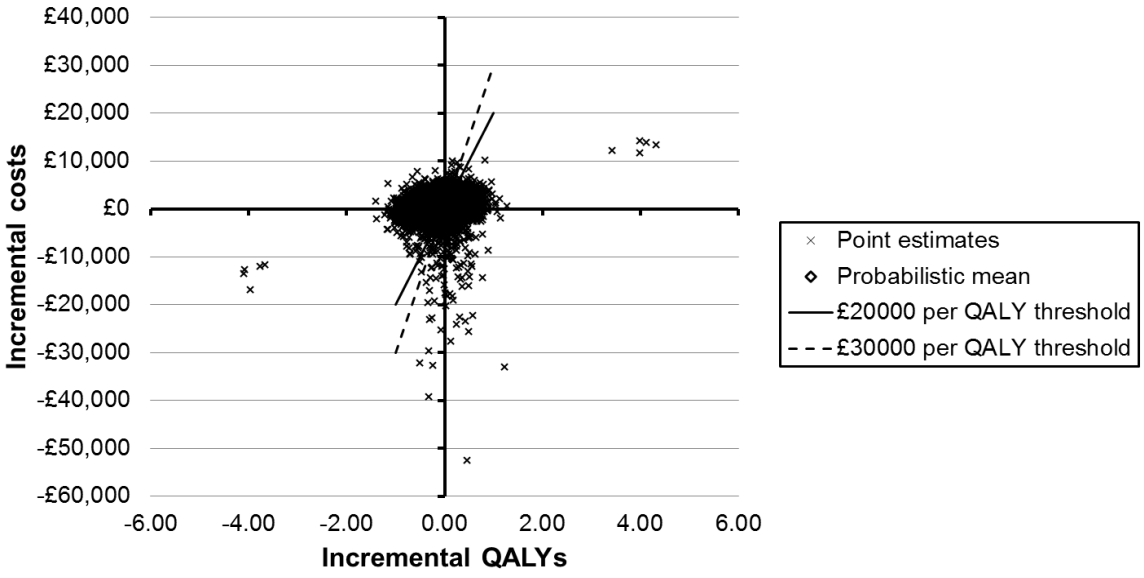
Figure 89: 95% confidence ellipses of costs and QALYs for DEX700 PRN and ranibizumab (50% discount for ranibizumab)



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

Figure 90 shows the scatter plot of incremental costs and QALYs for DEX700 PRN vs. ranibizumab. The incremental costs and QALYs span all four quadrants of the cost-effectiveness plane.

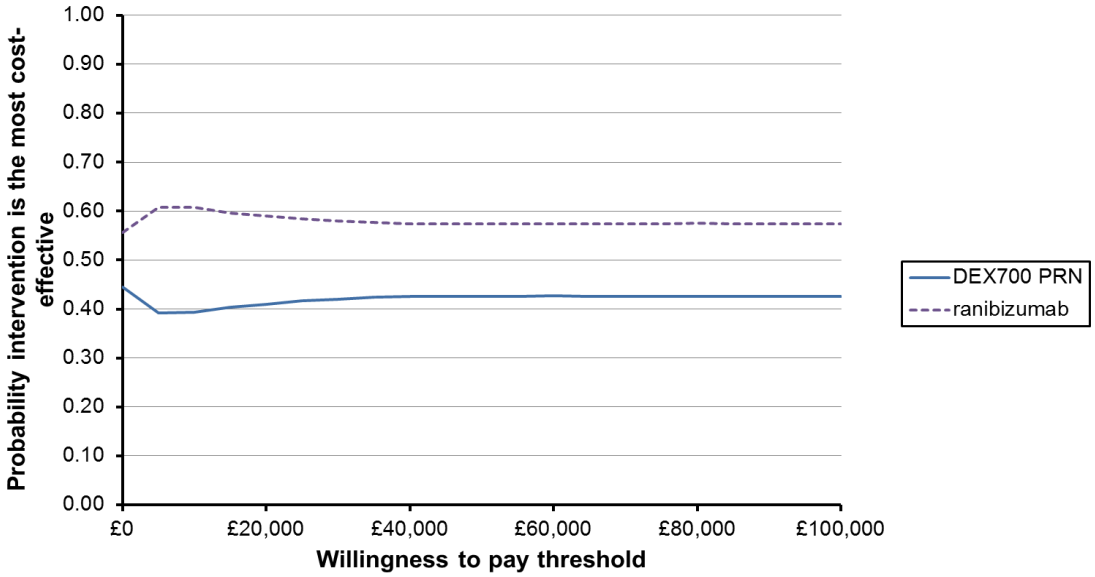
Figure 90: Scatter plot of incremental costs and QALYs for DEX700 PRN vs. ranibizumab (50% discount for ranibizumab)



Key: DEX, dexamethasone; PRN, *pro re nata*; QALY, quality-adjusted life year.

Figure 91 shows the cost-effectiveness acceptability curve for DEX700 PRN and ranibizumab based on the individual NMB at a range of willingness to pay thresholds to a maximum of £100,000 per QALY. This demonstrates that at a willingness to pay threshold of £20,000 per QALY gained DEX700 PRN is considered cost-effective compared with ranibizumab on 40.9% of occasions.

Figure 91: Cost-effectiveness acceptability curve – individual NMB (50% discount for ranibizumab)



Key: DEX, dexamethasone; NMB, net monetary benefit; PRN, *pro re nata*.

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The results of each scenario analysis discussed in Table 116 are presented below. For scenario 1 in each population the incremental analysis is presented with discounts to ranibizumab or fluocinolone acetonide of 0% (list price), 10%, 20%, 30% 40% and 50%. For all other scenarios in the pseudophakic population the incremental analysis is presented at a 50% discount for ranibizumab (providing the most pessimistic view of cost-effectiveness for DEX700). Where appropriate a discussion is provided considering smaller discounts for ranibizumab.

DMO patients who are considered unsuitable for non-corticosteroid therapy

The results of scenario analysis for the population of DMO patients who are considered unsuitable for non-corticosteroid therapy are presented below.

DEX700 PRN dominates watch and wait in the majority of scenarios, and hence can be considered a highly cost-effective treatment option for patients with DMO who are considered unsuitable for non-corticosteroid therapy.

In the scenario where the time horizon is reduced to 10 years DEX700 PRN no longer dominates watch and wait, however still remains cost-effective at a willingness to pay threshold of £20,000 per QALY with an ICER under £7,000 per QALY gained.

There are only three scenarios in which DEX700 PRN is no longer considered cost-effective compared with watch and wait at a willingness to pay threshold of £20,000 per QALY gained. These include shorter time horizons of 1 and 5 years, as the treatment costs of DEX700 PRN are incurred up-front whereas the benefits are realised over the longer-term in terms of avoiding the high costs of severe vision loss, and the scenario in which treatment was assumed to be administered only to patients affected in their WSE.

Scenario 1

Not applicable for this population.

Scenario 2

Not applicable for this population.

Scenario 3: Alternative utility regression equation using EQ-5D from MEAD

Table 137: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 3

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,413	6.6624			
Watch and wait	£21,882	6.6306	£1,469	-0.0318	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 4: Age-adjusted utilities

Table 138: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 4

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,413	5.7266			
Watch and wait	£21,882	5.6610	£1,469	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 5: Treatment duration 5 years with LOCF efficacy assumed in Years 4 and 5

Table 139: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 5

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,948	5.7478			
Watch and wait	£23,965	5.6691	£2,017	-0.0786	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 6: Treatment duration 5 years with stable vision assumed in Years 4 and 5

Table 140: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 6

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,245	5.7454			
Watch and wait	£21,265	5.6770	£20	-0.0684	DEX700 PRN

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

Scenario 7: Vision decline upon development of fellow eye involvement equal to one cycle of natural history of vision in DMO

Table 141: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 7

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,439	5.7419			
Watch and wait	£21,916	5.6763	£1,476	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 8: Stable vision following treatment cessation

Table 142: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 8

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£17,873	5.7527			
Watch and wait	£19,828	5.6781	£1,955	-0.0746	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 9: Time horizon = 1 year

Table 143: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 9

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£711	0.6012			
DEX700 PRN	£3,435	0.6027	£2,724	0.0015	£1,822,946*
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years. **Notes:** *DEX700 PRN vs. watch and wait.					

Scenario 10: Time horizon = 5 years

Table 144: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 10

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£7,214	2.6290			
DEX700 PRN	£10,785	2.6571	£3,571	0.0281	£127,034*

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

Scenario 11: Time horizon = 10 years

Table 145: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 11

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£15,649	4.4869			
DEX700 PRN	£15,985	4.5398	£337	0.0529	£6,365*

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

Scenario 12: Time horizon = 20 years

Table 146: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 12

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£23,175	6.3792			
Watch and wait	£25,429	6.3083	£2,254	-0.0709	DEX700 PRN dominates

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

Scenario 13: 100% unilateral treatment in the BSE

Table 147: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 13

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£23,585	5.6515			
Watch and wait	£32,139	5.5926	£8,554	-0.0590	DEX700 PRN dominates

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

Scenario 14: 100% unilateral treatment in the WSE

Table 148: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 14

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£5,104	5.7964			
DEX700 PRN	£9,468	5.8297	£4,364	0.0332	£131,276*
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years. **Notes:** *DEX700 PRN vs. watch and wait.					

Scenario 15: 100% bilateral treatment

Table 149: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 15

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£27,663	5.7017			
Watch and wait	£32,140	5.6095	£4,477	-0.0922	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 16: Hazard ratio for additional mortality due to DMO = 1.93[68]

Table 150: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 16

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,236	5.9890			
Watch and wait	£23,059	5.9205	£1,823	-0.0685	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 17: Hazard ratio for additional mortality due to DMO = 1.27[69]

Table 151: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 17

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£22,384	6.3315			
Watch and wait	£24,700	6.2590	£2,316	-0.0724	DEX700 PRN dominates

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

Scenario 18: Relative risk of mortality of 1.54 applied to patients whose BSE falls below 35 letters

Table 152: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 18

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£19,779	5.7128			
Watch and wait	£20,667	5.6201	£889	-0.0927	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 19: One-off costs of severe vision loss included

Table 153: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 19

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,414	5.7420			
Watch and wait	£21,884	5.6764	£1,470	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 20: All intravitreal injection procedures administered as a day case procedure 100% of the time

Table 154: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 20

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,684	5.7420			
Watch and wait	£21,882	5.6764	£197	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 21: All intravitreal injection procedures administered as a day case procedure 50% of the time

Table 155: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 21

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,049	5.7420			
Watch and wait	£21,882	5.6764	£833	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 22: DEX700 administered as a day case procedure on 50% of occasions; all other intravitreal injection procedures administered as an outpatient procedure 100% of the time

Table 156: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 22

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,049	5.7420			
Watch and wait	£21,882	5.6764	£833	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 23: Bilateral treatment is assumed to occur on the same day 100% of the time for anti-VEGF (average of 1 appointment) and 0% of the time for steroids (average of 2 appointments)

Table 157: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 23

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,467	5.7420			
Watch and wait	£21,882	5.6764	£1,415	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 24: Bilateral treatment is assumed to occur on the same day 50% of the time for anti-VEGF (average of 1.5 appointments) and 0% of the time for steroids (average of 2 appointments)

Table 158: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 24

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,467	5.7420			
Watch and wait	£21,882	5.6764	£1,415	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 25: Bilateral treatment is assumed to occur on the same day 50% of the time for anti-VEGF (average of 1.5 appointments) and 50% of the time for steroids (average of 1.5 appointments)

Table 159: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 25

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,358	5.7420			
Watch and wait	£21,882	5.6764	£1,523	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 26: Decreased rate of fellow eye involvement

Table 160: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 26

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£18,681	5.7539			
Watch and wait	£19,553	5.6937	£872	-0.0602	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 27: No fellow eye involvement

Table 161: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 27

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£18,001	5.7586			
Watch and wait	£18,632	5.7005	£631	-0.0581	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 28: Inclusion of discontinuation from watch and wait due to adverse events and other non-efficacy related reasons

Table 162: DMO patients who are considered unsuitable for non-corticosteroid therapy; scenario 28

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,413	5.7420			
Watch and wait	£20,640	5.6854	£228	-0.0566	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DMO patients who are considered insufficiently responsive to non-corticosteroid therapy

The results of scenario analysis for the population of DMO patients who are considered insufficiently responsive to non-corticosteroid therapy are presented below.

DEX700 PRN dominates watch and wait in the majority of scenarios, and hence can be considered a highly cost-effective treatment option for patients with DMO who are considered unsuitable for non-corticosteroid therapy.

In the scenario where the time horizon is reduced to 10 years DEX700 PRN no longer dominates watch and wait, however still remains cost-effective at a willingness to pay threshold of £20,000 per QALY with an ICER under £7,000 per QALY gained.

There are only three scenarios in which DEX700 PRN is no longer considered cost-effective compared with watch and wait at a willingness to pay threshold of £20,000 per QALY. These include shorter time horizons of 1 and 5 years, as the treatment

costs of DEX700 PRN are incurred up-front whereas the benefits are realised over the longer-term in terms of avoiding the high costs of severe vision loss, and the scenario in which treatment was assumed to be administered only to patients affected in their WSE.

In the comparison including fluocinolone acetonide DEX700 PRN is considered cost-effective if no discount is applied to fluocinolone acetonide.

Scenario 1: Inclusion of fluocinolone acetonide; variation of price of fluocinolone acetonide

Table 163: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 1; list price for fluocinolone acetonide

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. baseline (DEX700 PRN)
	Cost	QALY	Cost	QALY		
DEX700 PRN	£20,413	5.7420				
Watch and wait	£21,877	5.6765	£1,464	-0.0655	DEX700 PRN dominates	DEX700 PRN dominates
Fluocinolone acetonide	£22,365	5.8214	£1,953	0.0794	£24,591*	£24,591

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

Table 164: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 1; 10% discount to price for fluocinolone acetonide

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. baseline (DEX700 PRN)
	Cost	QALY	Cost	QALY		
DEX700 PRN	£20,413	5.7420				
Fluocinolone acetonide	£21,226	5.8214	£813	0.0794	£10,241*	£10,241
Watch and wait	£21,877	5.6765	£651	-0.1449	Fluocinolone acetonide dominates	DEX700 PRN dominates

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

Table 165: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 1; 20% discount to price for fluocinolone acetonide

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. baseline (Fluocinolone acetonide)
	Cost	QALY	Cost	QALY		
Fluocinolone	£20,086	5.8214				

acetonide						
DEX700 PRN	£20,413	5.7420	£326	-0.0794	Fluocinolone acetonide dominates	Fluocinolone acetonide dominates
Watch and wait	£21,877	5.6765	£1,790	-0.1449	Fluocinolone acetonide dominates	Fluocinolone acetonide dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.						

Table 166: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 1; 30% discount to price for fluocinolone acetonide

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. baseline (DEX700 PRN)
	Cost	QALY	Cost	QALY		
Fluocinolone acetonide	£18,947	5.8214				
DEX700 PRN	£20,413	5.7420	£1,466	-0.0794	Fluocinolone acetonide dominates	Fluocinolone acetonide dominates
Watch and wait	£21,877	5.6765	£2,930	-0.1449	Fluocinolone acetonide dominates	Fluocinolone acetonide dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.						

Table 167: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 1; 40% discount to price for fluocinolone acetonide

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. baseline (DEX700 PRN)
	Cost	QALY	Cost	QALY		
Fluocinolone acetonide	£17,808	5.8214				
DEX700 PRN	£20,413	5.7420	£2,605	-0.0794	Fluocinolone acetonide dominates	Fluocinolone acetonide dominates
Watch and wait	£21,877	5.6765	£4,069	-0.1449	Fluocinolone acetonide dominates	Fluocinolone acetonide dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.						

Table 168: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 1; 50% discount to price for fluocinolone acetonide

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. baseline (watch and wait)
	Cost	QALY	Cost	QALY		
Fluocinolone acetonide	£16,668	5.8214				
DEX700 PRN	£20,413	5.7420	£3,745	-0.0794	Fluocinolone	Fluocinolone

					acetonide dominates	acetonide dominates
Watch and wait	£21,877	5.6765	£5,209	-0.1449	Fluocinolone acetonide dominates	Fluocinolone acetonide dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.						

Scenario 2

Not applicable for this population.

Scenario 3: Alternative utility regression equation using EQ-5D from MEAD

Table 169: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 3

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,413	6.6624			
Watch and wait	£21,882	6.6306	£1,469	-0.0318	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 4: Age-adjusted utilities

Table 170: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 4

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,413	5.7266			
Watch and wait	£21,882	5.6610	£1,469	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 5: Treatment duration 5 years with LOCF efficacy assumed in Years 4 and 5

Table 171: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 5

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,948	5.7478			
Watch and wait	£23,965	5.6691	£2,017	-0.0786	DEX700 PRN dominates

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

Scenario 6: Treatment duration 5 years with stable vision assumed in Years 4 and 5

Table 172: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 6

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,245	5.7454			
Watch and wait	£21,265	5.6770	£20	-0.0684	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 7: Vision decline upon development of fellow eye involvement equal to one cycle of natural history of vision in DMO

Table 173: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 7

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,439	5.7419			
Watch and wait	£21,916	5.6763	£1,476	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 8: Stable vision following treatment cessation

Table 174: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 8

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£17,873	5.7527			
Watch and wait	£19,828	5.6781	£1,955	-0.0746	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 9: Time horizon = 1 year

Table 175: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 9

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£711	0.6012			
DEX700 PRN	£3,435	0.6027	£2,724	0.0015	£1,822,946*

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

Scenario 10: Time horizon = 5 years

Table 176: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 10

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£7,214	2.6290			
DEX700 PRN	£10,785	2.6571	£3,571	0.0281	£127,034*

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

Scenario 11: Time horizon = 10 years

Table 177: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 11

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£15,649	4.4869			
DEX700 PRN	£15,985	4.5398	£337	0.0529	£6,365*

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

Scenario 12: Time horizon = 20 years

Table 178: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 12

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£23,175	6.3792			
Watch and wait	£25,429	6.3083	£2,254	-0.0709	DEX700 PRN dominates

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

Scenario 13: 100% unilateral treatment in the BSE

Table 179: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 13

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£23,585	5.6515			
Watch and wait	£32,139	5.5926	£8,554	-0.0590	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 14: 100% unilateral treatment in the WSE

Table 180: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 14

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Watch and wait	£5,104	5.7964			
DEX700 PRN	£9,468	5.8297	£4,364	0.0332	£131,276*
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years. **Notes:** *DEX700 PRN vs. watch and wait.					

