NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from AbbVie

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Macular Society
   b. Royal College of Ophthalmologists

4. **Evidence Review Group report** prepared by BMJ-TAG

5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Mr Winfried Amoaku, Consultant Ophthalmologist & Assoc Professor/Reader in Ophthalmology – clinical expert, nominated by The Royal College of Ophthalmologists
   b. Stephen Scowcroft Director of Services – patient expert, nominated by Macular Society
   c. Bernadette Warren – patient expert, nominated by Macular Society
   d. Faruque Ghanchi, Consultant Ophthalmologist, nominated by Abbvie

8. **Technical engagement responses from consultees and commentators:**
   a. Alimera
   b. Novartis
   c. Roche

9. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ TAG

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dexamethasone intravitreal implant for treating diabetic macular oedema [ID3951]

Document B

Company evidence submission

January 2022

File name	Version	Contains confidential information	Date
ID3951_Ozurdex_NICE_STA_Document B_AIC_CIC	Final	Yes	10 Jan 2022

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

List of tables

List of figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the curve
BCVA	Best-corrected visual acuity
BRVA	Best-reported visual acuity
BRVO	Branch retinal vein occlusion
CFB	Change from baseline
CFT	Central foveal thickness
CI	Confidence interval
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CSR	Clinical study report
DRCR	Diabetic Retinopathy Clinical Research
DEX700	Dexamethasone 700 µg intravitreal implant in applicator (Ozurdex®)
DEX PS DDS	Dexamethasone posterior segment drug delivery system
DMO	Diabetic macular oedema
DDS	Drug delivery system
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group
ETDRS	Early Treatment Diabetic Retinopathy Study
ESS	Effective sample size
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IOP	Intraocular pressure
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LOCF	Last observation carried forward
LogMAR	Logarithm of the minimal angle of resolution
mITT	Modified intention-to-treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analyses
MAIC	Matching-adjusted indirect comparison
MD	Mean difference
OCT	Optical coherence tomography
OHT	Ocular hypertension
OR	Odds ratio
QALYs	Quality-adjusted life years

Abbreviation	Definition
RCT	Randomized controlled trial
RVO	Retinal vein occlusion
RWD	Real-world data
RWE	Real-world evidence
SD	Standard deviation
SLR	Systemic literature review
STC	Simulated treatment comparison
SmPC	Summary of product characteristics
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TA	Technology appraisal
TRAE	Treatment-related adverse event
VEGF	Vascular endothelial growth factor
VFQ-25	Visual Functioning Questionaire-25

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

Dexamethasone 700 µg intravitreal implant in applicator (Ozurdex®), hereinafter referred to as DEX700, is indicated for the treatment of adult patients with[1]:

- Visual impairment due to diabetic macular oedema (DMO) 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)
- Inflammation of the posterior segment of the eye presenting as non-infectious uveitis

DMO patients can be categorized as either phakic or pseudophakic, which are terms used to describe the status of a patient's lens.[2] Phakic refers to a patient with an intact natural lens, while pseudophakic refers to patients who have had their lens extracted and replaced with an intraocular lens.[2]

In July 2015, NICE issued guidance (technology appraisal [TA]349) on the use of DEX700 in DMO patients with pseudophakic lens who are unsuitable for, or insufficiently responsive to non-corticosteroid treatment. Although TA349 considered evidence for the use of DEX700 in the phakic and pseudophakic DMO patient population, the recommendation did not include DMO patients with phakic eyes. TA349 therefore only partially covers the European Medicines Agency (EMA) licensing indication for use of DEX700 in DMO patients.[1]

Table 1 presents a summary of previous NICE appraisals for DEX700 (TA349) and fluocinolone acetonide intravitreal implant (TA613) in the patient population of interest for this submission. In this appraisal, attempts have been made to address the challenges identified in these appraisals through substantial real-world evidence (RWE) data collection, the presentation of published clinical evidence including phakic

DMO patients and the inclusion of a range of alternative plausible scenarios in the cost-effectiveness model.

Further to this, since TA349 a change in the treatment pathway has been acknowledged. It is now understood that rather than watch and wait as was assumed in TA349, that the appropriate comparator for DMO patients with phakic eyes after an insufficient response to previous non-corticosteroid therapy is continued use of anti-vascular endothelial growth factors (anti-VEGFs), as per TA613.[3] In TA613 continued use of laser treatment was also considered, however, use of laser has declined further in recent years.[4, 5] Due to the lack of alternative treatments, these patients tend to continue to receive (sometimes frequent) anti-VEGF injections in an attempt to achieve a response. This continued administration poses a substantial burden on both patients and the healthcare system, with limited to no benefit being realized.[6]

In light of the changing comparator and newly available RWE, NICE has accepted a request to reappraise DEX700 for use in a broader population of DMO patients. Therefore, the population of focus for this submission is phakic DMO patients who are unsuitable for or insufficiently responsive to non-corticosteroid treatment, thus fully aligning with the licensed EMA indication for DEX700 (as defined in the scope, Table 2).

A summary of the key NICE appraisals and events that have preceded this submission are presented in Figure 1.

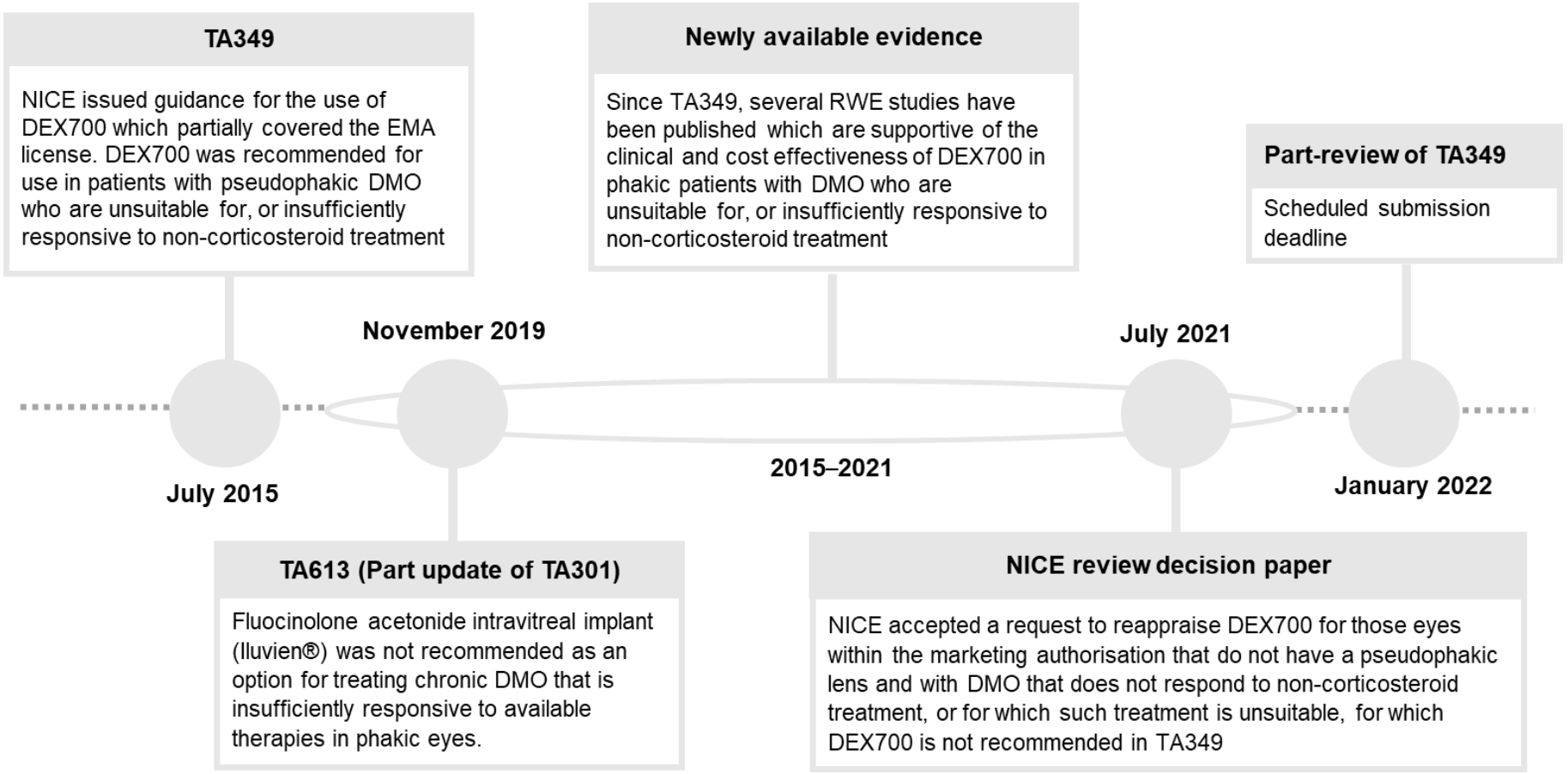
Table 1: Previous appraisals in the population of interest

Appraisal	Populations for which evidence was submitted	Comparators	Outcome	Rationale for outcome
TA349 DEX700 for treating DMO (Published 22 July 2015)	People with a pseudophakic lens with CRT of 400 micrometres or more	Ranibizumab	Not recommended	Compared with ranibizumab DEX700 was not considered a cost-effective use of NHS resources
	People with a pseudophakic lens with CRT less than 400 micrometres	Laser photocoagulation Bevacizumab	Not recommended	Compared with laser or bevacizumab DEX700 was not considered a cost-effective use of NHS resources
	People who do not have a pseudophakic lens and with DMO that does not respond to non-corticosteroid treatment or for whom such treatment is unsuitable	**Watch and wait**	**Not recommended**	**The Committee considered that the true value of the ICER compared with watch-and-wait would likely be greater than the ERG's exploratory base case ICER, which itself was greater than the usual willingness-to-pay threshold**
	People with a pseudophakic lens and with DMO that does not respond to non-corticosteroid treatment or for whom such treatment is unsuitable	Fluocinolone acetonide intravitreal implant	Recommended	When the exact discount for fluocinolone acetonide intravitreal implant was taken into account there was little difference in the total costs and QALYs of fluocinolone acetonide intravitreal implant and DEX700. Therefore, the cost-effectiveness of DEX700 is likely similar to that of fluocinolone acetonide intravitreal implant and DEX700 would provide an alternative option in this population.
TA613 Fluocinolone acetonide intravitreal implant (Iluvien) for	People with chronic diabetic macular oedema that is insufficiently responsive to available therapies in an eye with a natural lens (phakic eye), and	Usual care (anti-VEGF or laser)	Not recommended	The Committee concluded that because of the lack of clinical evidence in the population of interest, the cost-effectiveness estimates were too uncertain. Only a few patients in the

Appraisal	Populations for which evidence was submitted	Comparators	Outcome	Rationale for outcome
treating chronic DMO in phakic eyes after an inadequate response to previous therapy (Published 20 November 2019)	with symptomatic cataract			FAME trials and non-comparative studies used to support the company's submission had phakic eyes with symptomatic cataracts, and only very few patients had received anti-VEGFs before the FAME trials. Even the lowest plausible cost-effectiveness estimates were substantially higher than what can be considered a cost-effective use of NHS resources.

Key: CRT, central retinal thickness; DMO, diabetic macular oedema; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; QALY, quality-adjusted life years; RWE, real-world evidence; VEGF, vascular endothelial growth factor.
Notes: Bold text indicates population relevant to this appraisal.
Source: TA349[7], TA613[3]

Figure 1: Timeline of key NICE appraisals and events relevant to this submission



Key: DMO, diabetic macular oedema; EMA, European Medicines Agency; NICE, National Institute for Health and Care Excellence; RWE, real-world evidence; TA, technical appraisal.
Notes: A table of newly available RWE relevant to the decision problem has been provided in Section B.2.2.1.1.
Source: TA349[7]; TA613[3]; NICE Review Decision Paper.[8]

The main source of evidence for the use of DEX700 in patients with both pseudophakic and phakic DMO was provided by the Phase III randomized, sham-controlled trials MEAD-010 and MEAD-011; this is the evidence that was presented in NICE TA349 and relevant regulatory submissions. The analyses of the pseudophakic DMO populations from the MEAD trials were provided to support the use of DEX700 in these patients, whereas the analyses of the total intention-to-treat (ITT) populations were used to provide evidence for DEX700 in patients with phakic DMO in TA349. Given the ITT results for the MEAD trial populations were presented previously, NICE is aware of these data and that will therefore not be discussed in this submission. Instead, the results of a post-hoc analysis conducted for the phakic-only modified ITT (mITT) populations of the MEAD trials will be the primary focus of the submission (Section B.2.6.1), with these data also being used to inform the economic analyses.

As discussed in Section B.2.7, the management of phakic DMO patients in the MEAD trials was not fully aligned with management of these patients in the UK clinical practice, as confirmed through an advisory board conducted in 2021.[9] It is important to highlight that in TA349 the committee accepted that the outcomes of the sham-arm of the MEAD trials were a best-case scenario; the outcomes were an overestimation of the expected effectiveness of watch and wait in clinical practice. Further, the exploratory sub-analyses of the phakic-only mITT population from MEAD presented in Section B.2.7 indicate more favourable outcomes for DEX700 when the phakic population of MEAD was adjusted to more closely resemble the population of phakic DMO patients that would be eligible for treatment with DEX700 in UK clinical practice.