Scenario 15: 100% bilateral treatment

Table 181: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 15

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£27,663	5.7017			
Watch and wait	£32,140	5.6095	£4,477	-0.0922	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 16: Hazard ratio for additional mortality due to DMO = 1.93[68]

Table 182: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 16

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,236	5.9890			
Watch and wait	£23,059	5.9205	£1,823	-0.0685	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 17: Hazard ratio for additional mortality due to DMO = 1.27[69]

Table 183: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 17

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£22,384	6.3315			
Watch and wait	£24,700	6.2590	£2,316	-0.0724	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 18: Relative risk of mortality of 1.54 applied to patients whose BSE falls below 35 letters

Table 184: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 18

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£19,779	5.7128			
Watch and wait	£20,667	5.6201	£889	-0.0927	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 19: One-off costs of severe vision loss included

Table 185: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 19

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,414	5.7420			
Watch and wait	£21,884	5.6764	£1,470	-0.0656	DEX700 PRN dominates

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

Scenario 20: All intravitreal injection procedures administered as a day case procedure 100% of the time

Table 186: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 20

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,684	5.7420			
Watch and wait	£21,882	5.6764	£197	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 21: All intravitreal injection procedures administered as a day case procedure 50% of the time

Table 187: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 21

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,049	5.7420			
Watch and wait	£21,882	5.6764	£833	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 22: DEX700 administered as a day case procedure on 50% of occasions; all other intravitreal injection procedures administered as an outpatient procedure 100% of the time

Table 188: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 22

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£21,049	5.7420			
Watch and wait	£21,882	5.6764	£833	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 23: Bilateral treatment is assumed to occur on the same day 100% of the time for anti-VEGF (average of 1 appointment) and 0% of the time for steroids (average of 2 appointments)

Table 189: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 23

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,467	5.7420			
Watch and wait	£21,882	5.6764	£1,415	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 24: Bilateral treatment is assumed to occur on the same day 50% of the time for anti-VEGF (average of 1.5 appointments) and 0% of the time for steroids (average of 2 appointments)

Table 190: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 24

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,467	5.7420			
Watch and wait	£21,882	5.6764	£1,415	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 25: Bilateral treatment is assumed to occur on the same day 50% of the time for anti-VEGF (average of 1.5 appointments) and 50% of the time for steroids (average of 1.5 appointments)

Table 191: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 25

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,358	5.7420			
Watch and wait	£21,882	5.6764	£1,523	-0.0656	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 26: Decreased rate of fellow eye involvement

Table 192: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 26

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£18,681	5.7539			
Watch and wait	£19,553	5.6937	£872	-0.0602	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 27: No fellow eye involvement

Table 193: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 27

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£18,001	5.7586			
Watch and wait	£18,632	5.7005	£631	-0.0581	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

Scenario 28: Inclusion of discontinuation from watch and wait due to adverse events and other non-efficacy related reasons

Table 194: DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; scenario 28

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£20,413	5.7420			
Watch and wait	£20,640	5.6854	£228	-0.0566	DEX700 PRN dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DMO patients who are pseudophakic

The results of scenario analysis for the population of DMO patients who are pseudophakic are presented below.

Scenario 1: Price of ranibizumab

Table 195: DMO patients who are pseudophakic; scenario 1; list price for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£15,720	5.0886			
Ranibizumab	£21,724	5.2066	£6,004	0.1179	£50,905*

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

Table 196: DMO patients who are pseudophakic; scenario 1; 10% discount to price for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£15,720	5.0886			
Ranibizumab	£20,380	5.2066	£4,660	0.1179	£39,510*

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

Table 197: DMO patients who are pseudophakic; scenario 1; 20% discount to price for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£15,720	5.0886			
Ranibizumab	£19,036	5.2066	£3,316	0.1179	£28,116*

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

Table 198: DMO patients who are pseudophakic; scenario 1; 30% discount to price for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£15,720	5.0886			
Ranibizumab	£17,692	5.2066	£1,972	0.1179	£16,721*

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

Table 199: DMO patients who are pseudophakic; scenario 1; 40% discount to price for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£15,720	5.0886			
Ranibizumab	£16,348	5.2066	£628	0.1179	£5,327*

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

Table 200: DMO patients who are pseudophakic; scenario 1; 50% discount to price for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,004	5.2066			
DEX700 PRN	£15,720	5.0886	£716	-0.1179	Ranibizumab dominates

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

Scenario 2: Inclusion of laser, bevacizumab and watch and wait in incremental analysis

Table 201: DMO patients who are pseudophakic; scenario 2; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. baseline (laser)
	Cost	QALY	Cost	QALY		
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
DEX700 PRN	£15,720	5.0886	£6,318	-0.1491	Bevacizumab dominates	-£152,857
Watch and wait	£21,823	4.9824	£12,421	-0.2553	Bevacizumab dominates	-£87,199

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

Scenario 3: Alternative utility regression equation using EQ-5D from MEAD

Table 202: DMO patients who are pseudophakic; scenario 3; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,004	5.9439			
DEX700 PRN	£15,720	5.8862	£716	-0.0577	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 36% or less.

Scenario 4: Age-adjusted utilities

Table 203: DMO patients who are pseudophakic; scenario 4; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,004	5.1819			
DEX700 PRN	£15,720	5.0640	£716	-0.1179	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 27% or less.

Scenario 5: Treatment duration 5 years with LOCF efficacy assumed in Years 4 and 5

Table 204: DMO patients who are pseudophakic; scenario 5; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,830	5.2213			
DEX700 PRN	£18,067	5.0874	£2,237	-0.1339	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 17% or less.

Scenario 6: Treatment duration 5 years with stable vision assumed in Years 4 and 5

Table 205: DMO patients who are pseudophakic; scenario 6; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,818	5.2176			
DEX700 PRN	£16,647	5.0918	£829	-0.1258	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 27% or less.

Scenario 7: Vision decline upon development of fellow eye involvement equal to one cycle of natural history of vision in DMO

Table 206: DMO patients who are pseudophakic; scenario 7; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,009	5.2065			
DEX700 PRN	£15,742	5.0885	£733	-0.1180	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 26% or less.

Scenario 8: Stable vision following treatment cessation

Table 207: DMO patients who are pseudophakic; scenario 8; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£14,498	5.0981			
Ranibizumab	£14,718	5.2393	£219	0.1412	£1,554*

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

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 30% or less.

Scenario 9: Time horizon = 1 year

Table 208: DMO patients who are pseudophakic; scenario 9; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£3,555	0.5986			
Ranibizumab	£5,966	0.6020	£2,412	0.0035	£697,936*

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

DEX700 PRN is cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY.

Scenario 10: Time horizon = 5 years

Table 209: DMO patients who are pseudophakic; scenario 10; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£9,456	2.5789			
Ranibizumab	£12,327	2.6390	£2,871	0.0601	£47,729*

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

DEX700 PRN is cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY.

Scenario 11: Time horizon = 10 years

Table 210: DMO patients who are pseudophakic; scenario 11; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£13,132	4.2223			
Ranibizumab	£13,896	4.3233	£764	0.1010	£7,564*

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

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 40% or less.

Scenario 12: Time horizon = 20 years

Table 211: DMO patients who are pseudophakic; scenario 12; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,594	5.5306			
DEX700 PRN	£16,879	5.4076	£1,285	-0.1230	Ranibizumab dominates

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

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 22% or less.

Scenario 13: 100% unilateral treatment in the BSE

Table 212: DMO patients who are pseudophakic; scenario 13; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£12,822	5.0909			
DEX700 PRN	£17,823	4.9903	£5,001	-0.1006	Ranibizumab dominates

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

Scenario 14: 100% unilateral treatment in the WSE

Table 213: DMO patients who are pseudophakic; scenario 14; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£8,134	5.1530			
Ranibizumab	£11,403	5.2099	£3,269	0.0570	£57,384*

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

DEX700 PRN is cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY.

Scenario 15: 100% bilateral treatment

Table 214: DMO patients who are pseudophakic; scenario 15; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£18,100	5.2206			
DEX700 PRN	£21,368	5.0630	£3,268	-0.1576	Ranibizumab dominates

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

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 14% or less.

Scenario 16: Hazard ratio for additional mortality due to DMO = 1.93[68]

Table 215: DMO patients who are pseudophakic; scenario 16; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,451	5.5500			
DEX700 PRN	£16,620	5.4245	£1,170	-0.1255	Ranibizumab dominates

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

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 22% or less.

Scenario 17: Hazard ratio for additional mortality due to DMO = 1.27[69]

Table 216: DMO patients who are pseudophakic; scenario 17; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£16,100	6.0528			
DEX700 PRN	£17,952	5.9163	£1,852	-0.1365	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 16% or less.

Scenario 18: Relative risk of mortality of 1.54 applied to patients whose BSE falls below 35 letters

Table 217: DMO patients who are pseudophakic; scenario 18; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£14,937	5.2029			
DEX700 PRN	£15,109	5.0601	£173	-0.1428	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 27% or less.

Scenario 19: One-off costs of severe vision loss included

Table 218: DMO patients who are pseudophakic; scenario 19; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,007	5.2066			
DEX700 PRN	£15,725	5.0886	£718	-0.1179	Ranibizumab dominates

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

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 27% or less.

Scenario 20: All intravitreal injection procedures administered as a day case procedure 100% of the time

Table 219: DMO patients who are pseudophakic; scenario 20; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£16,847	5.0886			
Ranibizumab	£18,773	5.2066	£1,925	0.1179	£16,323*

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

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 46% or less.

Scenario 21: All intravitreal injection procedures administered as a day case procedure 50% of the time

Table 220: DMO patients who are pseudophakic; scenario 21; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
DEX700 PRN	£16,284	5.0886			
ranibizumab	£16,889	5.2066	£605	0.1179	£5,128*

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

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 36% or less.

Scenario 22: DEX700 administered as a day case procedure on 50% of occasions; all other intravitreal injection procedures administered as an outpatient procedure 100% of the time

Table 221: DMO patients who are pseudophakic; scenario 22; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,004	5.2066			
DEX700 PRN	£16,284	5.0886	£1,279	-0.1179	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 22% or less.

Scenario 23: Bilateral treatment is assumed to occur on the same day 100% of the time for anti-VEGF (average of 1 appointment) and 0% of the time for steroids (average of 2 appointments)

Table 222: DMO patients who are pseudophakic; scenario 23; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£14,655	5.2066			
DEX700 PRN	£15,767	5.0886	£1,113	-0.1179	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 24% or less.

Scenario 24: Bilateral treatment is assumed to occur on the same day 50% of the time for anti-VEGF (average of 1.5 appointments) and 0% of the time for steroids (average of 2 appointments)

Table 223: DMO patients who are pseudophakic; scenario 24; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,004	5.2066			
DEX700 PRN	£15,767	5.0886	£763	-0.1179	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 26% or less.

Scenario 25: Bilateral treatment is assumed to occur on the same day 50% of the time for anti-VEGF (average of 1.5 appointments) and 50% of the time for steroids (average of 1.5 appointments)

Table 224: DMO patients who are pseudophakic; scenario 25; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£15,004	5.2066			
DEX700 PRN	£15,673	5.0886	£668	-0.1179	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 27% or less.

Scenario 26: Decreased rate of fellow eye involvement

Table 225: DMO patients who are pseudophakic; scenario 26; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£14,325	5.1990			
DEX700 PRN	£14,776	5.0938	£450	-0.1052	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 29% or less.

Scenario 27: No fellow eye involvement

Table 226: DMO patients who are pseudophakic; scenario 27; 50% PAS discount assumed for ranibizumab

Technologies	Total		Incremental		ICER (cost per QALY)
	Cost	QALY	Cost	QALY	
Ranibizumab	£14,057	5.1960			
DEX700 PRN	£14,409	5.0958	£351	-0.1002	Ranibizumab dominates
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PRN, *pro re nata*; QALYs, quality-adjusted life years.					

DEX700 PRN becomes cost-effective compared with ranibizumab under this scenario at a willingness to pay threshold of £20,000 per QALY if the discount to ranibizumab is 31% or less.

7.7.10 What were the main findings of each of the sensitivity analyses?

Alternative utility regression using EQ-5D data: The results were not sensitive to the choice of utility values used within the model, with consistent results obtained when the choice of utility values were based on the VFQ-UI or the EQ-5D.

Age-adjusted utilities: Including an age adjustment for utilities had no impact on the results of the analysis. This is because there is no differential mortality assumed between treatment options and so the adjustment has the same impact to all treatment arms.

Increased treatment duration: These scenario analyses had no impact on the results in any population.

Vision decline upon development of fellow eye involvement: Assuming all eyes which develop DMO during the model duration receive one cycle of natural history of DMO has no impact on the results as the rate of fellow eye involvement is assumed to be independent of treatment arm and therefore this impacts all treatment arms equally.

Stable vision following treatment cessation: Assuming eyes with DMO have stable vision following the end of the initial treatment period in place of natural history has no impact on the results.

Time horizon: In all populations the time horizon of the analysis has a large influence on the results. This is because treatment costs are incurred upfront, whereas the costs of blindness are either incurred or avoided over the longer term.

Treated eye(s): Which eye is treated is an important driver of cost-effectiveness within the economic model. 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.

Mortality assumptions: Reducing the hazard ratio for mortality had minimal impact on the results as mortality is applied independent of treatment arm. Including additional mortality due to blindness did not impact on the results.

Increased cost of blindness: Increasing the cost of blindness in Year 1 had minimal impact on the results due to the short-term impact of this cost increase.

Variation in proportion of outpatient and day case procedures: The model was highly sensitive to changes in the assumptions around the setting of treatment administration in the pseudophakic population. Assuming an increasing proportion of day case procedures lead to increased costs, disadvantaging ranibizumab which is associated with higher numbers of injections. In contrast increasing the proportion of DEX700 procedures in the populations of patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy did not impact the results of the analysis with DEX700 remaining dominant compared with watch and wait.

Bilateral treatment administration assumptions: Varying the number of appointments required for bilateral administration of treatment did not have a large impact on the results of the analysis.

Fellow eye involvement rate: Removing or increasing the rate of fellow eye involvement did not have a large impact on the results.

Inclusion of discontinuation from watch and wait due to adverse events and other non-efficacy related reasons (DMO patients who are unsuitable for or insufficiently responsive to non-corticosteroid therapy only): Including discontinuation from watch and wait due to adverse events at the rate observed in the MEAD studies did not impact the results of the analysis.

Inclusion of fluocinolone acetonide (DMO patients who are insufficiently responsive to non-corticosteroid therapy only): The results were sensitive to the inclusion of fluocinolone acetonide within the analysis, particularly when a discount was applied to the price of fluocinolone acetonide.

Price of ranibizumab (DMO patients who are pseudophakic only): The results were sensitive to changes in the price of ranibizumab from list price to a 50% discount, with DEX700 PRN being considered cost-effective compared with ranibizumab at a range of discounts dependent on the scenario.

Inclusion of laser, bevacizumab and watch and wait (DMO patients who are pseudophakic only): The results of the analysis are highly sensitive to the choice of comparator treatments. If laser, bevacizumab and watch and wait are included in the incremental analysis both DEX700 PRN and ranibizumab are dominated by bevacizumab which is not widely available on the NHS.

7.7.11 What are the key drivers of the cost-effectiveness results?

The main drivers of the cost-effectiveness results in all populations considered include the proportion of intravitreal injection procedures being performed in the outpatient vs. the day case setting as treatment administration is a large part of the costs associated with treatment. This is particularly influential in the case of ranibizumab in the pseudophakic population, as the treatment burden is higher with this treatment. Therefore increases in the cost of the injection procedure have a

large impact on the cost-effectiveness particularly where ranibizumab is included in the analysis.

Other main drivers included the cost of, and proportion of patients with severe vision loss in their BSE who require residential care which is funded by the NHS. This is expected due to the high cost associated with residential care.

Another main driver of the cost-effectiveness results was the relative risk of improving or worsening vision obtained from the network meta-analysis. The network meta-analysis output was subject to a high level of uncertainty, with very wide credible intervals around the point estimates (section 6.6). As expected, the model is highly sensitive to changes in these parameters as efficacy of treatment in terms of the probability of improving, worsening or maintaining stable vision drives the QALYs and additionally the costs as efficacy influences the amount of the cost of severe vision loss being incurred (or avoided).

The model was also sensitive to the discount rate for costs, the probabilities of improving and worsening vision associated with natural history of DMO and the hazard ratio for the additional mortality due to DMO relative to a DM population.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

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.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

Not applicable

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

Not applicable

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Not applicable. The literature search for cost-effectiveness studies did not find any analyses suitable for comparison with the *de novo* analyses.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes, results for the three independent groups of patients included within the marketing authorisation for DEX700 have been presented.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The key strengths of the *de novo* economic model include the explicit modelling of both eyes of the patient. This adaptation allows treatment benefit in BSE, WSE and bilaterally treated patients to be modelled explicitly. It has been included to avoid the *ad-hoc* assumptions that have been necessary to model the impact of bilateral treatment in one-eye models submitted during previous technology appraisals.[83, 85]

The utility regression based on VFQ-UI data derived for the *de novo* model is a further strength of this economic evaluation. To our knowledge this is the first utility analysis that permits the calculation of utility values dependent on vision in both eyes. Previous utility analyses had, in general, only assessed utility in relation to one eye, usually the BSE. Moreover, this analysis uses a preference-based utility measure specifically designed to reflect vision-related quality of life. This has meant that in previous technology appraisals in DMO arbitrary adjustments have had to be made to attribute utility values to patients treated in the WSE or bilaterally, a limitation that is not present in the *de novo* analysis undertaken here.