Since the publication of TA349 in July 2015, several RWE studies have been published that further support the efficacy and safety of DEX700 (Sections B.2.6.2 and B.2.10.2, respectively). The visual outcomes reported for phakic DMO patients in the RWE studies are consistently better than those reported in the MEAD trials (Section B.2.6.2), demonstrating that MEAD presents an underestimation of efficacy for DEX700. The findings of these RWE studies also suggest that the treatment outcomes with DEX700 are consistent between pseudophakic DMO patients (the patient population that was reimbursed in July 2015) and phakic DMO patients (Section B.2.6.2.1).

Further to the new evidence for DEX700, a UK RWE audit was conducted on the continued use of anti-VEGFs in phakic DMO patients who are insufficient responders (Sections B.2.2.2.1, B.2.3.4 and B.2.6.4).[10] This study provides non-randomized controlled trial (non-RCT) real-world data from UK clinical practice for the comparator of interest. A retrospective analysis of Protocol T, a US-based randomized controlled trial, has also been included in support of this submission (Section B.2.2.2.2, B.2.3.5 and B.2.6.5). These studies further highlight that due to the current lack of alternative treatment options, patients continue to receive anti-VEGF treatment despite a suboptimal response.

Table 2 presents the decision problem for the submission.

Table 2: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Phakic DMO patients who are insufficiently responsive to or unsuitable for the non-corticosteroid treatment	As per final scope	Although the submission does consider the full population outlined in the final scope, the economic analysis only considers insufficient responders because there is no relevant additional evidence available to model this specific population beyond the data that was presented in TA349. However, given the high unmet need in this population, the clinical benefit of DEX700 and the limited size of this population (and therefore the small contribution this population would make to the overall cost-effectives in the broad population), consideration is given to this sub-population throughout the clinical evidence section
Intervention	Dexamethasone intravitreal implant	As per final scope	N/A
Comparator(s)	• Laser photocoagulation alone • Wait-and-wait (for people who are unsuitable for treatment with both anti-VEGFs and laser photocoagulation) The following technologies alone or in combination with laser photocoagulation:	Phakic DMO patients who are insufficiently responsive to non-corticosteroid treatment are: • Laser photocoagulation alone The following technologies alone or in combination with laser	Given the change in treatment pathway accepted in TA613, the economic analysis only considers anti-VEGF therapies. UK clinical feedback also confirms this is the only relevant comparator in the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Aflibercept (only if the eye has a central retinal thickness of 400 micrometres or more) • Bevacizumab (does not currently have a marketing authorization in the UK for this indication) • Ranibizumab (only if the eye has a central retinal thickness of 400 micrometres or more) Comparators for phakic DMO patients who are unsuitable for the available therapies: • Watch and wait	photocoagulation: • Aflibercept (only if the eye has a central retinal thickness of 400 micrometres or more) • Bevacizumab (does not currently have a marketing authorization in the UK for this indication) • Ranibizumab (only if the eye has a central retinal thickness of 400 micrometres or more)	insufficiently responsive population, which is the only population that is formally considered in the economic analysis
Outcomes	• Best corrected visual acuity (the affected eye) • Best corrected visual acuity (both eyes) • Central foveal subfield thickness • Central retinal thickness • Contrast sensitivity • Mortality • Need for cataract surgery • Adverse effects of treatment (including cataract formation and glaucoma) • Health-related quality of life, including the effects of changes in visual acuity	As per final scope	N/A
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 cost-effectiveness of treatments will be expressed in terms of incremental cost per quality-adjusted life year.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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 commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. Cost-effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.	The time horizon for estimating clinical- and cost-effectiveness is lifetime (40 years) and is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Longer time horizons are explored in scenario analyses. Costs are considered from an NHS and Personal Social Services perspective. There is no commercial arrangement for DEX700. Aflibercept and ranibizumab are subject to confidential patient access scheme discounts, these have therefore not been applied in this submission as the value of discount is not known. The presented cost-effectiveness analysis considers treatment in either the best or worst seeing eye, or in both eyes.	
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • Type of DMO (focal or diffuse, central involvement, ischaemic or non-ischaemic maculopathy) • Duration of DMO • Baseline visual acuity	Several exploratory sub-analyses of the phakic-only population from MEAD were conducted (Section B.2.6.4.1) to explore: • Timing of cataract surgery • Timing of DEX700 implant prior to cataract surgery	Exploratory post-hoc analysis of the MEAD data was performed to investigate the impact of some of the known limitations of the MEAD study. The sample size of the sub-populations is too small to draw firm conclusions from the results, and while a test of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• 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, aflibercept, ranibizumab or bevacizumab)	• Impact of lens opacity • Impact of diabetes duration • Impact of DMO duration • Impact of cataract surgery • Impact of prior treatment	statistical significance was performed, no claims for statistical significance are made.
Key: DMO, diabetic macular oedema; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; VEGF, vascular endothelial growth factor.			

B.1.2. Description of the technology being appraised

Dexamethasone 700 µg (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). DEX700 contains a PLGA matrix, which degrades to lactic acid and glycolic acid. When dexamethasone is consumed, degradation products are water and carbon dioxide, leaving no residue in the eye.[11] High concentrations of the drug are released during the initial 2 months, steadily declining over the following 4 months, with detectable levels of dexamethasone in the vitreous for up to 6 months following a single injection.[11]

Dexamethasone is a potent corticosteroid that reduces the levels of multiple inflammatory mediators (including the production of VEGF) which are involved in the multifactorial pathophysiology of DMO. Administration of dexamethasone results in improved visual acuity through the resolution of macular oedema and enables improved vision in patients without the need for monthly injections.

In the UK, DEX700 has existing market authorizations for use in DMO, retinal vein occlusion (RVO) and uveitis. The 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.

The recommended course of treatment is one DEX700 implant at approximately 6-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.

Table 3 presents a description of DEX700. The Summary of Product Characteristics (SmPC) and the European Public Assessment Report (EPAR) are presented in Appendix C.

Table 3: Technology being appraised

UK approved name and brand name	Dexamethasone 700 µg (DEX700) intravitreal implant in applicator (Ozurdex®)
Mechanism of action	DEX700 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. Dexamethasone is a potent corticosteroid that reduces the levels of multiple inflammatory mediators (including the production of VEGF) which are involved in the multifactorial pathophysiology of DMO. As a result, dexamethasone improves visual acuity through resolution of macular oedema, which is the key to effective long-term management of this condition.
Marketing authorisation/CE mark status	DEX700 was approved 27 July 2010; the label was renewed on 23 March 2015.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	DEX700 is indicated 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 • Macular oedema following either BRVO or CRVO • Inflammation of the posterior segment of the eye presenting as non-infectious uveitis
Method of administration and dosage	DEX700 is provided as a single intravitreal implant in applicator, containing 700 µg of dexamethasone. The recommended course of treatment is one DEX700 implant at approximately 6-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.
Additional tests or investigations	No additional tests or investigations are required.
List price and average cost of a course of treatment	The total cost of a course of DEX700 (assuming an average of [redacted] treatments over 5 years as per the economic base-case) is expected to be £5724 per treated eye.
Patient access scheme (if applicable)	N/A
Key: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DEX700,	

dexamethasone 700 µg intravitreal implant; DMO, diabetic macular oedema; VEGF, vascular endothelial growth factor.
Source: European Medicines Agency (Ozurdex SmPC).[1]

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease background

Diabetes is a serious chronic disease with a rising prevalence that is expected to affect 5 million people by 2025 and is one of the biggest threats to public health in the UK.[12, 13] Diabetes is categorized as either Type 1 (approximately 10% of all diagnosed cases in the UK), where the body's immune system attacks and destroys the cells that produce insulin; or Type 2 (approximately 90% of all diagnosed cases in the UK), where the body does not produce enough insulin, or the body's cells do not react to insulin.[13, 14]

DMO is a common, debilitating complication of diabetes resulting from diabetic retinopathy and is the most common cause of sight loss in people with diabetes.[15] Specifically, DMO is a swelling of the retina resulting from fluid leaking from blood vessels in the macula, which over time can lead to a loss of vision.[15] DMO can be unilateral (affecting only one eye) or bilateral (affecting both eyes).[16] DMO is a progressive disease that worsens with increased accumulation of fluid and proximity of the oedema to the centre of the macula.[17, 18]

The pathophysiology of DMO is multifactorial and complex, where chronic hyperglycaemia triggers a number of biochemical pathways which lead to the breakdown of the blood retinal barrier.[19] Inflammation is a central component of the pathophysiology of DMO and breakdown of the blood–retinal barrier leads to a build-up of fluid (oedema) in the macula: the central part of the retina responsible for central vision.[19, 20] Such accumulation of fluid causes thickening and swelling that impairs the ability of photoreceptor cells in the macula to sense light, causing blurring of vision.[19]

B.1.3.2 Epidemiology

In the UK, the prevalence of diabetes has been increasing exponentially over the past few decades. Indeed, the number of people diagnosed with diabetes rose from 1.4 million in 1996 to 3.5 million in 2015.[19] As of 2019, there were an estimated 4.9 million people in the UK living with diabetes.[13] Furthermore, as of 2020, the National Health Service (NHS) estimated that a record 2 million people in England are at risk of developing Type 2 diabetes (T2DM).[21] Strikingly, the prevalence of diabetes in the UK is estimated to rise to 5 million people by 2025.[13]

There is a scarcity of data on the incidence and progression of diabetic retinopathy and DMO[19]; however, the increase in prevalence of diabetes is likely to correlate with a rise in the prevalence of DMO, especially given diabetic retinopathy is the most common complication of diabetes.[19] It is estimated that approximately 90% all people with T1DM and approximately 67–80% of people with T2DM experience diabetic retinopathy within 15–20 years of diagnosis[15, 22, 23], and that one in three people living with diabetes for 20 years or more develop DMO.[24] In the UK, an estimated 7% of patients with diabetes will develop DMO[9], and the prevalence of sight loss (defined as central visual acuity < 6/6) as a result of DMO is estimated to affect 1–3% of all patients with diabetes in the UK.[25, 26]

The likelihood of developing DMO and sight loss is strongly associated with the duration of diabetes and the severity of diabetic retinopathy, with incidence increasing the longer diabetes persists.[27] The prevalence of diabetic retinopathy in patients with a diabetes duration of < 10 years is 20%, whereas the prevalence in patients with a diabetes duration of > 20 years is 76%.[19] As such, increasing age is a risk factor for developing DMO and for sight loss through DMO.[15] The development of DMO is also associated with poor management of diabetes.[19, 28] The Diabetes Control and Complications Trials (DCCT) showed that intensive therapy in patients with Type 1 diabetes mellitus (T1DM) reduced the risk for development and progression of diabetic retinopathy.[19] Similarly, the United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive control of blood glucose in patients with T2DM reduced the risk of microvascular end-points including the risk for retinal photocoagulation.[19]

B.1.3.3 Burden of disease

B.1.3.3.1 Clinical burden

Diabetic retinopathy and DMO are common vascular complications associated with both T1DM and T2DM. Other complications associated with diabetes include diabetic nephropathy, stroke, cardiovascular disease and diabetic neuropathy, as well as high rates of morbidity and mortality.[29] Diabetes also raises the risk for visual impairment due to cataracts and glaucoma, both of which are associated with as much as a five-fold prevalence increase in patients with diabetes compared with those without.[30-36] Cataracts is one of the most common causes of blindness in older-onset patients with diabetes and risk of its development appears to be greatest in non-insulin dependent patients[37], with a cataract rate of 13.5 per 1000 patient years reported in a large UK retrospective study for such patients.[38] Higher cataract rates are also seen in patients with T2DM who have had diabetes for a longer duration of time and in patients with worse glycaemic control.[32] In the population based Blue Mountains Eye Study, cataract formation resulted in a cumulative incidence of cataract surgery in patients with diabetes of 20.9% over 10 years.[39]

Patients with DMO experience significantly more comorbidities than in diabetes patients without DMO.[40-42] Indeed, higher rates of myocardial infarction, peripheral vascular disease and renal disease are reported in patients with diabetes and DMO compared with those with diabetes alone.[40] DMO is the most common cause of sight loss in people with diabetes[15], and complications of DMO such as cataract and glaucoma are leading causes of vision loss.[30] Development of cataracts is up to four times more likely in patients with diabetic retinopathy or DMO than in diabetes with no prior eye disorder.[31] In patients with DMO, the probability of losing two or more lines of visual acuity within 3 months is estimated to be 4.5%.[43] Furthermore, nearly half of patients with DMO will lose two or more lines of visual acuity within 2 years, and approximately a quarter of patients will lose three or more lines of visual acuity within 3 years.[43, 44] Note that a loss of two or more lines of visual acuity is equivalent to 10 or more letters in the visual acuity score (see Appendix L).[45] DMO patients with diabetes also have a much higher likelihood of developing vision loss compared with non-DMO patients with diabetes.[17, 31] Vision loss has a substantial impact on a patient's quality

of life by limiting social interactions and independence (Section B.1.3.3.3). Effective treatment is therefore critical for retaining vision in patients with DMO.

Poor management of DMO and diabetes leads to exacerbations of these complications and the concomitant burden of disease.[28, 29, 46] A patient's beliefs and behaviours regarding their condition are crucial to the successful control of diabetes, but high rates of non-compliance with recommended lifestyle changes, self-monitoring and medication are observed in practice.[46-50] Furthermore, vision loss may also complicate the management of other conditions by creating difficulties in medication adherence and management, for example, administering insulin or eye drops.[27]

B.1.3.3.2 Impact on life expectancy

Diabetes is associated with reduced life expectancy.[51, 52] In a study analysing data from the National Diabetes Audit and Office of National Statistics, the estimated life years lost in patients with Type 1 diabetes was 8.5 years for women and 7.0 years for men; for patients with T2DM, the estimated life years lost were 2.0 years for women and 1.4 years for men.[52] In patients with DMO, life expectancy is further reduced given the number of additional comorbidities.[40, 41] For instance, patients with DMO are at higher risk of macrovascular complications and mortality from cardiovascular disease and ischaemic heart disease than diabetes patients without DMO.[53, 54]

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.[53-55] In post-hoc analysis of patients enrolled in the Early Treatment Diabetic Retinopathy Study (ETDRS) of laser photocoagulation therapy in DMO, poor visual acuity was significantly associated with mortality in patients with diabetes.[55] In patients with Type 1 diabetes, 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% confidence interval [CI] 1.10, 2.75).[55] In patients with T2DM, 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 (95% CI 1.01, 1.83).[55]

B.1.3.3.3 Impact on patient's health-related quality of life

The visual impairment from DMO negatively impacts patients' physical and emotional functioning. A number of studies report on the damaging effect of DMO on vision: limiting a patient's 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 impact patients' mental well-being.[37, 56, 57] In addition, the fear of losing sight or independence causes emotional distress for many patients, particularly those with depressive disorder symptoms, which are often linked to diabetes.[58] Health-related quality of life (HRQL) appears to systematically decline as vision impairment and severity of DMO worsen.[59, 60] Specifically, progression from unilateral to bilateral vision impairment and progression from mild/moderate DMO to vision-threatening stages are important milestones in the reduction of patient HRQL.[59, 60]

Furthermore, limitations in physical and mental functioning due to visual impairment associated with DMO can compromise the patient's ability to successfully manage their diabetes and additional comorbidities. 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 importance of patient compliance and participation in their own disease management, this can increase the likelihood of developing other diabetic complications, and therefore reduce overall life expectancy. In a German study of 207 patients with diabetic retinopathy and DMO, patients stated that without eye problems, their diabetes care would be better.[62] Even in patients with a well-monitored and treated eye condition, the patient still experienced feelings of uncertainty and fear about how one's life will be affected by it in the future.[62]

The treatment and clinical management of DMO can also negatively impact patient HRQL. In a 5-year observational, multinational study of 30,514 patients with DMO, patients reported that injections caused stress and anxiety, and the most desired outcome from the perspective of patients was to achieve the same visual outcomes with fewer injections.[6] Patients also reported practical issues such as regular travelling and having to take leave from work to attend appointments.[6] The study estimated that over half of patients had an average of 19.1 appointments with healthcare

professionals, accounting for around 20 hours per patient over a 6-month period and that each injection appointment (including travel time) lasted on average 4.5 hours.[6]

B.1.3.3.4 Socioeconomic burden

In the UK, the latest NHS spending figures from 2019 showed that £14 billion was spent on the management of diabetes and its complications, accounting for about 10% of the annual NHS budget.[19, 63] The most comprehensive analysis to date, conducted in 2010/11, found that the direct cost of diabetes to the NHS was £9.8 billion.[63] However, given the large increase in prevalence since this time, the costs are likely to be much greater today. It should be noted that around 80% of the direct costs associated with diabetes are attributable to the complications of the disease, including (but not limited to), cardiovascular disease, excess in-patient days, kidney disease, neuropathy, stroke and diabetic retinopathy.[63]

Contributing to this economic burden are the high rates of non-compliance to treatment strategies for patients with diabetes, with many patients using health services several times per year due to poor treatment adherence.[40] The indirect costs of diabetes are also substantial, but the total cost is unknown. In 2012, the indirect costs of reduced productivity at work were estimated at nearly £9 billion (again, this is likely an underestimate today).[63] Of further note, the overall cost of diabetes in the UK is predicted to rise to £16.9 billion in 2035/36.[63]

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 diabetes patients without DMO.[64] One retrospective study of UK clinical practice estimated the costs solely related to DMO management.[26] The health and social care costs included those associated with diagnosing, treating and managing DMO, as well as downstream costs such as rehabilitation and residential care. The overall cost of illness for DMO was estimated at £116,296,038, translating to approximately £1,000 per patient per year (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. As with all ophthalmological conditions, the magnitude of direct and indirect costs associated with DMO rise significantly as the severity of the disease worsens, with insufficient

treatment, reduced patient independence and potentially vision loss all contributing.[65, 66] DMO is also thought to incur a substantial indirect cost, as vision loss may contribute to absenteeism and early retirement.[19]

Since 2010, the landscape of DMO management has changed substantially with the introduction of novel pharmaceutical therapies. However, rather than reduce the burden, these novel treatments have placed extreme pressure on the UK healthcare system.[19] Indeed, many recent therapies require multiple injections over a 12-month period, putting pressure on NHS resources, with capacity constraints and associated concerns on preventable sight loss incidence previously reported by the Royal National Institute of Blind People.[9] This is likely to have translated to increased healthcare costs for DMO. Furthermore, the costs attributed to DMO are expected to have steadily risen in correlation with the increasing prevalence of diabetes and associated conditions (see Section B.1.3.2). Moreover, clinicians highlighted that capacity issues that were prevalent before COVID-19 are likely to persist and may be exacerbated after COVID-19[9]; this will likely place further strain on the UK healthcare system.

B.1.3.4 Clinical care pathway and proposed positioning of the technology

B.1.3.4.1 UK clinical guidelines

NICE has not developed specific guidelines for treating diabetic retinopathy and DMO. The NICE guidelines for managing adults with T1DM (NG17[67]) and T2DM (NG28[68]) provide some recommendations for managing patients with diabetic eye disease, such as timings for when to screen patients; however, they do not include specific information for patients with DMO.

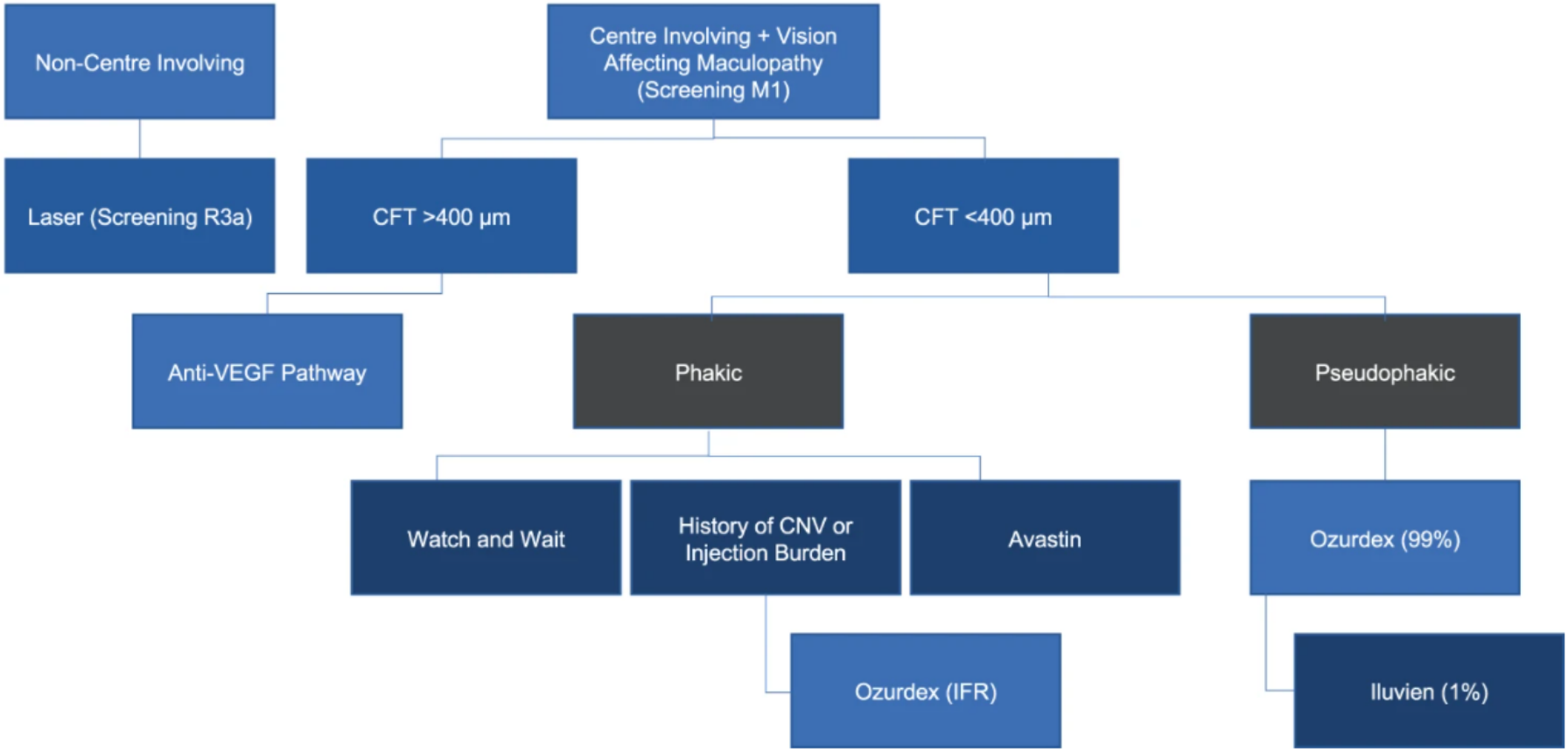
In 2012, the Royal College of Ophthalmologists published guidelines for the management of diabetic retinopathy[69]; however, given the changes to the treatment landscape of diabetic retinopathy and DMO over the past decade with the increased availability of diagnostic technologies and therapeutics, it is likely that these guidelines do not reflect the current clinical management of patients with DMO in the UK.[19]

In 2020, a UK Consensus Working Group was formed to address the perceived variations and lack of uniformity in DMO management in the UK and to provide

guidance to clinicians who manage patients with diabetic retinopathy.[19] The group included retinal specialists with expertise in managing diabetic eye disease, diabetologists, vitreoretinal surgeons and diabetic retinopathy experts. The group defined the current treatment pathway for DMO in the UK, which is based on whether a patient is centre-involving (i.e. where the fovea or immediate area around the fovea are affected) or non-centre-involving (i.e. extra-foveal), their central retinal thickness (CRT; i.e. > 400 µm or < 400 µm), and their lens status (i.e. phakic or pseudophakic).[19] The pathway for anti-VEGFs based on NICE TAs for eyes with CRT > 400 µm is presented in Figure 2.[19]

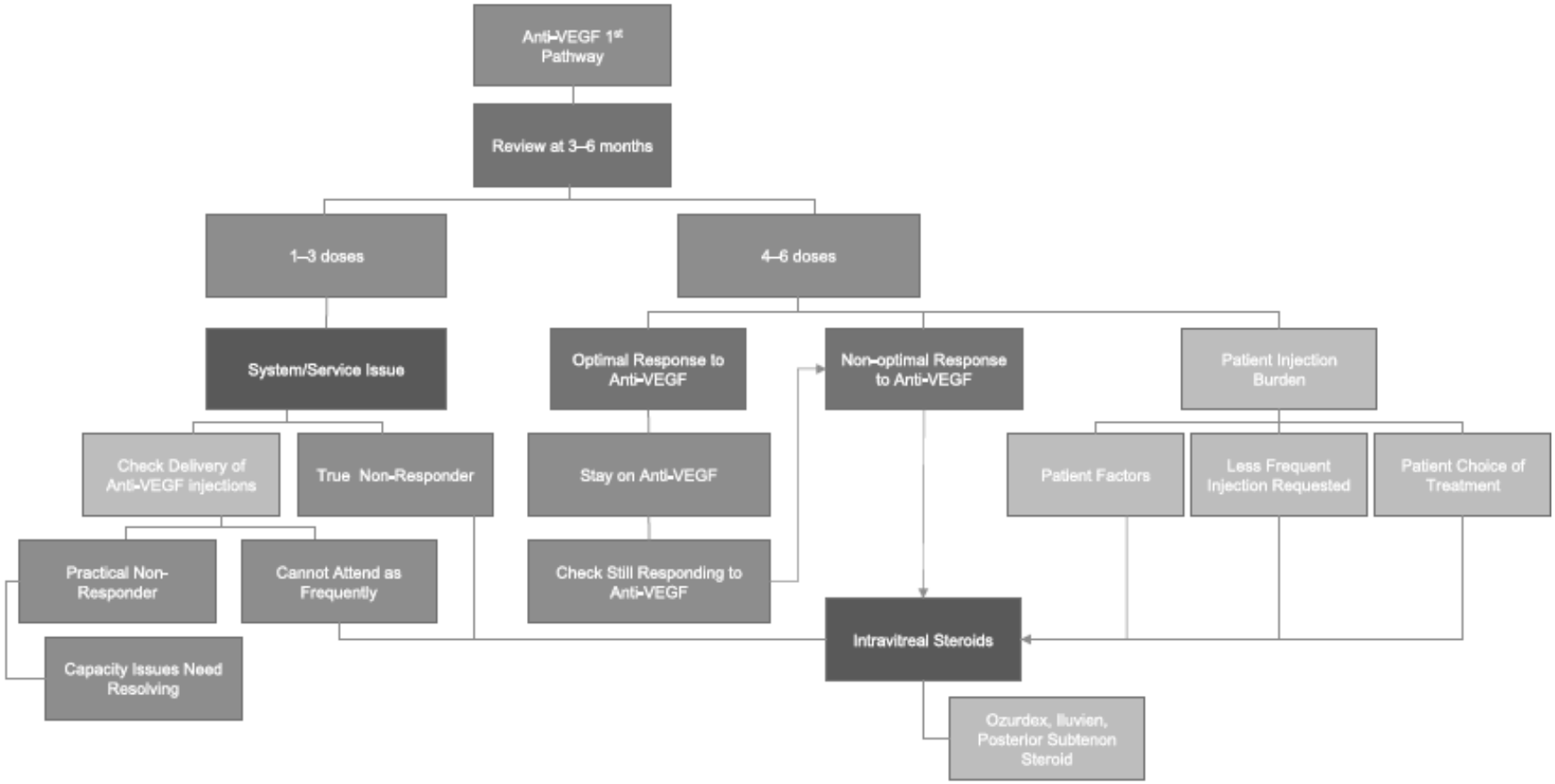
For patients with a CRT < 400 µm, dexamethasone intravitreal implant is the primary recommended treatment option for pseudophakic DMO patients, and either dexamethasone intravitreal implant, bevacizumab (Avastin®) or watch and wait are recommended for phakic DMO patients.[19] Anti-VEGFs are primarily recommended for patients with a CRT > 400 µm; however, intravitreal steroids (including dexamethasone intravitreal implant) are recommended for patients unsuitable for or insufficiently responsive to anti-VEGF therapy, or in patients who experience an injection burden with anti-VEGF (including those who cannot frequently attend appointments; Figure 3).[19] In the vast majority of literature, patients who are insufficiently responsive to non-corticosteroid treatment are defined as have < 5 letters gain at 6 months post-treatment.