The network meta-analysis performed to inform the economic modelling has modelled the relative risk of improving, worsening or maintaining stable vision within the same analysis. This therefore accounts for any correlation between these outcomes. Furthermore, the posterior distributions from the network meta-analysis samples were used in probabilistic analysis as described in section 7.6.3 to account for correlation between the parameter estimates within the probabilistic analysis. This is also considered a key strength of the analysis.

The key model structure and assumptions have been validated by clinicians at two advisory board meetings (detailed in appendix 14, section 10.14) and hence are felt to be robust and reflective of clinical practice for the treatment of DMO.

A weakness of the model is the lack of long-term evidence for the treatment of DMO both in terms of duration of treatment and progression of BCVA following treatment cessation. Clinicians have limited experience using pharmacologic treatments for DMO and hence assumptions about the long-term patient experience have been made and tested in scenario analyses.

Another weakness is the significant proportion of the MEAD study population (DEX700 and sham patients) who either discontinued from the study or were censored, forcing assumptions to be made about the evolution of BCVA in these patients. This introduces additional uncertainty regarding the true outcomes for these patients.

A further weakness is the lack of data for an appropriate watch and wait comparator arm, which means that the efficacy of watch and wait is likely to be overstated by the economic evaluation presented here.

The model includes a number of simplifying assumptions:

The assumption that the relative effect of treatments is constant irrespective of starting health state and constant over time may be a weakness of the model but given the evidence available this is considered the best assumption to make. In particular as the baseline transition probabilities to which the relative treatment effects are applied are allowed to vary over time.

To enable the network meta-analysis to be used to populate a Markov model structure the movements between visual acuity states were limited to a maximum of one visual acuity state in each cycle. This is a limitation of the model as it prevents extreme visual acuity gains or losses being modelled, which are clinically plausible. However, the application of three outcomes from a network meta-analysis within a Markov model structure is an improvement upon previous work of this type. Previous evaluations in DMO have benefitted from head-to-head patient-level data comparing the intervention against relevant comparators defined within the scope, whereas the sham comparator of the MEAD studies precluded a similar approach from being taken in order to satisfy the requirements of the scope for this appraisal. Given this, the methodology used for this appraisal, whilst subject to limitations, is considered the most robust analysis possible given the limited head-to-head data available.

Fellow eye involvement is assumed only to occur at the end of Years 1 and 2. This again is felt to be a justified assumption in order to allow treatment in the fellow eye to be dependent on the time at which DMO was developed whilst reducing the number of additional health states required to do this. Again, this could be considered a weakness; however it is believed to be a helpful simplification.

A further simplification is that the model assumes that the better-seeing eye (BSE) and worse-seeing eye (WSE) are defined at baseline and fixed throughout the time. 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). The exclusion of this functionality from the model is a limitation of the analyses presented here, as the true benefit of treatment (and equally the true detriment of a watch and wait strategy) may not be accurately captured.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Given existing data, not much more could be usefully done. There is a requirement for evidence on the long-term treatment requirements, and the long-term vision outcomes of patients with DMO as these are highly uncertain.

Furthermore, a randomised, controlled trial directly comparing all treatments for DMO would be preferred in order to directly model the relative treatment effects.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

As discussed in section 2, the 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.[41, 66] Applying this prevalence rate to the DM population in England and Wales as of 2013 (2,876,343) (DUK, 2014)[17], 80,538 individuals are estimated to require treatment for visual impairment due to DMO.

Up to 35% of the DMO population requiring treatment for visual impairment due to DMO (28,188 patients) may be considered unsuitable for non-corticosteroid therapy according to ophthalmologists currently practicing across England and Wales (see appendix 14, section 10.14). These patients, described in detail in section 2.6, would also be eligible for first-line or second-line treatment with DEX700. Bilateral DMO is observed in 36.4% of the MEAD clinical trial population[67], therefore this gives a total of 38,448 eyes of DMO patients who are considered unsuitable for non-corticosteroid therapy which are eligible for first- or second-line treatment with DEX700.

In addition, clinician opinion (see appendix 14, section 10.14) is that approximately 25% of all DMO patients (20,135 patients) are considered insufficiently responsive to non-corticosteroid therapy (based on anti-VEGF response given that laser monotherapy is rarely used in current clinical practice, see section 2.5), and are therefore eligible for second-line treatment with DEX700. Bilateral DMO is observed

in 36.4% of the MEAD clinical trial population[67], therefore this gives a total of 27,464 eyes of DMO patients who are considered insufficiently responsive to non-corticosteroid therapy which are eligible for second-line treatment with DEX700.

Further, we estimate based on MEAD trial data that 26.2% of these patients (21,101 patients) have a pseudophakic lens, and therefore are eligible for first- or second-line treatment with DEX700.[67] Bilateral DMO is observed in 36.4% of the MEAD clinical trial population[130], therefore this gives a total of 28,782 eyes with a pseudophakic lens which are eligible for first- or second-line treatment with DEX700.

These patient groups are not mutually exclusive and there will be cross-over between these estimates. For example, there will be some pseudophakic patients in the DMO population that will also be considered unsuitable for non-corticosteroid therapy. Therefore, the true number of eyes eligible for DEX700 in the UK will be less than this estimate though this is likely to increase in line with increasing prevalence and earlier development of DM.

Based on the difference in prevalence of DM in 2013 and 2012[17], the incidence of DM in 2013 was approximately 142,370 patients. Assuming that 2.8% of these patients had visual impairment due to DMO this gives an approximate incidence rate of 3,985 patients per year requiring treatment for visual impairment due to DMO. This gives an incidence of 1,395 DMO patients who are considered unsuitable for non-corticosteroid therapy, 997 DMO patients who are insufficiently responsive to non-corticosteroid therapy and 1,044 pseudophakic DMO patients. Assuming 36.4% of patients require bilateral treatment this gives an incidence of 1,903 eyes of DMO patients who are considered unsuitable for non-corticosteroid therapy, 1,360 eyes of DMO patients who are insufficiently responsive to non-corticosteroid therapy and 1,424 pseudophakic DMO eyes,.

Based on these estimates, the total number of eyes eligible for treatment with DEX700 over 5 years is provided in Table 227 to Table 229 for each population of interest.

Table 227: Eligible population – eyes of DMO patients who are unsuitable for non-corticosteroid therapy

	2015	2016	2017	2018	2019
Prevalent	38,448	0	0	0	0
Incident	1,903	1,903	1,903	1,903	1,903

Total	40351	42254	44157	46060	47962

Table 228: Eligible population – eyes of DMO patients who are insufficiently responsive to non-corticosteroid therapy

	2015	2016	2017	2018	2019
Prevalent	27,464	0	0	0	0
Incident	1,360	1,360	1,360	1,360	1,360
Total	28824	30184	31544	32904	34264

Table 229: Eligible population – eyes of DMO patients who are pseudophakic

	2015	2016	2017	2018	2019
Prevalent	28,782	0	0	0	0
Incident	1,424	1,424	1,424	1,424	1,424
Total	30206	31630	33054	34478	35902

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

It is assumed that the treatment options available are dependent on the patient population under consideration as described in Table 230.

Table 230: Current treatment options for DMO

Population covered by marketing authorisation for DEX700	Comparator treatments
DMO patients who are considered unsuitable for non-corticosteroid therapy	Watch and wait
DMO patients who are considered insufficiently responsive to non-corticosteroid therapy	Watch and wait Fluocinolone acetonide
DMO patients who are pseudophakic	Watch and wait Ranibizumab Bevacizumab Laser
Key: DEX, dexamethasone; DMO, Diabetic macular oedema.	

It is assumed that prevalent and incident cases of DMO are eligible for treatment with DEX700.

8.3 What assumption(s) were made about market share (when relevant)?

The current market share values for pharmaceutical treatments for the whole DMO population are provided in Table 231, based on IMS data.

Table 231: Current market share – pharmaceutical treatments only

Treatment	Market share
Ranibizumab	[redacted]
Bevacizumab	[redacted]
Fluocinolone acetonide	[redacted]
Aflibercept*	[redacted]
DEX700*	[redacted]
Key: DEX, dexamethasone. **Notes:** *Off-label use.	

The costing template for ranibizumab assumes that with the introduction of ranibizumab into the patient pathway 15% of patients will receive laser treatment and 10% of patients will receive no active treatment.[226] Based on this, assuming that laser accounts for 15% of the DMO market share and that 10% of all DMO patients will receive no active treatment (i.e. watch and wait), it is assumed that pharmaceutical treatments account for the remaining 75% of the market share, giving the current market share as detailed in Table 232.

Table 232: Current market share – all available strategies

Treatment	Market share
Watch and wait	[redacted]
Laser	[redacted]
Ranibizumab	[redacted]
Bevacizumab	[redacted]
Fluocinolone acetonide	[redacted]
Aflibercept*	[redacted]
DEX700*	[redacted]
Key: DEX, dexamethasone. **Notes:** *Off-label use.	

In the population of DMO patients who are unsuitable for non-corticosteroid therapies there is currently no first line treatment option available, and hence there is an unmet need in this patient population and it is assumed that the introduction of DEX700 will move patients who currently remain untreated on to treatment, based on the assumptions detailed in Table 233.

Table 233: Uptake of DEX700 – DMO patients who are unsuitable for non-corticosteroid therapy

	2015	2016	2017	2018	2019
Market share					
DEX700	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Watch and wait	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: DEX, dexamethasone.					

In the population of DMO patients who are insufficiently responsive to non-corticosteroid therapies it is assumed that the only treatment option available is fluocinolone acetonide which is shown to have a minimal market share, likely due to the restrictions placed on its use by its marketing authorisation[176] and NICE guidance[86], and hence there is an unmet need in this patient population and DEX700 will not displace the use of fluocinolone, instead it will move patients who currently remain untreated on to treatment, based on the assumptions detailed in Table 234.

Table 234: Uptake of DEX700 – DMO patients who are insufficiently responsive to non-corticosteroid therapy

	2015	2016	2017	2018	2019
Market share					
DEX700	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Watch and wait	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: DEX, dexamethasone.					

It is assumed that in the population of DMO patients who are pseudophakic DEX700 will displace the use of ranibizumab, laser, watch and wait and bevacizumab, based on the assumptions detailed in Table 235.

Table 235: Uptake of DEX700 – DMO patients who are pseudophakic

	2015	2016	2017	2018	2019
Market share					
DEX700	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Watch and wait	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: DEX, dexamethasone.					

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The costs included in the budget impact calculations are applied in line with the costs described for the cost-effectiveness model in section 7. The costs included are treatment acquisition, treatment administration, medical resource use and the cost of treatment for adverse events.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The costs and resource use assumed are consistent with the cost detailed in section 7.5 for the cost-effectiveness model. Patients were assumed to require treatment and monitoring at the rates assumed in the economic model, with a maximum duration of treatment assumed to be 3 years. Discontinuation from treatment was also applied at the rates assumed in the cost-effectiveness model.

8.6 Were there any estimates of resource savings? If so, what were they?

In the population of DMO patients who are pseudophakic, where the introduction of DEX700 into the treatment pathway is assumed to displace the use of ranibizumab and bevacizumab it is anticipated that there will be the potential for substantial resource savings due to the decreased treatment burden associated with DEX700. Ranibizumab and bevacizumab have a high burden to both patients and clinicians due to the high injection and monitoring frequency required, particularly at the start of treatment.

DEX700 is associated with a much lower treatment and monitoring burden and so the introduction of DEX700 would have a positive impact for patients who would not require as many visits, and also for clinicians who would need to see patients less frequently for both treatment and monitoring thus increasing the capacity of the clinic.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for the NHS in England and Wales is presented in Table 236 for the population of DMO patients who are unsuitable for non-corticosteroid therapy. This demonstrates that the introduction of DEX700 as a first line treatment option for DMO patients who are unsuitable for non-corticosteroid therapy may result in a cumulative budget impact of up to £27,057,924 over 5 years in a population where there is a clear unmet need for a treatment option.

Table 236: Estimated budget impact – DMO patients who are unsuitable for non-corticosteroid therapy

	Total annual cost in				
	2015	**2016**	**2017**	**2018**	**2019**
Pathway without DEX700	£618,286	£4,959,047	£8,438,959	£21,189,228	£22,157,895
Pathway with DEX700	£3,791,119	£12,689,389	£19,474,315	£23,585,539	£24,880,976
Budget impact of introducing DEX700	**£3,172,834**	**£7,730,342**	**£11,035,356**	**£2,396,311**	**£2,723,081**
	Total cumulative cost in				
	2015	**2016**	**2017**	**2018**	**2019**
Pathway without DEX700	£618,286	£5,577,333	£14,016,291	£35,205,519	£57,363,414
Pathway with DEX700	£3,791,119	£16,480,509	£35,954,823	£59,540,362	£84,421,338
Budget impact of introducing DEX700	**£3,172,834**	**£10,903,176**	**£21,938,532**	**£24,334,843**	**£27,057,924**
Key: DEX, dexamethasone; DMO, diabetic macular oedema.					

The estimated annual budget impact for the NHS in England and Wales is presented in Table 237 for the population of DMO patients who are insufficiently responsive to non-corticosteroid therapy. This demonstrates that the introduction of DEX700 as a second line treatment option for DMO patients who are insufficiently responsive to non-corticosteroid therapy may result in a cumulative budget impact of up to £20,829,587 over 5 years in a population where there is a clear unmet need for a treatment option.

Table 237: Estimated budget impact – DMO patients who are insufficiently responsive to non-corticosteroid therapy

	Total annual cost in				
	2015	**2016**	**2017**	**2018**	**2019**
Pathway without DEX700	£441,660	£3,542,403	£6,028,290	£15,136,321	£15,828,623
Pathway with DEX700	£2,708,107	£9,064,594	£14,787,657	£17,082,494	£18,164,030
Budget impact of introducing DEX700	**£2,266,448**	**£5,522,191**	**£8,759,367**	**£1,946,173**	**£2,335,408**
	Total cumulative cost in				
	2015	**2016**	**2017**	**2018**	**2019**
Pathway without DEX700	£441,660	£3,984,062	£10,012,352	£25,148,673	£40,977,295
Pathway with DEX700	£2,708,107	£11,772,701	£26,560,358	£43,642,852	£61,806,883
Budget impact of introducing DEX700	**£2,266,448**	**£7,788,639**	**£16,548,006**	**£18,494,179**	**£20,829,587**
Key: DEX, dexamethasone; DMO, diabetic macular oedema.					

The estimated annual budget impact for the NHS in England and Wales is presented for the population of DMO patients who are pseudophakic in Table 238 at list price for ranibizumab and in Table 239 for a 50% discount to ranibizumab. This demonstrates that the introduction of DEX700 as a first line treatment option for DMO patients who are pseudophakic could potentially result in significant cost savings to the NHS in England.

Table 238: Estimated budget impact – DMO patients who are pseudophakic, list price for ranibizumab

	Total annual cost in				
	2015	**2016**	**2017**	**2018**	**2019**
Pathway without DEX700	£339,124,367	£161,288,642	£93,792,732	£41,559,917	£42,048,717
Pathway with DEX700	£336,506,437	£155,869,719	£89,852,692	£39,720,315	£39,869,531
Budget impact of introducing DEX700	**-£2,617,930**	**-£5,418,923**	**-£3,940,040**	**-£1,839,602**	**-£2,179,186**
	Total cumulative cost in				
	2015	**2016**	**2017**	**2018**	**2019**
Pathway without DEX700	£339,124,367	£500,413,009	£594,205,741	£635,765,658	£677,814,375

Pathway with DEX700	£336,506,437	£492,376,156	£582,228,848	£621,949,163	£661,818,694
Budget impact of introducing DEX700	**-£2,617,930**	**-£8,036,853**	**-£11,976,893**	**-£13,816,495**	**-£15,995,681**
Key: DEX, dexamethasone; DMO, diabetic macular oedema.					

Table 239: Estimated budget impact – DMO patients who are pseudophakic, 50% discount for ranibizumab

	Total annual cost in				
	2015	**2016**	**2017**	**2018**	**2019**
Pathway without DEX700	£284,457,433	£131,404,896	£70,846,512	£36,795,791	£37,402,660
Pathway with DEX700	£282,386,172	£127,480,160	£68,742,170	£35,432,602	£35,781,001
Budget impact of introducing DEX700	**-£2,071,261**	**-£3,924,736**	**-£2,104,343**	**-£1,363,189**	**-£1,621,659**
	Total cumulative cost in				
	2015	**2016**	**2017**	**2018**	**2019**
Pathway without DEX700	£284,457,433	£415,862,329	£486,708,841	£523,504,632	£560,907,292
Pathway with DEX700	£282,386,172	£409,866,332	£478,608,502	£514,041,104	£549,822,105
Budget impact of introducing DEX700	**-£2,071,261**	**-£5,995,996**	**-£8,100,339**	**-£9,463,528**	**-£11,085,187**
Key: DEX, dexamethasone; DMO, diabetic macular oedema.					

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

In the populations of patients who are unsuitable for or insufficiently responsive to non-corticosteroid therapies there is an unmet need for a treatment option. The introduction of DEX700 into the treatment pathway for these patients could result in resource savings due to the prevention of clinical blindness which can occur as a result of DMO remaining untreated due to a lack of available therapies. These savings have not been captured in the budget impact calculations described here, but given the high annual cost of blindness per patient (£16,755, section 7.5.6) these savings could be substantial.

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10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

1. Name of the medicinal product

OZURDEX 700 micrograms intravitreal implant in applicator

2. Qualitative and quantitative composition

One implant contains 700 micrograms of dexamethasone.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Intravitreal implant in applicator.

Disposable injection device, containing a rod-shaped implant which is not visible. The implant is approximately 0.46 mm in diameter and 6 mm in length.

4. Clinical particulars

4.1 Therapeutic indications

OZURDEX is indicated for the treatment of adult patients with:

• visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy

• macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) (see section 5.1)

• inflammation of the posterior segment of the eye presenting as non-infectious uveitis

4.2 Posology and method of administration

OZURDEX must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Posology

The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended (see section 4.4).

DME

Patients treated with OZURDEX who have experienced an initial response and in the physician's opinion may benefit from retreatment without being exposed to significant risk should be considered for retreatment.

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

There is currently no experience of the efficacy or safety of repeat administrations in DME beyond 7 implants.

RVO and Uveitis

Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk (see section 5.1).

Patients who experience and retain improved vision should not be retreated. Patients who experience deterioration in vision, which is not slowed by OZURDEX, should not be retreated.

There is only very limited information on repeat dosing intervals less than 6 months (see section 5.1). There is currently no experience of repeat administrations in posterior segment non-infectious uveitis or beyond 2 implants in Retinal Vein Occlusion.

Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs (see section 4.4).

Special populations

Elderly (≥65 years old)

No dose adjustment is required for elderly patients.

Renal impairment

OZURDEX has not been studied in patients with renal impairment however no special considerations are needed in this population.

Hepatic impairment

OZURDEX has not been studied in patients with hepatic impairment; however no special considerations are needed in this population.

Paediatric population

There is no relevant use of OZURDEX in the paediatric population in

• diabetic macular oedema

• macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of OZURDEX in uveitis in the paediatric population have not been established. No data are available.

Method of administration

Single-use intravitreal implant in applicator for intravitreal use only.

Each applicator can only be used for the treatment of a single eye.

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).

The patient should be instructed to self-administer broad spectrum antimicrobial drops daily for 3 days before and after each injection. Before the injection, the periocular skin, eyelid and ocular surface should be disinfected (using for example drops of povidone iodine 5% solution on the conjunctiva as it was done in the clinical trials for the approval of OZURDEX) and adequate local anaesthesia should be administered. Remove the foil pouch from the carton and examine for damage (see section 6.6). Then, in a sterile field, open the foil pouch and gently place the applicator on a sterile tray. Carefully remove the cap from the applicator. Once the foil pouch is opened the applicator should be used immediately.

Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab. With the bevel of the needle up away from the sclera, advance the needle about 1 mm into the sclera then redirect toward the centre of the

eye into the vitreous cavity until the silicone sleeve is against the conjunctiva. Slowly press the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully pressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous.

Immediately after injecting OZURDEX, use indirect ophthalmoscopy in the quadrant of injection to confirm successful implantation. Visualisation is possible in the large majority of cases. In cases in which the implant cannot be visualised, take a sterile cotton bud and lightly depress over the injection site to bring the implant into view.

Following the intravitreal injection patients should continue to be treated with a broad spectrum antimicrobial.

4.3 Contraindications

OZURDEX is contraindicated in

• Hypersensitivity to the active substance or to any of the excipients as listed in section 6.1.

• Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

• Advanced glaucoma which cannot be adequately controlled by medicinal products alone.

• Aphakic eyes with ruptured posterior lens capsule.

• Eyes with Anterior Chamber Intraocular Lens (ACIOL), iris or transscleral fixated intraocular lens and ruptured posterior lens capsule.

4.4 Special warnings and precautions for use

Intravitreous injections, including those with OZURDEX, can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment. Proper aseptic injection techniques must always be used. In addition, patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within

30 minutes following the injection, and biomicroscopy between two and seven days following the injection.

Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay e.g. eye pain, blurred vision etc (see section 4.8).

All patients with posterior capsule tear, such as those with a posterior lens (e.g. due to cataract surgery), and/or those who have an iris opening to the vitreous cavity (e.g. due to iridectomy) with or without a history of vitrectomy, are at risk of implant migration into the anterior chamber. Implant migration to the anterior chamber may lead to corneal oedema. Persistent severe corneal oedema could progress to the need for corneal transplantation. Other than those patients contraindicated (see section 4.3) where OZURDEX should not be used, OZURDEX should be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored to allow for early diagnosis and management of device migration.

Use of corticosteroids, including OZURDEX, may induce cataracts (including posterior subcapsular cataracts), increased IOP, steroid induced glaucoma and may result in secondary ocular infections.

In the 3 year DME clinical studies, 59% of patients with a phakic study eye treated with OZURDEX underwent cataract surgery in the study eye (see section 4.8).

After the first injection the incidence of cataract appears higher in patients with non-infectious uveitis of the posterior segment compared with BRVO/CRVO patients. In BRVO/CRVO clinical studies, cataract was reported more frequently in patients with phakic lens receiving a second injection (see section 4.8). Only 1 patient out of 368 required cataract surgery during the first treatment and 3 patients out of 302 during the second treatment. In the non-infectious uveitis study, 1 patient out of the 62 phakic patients underwent cataract surgery after a single injection.

The prevalence of conjunctival haemorrhage in patients with non-infectious uveitis of the posterior segment appears to be higher compared with BRVO/CRVO and DME. This could be attributable to the intravitreous injection procedure or to concomitant use of topical and/or systemic corticosteroid or Non-steroidal anti-inflammatory medications. No treatment is required since spontaneous resolution occurs.

As expected with ocular steroid treatment and intravitreal injections, increases in intraocular pressure (IOP) may be seen. The rise in IOP is normally manageable with IOP lowering medication (see section 4.8). Of the patients experiencing an increase of IOP of ≥10 mm Hg from baseline, the greatest proportion showed this IOP increase between 45 and 60 days following an injection. Therefore, regular monitoring of IOP, irrespective of baseline IOP, is required and any elevation should be managed appropriately post-injection as needed. Patients of less than 45 years of age with macular oedema following Retinal Vein Occlusion or inflammation of the posterior segment of the eye presenting as non-infectious uveitis are more likely to experience increases in IOP.

Corticosteroids should be used cautiously in patients with a history of ocular viral (e.g. herpes simplex) infection and not be used in active ocular herpes simplex.

The safety and efficacy of OZURDEX administered to both eyes concurrently have not been studied. Therefore administration to both eyes concurrently is not recommended.

OZURDEX has not been studied in patients with macular oedema secondary to RVO with significant retinal ischemia. Therefore OZURDEX is not recommended.

A limited number of subjects with Type 1 diabetes were investigated in the Phase 3 studies, and the response to OZURDEX in these subjects was not significantly different to those subjects with Type 2 diabetes.

In RVO, anti-coagulant therapy was used in 2% of patients receiving OZURDEX; there were no reports of haemorrhagic adverse events in these patients. In DME, anti-coagulant therapy was used in 8% of patients. Among patients who used anti-coagulant therapy, the frequency of haemorrhagic adverse events was similar in the OZURDEX and sham groups (29% vs 32%). Among patients who did not use anti-coagulant therapy, 27% of OZURDEX treated patients reported haemorrhagic adverse events compared to 20% in the sham group. Vitreous haemorrhage was reported in a higher proportion of patients treated with OZURDEX who received anti-coagulant therapy (11%) compared with those not receiving anti-coagulant therapy (6%).

Anti-platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in up to 56% of patients. For patients using concomitant

and anti-platelet medication, haemorrhagic adverse events were reported in a slightly higher proportion of patients injected with OZURDEX (up to 29%) compared with the sham group (up to 23%), irrespective of indication or number of treatments. The most common haemorrhagic adverse event reported was conjunctival haemorrhage (up to 24%).

OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Systemic absorption is minimal and no interactions are anticipated.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown teratogenic effects following topical ophthalmic administration (see section 5.3). There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. Long-term systemic treatment with glucocorticoids during pregnancy increases the risk for intra-uterine growth retardation and adrenal insufficiency of the newborn child. Therefore, although the systemic exposure of dexamethasone would be expected to be very low after local, intraocular treatment, OZURDEX is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Dexamethasone is excreted in breast milk. No effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast-feeding unless clearly necessary.

Fertility

There are no fertility data available.

4.7 Effects on ability to drive and use machines

Patients may experience temporarily reduced vision after receiving OZURDEX by intravitreal injection (see section 4.8). They should not drive or use machines until this has resolved.

4.8 Undesirable effects

The adverse reactions considered related to OZURDEX treatment from the Phase III clinical trials (DME, BRVO/CRVO and uveitis) and spontaneous reporting are listed by MedDRA System organ class in the table below using the following convention:

Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

System organ class	Frequency	Adverse reaction
Nervous System Disorders	Common	Headache
	Uncommon	Migraine
Eye disorders	Very common	Intraocular pressure increased, cataract, conjunctival haemorrhage*
	Common	Ocular hypertension, cataract subcapsular, vitreous haemorrhage*, visual acuity reduced*, visual impairment/disturbance, vitreous detachment*, vitreous floaters*, vitreous opacities*, blepharitis, eye pain*, photopsia*, conjunctival oedema* conjunctival hyperaemia*
	Uncommon	Necrotizing retinitis, endophthalmitis*, glaucoma, retinal detachment*, retinal tear*, hypotony of the eye*, anterior chamber inflammation*, anterior chamber cells/flares*, abnormal sensation in eye*, eyelids pruritus, scleral hyperaemia*
General disorders and administration site conditions	Uncommon	Device dislocation* (migration of implant) with or without corneal oedema (see also section 4.4), complication of device insertion* (implant misplacement)

* indicates adverse reactions considered to be related to the intravitreal injection procedure (the frequency of these adverse reactions is proportional to the number of treatments given)

Diabetic Macular Oedema

The clinical safety of OZURDEX in patients with diabetic macular oedema was assessed in two phase 3 randomized, double-masked, sham-controlled studies. In both studies, a total of 347 patients were randomized and received OZURDEX and 350 patients received sham.

The most frequently reported adverse reactions across the entire study period in the study eye of patients who received OZURDEX were cataract and elevated IOP (see below).

In the 3 year DME clinical studies, at baseline, 87% of patients with a phakic study eye treated with OZURDEX had some degree of lens opacification/early cataract. The incidence of all observed cataract types (i.e. cataract cortical, cataract diabetic, cataract nuclear, cataract subcapsular, cataract lenticular, cataract) was 68% in OZURDEX treated patients with a phakic study eye across the 3 year studies. 59% of patients with a phakic study eye required cataract surgery by the 3 year final visit, with the majority performed in the 2nd and 3rd years.

Mean IOP in the study eye at baseline was the same in both treatment groups (15.3 mm Hg). The mean increase from baseline IOP did not exceed 3.2 mm Hg across all visits in the OZURDEX group with the mean IOP peaking at the 1.5 month visit post injection, and returning to approximately baseline levels by month 6 following each injection. The rate and magnitude of IOP elevation following OZURDEX treatment did not increase upon repeated injection of OZURDEX.

28% of patients treated with OZURDEX had a ≥ 10 mm Hg IOP increase from baseline at one or more visits during the study. At baseline 3% of patients required IOP-lowering medication(s). Overall, 42% of patients required IOP-lowering medications in the study eye at some stage during the 3 year studies, with the majority of these patients requiring more than one medication. Peak usage (33%) occurred during the first 12 months and remained similar from year to year.

A total of 4 patients (1%) treated with OZURDEX had procedures in the study eye for the treatment of IOP elevation. One patient treated with OZURDEX required incisional surgery (trabeculectomy) to manage the steroid-induced IOP elevation, 1 patient had a trabeculectomy owing to anterior chamber fibrin blocking the aqueous outflow leading to increased IOP, 1 patient had an iridotomy for narrow angle glaucoma and 1 patient had iridectomy due to cataract surgery. No patient required removal of the implant by vitrectomy to control IOP.

BRVO/CRVO

The clinical safety of OZURDEX in patients with macular oedema following central or branch retinal vein occlusion has been assessed in two Phase III randomised, double-masked, sham-controlled studies. A total of 427 patients were randomised to receive OZURDEX and 426 to receive sham in the two Phase III studies. A total of

401 patients (94%) randomised and treated with OZURDEX completed the initial treatment period (up to day 180).

A total of 47.3% of patients experienced at least one adverse reaction. The most frequently reported adverse reactions in patients who received OZURDEX were increased intraocular pressure (24.0%) and conjunctival haemorrhage (14.7%).

The adverse reaction profile for BRVO patients was similar to that observed for CRVO patients although the overall incidence of adverse reactions was higher for the subgroup of patients with CRVO.

Increased intraocular pressure (IOP) with OZURDEX peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. During the initial treatment period, 0.7% (3/421) of the patients who received OZURDEX required laser or surgical procedures for management of elevated IOP in the study eye compared with 0.2% (1/423) with sham.

The adverse reaction profile of 341 patients analysed following a second injection of OZURDEX, was similar to that following the first injection. A total of 54% of patients experienced at least one adverse reaction. The incidence of increased IOP (24.9%) was similar to that seen following the first injection and likewise returned to baseline by open-label day 180. The overall incidence of cataracts was higher after 1 year compared to the initial 6 months.

Uveitis

The clinical safety of OZURDEX in patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis, has been assessed in a single, multicentre, masked, randomised study.

A total of 77 patients were randomised to receive OZURDEX and 76 to receive Sham. A total of 73 patients (95%) randomised and treated with OZURDEX completed the 26-week study.

The most frequently reported adverse reactions in the study eye of patients who received OZURDEX were conjunctival haemorrhage (30.3%), increased intraocular pressure (25.0%) and cataract (11.8%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, anti-inflammatory agents, ATC code: S01BA01

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting oedema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response. Vascular Endothelial Growth Factor (VEGF) is a cytokine which is expressed at increased concentrations in the setting of macular oedema. It is a potent promoter of vascular permeability. Corticosteroids have been shown to inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular oedema.

Diabetic Macular Oedema

The efficacy of OZURDEX was assessed in two 3 year, multicentre, double-masked, randomised, sham-controlled, parallel studies of identical design which together comprised 1,048 patients (studies 206207-010 and 206207-011). A total of 351 were randomised to OZURDEX, 347 to dexamethasone 350 µg and 350 patients to sham.

Patients were eligible for retreatment based upon central subfield retinal thickness >175 microns by optical coherence tomography (OCT) or upon investigators interpretation of the OCT for any evidence of residual retinal edema consisting of intraretinal cysts or any regions of increased retinal thickening within or outside of the central subfield. Patients received up to 7 treatments at intervals no more frequently than approximately every 6 months.

Escape therapy was permitted at the investigator's discretion at any stage but led to subsequent withdrawal from the studies.

A total of 36% of OZURDEX treated patients discontinued study participation for any reason during the study compared with 57% of sham patients. Discontinuation rates due to adverse events were similar across treatment and sham groups (13% vs 11%). Discontinuation due to lack of efficacy was lower in the OZURDEX group compared to sham (7% vs 24%).

The primary and key secondary endpoints for studies 206207-010 and 011 are presented in Table 2. The vision improvement in the DEX700 group was confounded by cataract formation. Vision improvement was re-established upon removal of cataract.

Table 2: Efficacy in Studies 206207-010 and 206207-011 (ITT Population)

Endpoint	Study 206207-010		Study 206207-011		Pooled Studies 206207-010 and 206207-011	
	DEX 700 N = 163	Sham N = 165	DEX 700 N = 188	Sham N = 185	DEX 700 N = 351	Sham N = 350
Mean BCVA average change over 3 years, AUC approach (letters)	4.1	1.9	2.9	2.0	3.5	2.0
p-value	0.016		0.366		0.023	
BCVA ≥ 15-letter improvement from baseline at Year 3/Final (%)	22.1	13.3	22.3	10.8	22.2	12.0
p-value	0.038		0.003		< 0.001	
Mean BCVA change from baseline at year 3/final visit (letters)	4.1	0.8	1.3	-0.0	2.6	0.4
p-value	0.020		0.505		0.054	
OCT retinal thickness at center subfield mean average change over 3 years, AUC approach (µm)	-101.1	-37.8	-120.7	-45.8	-111.6	-41.9
p-value	<0.001		< 0.001		< 0.001	

The primary and key secondary endpoints for the pooled analysis for pseudophakic patients are presented in Table 3.

Table 3. Efficacy in Pseudophakic Patients (Pooled Studies 206207-010 and 206207-011)

Endpoint	DEX 700 N = 86	Sham N = 101	p-value
Mean BCVA average change over 3 years, AUC approach (letters)	6.5	1.7	< 0.001
BCVA ≥ 15-letter improvement from baseline at Year 3/Final visit (%)	23.3	10.9	0.024
Mean BCVA change from baseline at year 3/Final visit	6.1	1.1	0.004

OCT retinal thickness at center subfield mean average change over 3 years, AUC approach (µm)	-131.8	-50.8	< 0.001

The primary and key secondary endpoints for the pooled analysis for patients with any prior treatment are presented in Table 4.

Table 4. Efficacy in Patients with Any Prior Treatment (Pooled Studies 206207-010 and 206207-011)

Endpoint	DEX 700 N = 247	Sham N = 261	p-value
Mean BCVA average change over 3 years, AUC approach (letters)	3.2	1.5	0.024
BCVA ≥ 15-letter improvement from baseline at Year 3/Final visit (%)	21.5	11.1	0.002
Mean BCVA change from baseline at year 3/Final visit	2.7	0.1	0.055
OCT retinal thickness at center subfield mean average change over 3 years, AUC approach (µm)	-126.1	-39.0	< 0.001

BRVO/CRVO

The efficacy of OZURDEX was assessed in two multicentre, double-masked, randomised, sham-controlled, parallel studies of identical design which together comprised 1,267 patients who were randomized to receive treatment with dexamethasone 350 µg or 700 µg implants or sham (studies 206207-008 and 206207-009). A total of 427 were randomised to OZURDEX, 414 to dexamethasone 350 µg and 426 patients to sham.

Based on the pooled analysis results, treatment with OZURDEX implants showed statistically significantly greater incidence of responders, defined as patients achieving a ≥ 15 letter improvement from baseline in Best Corrected Visual Acuity (BCVA) at 90 days following injection of a single implant, when compared with sham ($p < 0.001$).

The proportion of patients achieving the primary efficacy measure of ≥ 15 letter improvement from baseline in BCVA following injection of a single implant is shown in Table 5. A treatment effect was seen at the first observation time point of day 30. The maximum treatment effect was observed at day 60 and the difference in the incidence of responders was statistically significant favouring OZURDEX compared with sham at all time points to day 90 following injection. There continued to be a numerically greater proportion of responders for a ≥ 15 letter improvement from

baseline in BCVA in patients treated with OZURDEX compared with sham at day 180.

Table 5. Proportion of Patients with ≥ 15 Letters Improvement from Baseline Best Corrected Visual Acuity in the Study Eye (Pooled, ITT Population)

	OZURDEX	Sham
Visit	N = 427	N = 426
Day 30	21.3 % [a]	7.5%
Day 60	29.3% [a]	11.3%
Day 90	21.8% [a]	13.1%
Day 180	21.5%	17.6%

[a] Proportion significantly higher with OZURDEX compared to sham ($p < 0.001$)

The mean change from baseline BCVA was significantly greater with OZURDEX compared to sham at all time points.