Figure 2: Existing UK treatment pathway for DMO



Key: CRT, central retinal thickness; CFT, central foveal thickness; CNV, choroidal neovascular membrane; DMO, diabetic macular oedema; IFR, individual funding request; VEGF, vascular endothelial growth factor.
Note: CRT and CFT are considered in the same box of the flow diagram.
Currently, some clinicians resort to IFRs in order to treat patients with DMO and CRT <400 µm who are not pseudophakic. However, this can be cumbersome and challenging on account of rejection due to financial constraints or poor appreciation of the clinical need. No further information was provided within the publication regarding IFR requests.
Source: Amoaku et al., 2020.[19]

Figure 3: Existing UK DMO 'anti-VEGF first-line' pathway: based on NICE TAs for eyes with CFT/CRT > 400 µm



Key: CRT, central retinal thickness; CFT, central foveal thickness; DMO, diabetic macular oedema; VEGF, vascular endothelial growth factor.
Source: Amoaku et al., 2020.[19]

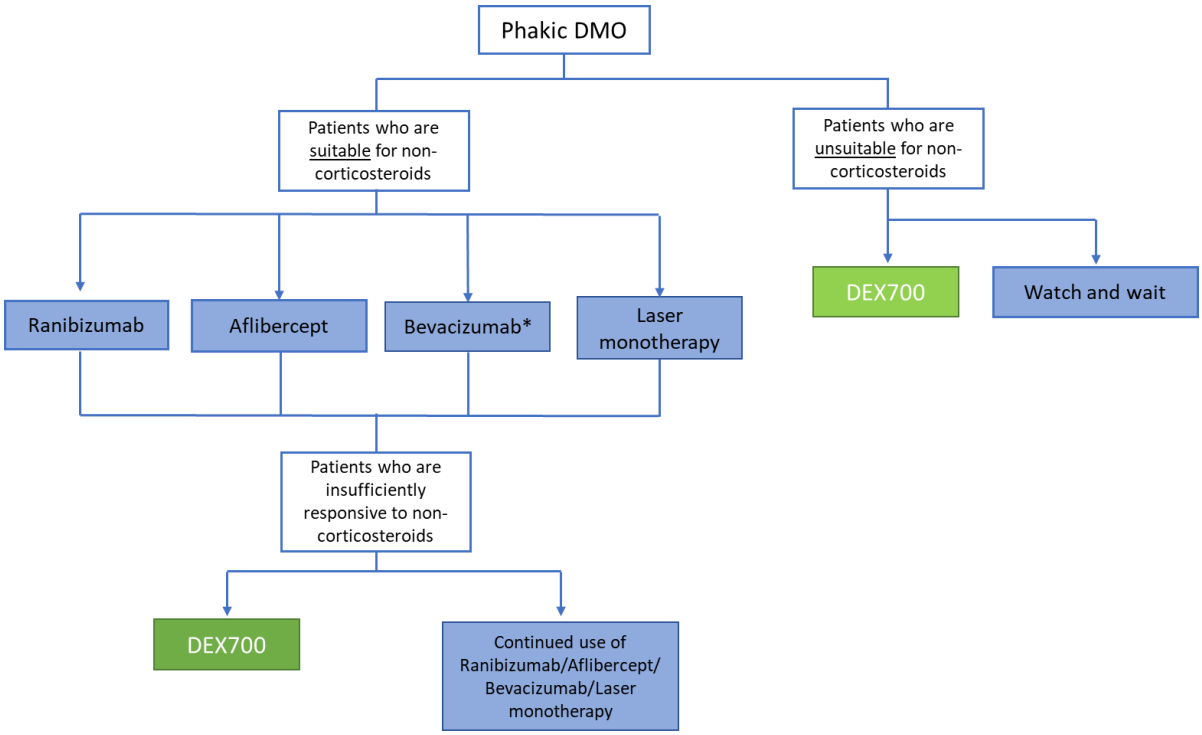
B.1.3.4.2 Current treatment options and relevant comparators for DEX700

To date, NICE have recommended pharmacological therapies for DMO patients in eyes with a CRT ≥ 400 µm. Current recommended pharmacological treatment options for patients with pseudophakic DMO who are unsuitable for or insufficiently responsive to non-corticosteroid treatment include the continued use of anti-VEGFs, ranibizumab (Lucentis®; TA274)[70], aflibercept (Eylea®; TA346)[71], fluocinolone acetonide intravitreal implant (Iluvien®; TA301)[72] and DEX700 (Ozurdex; TA349)[7].

Of note, bevacizumab does not currently have a marketing authorization in the UK and is not recommended by NICE; any use of bevacizumab is therefore deemed off-label.[19] In light of this, bevacizumab is not considered a relevant comparator to DEX700 and is not discussed in this submission. UK clinicians have highlighted that use of bevacizumab in this indication is extremely rare in clinical practice. This has been confirmed through the UK RWE audit, which identified only [redacted] of phakic DMO patients were treated with bevacizumab. Therefore, as use of bevacizumab in the UK is off-label, it is not included in the economic evaluation for the submission.

The comparators of DEX700 have evolved since TA349, where the comparator for phakic DMO patients who are insufficiently responsive to non-corticosteroid treatment was watch and wait. Figure 4 presents the current clinical pathway of care based on the available treatment guidelines for patients with phakic DMO in England, and the proposed placement of dexamethasone 700 µg (DEX700).

Figure 4: Clinical pathway of care for phakic DMO patients and proposed placement for DEX700



Key: DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema.
Notes: * Bevacizumab does not currently have a marketing authorization in the UK and is not recommended by NICE; any use of bevacizumab is therefore deemed off-label.[19] In light of this, bevacizumab is not considered a relevant comparator to DEX700 and is not discussed in this submission.

In phakic DMO patients who are insufficiently responsive to non-corticosteroid treatment, continued use of anti-VEGF (ranibizumab or aflibercept, or off-label use of bevacizumab), or (rapidly declining use of) laser monotherapy are the currently available options. Aligning with the NICE final scope for this submission, the anti-VEGFs (ranibizumab or aflibercept, or off-label use of bevacizumab), and laser monotherapy were also the agreed comparators for the fluocinolone (Iluvien®) appraisal (TA613).[72] In phakic DMO patients who are unsuitable for non-corticosteroid treatment, watch and wait is the only available treatment option.

B.1.3.4.3 The unmet clinical need and proposed use of DEX700

Patients with DMO have a high clinical burden, with the associated visual impairment having a substantial negative impact on the patients' quality of life. Currently, there are

limited treatment options for patients with phakic eyes and DMO who are insufficiently responsive to or unsuitable for non-corticosteroid treatment. These patients represent a large proportion of the DMO patient population in the UK: approximately 40% of patients with DMO do not respond completely or are suboptimal responders to anti-VEGF, and up to 5% of DMO patients are unsuitable for non-corticosteroid treatment.[73] In the UK RWE audit, 64.8% of patients were identified as insufficiently responding to anti-VEGF treatment (based on having gained less than 5 letters after 6 months of treatment), although this is likely to be an over-estimate of the true proportion of insufficient responders due to the limitations of the study (Section B.2.6.4). Although the proportion of patients who are unsuitable for non-corticosteroid treatment is much lower, they represent a population with substantial unmet need given there are no recommended active treatment options.

The continued use of anti-VEGFs in patients who are insufficiently responsive to treatment is problematic for several reasons. Anti-VEGFs have a short-term duration of effectiveness and can require frequent administration and monitoring to achieve optimum efficacy, which poses a significant burden to both patients and the healthcare system.[6] Patients who are insufficiently responsive to anti-VEGFs require more frequent injections, even if the patient is not getting an effective response[9], which further increases the burden on both patients and the healthcare system. As previously discussed (Section B.1.3.3.3), frequent injections cause stress, anxiety and practical issues for patients, as well as potentially increasing the small risk of injection procedure related adverse events such as endophthalmitis and retinal haemorrhage. Therefore, the continued use of anti-VEGFs increases the patient burden and risk without providing additional clinical benefit.

Pertaining to this, clinicians have highlighted the prevalence of capacity issues in ophthalmology services in the UK, which are likely to have been exacerbated by COVID-19 and are expected to persist for some time after.[9, 74] Therefore, continued use of anti-VEGFs is adding to the existing burden and alternative options that can provide benefit to patients whilst reducing burden on the health system are increasingly important, as highlighted by the Royal College of Ophthalmologists in their guidance for the management of ophthalmology services during the COVID-19 pandemic.[75] Capacity constraints can cause further issues for patients who are

insufficiently responsive to anti-VEGFs, as patients will require a significant number of injections over a prolonged period in an attempt to achieve any level of response.[76] As presented in Section B.2.6.5.2, Protocol T reported on the frequency of anti-VEGF injections in visually impaired patients with patients centre-involved DMO. Protocol T was a randomized, double-masked trial and therefore all patients enrolled into the trial followed a strict monitoring schedule. Of note, the baseline characteristics reported in Protocol T were not aligned with those presented in the MEAD trials (as discussed in Section B.2.3.5.1). At the 2-year follow up, patients had received a mean of [redacted] anti-VEGF injections and the mean change in best-corrected visual acuity (BCVA) from baseline was [redacted] letters. This therefore suggests with a high injection frequency, there is some long-term gain in patients that were initially classified as insufficient responders (Section B.2.6.5). When comparing to the UK RWE audit (Section B.2.6.4), patients received an average of [redacted] injections and the mean change from baseline BCVA in insufficient responders was [redacted] letters at the 2-year follow up.[10] This therefore suggests that a much lower number of anti-VEGF injections does not result in the same long-term gains in BCVA. Furthermore, the BEVORDEX study compared the outcomes of eyes with DMO randomised to either DEX700 injections or bevacizumab over 2 years. A mean of 9 DEX700 injections were administered in comparison to 19.2 anti-VEGF injections. This study demonstrates the high burden of anti-VEGF injections in comparison to DEX700, with a similar proportion of eyes from each treatment arm gaining ≥10 letters at 5 years from enrolment in the BEVORDEX trial.

Since anti-VEGFs and DEX700 have been available for use, the treatment landscape for DMO patients has evolved, and use of laser monotherapy has reduced. Laser monotherapy has also been shown to have limited efficacy, and rather than improve vision, laser therapy slows the deterioration of vision in patients with DMO in the majority of patients.[4, 5] Furthermore, laser photocoagulation can reduce the risk of moderate vision loss in DMO, but most patients do not regain visual acuity that has been lost.[77-79] As part of the fluocinolone acetonide reappraisal (TA613), it was suggested that laser therapies were used in 28% of patients with DMO; however, recent reviews of the treatment landscape suggest the percentage of DMO patients treated with laser is lower.[80, 81] This view was supported by clinicians at an advisory

board conducted in 2021 who indicated that lasers are used less frequently, suggesting that the rates of use may be down 15–20% since TA613.[9, 81] Furthermore, laser monotherapy is not recommended for use in patients with clinically significant DMO where the centre of the macula is involved[9], and has progressively been phased out as it resulted in macular scars that increased in size over time and could potentially lead to secondary vision loss.[80] Due to the reduced use and limited efficacy, laser therapy is not deemed a relevant comparator to DEX700, however some limited use of laser is explored in economic scenario analyses.