In each Phase III study and the pooled analysis, the time to achieve ≥ 15 letters (3-line) improvement in BCVA cumulative response curves were significantly different with OZURDEX compared to sham ($p < 0.001$) with OZURDEX treated patients achieving a 3-line improvement in BCVA earlier than sham treated patients.

OZURDEX was numerically superior to sham in preventing vision loss as shown by a lower of proportion of patients experiencing deterioration of vision of ≥ 15 letters in the OZURDEX group throughout the 6-month assessment period.

In each of the phase III studies and the pooled analysis, mean retinal thickness was significantly less, and the mean reduction from baseline was significantly greater, with OZURDEX (-207.9 microns) compared to sham (-95.0 microns) at day 90 ($p < 0.001$, pooled data). The treatment effect as assessed by BCVA at day 90 was thus supported by this anatomical finding. By Day 180 the mean retinal thickness reduction (-119.3 microns) compared with sham was not significant.

Patients who had a BCVA score of <84 OR retinal thickness > 250 microns by optical coherence tomography OCT and in the investigator's opinion treatment would not put the patient at risk; were eligible to receive an OZURDEX treatment in an open label extension. Of the patients who were treated in the open label phase, 98% received an OZURDEX injection between 5 and 7 months after the initial treatment.

As for the initial treatment, peak response was seen at Day 60 in the open label phase. The cumulative response rates were higher throughout the open label phase

in those patients receiving two consecutive OZURDEX injections compared with those patients who had not received an OZURDEX injection in the initial phase.

The proportion of responders at each time point was always greater after the second treatment compared with the first treatment. Whereas, delaying treatment for 6 months results in a lower proportion of responders at all time points in the open label phase when compared with those receiving a second OZURDEX injection.

Uveitis

The clinical efficacy of OZURDEX has been assessed in a single, multicentre, masked, randomised study for the treatment of non-infectious ocular inflammation of the posterior segment in patients with uveitis.

A total of 229 patients were randomised to receive dexamethasone 350 µg or 700 µg implants or sham. Of these, a total of 77 were randomised to receive OZURDEX, 76 to dexamethasone 350 µg and 76 to sham. A total of 95% of patients completed the 26-week study.

The proportion of patients with vitreous haze score of 0 in the study eye at week 8 (primary endpoint) was 4-fold higher with OZURDEX (46.8%) compared to Sham (11.8%), $p < 0.001$. Statistical superiority was maintained up to and including week 26 ($p \leq 0.014$) as shown in Table 6.

The cumulative response rate curves (time to vitreous haze score of 0) were significantly different for the OZURDEX group compared to the Sham group ($p < 0.001$), with patients receiving dexamethasone showing an earlier onset and greater treatment response.

The reduction in vitreous haze was accompanied by an improvement in visual acuity. The proportion of patients with at least 15 letters improvement from baseline BCVA in the study eye at week 8 was more than 6-fold higher with OZURDEX (42.9%) compared to Sham (6.6%), $p < 0.001$. Statistical superiority was achieved at week 3 and maintained up to and including week 26 ($p < 0.001$) as shown in Table 6.

The percent of patients requiring escape medications from baseline to week 8 was nearly 3-fold less with OZURDEX (7.8%) compared to Sham (22.4%), $p = 0.012$.

Table 6. Proportion of Patients with Vitreous Haze Score of Zero and ≥ 15 Letters Improvement from Baseline Best Corrected Visual Acuity in the Study Eye (ITT Population)

Visit	Vitreous Haze Score of Zero		BCVA improvement from baseline of ≥15 letters	
	DEX 700 N = 77	Sham N = 76	DEX 700 N = 77	Sham N = 76
Week 3	23.4%	11.8%	32.5%[a]	3.9%
Week 6	42.9%[a]	9.2%	41.6%[a]	7.9%
Week 8	46.8%[a]	11.8%	42.9%[a]	6.6%
Week 12	45.5%[a]	13.2%	41.6%[a]	13.2%
Week 16	40.3%[b]	21.1%	39.0%[a]	13.2%
Week 20	39.0%[c]	19.7%	40.3%[a]	13.2%
Week 26	31.2%[d]	14.5%	37.7%[a]	13.2%

[a] $p < 0.001$; [b] $p = 0.010$; [c] $p = 0.009$; [d] $p = 0.014$

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with

OZURDEX in all subsets of the paediatric population for retinal vascular occlusion and also for diabetic macular oedema. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Plasma concentrations were obtained from a subset of 21 patients in the two RVO, 6-month efficacy studies prior to dosing and on days 7, 30, 60, and 90 following intravitreal injection of a single intravitreal implant containing 350 µg or 700 µg dexamethasone. Ninety-five percent of the plasma dexamethasone concentration values for the 350 µg dose group and 86% for the 700 µg dose group were below the lower limit of quantitation (0.05 ng/ml). The highest plasma concentration value of 0.094 ng/ml was observed in one subject from the 700 µg group. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

Plasma concentrations were obtained from a subgroup of patients in the two DME pivotal studies prior to dosing and on days 1, 7, and 21, and months 1.5 and 3 following intravitreal injection of a single intravitreal implant containing 350 µg or 700 µg dexamethasone. One hundred percent of the plasma dexamethasone concentration values for the 350 µg dose group and 90% for the 700 µg dose group

were below the lower limit of quantitation (0.05 ng/ml). The highest plasma concentration value of 0.102 ng/ml was observed in 1 subject from the 700 µg group. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In a 6-month monkey study following a single intravitreal injection of OZURDEX the dexamethasone vitreous humour Cmaxwas 100 ng/ml at day 42 post-injection and 5.57 ng/ml at day 91. Dexamethasone remained detectable in the vitreous at 6 months post-injection. The rank order of dexamethasone concentration was retina > iris > ciliary body > vitreous humour > aqueous humour > plasma.

In an in vitro metabolism study, following the incubation of [14C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humour, and sclera tissues for 18 hours, no metabolites were observed. This is consistent with results from rabbit and monkey ocular metabolism studies.

Dexamethasone is ultimately metabolised to lipid and water soluble metabolites that can be excreted in bile and urine.

The OZURDEX matrix slowly degrades to lactic acid and glycolic acid through simple hydrolysis, then further degrades into carbon dioxide and water.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at doses considered sufficiently in excess of the maximum dose for human indicating little relevance to clinical use.

No mutagenicity, carcinogenicity, reproductive or developmental toxicity data are available for OZURDEX. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application.

Dexamethasone exposure to the healthy/untreated eye via contralateral diffusion has been observed in rabbits following delivery of the implant to the posterior segment of the eye.

6. Pharmaceutical particulars

6.1 List of excipients

• Ester terminated 50:50 poly D,L-lactide-co-glycolide.

• Acid terminated 50:50 poly D,L-lactide-co-glycolide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1 pack contains:

1 sustained release sterile implantable rod shaped implant containing 700 micrograms of dexamethasone, located in the needle (stainless steel) of a disposable applicator.

The applicator consists of a plunger (stainless steel) within a needle where the implant is held in place by a sleeve (silicone). The plunger is controlled by a lever on the side of the applicator body. The needle is protected by a cap and the lever by a safety tab.

The applicator containing the implant is packaged in a sealed foil pouch containing desiccant.

6.6 Special precautions for disposal and other handling

OZURDEX is for single use only.

Each applicator can only be used for the treatment of a single eye.

If the seal of the foil pouch containing the applicator is damaged, do not use. Once the foil pouch is opened the applicator should be used immediately.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Allergan Pharmaceuticals Ireland, Castlebar Road, Co. Mayo, Westport, Ireland

8. Marketing authorisation number(s)

EU/1/10/638/001

9. Date of first authorisation/renewal of the authorisation

27/07/2010

10. Date of revision of the text

08/2014.Version 4.

Detailed information on this medicinal product is available on the website of the European Medicines Agencyhttp://www.ema.europa.eu/.

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Electronic databases presented in Table 240 were searched.

Table 240: Electronic databases searched to identify the RCT clinical evidence base

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

10.2.2 The date on which the search was conducted.

Original searches were conducted on 13th February 2014 and update searches were conducted on 17th July 2014.

10.2.3 The date span of the search.

No date limits were applied in the original searches conducted in February 2014. Coverage of each database is presented in Table 240.

A date limit of 2014 – current was applied in update searches conducted in July

10.2.4 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).

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

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

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

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+")

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Additional searches were conducted in clinicaltrials.gov along with the following conference proceedings:

- 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)

10.2.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria applied to the search results are presented in Table 241.

Table 241: Eligibility criteria applied to systematic search results identifying the clinical evidence base of RCTs

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)
Key: BCVA, best corrected visual acuity; CRT, central retinal thickness; 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.	

10.2.7 The data abstraction strategy.

One reviewer extracted pre-defined data items from included trials. A second reviewer verified the extracted data against the original source document. In case of disagreement between the two reviewers, a third would have extracted data and final results attained by consensus but this was not necessary.

The pre-defined data extraction table comprised data items related to the basic characteristics of each selected study and study results and was developed based on conventions in to systematic reviews; taking into account information of relevance to the treatment of DMO, pre-define data of interest to HTA bodies and specific requirements for subsequent quantitative synthesis.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

10.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Quality assessment of all RCTs presented in section 6.5 is detailed in Table 242.

Table 242: Quality assessment of DEX700 RCTs

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		

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

As per section 10.2.1

10.4.2 The date on which the search was conducted.

As per section 10.2.2

10.4.3 The date span of the search.

As per section 10.2.3

10.4.4 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).

As per section 10.2.4

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

As per section 10.2.5

10.4.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria applied to the search results are presented in Table 243.

Table 243: Eligibility criteria applied to RCT systematic search results to identify the evidence base for MTC

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) • 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 Outcomes (one or more of the following) • Proportion of patients achieving at least a 10 letter gain from baseline at 12 months • Proportion of patients achieving at least a 10 letter loss from baseline at 12 months 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 Comparators • Other active therapy Outcomes • Non-vision or anatomical related efficacy measures Study design • Prospective non-RCTs • Single arm trials • Observational studies Study duration • <6 months (24 weeks)
Key: BCVA, best corrected visual acuity; CRT, central retinal thickness; 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.	

10.4.7 The data abstraction strategy.

As per section 10.2.7

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

Quality assessment of RCTs presented in section 6.7 that are not included in quality assessment presented in section 10.3.1 is detailed in Table X.

Table 244: Quality assessment of comparator RCTs

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		

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Electronic databases presented in Table 245 were searched.

Table 245: Electronic databases searched to identify the RCT clinical evidence base

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

10.6.2 The date on which the search was conducted.

All searches were conducted on 18th July 2014.

10.6.3 The date span of the search.

No date limits were applied. Coverage of each database is presented in Table 245.

10.6.4 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).

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

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

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

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+")

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Additional searches were conducted in clinicaltrials.gov along with the following conference proceedings:

- 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)

10.6.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria applied to the search results are presented in Table 246.

Table 246: Eligibility criteria applied to systematic search results identifying the non-RCT clinical evidence

Inclusion criteria	Exclusion criteria
Population • Adult • Unilateral or bilateral DMO associated to DM • Pre-treated or treatment-naïve Intervention • Intravitreal dexamethasone 700ug • 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 • Prospective non-RCTs • Single arm trials • Observational studies Study duration • ≥6 months (24 weeks)	Population • Paediatric • Diabetic retinopathy patients without associated DMO • Macular oedema not associated to DM • DMO subgroup of <5 patients Interventions • Laser photocoagulation • Anti-VEGF therapy • Non-dexamethasone corticosteroids • Local corticosteroids Outcomes • Non-vision or anatomical related efficacy measures Study design • Randomised controlled trials • Case reports • Case series with <5 patients Study duration • <6 months (24 weeks)
Key: BCVA, best corrected visual acuity; CRT, central retinal thickness; 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.	

10.6.7 The data abstraction strategy.

One reviewer extracted top line data items from included trials. A second reviewer verified the extracted data against the original source document when summarising the evidence base. In case of disagreement between the two reviewers, a third would have extracted data and final results attained by consensus but this was not necessary.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Quality assessment of non-RCTs presented in section 6.8 is presented in Table X.

Table 247: Quality assessment of DEX700 non-RCTs

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

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

As per section 10.2.1

10.8.2 The date on which the search was conducted.

As per section 10.2.2

10.8.3 The date span of the search.

As per section 10.2.3

10.8.4 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).

As per section 10.2.4

10.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

As per section 10.2.5

10.8.6 The inclusion and exclusion criteria.

As per section 10.2.6

10.8.7 The data abstraction strategy.

As per section 10.2.7

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

As per section 10.3.1

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The databases searched, service provider used and coverage are presented in Table 248 for the initial review and Table 249 for the updated review.

Table 248: Summary of databases searched – initial searches

Database/website		Provider/Interface	Coverage
	Medline and Medline in Process & Other Non-Indexed citations	Ovid	1948-present
	Embase	Ovid	1974-Febuary 21st
	Cochrane library: NHS EED	Wiley Interscience	1995-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
	EconLit	Ovid	1886 to January 2014

Table 249: Summary of databases searched – updated searches

Database/website		Provider/Interface	Coverage
	Medline and Medline in Process & Other Non-Indexed citations	Ovid	1948-present
	Embase	Ovid	1974-July 16th
	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
	EconLit	Ovid	1886 to January 2014

10.10.2 The date on which the search was conducted.

Response

10.10.3 The date span of the search.

Response

10.10.4 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).

The search terms used are detailed below.

STRATEGIES FOR THE COST EFFECTIVENESS OF DEX700 OR ALTERNATIVE THERAPIES FOR THE TREATMENT OR DIABETIC MACULAR OEDEMA (DMO) IN PATIENTS WITH DM

Medline and Medline in Process & Other Non-Indexed citations: Ovid. 1946 to Present
24th February 2014

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

Embase: Ovid.
24th February 2014

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	

Cochrane Library: Wiley Interscience.
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
24th February 2014

#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

CINAHL: EBSCO.
24th February 2014

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+")

EconLit: Ovid.
24th February 2014

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

The search terms used for the search updates are detailed below.

STRATEGIES FOR THE COST EFFECTIVENESS OF OZURDEX OR ALTERNATIVE THERAPIES FOR THE TREATMENT OR DIABETIC MACULAR OEDEMA (DMO) IN PATIENTS WITH DM

Medline and Medline in Process & Other Non-Indexed citations: Ovid.
1946 to Present
17th July 2014

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. 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

63. limit 62 to yr="2014 -Current"

Embase: Ovid.
17th July 2014

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	
59. limit 58 to yr="2014 -Current"	

Cochrane Library: Wiley Interscience.
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
17th July 2014

#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 Publication Year from 2014 to 2014

CINAHL: EBSCO.
17th July 2014

S54	S37 AND S53 Limiters - Published Date: 20140101-
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	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+")

EconLit: Ovid.
17th July 2014

1. dexamethasone.tw.
2. ozurdex.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

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Additional searches for relevant NICE guidance was also conducted.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

	Study name Pershing *et al.*[227] (2014)

Study question	Grade (yes/no/not clear/N/A)	Comments
Study design		
1. Was the research question stated?	No	No clear question stated
2. Was the economic importance of the research question stated?	N/A	No question stated
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Societal perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Available treatments in US plus natural history to represent undiagnosed DMO
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	No	Not stated explicitly; implied cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Key clinical trials were referenced
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	Based on multiple studies
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	None reported
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	ICER: cost per QALY gained
12. Were the methods used to value health states and other benefits stated?	Yes	Linear regression modelling of time-trade off utilities for patients across a spectrum of eye diseases

13. Were the details of the subjects from whom valuations were obtained given?	No	Not stated explicitly, references to original study is provided
14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes/No	Unit cost sources given, quantities not given
18. Were currency and price data recorded?	Yes	2010 US$
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Consumer Price Index deflators
20. Were details of any model used given?	Yes	Markov model, 6 vision related health states, on/off treatment.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	Yes	3% annually
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Confidence intervals and distribution for sensitivity analysis provided for uncertain parameters
27. Was the approach to sensitivity analysis described?	Yes	Deterministic and probabilistic
28. Was the choice of variables for sensitivity analysis justified?	No	

29. Were the ranges over which the parameters were varied stated?	Yes	Confidence intervals
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	N/A	No question stated
34. Did conclusions follow from the data reported?	Yes	Final paragraph provides conclusions
35. Were conclusions accompanied by the appropriate caveats?	Yes	Study limited by outcomes for strategies obtained from different publications
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Key: DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; US, United States.		

	Study name: Stein *et al.*[228] (2013)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Compared cost-effectiveness of several different treatment options for patients with newly diagnosed CSDMO
2. Was the economic importance of the research question stated?	Yes	Over $1.6 billion spent annually on ranibizumab which is 7x more expensive than bevacizumab, therefore rigorous cost-effectiveness analysis important to policymakers seeking cost savings in the US health care system
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Policymaker in US health care system
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	DRCR.net trial
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	None included

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	ICER and NMB
12. Were the methods used to value health states and other benefits stated?	Yes	Utility scores from Brown *et al*., 2003
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	2011 US$
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Markov model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Standard method used in general health technology assessments, has been used in prior cost-effectiveness analyses for CSDMO
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	25 years (approximately life time)
23. Was the discount rate stated?	Yes	3% per year
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	

27. Was the approach to sensitivity analysis described?	Yes	One-way, 2-way, scenario, probabilistic sensitivity analyses
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	Ranibizumab only cost-effective for those willing to pay at least $71,271 per QALY, bevacizumab cost-effective for those willing to pay at least $11,138 per QALY
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations section provided
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Key: CSDMO, clinically significant diabetic macular oedema; DRCR.net, Diabetic Retinopathy Clinical Research Network; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year; US, United States		

	Study name: Dewan *et al.*[205] (2012)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Economic evaluation based on PROTOCOL I to provide direction to policy makers considering how to best incorporate the study's results into clinical practice
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Payer perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Trial comparators were used to allow incorporation of results into practice
5. Were the alternatives being compared clearly described?	No	Reference to trial provided but not clearly defined within publication.
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	PROTOCOL I
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	References PROTOCOL I but does not describe it in detail
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	No evidence synthesis was performed
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	ICER (cost per VA letter gained)

12. Were the methods used to value health states and other benefits stated?	N/A	No health states, benefits simply VA letters gained
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	2010 Medicare allowable charges, quantities from PROTOCOL I
18. Were currency and price data recorded?	Yes	2010 US$
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	Markov model using microsimulation
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	104 weeks
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	Univariate

28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	33% to 300%
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Key: ICER, incremental cost-effectiveness ratio; US, United States; VA, visual acuity		

	Study name: Mitchell *et al.*[44] (2012)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Evaluate the cost-effectiveness of ranibizumab from a UK payer perspective when used as a monotherapy or in combination with laser compared with laser alone
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	UK payer
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Laser current standard of care
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	RESTORE and assumptions from other trials
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	RESTORE study summarised sufficiently
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	ICER (incremental cost per QALY gained)

12. Were the methods used to value health states and other benefits stated?	Yes	Derived from RESTORE trial EQ-5D data
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Patients in RESTORE trial
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Unit cost details explained, assumptions noted
18. Were currency and price data recorded?	Yes	2010 UK£
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Hospital and Community Health Services index
20. Were details of any model used given?	Yes	Markov model described
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	15 years
23. Was the discount rate stated?	Yes	3.5% per year
24. Was the choice of rate justified?	Yes	Consistent with NICE reference case (UK standard)
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	Univariate and probabilistic (PSA)

28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	Univariate ranges stated. PSA in supplementary information.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	States limitations of analysis
36. Were generalizability issues addressed?	Yes	Excluded some subgroups from trials
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Key: EQ-5D, EuroQol 5 dimension health questionnaire; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; UK, United Kingdom		

	Study name: Smiddy *et al.*[229] (2012)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Assess cost-effectiveness of specific clinically relevant situations involving subsets of patients with DMO
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	No	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Index study for each treatment
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	None included
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	US Dollars per line saved; US Dollars per QALY

12. Were the methods used to value health states and other benefits stated?	Yes	QALYs calculated as 0.03 QALYs per incremental line of vision gained
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	Numbers of follow-up visits, OCT scans, FA and treatments needed were given
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Lower visit schedule than in trials to mimic actual use, unit costs from Medicare-allowable costs
18. Were currency and price data recorded?	Yes	2011 US$
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	N/A	No model used
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	1 year costs; benefits at 1 year assumed durable to lifetime
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	N/A	None reported

28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	No comparison made
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Key: DMO, diabetic macular oedema; QALY, quality-adjusted life year; US, United States;		

	Study name: Smiddy *et al.*[230] (2011)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Estimate cost per line of vision saved and cost per line-year of vision saved for representative therapeutic regimens
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	Used treatments included in trials; no incremental analysis performed – no direct comparisons
5. Were the alternatives being compared clearly described?	No	
6. Was the form of economic evaluation stated?	Yes	Cost utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Index study for each treatment
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	None included
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Costs, lines of VA gained vs. natural history, QALYs

12. Were the methods used to value health states and other benefits stated?	Yes	0.03 QALYs per line gained vs. natural history
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	Numbers of follow-up visits, OCTs, FAs and treatments reported
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Adapted trial data to non-trial setting
18. Were currency and price data recorded?	Yes	2010 US$
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	N/A	No model used
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Efficacy results at 1 year assumed to be durable to life time; 1 year of costs assumed
23. Was the discount rate stated?	N/A	No discounting
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	None included
27. Was the approach to sensitivity analysis described?	N/A	Not included

28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	All treatments vs. natural history, which is not relevant for current treatment decisions
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Key: QALY, quality-adjusted life year; VA, Visual acuity; OCT, optical coherence tomography ; FA, fluocinolone acetonide intravitreal implant; US, United States;		

	Study name: Sharma et al.[231] (2000)	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Determine the cost-effectiveness of grid laser
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Third-party insurer
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	No	
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	ETDRS study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	None included
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per QALY
12. Were the methods used to value health states and other benefits stated?	Yes	TTO
13. Were the details of the subjects from whom valuations	Yes	100 diabetic retinopathy patients

were obtained given?		
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	1999 US$
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	Decision tree
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	40 years (life time)
23. Was the discount rate stated?	Yes	5%
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	No explanation for lack of discounting in base case
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Not clear	Confidence intervals for VA progression reported
27. Was the approach to sensitivity analysis described?	Yes	Univariate sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	One-way sensitivity analysis table gives range of variation
30. Were relevant alternatives	Yes	

compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Key: ETDRS, Early Treatment of Diabetic Retinopathy Study; QALY, quality-adjusted life year; TTO, time-trade-off ; US, united states; VA, visual acuity		

	Study name: NICE guidance TA301[86]	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Comparison of fluocinolone acetonide intravitreal implant with 'optimised standard of care' in the FAME trials for a cohort of patients with chronic DMO
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	UK NHS
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	FAME trials
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	None reported
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Incremental cost per QALY

12. Were the methods used to value health states and other benefits stated?	Yes	Utility values from Brown *et al*. (2000)
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Better-seeing eye population with age-related macular degeneration
14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Markov model, 14 health states
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	15 years
23. Was the discount rate stated?	Yes	3.5% annually
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	

28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Key: DMO, diabetic macular oedema; QALY, quality-adjusted life year; UK, united Kingdom;		

	Study name: NICE guidance TA274[84]	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Clinical and cost-effectiveness of ranibizumab monotherapy and ranibizumab plus laser photocoagulation compared with laser photocoagulation alone
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	UK NHS
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	RESTORE study, DRCR.net study, epidemiological literature
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Not included
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per QALY gained

12. Were the methods used to value health states and other benefits stated?	Yes	EQ-5D data from RESTORE
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Patients in RESTORE
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	Numbers of treatments and visits reported
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	2009 UK£
19. Were details of price adjustments for inflation or currency conversion given?	Not clear	States “costs updated of adjusted for inflation as appropriate” but does not provide detail
20. Were details of any model used given?	Yes	Markov model with 3-monthly cycles, 8 health states of 10-letter categories between 75 and 36 letters
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	15 years
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	

27. Was the approach to sensitivity analysis described?	Yes	Deterministic sensitivity analyses, probabilistic sensitivity analyses, subgroup analyses
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Key: DRCR.net, Diabetic Retinopathy Clinical Research Network; EQ-5D, EuroQol-five dimensions questionnaire; QALY, quality-adjusted life year; UK, united Kingdom;		

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline

- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

The databases searched, service provider used and coverage are presented in Table 250 for the initial review and Table 251 for the updated searches.

Table 250: Summary of databases searched – initial searches

Database/website		Provider/Interface	Coverage
	Medline and Medline in Process & Other Non-Indexed citations	Ovid	1948-present
	Embase	Ovid	1974-Febuary 21st
	Cochrane library: NHS EED	Wiley Interscience	1995-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
	EconLit	Ovid	1886 to January 2014

Table 251: Summary of databases searched – updated searches

Database/website		Provider/Interface	Coverage
	Medline and Medline in Process & Other Non-Indexed citations	Ovid	1948-present
	Embase	Ovid	1974-July 16th
	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
	EconLit	Ovid	1886 to January 2014

10.12.2 The date on which the search was conducted.

Initial searches were conducted on 24 February 2014. Updated searches were conducted on 17 July 2014.

10.12.3 The date span of the search.

No date limits were applied to the initial searches, therefore the date span of the search is as per the coverage column of Table 250 in section 10.12.1. For the updated searches a date limit of 2014 was applied.

10.12.4 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).

The search terms used for the initial searches are detailed below.

UTILITY SEARCHES FOR DIABETIC MACULAR OEDEMA (DMO) IN PATIENTS WITH DM

Medline and Medline in Process & Other Non-Indexed citations: Ovid. 1946 to Present
24th February 2014

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

Embase: Ovid.
24th February 2014

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

Cochrane Library: Wiley Interscience.
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
24th February 2014

#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: [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
#22	thirty six:ti,ab,kw
#23	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
#24	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
#25	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
#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
#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

CINAHL: EBSCO.
24th February 2014

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+")

EconLit: Ovid.
24th February 2014

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

The search terms used for the search updates are detailed below.

UTILITY SEARCHES FOR DIABETIC MACULAR OEDEMA (DMO) IN PATIENTS WITH DM

Medline and Medline in Process & Other Non-Indexed citations: Ovid.
1946 to Present
17th July 2014

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 hrqol 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
48. limit 47 to yr="2014 -Current"

Embase: Ovid.
17th July 2014

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 hrqol 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
47. limit 46 to yr="2014 -Current"

Cochrane Library: Wiley Interscience.
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
17th July 2014

#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: [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
#22	thirty six:ti,ab,kw
#23	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
#24	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
#25	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
#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
#28	5d:ti,ab,kw
#29	hql or hqol or h qol or hrqol 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 Publication Year from 2014 to 2014

CINAHL: EBSCO.
17th July 2014

S45	S9 AND S44 Limiters - Published Date: 20140101-
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 hrqol or hr qol) or AB (hql or hqol or h qol or hrqol 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+")

EconLit: Ovid.
17th July 2014

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

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Additional searches for relevant NICE guidance was also conducted.

10.12.6 The inclusion and exclusion criteria.

See section 7.4.5.

10.12.7 The data abstraction strategy.

All relevant articles were retrieved in full text, read and data extracted into the requested template.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase

- Medline (R) In-Process
- NHS EED
- EconLIT.

The databases searched, service provider used and coverage are presented in Table 252 for the initial review and Table 253 for the updated searches.

Table 252: Summary of databases searched – initial searches

Database/website		Provider/Interface	Coverage
1.	Medline and Medline in Process & Other Non-Indexed citations	Ovid	1948-present
2.	Embase	Ovid	1974-Febuary 21st
3.	Cochrane library: NHS EED	Wiley Interscience	1995-present
4.	Health Technology Assessment Database (HTA)	Wiley Interscience	1995-present
5.	Database of Abstracts of Review of Effects (DARE)	Wiley Interscience	1995-present
6.	Cumulative Index to Nursing and Allied Health Literature (CINAHL)	EBSCO	1982-present
7.	EconLit	Ovid	1886 to January 2014

Table 253: Summary of databases searched – updated searches

Database/website		Provider/Interface	Coverage
	Medline and Medline in Process & Other Non-Indexed citations	Ovid	1948-present
	Embase	Ovid	1974-July 16th
	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
	EconLit	Ovid	1886 to January 2014

10.13.2 The date on which the search was conducted.

Searches were conducted on 24 February 2014. Updated searches were conducted on 17 July 2014.

10.13.3 The date span of the search.

No date limits were applied to the initial searches, therefore the date span of the search is as per the coverage column of Table 252 in section 10.12.1. For the updated searches a date limit of 2014 was applied.

10.13.4 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).

The search terms used for the initial searches are detailed below.

COST AND RESOURCE VALUES RELATING TO DIABETIC MACULAR OEDEMA (DMO) IN PATIENTS WITH DM

Medline and Medline in Process & Other Non-Indexed citations: **Ovid. 1946 to Present**
24th February 2014

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

Embase: Ovid.
24th February 2014

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

Cochrane Library: Wiley Interscience.
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
24th February 2014

#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

CINAHL: EBSCO.
24th February 2014

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+")

EconLit: Ovid.
24th February 2014

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

The search terms used for the search updates are detailed below.

COST AND RESOURCE VALUES RELATING TO DIABETIC MACULAR OEDEMA (DMO) IN PATIENTS WITH DM

Medline and Medline in Process & Other Non-Indexed citations: Ovid.
1946 to Present
17th July 2014

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
37. limit 36 to yr="2014 -Current"

Embase: Ovid.
17th July 2014

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
31. limit 30 to yr="2014 -Current"

Cochrane Library: Wiley Interscience.
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
17th July 2014

#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 Publication Year from 2014 to 2014

CINAHL: EBSCO.
17th July 2014

S28	S9 AND S27 Limiters - Published Date: 20140101-
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+")

EconLit: Ovid.
17th July 2014

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

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Additional searches for relevant NICE guidance were also conducted.

10.13.6 The inclusion and exclusion criteria.

See section 7.5.3.

10.13.7 The data abstraction strategy.

All relevant articles were retrieved in full text, read and data extracted into the requested template.

10.14 Appendix 14: Key opinion leader input

10.14.1 Advisory board meeting 12th December 2013.

The advisory board meeting was convened on 12th December 2013 to provide advice on the upcoming submission to NICE for DEX700 for the treatment of DMO. The meeting included 7 clinical key opinion leaders from across England in addition to representatives from Allergan and BresMed. The agenda for the meeting is provided in Table 254.

Table 254: Agenda: Advisory board meeting 12th December 2013

Time	Topic
09.45 -10.00	Arrivals + tea and coffee
10.00-10.15	Introductions and meeting objectives
10.15-11.00	Current challenges for the optimal management of DMO
11.00 -11.15	Tea and coffee break
11.15 – 11.30	Overview of DEX700 cost effectiveness model and associated clinical assumptions
11.30 – 12.30	Validation of DEX700 clinical assumptions within cost effectiveness model
12.30 – 13.00	Lunch (buffet style)
13.00 – 14.00	DEX700 in DMO – Phase III data presentation + Q&A
14.00 – 15.00	Strengths and weakness associated with the DEX700 Phase III data
15.00-15.15	Tea and coffee break
15.15 – 15.50	Preparing for a successful NICE submission
15.50 – 16.00	Summary and close

The objectives of the meeting were

- To understand the current clinical practice for the management of DMO, challenges faced as part of this and resulting unmet need for patients
- To validate key clinical assumptions within the DEX700 cost-effectiveness model
- To present and take feedback on Phase III clinical data for DEX700 (MEAD studies)

Current clinical practice for DMO

The clinical pathway for DMO that was presented at the NICE scoping meeting was presented for comment and feedback.

Attendees recognised the pathway but considered it basic with no explicit reference to criteria relating to central retinal thickness and no clear differentiation for which patients should receive fluocinolone acetonide as

there is no clear definition of “insufficiently responsive”. Attendees felt that the assumption within the pathway that anti-VEGF would be given in combination with laser was not necessarily ideal for the patient, agreeing that this should be depicted as “anti-VEGF and/or laser photocoagulation”. All attendees agreed that the management of patients with DMO is dependent on the individual patient who may have one or both eyes affected.

An unmet need was identified for patients in England who do not meet the criteria for anti-VEGF therapy based on central retinal thickness.

Impact of intravitreal injections on service capacity

The majority of attendees agreed that the lack of capacity within the local service was a significant problem and an on-going challenge. The monthly injections and regular monitoring appointments that are part of the ranibizumab regimen for example are considered ‘a large burden’ to patients and to those involved in the planning and delivering of ophthalmology services. Qualified personnel are required to deliver and administer the procedure but departments are ‘chronically understaffed’. Consequently, waiting times have increased in some departments that cannot provide appointments according to the treatment or monitoring schedule.

Attendees noted that if the required treatment regimen cannot be implemented the full potential/effect of the therapy is unlikely to be realised, leading to a waste of budget and poor patient experience/outcomes.

It was also noted that patients with macular thickening that do not meet the criteria for ranibizumab set by NICE could receive unlicensed medications such as bevacizumab or triamcinolone, which have a detrimental impact on capacity. The average consultation for example can take 45 minutes or more due to the additional time required to ensure the patient consents to treatment and understands why it is suitable for them (despite the packaging which states the product should not to be used in eyes).

Validation of key clinical assumptions within the economic model

A brief overview of the structure of the *de novo* economic model was presented to attendees for comment. The model structure was well received,

and attendees were pleased that bilateral DMO had been included as an explicit option.

This was followed by presentation and discussion of four key clinical assumptions within the model

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

Attendees felt that there were three key reasons for discontinuation:

- Lack of response, or loss of efficacy
- Adverse event(s)
- Patient (or physician) choice

Attendees felt that in practice, the initial therapy and reason for discontinuation would dictate the next line of treatment. If a patient discontinues treatment due to a loss of efficacy, a new class of treatment will likely be prescribed, with preference for pharmacological treatment over laser photocoagulation. However, the second-line treatment may not be as effective as if it had been used first line. The choice of therapy could also depend on patient characteristics such as age and also the quality of vision. For example there is a reluctance to prescribe steroids in younger patients or patients with a family history of glaucoma due to the potential side effects.

If a patient discontinues due to an adverse event, a new class of treatment would be also likely be prescribed with consideration of the nature of the adverse event. The efficacy of the second-line treatment in this instance would be expected to be similar to the efficacy of the treatment if it had been given first-line. In addition, if a patient chooses to discontinue a particular treatment, the second-line treatment would also be expected to be as effective as if it had been used first-line. Whilst patients are most concerned with the burden of the regimen and potential side effects, they are often heavily influenced by their consultant. Attendees confirmed that patients may not necessarily/always receive another treatment after discontinuation.

Assumption 2: A maximum of 5 years of treatment has been programmed in the model, with patients receiving no treatment beyond this.

A proportion of attendees felt it would be reasonable to expect some patients to still be on treatment after 5 years (although there is uncertainty regarding how well the patient would be doing or what exactly would be happening to them). This was justified by their experience of treating patients for wet age-related macular degeneration and their perception of DM patients who have long-term problems and treatment needs.

Conversely other attendees felt that there is nothing to suggest this would be the case in DMO. Furthermore, some attendees suggested it is likely patients would stop treatment before 5 years if a patient had chronic unresponsive DMO. Attendees agreed that there is a large number of reasons why a patient may stop treatment before 5 years and these will often be 'patient specific' or 'locally variable'.

Assumption 3: If a patient develops DMO in their fellow eye the second eye is treated in line with the remaining schedule of treatment for the initially affected eye. The efficacy of treatment is assumed equal in both eyes.

Attendees felt that each eye should be judged individually and differences in treatment regimens need to be accounted for i.e. the 2nd eye needs to incorporate the intensive treatment period in year one (as per the first eye) rather than following the remaining schedule of the first eye.

It is noted that in response to this feedback the assumption was changed and is now as described in section 7.3.2.

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.

DEX700 Phase III clinical trial data

Key data from the recently completed Phase III MEAD studies were presented to attendees. Attendees asked clarifying questions about the data presented and the data were discussed.