Overall, there remains a substantial unmet clinical need for a new treatment option for patients with phakic eyes and DMO who are insufficiently responsive to or unsuitable for non-corticosteroid treatment, one that is safe, effective and reduces the burden on patients and society. The unmet need in these patients is recognized by the clinical community. As such, the proposed target population for DEX700 (in addition to the current recommendation [TA349]) is patients with phakic eyes and DMO who are insufficiently responsive to or unsuitable for non-corticosteroid treatment. This use of DEX700 in phakic DMO patients is supported by the UK Consensus Working Group (see Section B.1.3.4.2).[19] In addition, clinicians expressed a clear desire to use DEX700 in phakic DMO patients.

B.1.4. Equality considerations

No equality considerations relating to the use of DEX700 have been identified or are anticipated.

B.2. Clinical effectiveness

- **The MEAD trials are the most robust data source providing evidence for the use of DEX700 in phakic DMO patients who are unsuitable for, or insufficiently responsive to non-corticosteroid treatment[82]**
  - DEX700 (n = [redacted]) resulted in a greater mean change in BCVA measured from baseline to 39 months compared to sham (n = [redacted]), although the results were not statistically significant ([redacted] versus [redacted] letters, respectively; [redacted])[82]
  - At 39 months, a significantly greater number of DEX700 patients achieved a BCVA improvement of ≥ 10 letters and ≥ 15 letters from baseline compared to sham ([redacted] and [redacted], respectively)[82]

- **Outcomes in the sham arm were considered as a best-case scenario of the expected effectiveness of watch and wait patients in clinical practice, and therefore considered an overestimation of the outcomes of watch and wait therapy**
- **MEAD subgroup analyses assess the impact of DEX700 in phakic DMO patients who more closely resemble those treated in UK clinical practice[83]**
  - Exploratory sub-analyses were performed to assess the impact of the timing of cataract surgery/DEX700 injection prior to cataract surgery, lens opacity, prior treatment and cataracts on visual outcomes[6]
- **Published RWE studies of DEX700 suggest that visual outcomes may be better than the DEX700 arm of the MEAD studies**
  - Several RWE studies demonstrate a clinical benefit with DEX700 in DMO patients who are insufficiently responsive to anti-VEGFs; published RWE reported no statistical difference between phakic and pseudophakic DMO patients receiving DEX700 for the mean maximum BCVA change from baseline to final follow-up[84-90]
- **A UK RWE audit was conducted of [redacted] eyes ([redacted] patients) who underwent treatment for DMO with anti-VEGFs[10]**
  - At 6 months, [redacted]% of eyes had a suboptimal response to treatment (i.e. a ≤ 5 letter gain) and despite an average of [redacted] and [redacted] injections, mean change from baseline BCVA in insufficient responders was [redacted] and [redacted] letters at 2 and 4 years
- **Indirect treatment comparisons (ITCs) were subject to high levels of uncertainty, mainly driven by differences in baseline BCVA across evidence sources, resulting in inconclusive results**

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify randomized controlled trial (RCT) data and RWE for phakic DMO patients who are unsuitable for or insufficiently responsive to non-corticosteroid treatment. This SLR covered a broad range of interventions used globally; the results of the SLR were then further refined to align with the decision problem addressed in this submission. Of the 44 studies (extracted from 94 publications) identified by the SLR, 25 evaluated the use of DEX700. Full details of the process and methods used to identify and select the relevant evidence are presented in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

Table 4 presents a summary of the evidence presented in this submission, either in support of the use of DEX700 in phakic DMO patients, or to present RWE for comparator treatments.

Table 4: Summary of evidence used in the submission

Study name	Primary clinical evidence	Supportive clinical evidence	Economic model base case
DEX700			
MEAD-010/MEAD-011	✓	×	✓
MEAD-010/MEAD-011 subgroup analyses	×	✓	×
DEX700 published RWE studies	×	✓	×
French RWD	×	✓	×
Comparator treatments			
UK RWE audit	✓	×	✓
Protocol T	×	✓	×

Key: DEX700, dexamethasone 700 µg; RWD, real-world data; RWE, real-world evidence.
Notes: A full list of published RWE studies is provided in Section B.2.2.1.1 (Table 6). Of note, the efficacy for the comparator is based on the sham data presented in MEAD. Efficacy data from the UK RWE audit has been used to inform treatment costs and scenario analysis only.

B.2.2.1 Available evidence for DEX700

The clinical SLR identified seven RCTs, of which two were considered the most robust data sources providing evidence for the use of DEX700 in phakic DMO patients who are unsuitable for or insufficiently responsive to non-corticosteroid: MEAD-010 and MEAD-011. Table 5 provides a summary of the two MEAD trials. The MEAD trials provide information on 1,048 patients relevant to the decision problem, with a maximum follow-up of 39 months.

Table 5: Clinical effectiveness evidence

Study title	MEAD-010	MEAD-011
Trial number	NCT00168389	NCT00168337
Study design	Phase 3, multicentre, masked, randomized, sham-controlled trial	
Population	Patients aged > 18 years diagnosed with Type 1 or 2 diabetes mellitus who had fovea-involved macular oedema associated with diabetic retinopathy and had been previously treated with medical or laser therapy. Treatment-naïve patients who had refused laser treatment or who, in the opinion of the investigator, would not benefit from laser treatment were also enrolled.	
Intervention	700 µg dexamethasone posterior segment drug delivery system applicator system (DEX700) 350 µg dexamethasone posterior segment drug delivery system applicator system (DEX350)	
Comparator	Needleless applicator system (Sham)	
Indicate if trial supports application for marketing authorization (yes/no)	Yes	Yes
Indicate if trial used in the economic model (yes/no)	Yes	Yes
Rationale for use/non-use in the model	Supportive evidence for the use of DEX700 in phakic DMO patients.	
Reported outcomes specified in the decision problem	• Best corrected visual acuity (the affected eye) • Best corrected visual acuity (both eyes) • Central foveal subfield thickness • Central retinal thickness • Contrast sensitivity • Mortality • Need for cataract surgery • Adverse effects of treatment (including cataract formation and glaucoma) • Health-related quality of life, including the effects of changes in visual acuity	
All other reported outcomes	N/A	

Key: BCVA, best-corrected visual acuity; CRT, central retinal thickness; DMO, diabetic macular oedema.
Source: Boyer et al. 2014.[82]

B.2.2.1.1 Published DEX700 studies

Two MEAD sub-analyses (Maturi et al. 2016[91] and Augustin et al. 2015) have been identified for inclusion within the published DEX700 studies, and are further discussed within Sections B.2.3.2 and B.2.6.2. A further supportive RCT (Cornish et al. 2021[92]; BEVORDEX) was identified by the SLR for inclusion and has been used later within the submission.

The SLR also identified 21 RWE studies. The SLR inclusion criteria (as presented in Appendix D.1.2) was set to address the decision problem of interest, however given the highly specific patient population of interest, limited evidence was identified. Therefore, a number of RWE studies relevant to the decision problem that did not meet the inclusion criteria of the SLR that were known to AbbVie are also included in this submission. Table 6 presents a list of all published RWE studies identified for inclusion and cross-references to their relevant sections within the submission.

Of note, five published RWE studies have presented results for concomitant use of DEX700 with other treatments, primarily anti-VEGFs. These studies have been highlighted grey in Table 6 below, and further discussed in Section B.2.3.2.

Table 6: Summary of real-world evidence

Study	Section(s)
Studies identified from the SLR	
Pareja-Ríos et al. 2018[93]	B.2.3.2, B.2.6.2.2, B.2.10.2
Kaldırım et al. 2020[85]	B.2.3.2, B.2.6.2.1, B.2.6.2.2
Mathis et al. 2020[87]	B.2.3.2, B.2.6.2.1, B.2.10.2, B.2.6.2.4
Chatziralli et al. 2017[94]	B.2.3.2, B.2.6.2.2, B.2.10.2
Aydin et al. 2019[95]	B.2.3.2, B.2.6.2.2, B.2.10.2
Zhioua et al. 2015[96]	B.2.3.2, B.2.6.2.2, B.2.10.2
Cavalleri et al. 2019[97]	B.2.3.2, B.2.6.2.2, B.2.10.2
Al-khersan et al. 2019[98]	B.2.3.2, B.2.10.2
Al-khersan et al. 2017[99]	B.2.3.2, B.2.10.2
Cicinelli et al. 2017[100]	B.2.3.2, B.2.6.2.2, B.2.10.2
Park & Park, 2020[101]	B.2.3.2, B.2.10.2
Iglicki et al. 2019[102]	B.2.3.2, B.2.6.2.2, B.2.6.2.3, B.2.10.2
Akıncıoğlu et al. 2019[103]	B.2.3.2, B.2.10.2
Scaramuzzi et al. 2015[104]	B.2.3.2, B.2.10.2
De Geronimo et al. 2019[105]	B.2.3.2, B.2.6.2.2, B.2.10.2

Bansal et al. 2016[106]	B.2.3.2, B.2.6.2.2
Augustin et al. 2015[107]	B.2.3.2, B.2.6.2.2, B.2.10.2
Hsia et al. 2021[108]	B.2.3.2, B.2.6.2.2, B.2.10.2
Al-Latayfeh et al. 2021[109]	B.2.3.2, B.2.6.2.2, B.2.10.2
Bux et al. 2021[110]	B.2.3.2, B.2.6.2.2, B.2.10.2
Singer et al. 2018 (REINFORCE)[89]	B.2.3.2, B.2.6.2.1
Studies known to AbbVie	
Kodjikian et al. 2018[81]	B.2.3.2, B.2.6.2, B.2.10.2
Malclès et al. 2017 (RELDEX)[86]	B.2.3.2, B.2.6.2.1, B.2.10.2, B.2.6.2.4
Mello Filho et al. 2017[88]	B.2.3.2, B.2.6.2.1
Guigou et al. 2015[84]	B.2.3.2, B.2.6.2.1, B.2.10.2
Maturi et al, 2016[91]	B.2.3.2, B.2.10.2
Rosenblatt et al. 2020	B.2.3.2, B.2.6.2.2, B.2.10.2
Sharma et al, 2020[111]	B.2.3.2, B.2.10.2
Wallsh et al. 2020[90]	B.2.3.2, B.2.6.2.1
Kabanarou et al. 2020[112]	B.2.3.2, B.2.10.2, B.2.6.2.4
Garcia Layana et al. 2019[113]	B.2.3.2, B.2.6.2.3,
Bilgic et al. 2019[114]	B.2.3.2, B.2.6.2.3, B.2.10.2
Busch et al. 2019[76]	B.2.3.2, B.2.6.2.2
Unsal et al. 2017[115]	B.2.3.2, B.2.6.2.2
Hernández Martínez et al. 2020[116]	B.2.3.2, B.2.6.2.2
Demir et al. 2020[117]	B.2.3.2, B.2.6.2.2
Ozsaygili & Duru. 2020[118]	B.2.3.2, B.2.6.2.3, B.2.10.2
Menezo et al. 2019[119]	B.2.3.2, B.2.6.2.3, B.2.10.2
Rajesh et al. 2019[120]	B.2.3.2, B.2.10.2
Rezkallah et al. 2021[121]	B.2.3.2, B.2.10.2
Pinto et al. 2021[122]	B.2.3.2, B.2.6.2.3, B.2.10.2
Goldberg et al. 2021[123]	B.2.3.2, B.2.6.2, B.2.10.2
Modi et al. 2021[124]	B.2.3.2, B.2.6.2, B.2.10.2
Notes: Boxes highlighted in grey represent studies which reported on the concomitant use of DEX700 injections and other treatments, primarily anti-VEGFs.	

B.2.2.1.2 French RWD

In addition to the DEX700 RWE studies introduced in Section B.2.2.1.1, one additional collaborative study by AbbVie and PI was conducted to explore outcomes of DEX700 in treatment-naïve and/or previously treated DMO patients with phakic and pseudophakic eyes. Existing databases have been used to provide data, all of which have previously reported and published outcomes in phakic DMO:

- RELDEX 1 and RELDEX 2
- SAFODEX 1 and SAFODEX 2
- NAVEDEX

Further details on the methodology and results of the trial are presented in Section B.2.3.4 and B.2.6.4, respectively.

B.2.2.2 Available evidence for comparators

B.2.2.2.1 UK RWE audit

A UK RWE audit of UK clinical practice was conducted to identify the proportion of phakic DMO patients who were insufficient responders after the initial 3 and 6 months of anti-VEGF injections. Further details on the methodology and results of the trial are presented in Section B.2.3.3 and B.2.6.4, respectively.

B.2.2.2.2 Post-hoc analysis of Protocol T

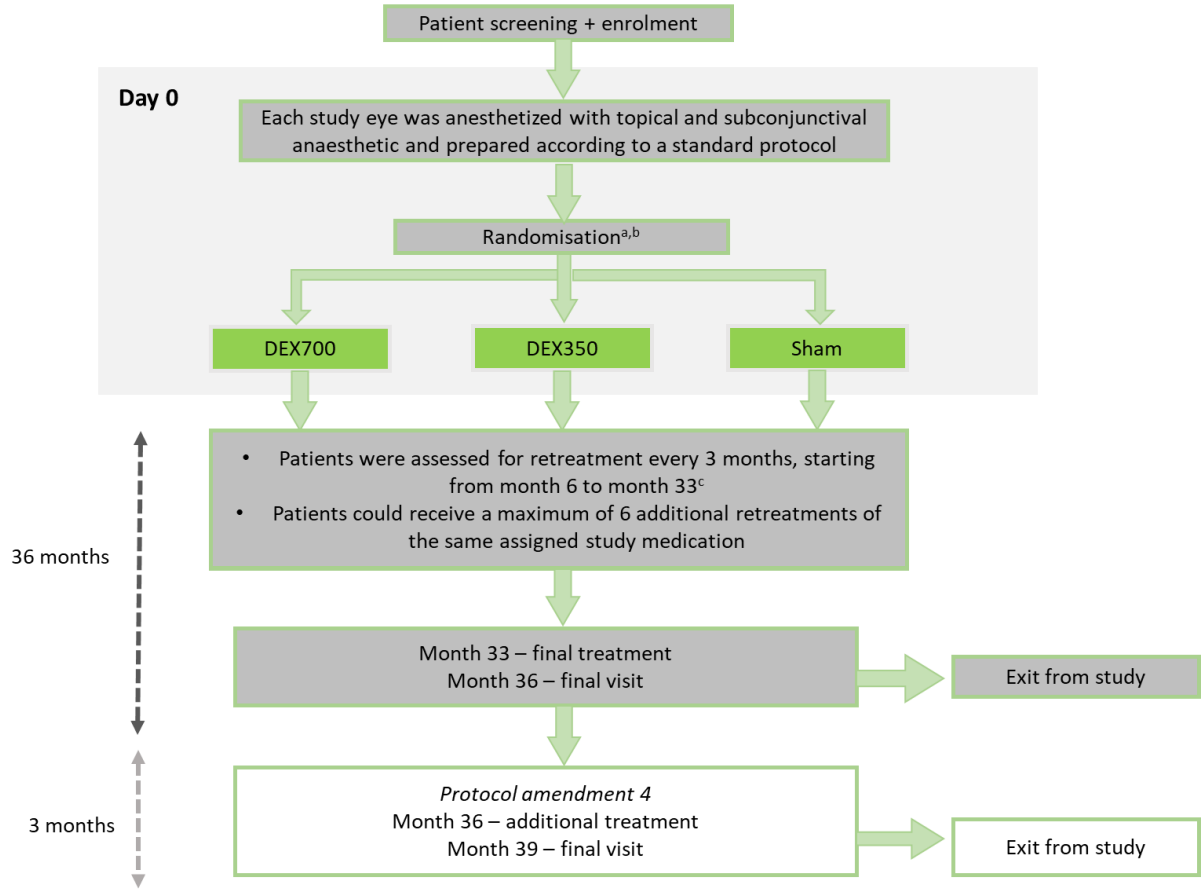
Also in support of this submission is a retrospective analysis of publicly available data from the Protocol T study. Protocol T was a US-based randomized controlled trial conducted to assess outcomes in patients with DMO receiving anti-VEGF treatment (aflibercept, ranibizumab or bevacizumab) over a period of 2 years (followed by a 5-year follow-up extension study).[125, 126] Results have also been published investigating outcomes based on initial response to anti-VEGF.[127] Further details on the methodology and results of the trial are presented in Section B.2.3.5 and B.2.6.5, respectively.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 MEAD-010 and MEAD-011

MEAD-010 and MEAD-011 were two 3-year, Phase III, multicentre, masked, randomized, sham-controlled trials designed to assess the safety and efficacy of DEX700 and DEX350 (i.e. dexamethasone 350 µg intravitreal implant in applicator) in patients with DMO.[82]

Figure 5: Study design schematic (MEAD-010 and MEAD-011)



Key: DEX350, Dexamethasone 350 µg intravitreal implant; DEX700, Dexamethasone 700 µg intravitreal implant; OCT, optical coherence tomography.
Notes: [a]Patients randomized to active treatment (DEX350 or DEX700) had the study drug placed into the vitreous through the pars plana using the Dexamethasone posterior segment drug delivery system (DEX PS DDS). Patients randomized to Sham treatment had the needleless applicator pressed against the conjunctiva to preserve masking.
[b]At the visit preceding the study treatment procedure, the patient was given a bottle of gatifloxacin or ofloxacin ophthalmic solution (where available); otherwise an ophthalmic fluoroquinolone (such as ciprofloxacin) or an ophthalmic aminoglycoside (such as gentamicin or tobramycin) was used. Patients were to instil a drop in the study eye 4 times per day for 3 days prior to the study treatment procedure, up to 4 times per day on the day of the procedure, and 4 times per day for 3 days post-operatively.
[c]Patients were eligible for retreatment if retinal thickness in the 1 mm central macular subfield by OCT was > 175 µm or upon investigator interpretation of the OCT for any evidence of residual retinal oedema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the centre subfield).

Study visits were scheduled every 1.5 months during the first year and every 3 months during Years 2 and 3.[82] In addition, patients were seen at safety visits 1, 7, and 21 days after study treatment or retreatment. After a study protocol amendment in May 2010, patients who had not yet completed the study and who met retreatment eligibility criteria were retreated at Month 36 and followed at an additional study visit at Month

39. Over 50% of patients had completed or discontinued the study before the protocol amendment.[82]

Table 7 presents an overview of the methodology of the MEAD trials; note that the trial design, endpoints and patient eligibility criteria were consistent between the two trials.

Table 7: Summary of MEAD study methodology

Trial name	MEAD-010	MEAD-011
Location	59 study centres in 10 countries (Australia, Canada, Czech Republic, Germany, Israel, Philippines, Portugal, South Africa, Spain and the US)	72 study centres in 14 countries (Brazil, Canada, Colombia, France, Hungary, India, Italy, New Zealand, Poland, Singapore, South Korea, Taiwan, the UK and the US)
Trial design	Multicentre, masked, randomized, sham-controlled, Phase III study (36–39 months) designed to assess the efficacy and safety of 700 µg and 350 µg dexamethasone posterior segment drug delivery system in the treatment of patients with DMO	
Key eligibility criteria for patients	**Inclusion criteria** • Aged ≥ 18 years • Diagnosis of Type 1 or Type 2 diabetes mellitus • 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 ≥ 300 µm by OCT – Negative pregnancy test – Written informed consent, written data protection consent, and 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 4 mg 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 **Exclusion criteria** • Uncontrolled systemic disease or current immunosuppressive diseases	

Trial name	MEAD-010	MEAD-011
	• Initiation of medical therapy for diabetes mellitus 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 > 23 mmHg if taking no anti-glaucoma medications or IOP > 21 mmHg if taking one anti-glaucoma medications or taking two or more anti-glaucoma medications • Aphakia or presence of anterior chamber intraocular lens • Active optic disc or retinal neovascularization • Active or history of choroidal neovascularization • 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 triamcinolone • History of use of intravitreal bevacizumab, ranibizumab, or pegaptanib	
Settings and locations where the data were collected	Each site had a treating investigator who administered the study treatment and performed post-injection safety evaluations up to Day 21 after each treatment.	
Trial treatments	**Interventions** 700 µg dexamethasone posterior segment drug delivery system applicator system (DEX700) 350 µg dexamethasone posterior segment drug delivery system applicator system (DEX350) **Comparator**	

Trial name	MEAD-010	MEAD-011
	Needleless applicator system (Sham)	
Permitted and disallowed concomitant medication	Therapy considered necessary for the patient's welfare could be given at the discretion of the investigator: • **Treatment of elevated IOP**: for elevated IOP in the study eye up to 30 mmHg, the need for treatment was at the discretion of the investigator, based on the patient's risk factors for optic nerve damage. For IOP > 30 mmHg, consultation with a glaucoma specialist was recommended • **PRP**: it was expected that some patients would develop proliferative diabetic retinopathy within the study period. The decision to perform PRP was left to the discretion of the investigator and the patient. Efforts were to be made to avoid PRP within 30 days prior to a retreatment visit • **Cataract surgery**: it was expected that some patients would develop cataracts within the study period. The decision to perform cataract surgery was left to the discretion of the investigator and the patient. Efforts were to be made to avoid cataract surgery within 30 days prior to a retreatment visit. The surgery was to take place within 3 months of the last retreatment. For sites that were selected to measure endothelial cell density, and whose patients underwent cataract surgery during the study, endothelial cell density measurements were to be performed pre- and post-surgery within 2 months before and within 1 to 3 months after the surgery • Topical steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) were allowed up to 6 weeks following cataract surgery, if required per postoperative standard practice • **Inflammatory condition in the non-study eye**: if there was an inflammatory condition in the non-study eye, topical steroids or periocular or intravitreal steroid injections could be used • **Macular oedema in the non-study eye**: macular oedema in the non-study eye could be treated with laser and/or local therapies (e.g. topical, periocular, intravitreal). Systemic therapies (e.g. oral or parenteral steroids, systemic anti-VEGFs) and doses of intravitreal anti-VEGFs higher than the doses detailed in the exclusion criteria were not to be used • **Use of systemic NSAIDs**: if systemic NSAIDs (e.g. Celebrex® [celecoxib], and ibuprofen) were regularly used prior to enrolment, those medications could be continued during the study The following were prohibited during the study: • Dexamethasone during the first 90 days of the study in any form or route for patients who participated in therapeutic drug monitoring • Systemic steroids • Immunosuppressants (e.g. cyclosporine), immunomodulators (e.g. interferon), antimetabolites and alkylating agents (e.g. 5-fluorouracil, cyclophosphamide), or other chemotherapeutic	

Trial name	MEAD-010	MEAD-011
	agents except for topical ocular cyclosporine (RESTASIS®) • Warfarin or heparin • Additional non-study procedures or surgery in the study eye except for cataract surgery or PRP • Dialysis • Escape therapy for macular oedema in the study eye including intravitreal steroids other than the study medication, periocular steroids, laser or surgical treatments for macular oedema, anti-VEGF therapy, systemic anti-VEGF therapy, and other pharmacologic therapy for macular oedema	
Primary outcomes (including scoring methods and timings of assessments)	Mean BCVA average change from baseline[a]. BCVA was measured using the ETDRS method. Average change in the study eye was measured using the AUC approach.	
Other outcomes used in the economic model/specified in the scope	• Proportion of patients receiving treatment • Treatment discontinuation rates • Rate of cataract surgery • AE rates (including elevated intraocular pressure)	
Pre-planned subgroups	Patients were analysed by: • The duration of diabetes • The duration of DMO • Their baseline HbA1c • Prior laser treatment (yes/no) • Treatment-naïve (yes/no) • Their lens status at baseline • NPDR severity at baseline • Country	

Key: AE, adverse event; AUC, area under curve; BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DMO, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; GFR, glomerular filtration rate; HbA1c, haemoglobin A1c; IOP, intraocular pressure; NPDR, non-proliferative diabetic retinopathy; NSAIDs, non-steroidal anti-inflammatory drugs; OCT, optical coherence tomography; OHT, ocular hypertension; PRP, panretinal photocoagulation.
Notes: [a], the primary outcome measure of clinical efficacy for Europe was mean change in average BCVA from baseline. 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. This amendment was in line with changes in regulatory precedent and standard of care for DMO in the period over which the MEAD studies were conducted.
Source: Boyer et al. 2014[82]; MEAD-010 CSR[128]; MEAD-011 CSR.[129]

B.2.3.1.1 Patient baseline demographics and disease characteristics of patients in the MEAD studies

Table 8 presents the pooled baseline demographics and disease characteristics for phakic DMO patients in the MEAD-010 and MEAD-011 studies. Patient disposition data for the MEAD studies are presented in Appendix D.3, alongside a Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow for each trial. At the time the MEAD trials were designed, there were no approved pharmacologic treatments for DMO, and therefore anti-VEGFs were not widely used by patients enrolling into the study. In total, only [redacted] of patients treated with DEX700 had received prior anti-VEGF treatment.

Overall, the baseline demographics and disease characteristics were well balanced between treatment arms. However, several baseline characteristics are worth noting, including the proportion of patients with lens opacity and the proportion of patients with pre-existing cataracts. Of note, patients who are diagnosed with a cataract may not concurrently experience clinically significant lens opacity, and therefore the patients' vision will not be affected. If the patient develops lens opacity which affects their visual acuity, the patient may be put forward for cataract extraction.

In the MEAD trials, [redacted] of phakic DMO patients had pre-existing cataracts at baseline. As presented in Section B.2.3.4.1, the proportion of patients in UK clinical practice with pre-existing cataracts tends to be lower, with the UK RWE audit reporting [redacted] of phakic DMO patients having pre-existing cataract, and the published RWE reporting 40%.[130] In the DEX700 group of the MEAD trials, the proportion of patients with lens opacity at baseline was confirmed in [redacted] of patients, and labelled as questionable in a further [redacted] of patients. Although the UK RWE audit did not provide sufficient information to accurately estimate the proportion of phakic DMO patients with lens opacity, clinical experts have stated that this tends to be much lower in UK clinical practice. As the baseline characteristics in the MEAD trials tend to be poorer than those observed in clinical practice, the outcomes of MEAD can be classified as being conservative.