With regard to safety outcomes the attendees noted that IOP elevation would be acceptable if is transient and manageable and does not require increased monitoring appointments. The attendees also felt that the ITT data includes patients who received cataract surgery and therefore this dilutes the positive effect of DEX700 on BCVA outcomes in an AUC analysis.

10.14.2 Advisory board meeting 15th April 2014.

The advisory board meeting was convened on 15th April 2014 to provide advice on the upcoming submission to NICE for DEX700 for the treatment of DMO. The meeting included 4 clinical key opinion leaders from across England (including some who attended both advisory board meetings) and one health economic advisor in addition to representatives from Allergan and BresMed. The agenda for the meeting is provided in Table 255.

Table 255: Agenda: Advisory board meeting 15th April 2014

Time	Topic
09.45 - 10.00	Arrivals + tea and coffee
10.00 - 10.15	Introductions and meeting objectives
10.15 - 11.00	NICE submission timelines and draft Scope
11.00 - 11.15	Tea and coffee break
11:15 - 11:30	Economic modelling recap and update
11:30 - 12:40	Understanding the treatment algorithm for different patient populations
12.40 - 13.10	Lunch
13:10 - 14:20	Understanding the treatment algorithm for different patient populations (continued)
14:20 - 15:00	Modelling the management of treatment related adverse events
15.00 - 15.15	Tea and coffee break
15.15 - 15.45	Preparing for a successful NICE submission
15:45 - 15:50	Availability for a further advisory board meeting in July
15.50 - 16.00	Summary and close

The objectives of the meeting were

- Feedback on the revised draft NICE scope
- Validation of changes to the *de novo* economic model
- To understand the specific treatment pathways for different patient populations
- To understand the management of adverse events of treatments for DMO

Draft NICE scope feedback

The draft pre-invitation scope was presented to attendees. Specific reference was made to the wording for the inclusion of bevacizumab “for patients for whom ranibizumab and fluocinolone acetonide are unsuitable”, asking clinical attendees how they would define this population. Attendees suggested this could be based on NICE guidance and restrictions placed on the use of these treatments to identify patients for whom there is no other option available, e.g.

phakic patients with DMO and a central retinal thickness of less than 400 microns. One attendee noted that a main problem they experience in their practice is that very few patients go straight from screening to clinics and have a retinal thickness of more than 400 microns. This leaves very few treatment options, clinicians can wait and see if the retina thickness increases to 400 microns or more, in which case ranibizumab is used, or treat the patient with laser or bevacizumab if it is available.

The clinical attendees were asked if they would follow a path of watch and wait, and if so how long do they wait? Attendees commented that the path of watch and wait is only generally followed if the vision is not affected. Traditionally DMO treatment is thought of as a means to stop progression rather than gaining back vision that has been lost. It was also suggested that watch and wait has been shown to be a good strategy as the ETDRS study showed that 50% of patients had reasonable vision after 3 years with no treatment. The attendees were asked how often patients would be monitored if they were on a strategy of watch and wait, attendees advised that the Royal College of Ophthalmologists recommends monitoring once every 4 months.

Validation of updated economic modelling clinical assumptions

The model structure was reviewed briefly and updates made to the economic model assumptions following the previous advisory board meeting were presented.

Assumption 1: Fellow eye involvement

Based on feedback from the previous advisory board meeting, a change to the assumptions regarding fellow eye involvement was presented. In the revised model unilateral patients are only allowed to have fellow eye involvement within the first 2 years. When a patient develops DMO in the second eye the model assumes that both eyes are treated with the same initial intensity; the first eye continues as it was and the second eye is treated for up to a maximum of 5 years from the point of development of DMO. To allow this to be modelled, fellow eye involvement was limited to the end of Year 1 or Year 2 due to the need for further health states to monitor the time of development of DMO given the memoryless property of the model. This

was further supported by the MEAD data, which demonstrated a higher rate of fellow eye involvement in Years 1 and 2 compared with Year 3.

Attendees felt that assuming development of fellow eye DMO in the first 2 years only is acceptable; there is no data beyond this as most studies focus on one eye, which makes it difficult to argue against the 2 years currently used. Attendees also noted that after 3 years it is expected that the one of the eyes (not specifically the second eye) will have settled so the amount of bilateral patients should become approximately constant.

Treatment algorithm

Given that at the time of the advisory board meeting the terms of the marketing authorisation for DEX700 had not been confirmed, the attendees were asked to discuss the treatment algorithm for a number of possible populations of DMO patients, to aid the understanding of the relevant comparators and treatment pathways for different patient groups.

Management of adverse events of treatments for DMO

The clinical advisors were asked how they would typically manage adverse events of treatments for DMO.

Raised intraocular pressure

Feedback was that, in general, patients would be started on medical treatment if they reached an IOP ≥30mmHg, and that treatment would continue if the pressure was consistently high at future visits.

The clinicians were asked what treatments would be used. It was indicated that latanoprost followed by Cosopt® would typically be prescribed. The economic advisor indicated that data on drug usage may provide useful information. However, adverse events are rarely a key driver of economic results. This level of complexity in the costing of adverse events may be overly-complicated for something that is not likely to influence the results.

The clinicians were asked what would be the average duration of medication for raised IOP resulting from intravitreal injections with DEX700. The response was that if patients were to be re-treated they would remain on the pressure-lowering medication.

Attendees indicated that, regardless of treatment for DMO, patients with IOP ≥40mmHg would be considered for surgical intervention, which would likely be a Trabeculectomy.

Endophthalmitis

Feedback was that all patients would receive a vitreous biopsy or a vitrectomy, accompanied by intravitreal antibiotics.

10.14.3 Clinician interviews July-August 2014.

Following the advisory board meetings, further questions were identified as relevant to the submission process that required clinical input. Two clinicians who were in attendance at both advisory board meetings agreed to be interviewed to gain answers to these questions. A first set of interviews were conducted individually on 2nd and 3rd July 2014 and the questions were sent out to the clinicians in advance of this. A second meeting was held with both clinicians simultaneously on 5th August 2014 where some further guidance and clarification was provided.

The questions asked and answers provided in the first set of interviews (2nd - 3rd July 2014) are detailed below.

Considering the following medical appointments/tests for DMO patients

- Routine consultation appointment
- OCT
- Fluorescein angiography
- Ophthalmoscopy
- Tonometry

a. Would you expect any of these to be required equally for all DMO patients regardless of treatment received?

Clinician 1:

An IOP check (tonometry) is a minor part of a routine appointment.

Would expect monthly monitoring for ranibizumab, for steroid treatments would monitor 3-4 months post injection, for DEX700 this would be to determine whether re-treatment is needed.

Clinician 2:

With the exception of fluorescein angiography, which would be given at baseline only for treated patients, all of the resources listed would be given at all monitoring appointments.

DEX700 patients would additionally require tonometry (IOP check) every 8 weeks if they have been treated; if they are not re-treated this would revert back to usual care monitoring of every 4 months.

b. Which (if any) may be “grouped” into one appointment? (i.e. can we assume one visit with one cost incorporating a combination of tests and/or monitoring?)

Clinician 1:

Routine consultations, OCT, ophthalmoscopy and tonometry could all occur within one visit.

Clinician 2:

Routine consultations, OCT, ophthalmoscopy and tonometry could all occur within one visit; however, DEX700 patients may need additional tonometry.

c. Which (if any) can occur as part of a treatment visit? (i.e. can we assume any of these would occur at a treatment visit therefore incur no additional visits or costs unless a patient required more than the number of treatment visits?)

Clinician 1:

60-70% of centres will operate a two-stop system, whereby a patient attends an assessment visit to determine whether they need re-treatment, which will include regular monitoring. If the patient does require treatment this would require a separate appointment for treatment only. This therefore delays the treatment, often into the next month and may limit the capacity of centres to administer monthly injections of ranibizumab.

The remaining centres operate a one-stop system where the patient is referred for re-treatment and seen that day. However, this has large implications for capacity because appointments may need to be kept free. These may never filled or patients may have to wait for a very long time.

Clinician 2:

The cost of monitoring would be a separate cost to the treatment administration visit costs.

2. What dose of bevacizumab is used to treat DMO and is the dosing regimen adopted in line with the recommended regimen for ranibizumab?
    a. i.e. three loading doses with additional treatment administered on an “as needed” basis

Clinician 1:

The dose used is 1.25mg in 0.05ml, and the dosing regimen is in line with that for ranibizumab.

Clinician 2:

The dose used is 1.25mg in 0.05ml, and the dosing regimen is in line with BOLT, which mirrors the dosing regimen for ranibizumab.

3. Is the mETDRS protocol still the most commonly adopted treatment regimen for laser therapy? (i.e. argon green laser applied every 3-4 months on an “as needed” basis)

Clinician 1:

Yes.

Clinician 2:

Yes.

4. Are alternative laser technologies comparable in regard to treatment regimen and clinical efficacy? (e.g. krypton red laser, dye yellow laser, diode laser, sub-threshold micropulse diode laser)

Clinician 1:

There is no RCT evidence available; the only evidence available is from small retrospective studies. Personal preference is for argon green laser, especially if the leakage is outside of the fovea.

Clinician 2:

Krypton red laser and diode laser are not used.

There are no trials to prove that all of the types of laser have equal efficacy, but clinicians generally assume they are equivalent. Dye yellow laser and micropulse diode lasers are thought to be safer for macular use where there is a higher risk of complications when using laser.

5. When treating bilaterally would you treat both eyes in the same visit or require two separate visits?

Clinician 1:

Anti-VEGF treatments may be given at the same visit. Currently steroid treatment would be given at separate visits. However, there is a movement towards administration of steroid in both eyes at the same visit.

Clinician 2:

For anti-VEGF treatments both eyes may be treated in the same visit. Laser would be treated in the same visit. For steroid treatments two treatment visits would usually be required to treat both eyes, due to the risks of increased IOP and the more complex injection procedure, it is necessary to confirm there are no complications before injecting the second eye. The average time between injections in each eye would be two weeks for DEX700, longer for fluocinolone acetonide.

At the follow-up meeting held on 5th August 2014 the clinicians were asked to provide input on a number of points regarding the submission, these are detailed below.

1. Clarification on the population of patients who are considered unsuitable for non-corticosteroid therapies

The clinicians agreed that the following cohorts of patients would be considered unsuitable for non-corticosteroid therapies:

- Patients with centre-involved macular oedema and CRT <400µm with associated vision loss
- Patients with high-risk comorbidities
  - Patients with high cardiovascular risk
  - Patients requiring regular dialysis
- Patients unable to attend regular injection appointments
  - Patients that live far away from clinics
  - Working population
- Patients who refuse non-corticosteroid therapies
  - Patients who suffer anxiety associated with frequent anti-VEGF therapy
- Pregnant women
- Patients with prior vitrectomy
- Patients with long-standing cysts

2. Clarification on the number of appointments that would be required for bilateral treatment

The clinicians agreed that bilateral treatment with any treatment may be performed in both eyes in the same day; however this is very much based on clinician preference. In general, the clinicians estimated that bilateral anti-VEGF treatment would be injected into both eyes on the same day around 50% of the time (i.e. an average of 1.5 administration appointments required for bilateral treatment with anti-VEGF). They further advised that bilateral DEX700 treatment would also be administered to both eyes in the same day in some cases, as the new needle for DEX700 means that there is a lower risk of complications of the procedure; but that the proportion of bilateral DEX700 treatments occurring on the same day would be expected to be lower than that for anti-VEGF treatments. It was generally agreed that these estimates are highly uncertain and so sensitivity analyses should be included to address the impact of these uncertainties within the economic model.

10.14.4 Advisory board meeting 5th September 2014.

The advisory board meeting was convened on 5th September 2014 to provide advice on the upcoming submission to NICE for DEX700 for the treatment of DMO, in light of the recent extension to the marketing authorisation. The meeting included 4 clinical key opinion leaders from across England (including one who attended all previous advisory board meetings) in addition to representatives from Allergan and BresMed. The agenda for the meeting is provided in Table 256.

Table 256: Agenda: Advisory board meeting 5th September 2014

Time	Topic
12.00 – 12.20	Arrivals + Lunch
12.20 – 12.30	Introductions and meeting objectives
12.40 – 13.00	NICE submission timelines, Scope & License interpretation
13.00 – 13.30	Ozurdex MEAD Clinical data
13.30 – 14.00	Ranibizumab in DMO - RESPONSE
14.00 – 14.15	Judging response to Ranibizumab in DRCR.net Protocol I
14.15 – 14.30	Proposal of criteria
14.40 – 15.00	Discussion and alignment on proposed criteria
15.00 – 15.40	Review of cases
15.40 – 16.00	Refinement of criteria
16.00	Close

The objectives of the meeting were

- Validation of the populations covered within the license for DEX700 in DMO, including estimation of the proportion of DMO patients who fall into each population
- To reach a consensus on the criteria to identify patients who are “unsuitable” for non-corticosteroid therapy
- To reach a consensus on the criteria to identify “insufficient response” to non-corticosteroid therapy

Prior to the meeting draft criteria were developed following discussions with clinicians.

Validation of populations covered by the license for DEX700 in DMO

The consensus reached in terms of the proportion of DMO patients who met criteria considered to be covered by the license terms for DEX700 in DMO are summarised in Table 257.

Table 257: Summary of population estimates

Population	Percentage estimate of total DMO population	Percentage estimate of total DMO population that would consider treating with DEX700
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 dialysis, prison population	20%	12%
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%
Pseudophakic patients		
Pseudophakic	25%	-

Criteria to identify patients who are "unsuitable" for non-corticosteroid therapy

A list of potential patient groups that were unsuitable for anti-VEGF was presented and discussed:

- Patients with centre-involved macular oedema & CRT <400µm with associated vision loss
    - Note that whilst ~85% of patients present with CRT <400µm in clinical practice since national screening for DR was initiated, not many also have associated visual impairment and thus considered for pharmaceutical treatment
- Patients unable to attend regular appointments (visit schedule and injection burden)
    - Anti-VEGF injection "did not attend" (DNA) rate approximately 20% across clinics. The majority of these are due to the impractical patient burden of monthly injection regimens
- Patients with high risk comorbidities
- Other criteria with smaller patient numbers:
    - Patients that don't meet HTA restrictions or clinical guideline criteria (NICE restrictions on ranibizumab, fluocinolone acetonide)
    - Patients who are pregnant or planning a family
    - Patients with vitrectomised eyes
    - Patients who refuse non corticosteroid because of anxiety associated with frequent injections

Criteria to identify patients who are "insufficiently responsive" to non-corticosteroid therapy

The proposed criteria were presented:

- Despite recent repeated dosing:
    - OCT evidence of any central 5 ETDRS zones > 300 µm due to macular oedema, and
    - Visual impairment due to DMO, and
    - Potential for visual improvement or stabilisation in oedema can be improved

Four case studies were presented, and the above draft criteria were tested against them to see how well the above statement held up.

The criteria were then refined:

- Repeat dosing:
    - Six injections was suggested as the minimum before moving on to steroid treatment. The attendees stated it should be a clinical decision at what point to move on to a follow-on therapy and adding a specific number would limit freedom
- OCT evidence of any central 5 ETDRS zones > 300 µm due to macular oedema
    - Attendees discussed and debated how many zones would be necessary. Some attendees confirmed that they just concentrate on the central zone (the centre 1000 µm). “5 central zones” could be changed to “centre involving” to allow a bit more freedom of choice
    - Laser therapy would not tend to be used on the central 5 zones, so keeping this as 5 sections was finally agreed
        - This would be specific to a central retinal thickness of > 300 µm in any of the 5 central zones (not just the central 1000 µm)
        - This would allow treatment of ‘the more difficult patient’ that may have just less than 300 µm in most of these zones, but in the opinion of the clinician, may benefit from Ozurdex treatment
- Visual impairment due to DMO
    - There was a suggestion to an extra ‘qualifier’ regarding whether or not the patient reports no benefit
        - It was discussed that if the patient reported no benefit, the clinicians would stop treatment at this point anyway, so would not need to be added into the definition

    - The “visual impairment due to DMO” and “OCT evidence of CRT >300 µm” in the opinion of the clinicians seem to be linked together, and separate from the issue of potential improvement. A decision was agreed to merge these statements
- Potential for visual improvement or stabilisation in oedema can be improved
    - It was agreed that this is dependent on experience of analysing OCT images, and viewing how much ERM is remaining, quality of macular and so on
        - It was decided against defining this too much as clinical judgement is important here
    - The potential for vision to decline if oedema was to worsen was discussed as an additional ‘qualifier’ as there are many patients on treatment that are not improving, but they may worsen if treatment is discontinued
    - After considering the possibility of a patient with visual impairment and retinal thickening but the clinician had no confidence that the macular could recover if oedema was resolved, it was decided to add an “OR” between the two statements

The final consensus statement was:

Response to anti-VEGF can be considered as insufficient if despite recent repeated dosing there is visual impairment due to DMO that is >300 micron in any of the five central ETDRS zones or in the opinion of the treating clinician that there is potential for further visual improvement if oedema can be resolved further by alternative therapies.

10.15 Appendix 15: Supplementary efficacy data

10.15.1 DEX700 transition probability matrices.

The transition probabilities for DEX700 are provided in Table 258 for the mITT population (applied for DMO patients who are considered insufficiently responsive to non-corticosteroid therapy and DMO patients who are considered unsuitable for non-corticosteroid therapy) and Table 259 for the pseudophakic population.

Table 258: Transition probability matrices, DEX700 treatment arm; mITT population

Month 0-3		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 3-6		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 6-9		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 9-12		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 12-15		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 15-18		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 18-21		To					
		HS1	HS2	HS3	HS4	HS5	HS6
r o	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 21-24		To					
		HS1	HS2	HS3	HS4	HS5	HS6
r o	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 24-27		To					
		HS1	HS2	HS3	HS4	HS5	HS6
r o	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 27-30							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 30-33							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 33-36							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: HS, health state.

Source: Allergan Mead Data on File[194]

Table 259: Transition probability matrices, DEX700 treatment arm; pseudophakic subgroup

Month 0-3							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 3-6							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 6-9							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 9-12							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 12-15							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 15-18							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 18-21							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 21-24							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 24-27							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 27-30							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 30-33							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month 33-36							
		To					
		HS1	HS2	HS3	HS4	HS5	HS6
From	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: HS, health state.