Table 8: Patient baseline demographics and disease characteristics of phakic DMO patients in the MEAD trials (pooled data)

	DEX700 (n = [redacted])	Sham (n = [redacted])
Mean age, years (SD)	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Treated eye, n (%)		
Better seeing eye	[redacted]	[redacted]
Worse seeing eye	[redacted]	[redacted]
Bilateral DMO, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior laser, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior anti-VEGF, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
BCVA < 50 letters, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Treatment-naïve at baseline, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
DMO duration > 1.3 years[a], n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
DMO duration ≥ 3 years, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
CRT ≥ 400 microns, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Cataract, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Lens opacity, n (%)		
Questionable	[redacted]	[redacted]
Present	[redacted]	[redacted]
Absent	[redacted]	[redacted]

Key: CRT, central retinal thickness; DMO, diabetic macular oedema; SD, standard deviation; VEGF, vascular endothelial growth factor.
Notes: [a] A DMO duration of 1.3 years was based on the median of the intention-to-treat population of the MEAD clinical trials.
Source: AbbVie, 2021 (MEAD subgroup analysis – baseline characteristics).[131]; Exploratory analysis slide deck, version 2.2. [83]

B.2.3.2 DEX700 real-world evidence studies

As presented in Section B.2.2, 43 RWE studies deemed relevant to the decision problem have been published since the TA349 submission in July 2015, of which, 21 were identified from the SLR and 22 were known to AbbVie. Further details on the SLR conducted for this submission are presented in Appendix D.1, and the methodology of the 43 included RWE studies are presented in Appendix M.1.1.

A review of real-world observational studies was conducted on PubMed to identify all articles investigating the efficacy of anti-VEGFs (ranibizumab, aflibercept and bevacizumab) and DEX700 in DMO patients between 2005 and 2016.[81] Each of the included studies primarily reported on the change in visual acuity from baseline. The initial PubMed search, followed by primary screening identified 32 studies evaluating the efficacy of anti-VEGF, and 31 evaluating the efficacy of DEX700, totalling 6,842 eyes and 1,703 eyes, respectively. Results of this review are presented in Section B.2.6.2.

Of the remaining 42 studies, the number of patients treated with DEX700 in each study ranged from 12 to 1,434. The number of phakic and pseudophakic DMO patients was presented in 37 (90.2%) studies, in which most studies enrolled a fairly even ratio of phakic to pseudophakic DMO patients.

Of note, two of the 41 studies reported on a sub-analyses of the pooled MEAD trials, and therefore present an overlapping patient population with the patients acknowledged within Sections B.2.3.1 and B.2.6.1 of this submission.[91, 107]

Seven RWE studies reported on the visual outcomes in patients with phakic DMO versus pseudophakic DMO (Section B.2.6.2.1), 21 RWE studies reported on the clinical benefit with DEX700 in DMO patients who are insufficiently responsive to anti-VEGFs (Section B.2.6.2.2) and seven RWE studies reported on the outcomes of treatment-naïve patients with DMO (Section B.2.6.2.3).

Out of the 38 studies where length of follow-up was reported, 34 studies had a follow-up period of at least 6 months. A range of study outcomes were measured, although most studies reporting on efficacy had change in BCVA from baseline as the primary outcome.

Studies reporting on safety outcomes primarily reported the proportion of patients with cataracts, or the proportion of patients requiring cataract surgery (Section B.2.10.2.1). Several studies also reported on the change in intraocular pressure (IOP) and any related adverse events (AEs) or administered medication during the study follow-up (Section B.2.10.2.2).

B.2.3.2.1 Patient baseline demographics and disease characteristics

Baseline characteristics were well balanced among the published RWE studies. Summaries of the patient baseline demographics and disease characteristics of all relevant published RWE studies are provided in Appendix M.1.1.1.

As introduced in Section B.2.3.2, a review was conducted to identify articles on the efficacy of anti-VEGF and DEX700 for treating DMO patients.[81] For the anti-VEGF studies, patients had a mean BCVA of 57.3 letters, with a range of 38 – 72 letters. The mean follow-up was 15.6 months (6–48 months). In the DEX700 studies, patients had a mean BCVA of 51.5 letters (range: 18.8 – 72.5 letters), and the mean follow-up was 10.3 months (6 – 36 months).

In most studies, the mean patient age fell between 65 and 70 years, and approximately 50–60% of patients were male. The mean duration of diabetes ranged from 8.7 to 23.1 years. A high proportion of patients had undergone previous DMO treatment, including anti-VEGF treatments (e.g. ranibizumab and/or bevacizumab), focal/grid laser and steroid injections (e.g. triamcinolone). Anti-VEGFs were the most commonly administered prior treatment. In MEAD, anti-VEGFs were only previously administered in [redacted] of phakic DMO patients.[131] Four RWE studies reported on treatment-naïve DMO patients. In MEAD, [redacted] of phakic DMO patients were treatment-naïve.[131]

Five studies reported the concomitant use of DEX700 with other treatments during the study follow-up.[89, 90, 102, 123, 124] Three studies specified the concomitant use of anti-VEGFs[90, 123, 124], one study specified the concomitant use of anti-VEGFs, fluocinolone acetonide implant, macular laser and/or pars plana vitrectomy with internal limiting membrane peeling[102] and the remaining study did not specify which treatments were used alongside DEX700.[89] The outcomes presented from these five studies should therefore be considered with this in mind.

Mean baseline BCVA was measured in approximate ETDRS letters in 18 studies, and logarithm of the minimal angle of resolution (LogMAR) in 16 studies. The mean baseline BCVA ranged from 29.6 to 64.2 letters, although a high majority of studies reported a baseline BCVA between 50 to 60 letters.[84, 86-89, 92, 94, 105, 107, 119, 122] In the studies that reported mean BCVA by LogMAR, the baseline values ranged from 0.44 to 0.88, with the majority reportedly between 0.50 and 0.70.[76, 85, 88, 99, 102-105, 117, 120] In the MEAD trials, the mean ETDRS at baseline for the DEX700 arm was [redacted] letters which aligns with that reported within the published RWE studies. The UK RWE audit did however report a higher mean baseline BCVA of [redacted] letters. Clinical experts have acknowledged that DMO patients in UK clinical practice are normally treated sooner in the treatment pathway, resulting in the patient having a higher baseline BCVA. Due to the limited treatment options available prior to 2015, a larger proportion of patients in the MEAD trial may have had DMO for a longer period of time. As the UK RWE audit observed UK clinical practice at a later timepoint (i.e. between 2015 and 2020), patients received anti-VEGF treatment which is now an established treatment option in UK clinical practice.

The published RWE did not provide sufficient information to accurately estimate the proportion of phakic DMO patients with lens opacity or presence of cataract at baseline. Section B.2.10.2.1 presents the proportion of phakic DMO patients with cataract progression and/or the proportion who underwent cataract surgery during the study follow-up.

B.2.3.3 French RWD

The French real-world data (RWD) study analysed pooled data from five chart review studies to explore outcomes following treatment with DEX700 in treatment-naïve or previously treated phakic eyes of DMO patients.[132] Outcomes were compared to those of pseudophakic eyes in order to demonstrate the absence of any significant differences in terms of efficacy, durability (i.e. number of injections) and safety.

RELDEX 2 and SAFODEX 2 included eyes of consecutive DMO patients at two hospitals in France who had received DEX700 between October 2010 and July 2017.

NAVEDEX included treatment-naïve patients who had received at least one DEX700 injection between 2011 and 2016 in 11 French centres. The inclusion criteria included treatment naïve patients who had not received any DMO treatment before, except for focal laser > 3 months prior to the study.

B.2.3.3.1 Patient baseline demographics and disease characteristics

In total, [redacted] eyes of [redacted] DMO patients were included in the study, with a mean age of [redacted] (standard deviation [SD] [redacted]) years. Baseline characteristics were well balanced between phakic and pseudophakic population. The mean (SD) baseline visual acuity was [redacted] ([redacted]) and [redacted] ([redacted]) in the phakic and pseudophakic populations, respectively.. Further baseline demographics have been presented in Appendix M.2.

B.2.3.4 UK RWE audit

A UK RWE audit was conducted to understand the potential unmet need in phakic DMO patients who have been treated with anti-VEGF injections.[10] This retrospective, cohort study used data from the electronic patient record database (Medisoft) of two ophthalmology centres in the UK between 2015 and March 2020.

The primary objective of the study was to identify the proportion of phakic DMO patients who were insufficient responders to initial anti-VEGF injections evaluated at month 3 and month 6, and to provide long-term data on visual acuity and anatomical outcomes for these patients.

B.2.3.4.1 Patient baseline demographics and disease characteristics

A total of [redacted] eligible eyes from [redacted] patients have undergone treatment for DMO with anti-VEGFs.[10] A summary table of the baseline characteristics of the patients enrolled in the UK RWE audit is presented in Appendix M.3.1.

The mean age for first anti-VEGF (first eye) is [redacted] years (SD [redacted]), with majority of patients being between [redacted] and [redacted] years at first treatment. At baseline, [redacted] ([redacted]) had no pre-existing cataract, whilst [redacted] ([redacted]) had evidence of pre-existing cataract. The mean best-reported visual acuity (BRVA) at baseline was relatively high ([redacted] letters), with [redacted] of patients reporting a mean baseline BRVA of >70 letters.

B.2.3.5 Post-hoc analysis of Protocol T

Protocol T was a US multicentre, randomized, double-masked trial conducted by the Diabetic Retinopathy Clinical Research (DRCR) Retina Network to compare the efficacy and safety of anti-VEGFs in the treatment of visually impaired patients with centre-involved DMO. Each patient was randomly assigned in a 1:1:1 ratio for treatment with aflibercept (2.0 mg), bevacizumab (1.25 mg), or ranibizumab (0.3 mg) which were administered as often as every 4 weeks.

A retrospective analysis of the publicly available 2-year data from the Protocol T study was conducted to assess whether the reported findings in patients who were insufficiently responsive after 12 weeks of treatment were consistent between phakic and pseudophakic eyes, and robust to alternative definitions of insufficient response.[127] The analysis pooled data from the 3 randomized anti-VEGF treatments and assessed the primary outcomes of BCVA change from baseline and 10-letter BCVA improvement at weeks 52 and 104.

B.2.3.5.1 Patient baseline demographics and disease characteristics

In total, [redacted] eyes met the inclusion criteria, in which [redacted] ([redacted]) were phakic and [redacted] ([redacted]) were pseudophakic at baseline. Phakic DMO patients were younger than pseudophakic DMO patients ([redacted] versus [redacted] years, respectively), and presented with a shorter duration of diabetes ([redacted] versus [redacted] years) and greater CRT ([redacted] versus [redacted] µm) at baseline, but had similar mean BCVA at baseline ([redacted] versus [redacted] letters).

The baseline characteristics reported in Protocol T were not fully aligned with those presented in the MEAD trials. Patients in Protocol T had a higher mean baseline BCVA ([redacted] letters) compared with patients enrolled into the MEAD trials ([redacted] and [redacted] letters in the DEX700 and Sham arms of MEAD, respectively). Furthermore, a higher proportion of patients were treatment-naïve in Protocol T ([redacted]) compared to MEAD ([redacted] and [redacted] in the DEX700 and Sham arms of MEAD, respectively).

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

For the MEAD trials, the primary outcome measure of clinical efficacy for Europe was mean change in average BCVA from baseline. 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. This amendment 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 five letters) is clinically meaningful.[133]

The primary outcome of mean BCVA average change from baseline was assessed using the area under the curve (AUC) approach, which considers the effect of multiple treatments and observation times during the entire 3-year study period. 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 and was accepted during TA349.[7, 134]

Table 9: Summary of statistical analyses, MEAD trials

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
MEAD-010 MEAD-011	The primary efficacy objective was to demonstrate that DEX700 and/or DEX350 is more effective than Sham in improving BCVA. For the primary efficacy analyses, the null hypothesis was that there was no difference between DEX700 (or DEX350) and Sham in the change in average BCVA from baseline. The alternative hypothesis was that a difference exists between the DEX700 (or DEX350) and Sham treatment arms.	The primary analysis of change in average BCVA 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, their average change from baseline was 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 1 error at 5% for the two between-group comparisons. The comparison of DEX700 versus Sham was considered statistically significant if the p-value was ≤ 0.05. If the comparison of DEX700 versus Sham was significant at the 0.05 level,	The sample size calculation was based on the primary efficacy analysis of the change in average BCVA from baseline in the study eye comparing each DEX PS DDS dose and Sham. From two 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 four-letter mean difference (delta) in the change in average BCVA 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	The primary analysis included all randomized eyes and followed the ITT principle with missing value imputed by last observation carried forward except for AUC analysis that was conducted using observed data. Secondary analyses included all randomized eyes with missing value based on multiple imputation; and observed data in the per-protocol population (defined as randomized patients with no major protocol violations).

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		the comparison of DEX350 versus Sham was 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 considered statistically significant, regardless of its p-value. In addition, 2-sided 95% CIs were constructed for the three between-group differences based on the ANCOVA model.	sample size of 170 patients per arm (510 patients total) had a power of 86% (two-sided alpha of 0.05). The power calculation, using nQuery Advisor 6.01, was based on two sample t-tests with equal variances. The treatment difference and variance were estimated from two completed Allergan studies, 206207-008 and 206207-009, in RVO.	

Key: ANCOVA, analysis of covariance; AUC, area under the curve; BCVA, best corrected visual acuity; CI, confidence intervals; DMO, diabetic macular oedema; ITT, intention-to-treat; PS DDS, posterior segment drug delivery system; RVO, retinal vein occlusion.