Source: Allergan Mead Data on File[194]

10.16 Appendix 16: Disaggregated discontinuation data

Table 260 and Table 261 detail the proportion of patients who discontinue from treatment during each year, due to adverse events and other non-efficacy related reasons or due to lack or loss of efficacy of treatment. This is calculated using the proportion of patients remaining on treatment from the previous cycle.

Table 260: Discontinuation; All DMO (DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy)

Treatment	Discontinuation due to adverse events and other non-efficacy related reasons			Discontinuation due to lack (or loss) of efficacy			Reference
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	
DEX700 PRN	5.19%	9.56%	6.15%	3.46%	5.79%	4.98%	MEAD[194]
Watch and wait	10.86%†	8.33%†	3.50%†	15.85%	19.12%	7.85%	MEAD[194] (note no discontinuation due to adverse events and other reasons from watch and wait in the base case)
Fluocinolone acetonide†	0.00%	20.00%	7.20%	0.00%	0.00%	0.00%	FAME[163, 173, 198] (note rates reported at Year 2 and 3 only, reasons not clearly specified so assumed due to other reasons)

Key: DEX, dexamethasone; DMO, diabetic macular oedema; PRN, pro re nata.

Notes: *DMO patients who are insufficiently responsive to non-corticosteroid therapy only; †scenario analysis only.

Table 261: Discontinuation; DMO patients who are pseudophakic

Treatment	Discontinuation due to adverse events and other non-efficacy related reasons			Discontinuation due to lack (or loss) of efficacy			Reference
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	

DEX700 PRN	5.88%	11.76%	5.93%	4.71%	9.41%	5.88%	MEAD[194]
Watch and wait**	0.00%	0.00%	0.00%	13.60%	15.22%	2.77%	MEAD[194] (note no discontinuation due to adverse events and other reasons from watch and wait in the base case)
Ranibizumab	9.48%	5.40%	3.24%	0.86%	0.00%	0.00%	RESTORE[100, 114, 199]* (note no discontinuation due to lack or loss or efficacy during Year 2 or 3)
Bevacizumab**	0.00%	14.29%	6.12%	0.00%	0.00%	0.00%	BOLT[99, 200] to Year 2 then extrapolated* (note no discontinuation during Year 1; no reason for discontinuation specified so all assumed due to other reasons)
Laser**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Allergan analysis of PROTOCOL I[201] to Year 2 then extrapolated*† (note no discontinuation due to adverse events and other reasons during Year 1)

Key: DEX, dexamethasone; DMO, diabetic macular oedema, PRN, *pro re nata*.

Notes: *Based on the ITT population in the absence of published data for pseudophakic patients; †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; **Scenario analysis only.

10.17 Appendix 17: Scenario analysis: Additional mortality due to severe vision loss

If increased mortality is assumed for patients in whom the BSE falls into the severe vision loss health state (Health State 1, BCVA ≤ 38 letters, considered clinical blindness), an increased mortality rate is applied to Health State 1 in the BSE of 1.54 times that of the general population.[77] To ensure that the total mortality experienced by the patient is equal across both eyes (so that both eyes carry equal weight and mortality is applied equally across the BSE and the WSE), an adjustment is applied to the mortality for the proportion of patients whose WSE falls into in Health State 1.

The adjustment is applied 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 is therefore calculated for each type of patient (on initial treatment versus discontinued from initial treatment and unilateral versus bilateral DMO)

10.18 Appendix 18: Supplemental utility data

10.18.1 Association between VFQ-UI and BCVA

Figure 92 and Figure 93 present the association between VFQ-UI and BCVA in the BSE and BCVA in the WSE at baseline in the form of a scatter-plot with fitted line. As expected, at baseline the associations between both VFQ-UI score and BCVA in the BSE and BCVA in the WSE are positive and are statistically significant; however there is a large amount of variation in the estimates. A clear ceiling and floor effect is observed.

[redacted] **Scatterplot of Baseline VFQ-UI Score vs BCVA in the BSE**

[redacted]

Key: BCVA, best-corrected visual acuity; BSE, better-seeing eye; VFQ-UI, visual functioning questionnaire utility index.
Source: Allergan MEAD Data on File[194]

[redacted] **Scatterplot of Baseline VFQ-UI Score vs BCVA in the WSE**

[redacted]

Key: BCVA, best-corrected visual acuity; VFQ-UI, visual functioning questionnaire utility index; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File[194]

Figure 94 and Figure 95 present the association between VFQ-UI and BCVA in the BSE and BCVA in the WSE in the pooled visits in the form of a scatter-plot with fitted line. As expected, at baseline the associations between both VFQ-UI score and BCVA in the BSE and BCVA in the WSE are positive and are statistically significant; however there is a large amount of variation in the estimates. A clear ceiling and floor effect is observed.

[redacted] **Scatterplot of VFQ-UI Score vs BCVA in the BSE in Pooled Visits**

[redacted]

Key: BCVA, best-corrected visual acuity; BSE, better-seeing eye; VFQ-UI, visual functioning questionnaire utility index.
Source: Allergan MEAD Data on File[194]

[redacted] **Scatterplot of VFQ-UI Score vs BCVA in the WSE in Pooled Visits**

[redacted]

Key: BCVA, best-corrected visual acuity; VFQ-UI, visual functioning questionnaire utility index; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File[194]

10.18.2 Association between EQ-5D and BCVA

Figure 96 and Figure 97 present the association between EQ-5D and BCVA in the BSE and BCVA in the WSE at baseline in the form of a scatter-plot with fitted line. A clear ceiling effect is demonstrated, with a large number of observed EQ-5D values of 1.

[redacted] **Scatterplot of Baseline EQ-5D Score vs BCVA in the BSE**

[redacted]

Key: BCVA, best-corrected visual acuity; BSE, better-seeing eye; EQ-5D, EuroQol 5-dimension.
Source: Allergan MEAD Data on File[194]

[redacted] **Scatterplot of Baseline EQ-5D Score vs BCVA in the WSE**

[redacted]

Key: BCVA, best-corrected visual acuity; EQ-5D, EuroQol 5-dimension questionnaire; WSE, worse-seeing eye.
Source: Allergan MEAD Data on File[194]

10.18.3 Impact of adverse events on utility

Regression equations were performed to determine the impact of raised IOP (with coefficients for IOP Change ≥10mmHg or IOP-Medication or for IOP ≥30mmHg or IOP-Medication) and of cataract (with coefficients for cataract in the WSE and cataract in the BSE or for cataract surgery) on VFQ-UI score. Each adverse event indicator was recorded at each visit. The results of these regressions are shown in Table 262. No coefficients related to adverse events of treatment were statistically significant at the 5% significance level and all were very small (<0.01). Therefore the impact of adverse events on utility was not modelled.

Table 262: supplementary utility regression equations: Impact of adverse events on VFQ-UI score

Parameters	Number of observations	Mean	SE	P-value
Impact of IOP Change ≥10mmHg or IOP-Medication				
Constant	[redacted]	[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]	[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]	[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]	[redacted]
$Coefficient_{BSE}$		[redacted]	[redacted]	[redacted]
$Coefficient_{WSE}$		[redacted]	[redacted]	[redacted]
$Coefficient_{cataract\ surgery}$		[redacted]	[redacted]	[redacted]

Key: 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

Source: Allergan Mead Data on File[194]

10.19 Appendix 19: Visual Acuity Ranges and Notations (Precision Vision, 2014)

RANGES (ICD-9-CM)		EQUIVALENT NOTATIONS		TRUE SNELLEN FRACTIONS (numerator = test distance)					MAgnification Requirement		Visual Acuity Score (letter count)
		Decimal	US	6.3 m	*6 m (Britain)*	5 m (Europe)	4 m (ETDRS)	1 m (Low Vision)	MAR (1/V)	Log MAR	
(Near-) Normal Vision	Range of Normal Vision	1.6	20/12.5	6.3/4	*6/3.8*	5/3.2	4/2.5	1/0.63	0.63	–0.2	110
		1.25	20/16	6.3/5	*6/4.8*	5/4	4/3	1/0.8	0.8	–0.1	105
		1.0	**20/20**	**6.3/6.3**	***6/6***	**5/5**	**4/4**	**1/1**	**1.0**	**0**	**100**
		0.8	20/25	6.3/8	*6/7.5*	5/6.3	4/5	1/1.25	1.25	+0.1	95
	Mild Vision Loss	0.63	20/32	6.3/10	*6/9.5*	5/8	4/6.3	1/1.6	1.6	0.2	90
		0.5	20/40	6.3/12.5	*6/12*	5/10	4/8	1/2	2.0	0.3	85
		0.4	20/50	6.3/16	*6/15*	5/12.5	4/10	1/2.5	2.5	0.4	80
		0.32	20/63	6.3/20	*6/19*	5/16	4/12.5	1/3.2	3.2	0.5	75
Low Vision	Moderate Vision Loss	0.25	20/80	6.3/25	*6/24*	5/20	4/16	1/4	4	0.6	70
		0.20	20/100	6.3/32	*6/30*	5/25	4/20	1/5	5	0.7	65
		0.16	20/125	6.3/40	*6/38*	5/32	4/25	1/6.3	6.3	0.8	60
		0.125	20/160	6.3/50	*6/48*	5/40	4/32	1/8	8	0.9	55
	Severe Vision Loss	**0.10**	**20/200**	**6.3/63**	***6/60***	**5/50**	**4/40**	**1/10**	**10**	**+1.0**	**50**
		0.08	20/250	6.3/80	*6/75*	5/63	4/50	1/12.5	12.5	1.1	45
		0.063	20/320	6.3/100	*6/95*	5/80	4/63	1/16	16	1.2	40
		0.05	20/400	6.3/125	*6/120*	5/100	4/80	1/20	20	1.3	35
	Profound Vision Loss	0.04	20/500	6.3/160	*6/150*	5/125	4/100	1/25	25	1.4	30
		0.03	20/630	6.3/200	*6/190*	5/160	4/125	1/32	32	1.5	25
		0.025	20/800	6.3/250	*6/240*	5/200	4/160	1/40	40	1.6	20
		0.02	0/1000	6.3/320	*6/300*	5/250	4/200	1/50	50	1.7	15
(Near-) Blind-ness	Near-Blindness	0.016	20/1250	6.3/400	*6/380*	5/320	4/250	1/63	63	1.8	10
		0.0125	20/1600	6.3/500	*6/480*	5/400	4/320	1/80	80	1.9	5
		0.01	**20/2000**	**6.3/630**	***6/600***	**5/500**	**4/400**	**1/100**	**100**	**+2.0**	**0**
		---	---	---	---	---	---	---			---
	Blindness	No Light Perception (NLP)									

10.20 Appendix 20: Baseline characteristics of pseudophakic subgroups

	MEAD-010		MEAD-011		Study 024		PLACID	
	DEX700 (n=44)	**Sham (n=50)**	**DEX700 (n=42)**	**Sham (n=51)**	**DEX700 ([redacted])**	**RAN [redacted]**	**DEX700 + laser (n=35)**	**Laser (n=32)**
Demographics								
Age, mean years (SD)	67.55 (7.97)	65.78 (8.77)	67.50 (8.43)	68.61 (8.62)	[redacted]	[redacted]	69.1 (10.75)	69.1 (7.59)
Male, n (%)	29 (65.9)	32 (64.0)	23 (54.8)	29 (56.9)	[redacted]	[redacted]	17 (48.6)	17 (53.1)
Caucasian, n (%)	39 (88.6)	45 (90.0)	21 (50.0)	34 (66.7)	[redacted]	[redacted]	27 (77.1)	20 (62.5)
Disease characteristics								
Duration of DM, mean years (SD)	16.86 (8.83)	16.71 (8.32)	15.43 (8.19)	120.96 (11.49)	[redacted]	[redacted]	6.2 (NR)	21.7 (23.52)
Type 2 DM, n (%)	44 (100)	44 (88.0)	37 (88.1)	46 (90.2)	[redacted]	[redacted]	29 (82.9)	25 (78.1)
Baseline HbA1c, mean % (SD)	7.48 (0.91)	7.47 (0.88)	7.52 (1.13)	7.22 (1.05)	[redacted]	[redacted]	7.5 (1.39)	7.3 (1.01)
IOP in study eye, mean mmHg (SD)	14.89 (2.86)	15.64 (3.36)	15.14 (2.46)	14.86 (3.19)	[redacted]	[redacted]	15.3 (2.69)	15.4 (2.45)
≥ Severe DR, n (%)	20 (45.5)	18 (36.0)	22 (52.4)	18 (35.3)	[redacted]	[redacted]	NR	NR
Duration of DMO, mean months (SD)	24.77 (22.53)	42.06 (37.23)	23.40 (23.66)	28.43 (24.75)	[redacted]	[redacted]	31.1 (25.95)	49.4 (45.73)
Duration of DMO ≥3 years, n (%)*	11 (25.0)	23 (46.0)	8 (19.0)	15 (29.4)	[redacted]	[redacted]	10 (28.6)	17 (53.1)
Baseline VA, mean letters (SD)	55.52 (11.25)	55.88 (9.95)	55.10 (9.23)	56.06 (7.50)	[redacted]	[redacted]	56.2 (9.72)	56.0 (10.28)

	MEAD-010		MEAD-011		Study 024		PLACID	
	DEX700 (n=44)	**Sham (n=50)**	**DEX700 (n=42)**	**Sham (n=51)**	**DEX700 ([redacted])**	**RAN [redacted]**	**DEX700 + laser (n=35)**	**Laser (n=32)**
Baseline CRT, mean µm (SD)	430.66 (167.03)	475.38 (129.62)	493.24 (165.63)	475.22 (130.53)	[redacted]	[redacted]	467.9 (125.61)	461.1 (129.94)
CRT ≥400 µm, n (%)*	22 (50.0)	33 (66.0)	27 (64.3)	35 (68.6)	[redacted]	[redacted]	23 (65.7)	19 (59.4)
Study eye was BSE, n (%)	10 (22.7)	9 (18.0)	11 (26.2)	13 (25.5)	[redacted]	[redacted]	6 (17.1)	5 (15.6)
Bilateral DMO, n (%)	13 (29.5)	16 (32.0)	19 (45.2)	18 (35.3)	[redacted]	[redacted]	15 (42.9)	19 (59.4)
Treatment history for DMO in the study eye								
Treatment naïve, n (%)	8 (18.2)	7 (14.0)	13 (31.0)	11 (21.6)	[redacted]	[redacted]	6 (17.1)	9 (28.1)
Prior laser, n (%)	33 (75.0)	39 (78.0)	25 (59.5)	34 (66.7)	[redacted]	[redacted]	29 (82.9)	23 (71.9)
Prior anti-VEGF, n (%)	4 (9.1)	8 (16.0)	4 (9.5)	5 (9.8)	[redacted]	[redacted]	1 (3.1)	2 (5.7)
Prior steroid, n (%)	14 (31.8)	14 (28.0)	13 (31.0)	11 (21.6)	[redacted]	[redacted]	4 (11.4)	3 (9.4)

Key: BSE, better seeing eye; CRT, central retinal thickness; DEX, dexamethasone; DM, diabetes mellitus; DMO, diabetic macular oedema; DR, diabetic retinopathy; HbA1c, glycated hemoglobin; IOP, intraocular pressure; RAN, ranibizumab; SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor

10.21 Appendix 21: Additional analyses of subgroups of patients with prior treatment

Table 263 presents a summary of the key efficacy results in the subgroup of patients with prior anti-VEGF and without prior steroid therapy. Table 264 presents a summary of the key efficacy results in the subgroup of patients with prior laser treatment and without prior steroid therapy. Table 265 presents a summary of the key efficacy results in the subgroup of patients with prior laser or prior anti-VEGF and without prior steroid therapy.

Importantly, the sample size of patients in the subgroup that had prior anti-VEGF therapy and no prior steroid therapy was relatively small in each study [redacted]

Table 263: Efficacy in Patients with Prior anti-VEGF and Without Prior Intravitreal Steroid Therapy

	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 center subfield mean average change over 3 years, AUC approach (µm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Difference from sham p = < 0.05

Key: AUC, area under the curve; BCVA, best corrected visual acuity; 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 264: Efficacy in Patients with Prior Laser and Without Prior Intravitreal Steroid Therapy

	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 center 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

Key: AUC, area under the curve; BCVA, best corrected visual acuity; 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 265: Efficacy in Patients with Prior Anti-VEGF or Laser and Without Prior Intravitreal Steroid Therapy

	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 center 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

Key: AUC, area under the curve; BCVA, best corrected visual acuity; 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

10.22 Appendix 22: MTC code

WINBUGS MODELS

 # Baseline model (probit link) for sham/no treatment arms only for patients losing 10 or more letters

```
model{

# Loop through the trial reference baselines
for(i in 1:NObs){

# Likelihood and link functions for the sample data
rbase[i] ~ dbin(pbase[i], nbase[i])
probit(pbase[i]) <- mubase[i]

# Random effects distribution for the baseline response rate on the probit
scale
mubase[i] ~ dnorm(mean.base, precb)
}

# Vague prior distributions for the baseline response rate and between
study SD on the probit
# scale

mean.base ~ dnorm(0, 0.01)

precb <- 1/(taub*taub)

taub ~ dunif(0,2)

popn.mean <- phi(mean.base)
}
```

10.23 Appendix 23: Clinical trials search for DEX700 in DMO studies for which no results have been made available to date

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-randomised	DEX700	Bevacizumab PRN	50	June 2013	December 2015	October 2014	Currently recruiting
NCT01571232	Phase 2, open-label	DEX700	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	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	DEX700	NA	24	December 2012	NR	June 2014	Currently recruiting

Study ID	Study Type	Intervention	Control	Enrolment	Study start date	Study Completion Date	Primary Completion Date	Status
	trial							
NCT01788475	RCT	DEX700 3 monthly	DEX700 6 monthly 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								

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such

public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

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

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be ‘blacked out’ from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of ‘academic in confidence’ information. The ‘stripped’ version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE’s website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the ‘stripped’ version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The

Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.