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

The MEAD study adhered to the tenets of the Declaration of Helsinki and was compliant with the Health Insurance Portability and Accountability Act of 1996. The study protocol was approved by an institutional review board or independent ethics committee at each site, and all patients provided written informed consent.[82]

The study personnel who collected efficacy data, and a follow-up investigator who performed safety evaluations at other study visits, were masked to the treatment assignment, and patients were also masked.[82]

Each site used an interactive voice-response or web-response system to assign randomization numbers to patients.[82] Treatment assignment was based on enrolment order and a computer-generated randomization scheme provided by the sponsor. Study treatment was administered after all baseline evaluations. An applicator system was used to inject DEX700 into the vitreous of the study eye through the pars plana. In the sham procedure, a needleless applicator was pressed against the conjunctiva of the study eye.[82]

The quality assessments of MEAD-010 and MEAD-011 are presented in Appendix D.4.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1 MEAD trials

This section presents the pooled results of the post-hoc analyses of phakic DMO patients from the ITT population from the MEAD clinical trials (i.e. the mITT population). The full phakic population has been used to support this submission as there was no reason to believe outcomes would differ between DMO patients who are either insufficiently responding to prior treatment, or unsuitable for treatment with non-corticosteroid treatment (Section B.2.6.2.1). This aligns with the evidence previously presented in TA349 in which the pseudophakic population was reimbursed.[7] Furthermore, exploratory analyses of phakic patients in MEAD have demonstrated no material differences between the pre-treated and naïve subgroups in MEAD (Section

B.2.7.3).Of note, patients in the MEAD trials who required rescue therapy were excluded from the analyses, as per the study exclusion criteria. In TA349, the committee therefore accepted that the outcomes of the sham arm were considered as a best-case scenario of the expected effectiveness of watch and wait patients in clinical practice. As such, the results of the sham arm in the following sections are also considered an overestimation of the outcomes of watch and wait therapy.

B.2.6.1.1 Best corrected visual acuity

In the mITT population, DEX700 resulted in a [redacted] mean change in average BCVA (AUC approach) measured from baseline to 39 months compared with sham, although the results were not statistically significant ([redacted] versus [redacted] of ETDRS letters, respectively; [redacted]).[135] Figure 6 presents the change in BCVA from baseline in the study eye. In the DEX700 arm, there was a [redacted] in mean change in BCVA between 18–30 months. Based on feedback received from an expert panel discussion, this is caused by a high proportion of patients developing or experiencing progression of cataracts such that it impacted their vision and in whom the cataract had not yet been removed. Furthermore, the visual outcomes in the DEX700 group were seen to improve following this period, when many of these cataracts were extracted; however, as this occurred toward the end of the MEAD study, it is unknown whether the visual acuity would have continued to improve. Post-hoc exploratory analyses were conducted to investigate the impact of early versus late cataract extraction (Section B.2.7.1.1), lens opacity (Section B.2.7.1.1), and cataract surgery (Section B.2.7.2) on a patient's BCVA.

Figure 6: Change in BCVA (ETDRS letters) from baseline in phakic study eyes (LOCF analysis)

Key: BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward.
Source: AbbVie, 2021 (MEAD post-hoc analyses – Figures).[136]

At 39 months, a [redacted] of patients treated with DEX700 achieved a BCVA [redacted] of ≥ 10 letters from baseline compared with those receiving sham ([redacted] versus [redacted]; [redacted]).[135] Furthermore, a [redacted] of patients treated with DEX700 achieved a BCVA [redacted] of ≥ 15 letters from baseline to 39 months compared with those receiving sham ([redacted] versus [redacted]; [redacted]; Figure 7).[135]

Figure 7: Proportion of patients with BCVA improvement of ≥ 15 letters from baseline

Key: BCVA, best corrected visual acuity.
Source: AbbVie, 2021 (MEAD post-hoc analyses – Figures).[136]

B.2.6.1.2 Central retinal thickness

In the mITT population, DEX700 resulted in a [redacted] in CRT from baseline to 39 months compared with sham ([redacted] versus [redacted]; [redacted]).[135] Figure 8 presents the change in study eye CRT from baseline to 39 months for patients in the mITT.

Figure 8: Change in CRT from baseline in phakic study eyes (LOCF analysis)

Key: CRT, central retinal thickness; LOCF, last observation carried forward.
Source: AbbVie, 2021 (MEAD post-hoc analyses – Figures).[136]

B.2.6.1.3 Health-related quality of life outcomes

For the post-hoc analysis of phakic DMO patients from the MEAD studies, patient-reported outcomes were assessed using the National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25). The VFQ-25 consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item.[137] The overall composite score was calculated by averaging all 11 vision-targeted subscale scores, excluding the general health score.[137]

Table 10 presents the average change in VFQ-25 scores from baseline to 39 months. Note that patient-reported outcome data were not available for all patients in the mITT; the number of patients included in the analysis are indicated in Table 10. Overall, there were .

Table 10: Average change in VFQ-25 scores from baseline to 39 months

VFQ-25 parameter	DEX700 (n = [redacted])	Sham (n = [redacted])	p-value
Mean (SD) Overall Composite Score	[redacted]	[redacted]	[redacted]
Mean (SD) General Vision[a]	[redacted]	[redacted]	[redacted]
Mean (SD) Difficulty with Near Vision	[redacted]	[redacted]	[redacted]
Mean (SD) Difficulty with Distance Vision	[redacted]	[redacted]	[redacted]
Mean (SD) Mental Health Symptoms due to Vision	[redacted]	[redacted]	[redacted]

Key: SD, standard deviation; VFQ-25, Visual Functioning Questionnaire-25.
Notes: [a] The analysis included 243 patients in the DEX700 arm and 231 patients in the sham arm.
Source: AbbVie, 2021 (MEAD post-hoc analyses – Tables).[135]

B.2.6.2 DEX700 real-world evidence studies

As presented in Section B.2.2, 43 published RWE studies have been identified as relevant to the decision problem. These RWE studies demonstrate similar outcomes in phakic and pseudophakic DMO patients following treatment with DEX700 (Section B.2.6.2.1). Compared to phakic DMO patients in the MEAD trials, better outcomes were reported in the published RWE studies for both treatment-naïve phakic DMO patients (Section B.2.6.2.3), and phakic DMO patients who were insufficiently responsive to prior anti-VEGF therapy (Section B.2.6.2.2). Furthermore, in phakic DMO patients who switch from anti-VEGFs to DEX700, RWE studies demonstrate that clinical outcomes are better the earlier the patient switches (Section B.2.6.2.4). RWE has also demonstrated that visual outcomes are better when DEX700 is administered shortly prior to, or at the same time as cataract surgery (Section B.2.6.2.4).

As introduced in Section B.2.3.2, a literature review was performed to identify studies which evaluate the efficacy of anti-VEGF and DEX700 in DMO (phakic and pseudophakic) patients.[81] In all included DEX700 studies, the mean gain in visual acuity was consistently ≥ 5 letters; this was not replicated within the anti-VEGF studies, with many studies failing to demonstrate a gain of ≥ 5 letters. When assessing the subgroup of patients with the lowest baseline visual acuity (< 50 letters), there is a marked difference in gain of visual acuity from baseline between the anti-VEGF studies (+4.3 letters) and the DEX700 studies (+10.5 letters), although the baseline

visual acuity is relatively similar (anti-VEGFs, 42.4 letters; DEX700 39.4 letters). The greatest difference in mean change between DEX700 studies and anti-VEGF studies was however seen in the subgroup of patients with baseline visual acuity of > 60 letters, with a mean gain of 3.1 letters in the anti-VEGF studies, and 8.8 letters in the DEX700 studies, resulting in a mean final visual acuity of 65.3 letters and 68.4 letters, respectively. This therefore supports that, even if there is a possibility of a ceiling effect, the mean visual acuity gain seen following treatment with DEX700 is not only due to the lower mean baseline visual acuity, but also persists in a subgroup of patients with a higher baseline visual acuity. Although this review reports on a pooled analysis of both the phakic and pseudophakic DMO patients, outcomes have been demonstrated to be similar across both populations (Section B.2.6.2.1).

The mean number of injections ranged from just one injection to 5.9 DEX700 injections, although the studies reporting one injection also had a much shorter study follow-up period of less than one year. Of note, the mean number of DEX700 injections administered in DEX700 arm of the MEAD trials was 4.1 over 3 years.[82] In the UK RWE audit, the overall mean number of anti-VEGF injections administered within 6 months was [redacted] (Section B.2.6.4.1).

The safety analyses, including the proportion of DMO patients with cataracts, are presented in Section B.2.10.2.

B.2.6.2.1 Outcomes in patients with phakic DMO versus pseudophakic DMO

In total, seven published RWE studies have reported on the difference in clinical benefit between phakic and pseudophakic DMO patients following treatment with DEX700, A summary of relevant published RWE studies has been provided in Appendix M.1.2.1.

Visual outcomes are reported to be similar in both phakic and pseudophakic DMO patients.[84-90] Only one study (N = 177) reported the exact mean maximum BCVA change from baseline for both the phakic and pseudophakic DMO patients, in which the phakic patients had an increase of 12.2 letters, and the pseudophakic patients had an increase of 11.5 letters.[89] Although this study reported on the concomitant use of DEX700 with other DMO treatments, patients treated with DEX700 alone reported a numerically higher maximum improvement in BCVA after 1 and 3 DEX700 injections

compared to patients treated with DEX700 and other treatments (9.4 versus 8.6 letters, and 7.9 versus 5.9 letters, respectively). However, of the four studies that tested for significance, no statistical difference was identified between phakic and pseudophakic DMO patients for the mean maximum BCVA change from baseline to final follow-up.[85-87, 90]

A comparison of outcomes for the phakic and pseudophakic DMO population has also been conducted in the French RWD study (Section B.2.6.3). A similar number of injections were administered in phakic and pseudophakic eyes ([redacted] [SD [redacted]] and [redacted] [SD [redacted]], respectively). The mean change in BCVA was never significantly inferior in phakic patients and was numerically superior at months 2, 24 and 36 (Figure 9).

It can therefore be concluded that, in general, the lens status of the patient (i.e. phakic or pseudophakic) has little effect on visual outcomes following treatment with DEX700.

B.2.6.2.2 Switching from anti-VEGFs to DEX700

Several published RWE studies have demonstrated a clinical benefit with DEX700 in patients with DMO who are insufficiently responsive to anti-VEGFs. Of the 43 published RWE studies, 17 reported on patients who had switched from anti-VEGF treatment to DEX700, one of which was a sub-analysis of the MEAD trials.[107] Previous anti-VEGF treatments included aflibercept, ranibizumab and bevacizumab.

A sub-analysis of MEAD demonstrated that DEX700 significantly improved visual outcomes in previously treated patients.[107] It was concluded that although phakic eyes are at high risk of cataract progression after multiple DEX700 injections, treatment with DEX700 can still be justified in phakic DMO patients who have not responded to other treatment. Persistent DMO can lead to irreversible vision loss, whereas patients who develop cataract during DEX700 treatment recover vision gain after cataract extraction (Section B.2.7.2).

Furthermore, patients who switch from anti-VEGFs to DEX700 earlier in their treatment plan tend to have better outcomes than patients who switched later.[76] Two studies (N = 58 and N = 68) compared the mean change in BCVA in an early switch (received three consecutive monthly injections) and late switch group (received six consecutive monthly injections).[116, 117] The mean change in BCVA was seen to

increase to a greater extent in patients who switched treatment to DEX700 injections after only 3 prior anti-VEGF injections, with one study reporting a statistically significant increase at 6 months,[117] and another reporting a statistically significant increase at 24 months.[116] These data therefore argue in favour of administering DEX700 more quickly as a second-line therapy.

B.2.6.2.3 Visual outcomes in treatment-naïve patients with DMO

Seven studies reported on the visual outcomes of treatment-naïve DMO patients. A summary of the relevant RWE studies reporting visual outcomes in treatment-naïve patients with DMO is provided in Appendix M.1.2.3.

A much smaller proportion of studies reported on treatment-naïve DMO patients treated with DEX700 as DEX700 is currently a second-line treatment in routine practice. Two studies reported specifically on phakic DMO patients who were treatment-naïve, one of which was a Delphi panel.[113, 114] More than 94% of experts agreed that DEX700 can be used as first-line therapy for DMO in phakic patients who are candidates for cataract surgery.[113] Furthermore, DEX700 implants reduce the number of visits compared to other therapeutic regimens and facilitate compliance.[113]

The five remaining RWE studies reported on the pooled phakic and pseudophakic treatment-naïve population. All five studies reported a significant increase in BCVA from baseline at the end of their respective follow-up period.[102, 110, 118, 119, 122]

B.2.6.2.4 Timing of DEX700 injections

In total, four studies reported on the timing of DEX700 injections compared with cataract surgery.[86, 87, 112, 113] Clinical experts have acknowledged that DEX700 is usually given shortly prior to, or at the same time as cataract surgery.[9] This was not the case in the MEAD trials due to the strict re-treatment schedule. In RWE studies, DMO patients were treated with DEX700 ahead of a planned cataract surgery, as recently recommended in the European guidelines for DMO management.[80]

Three of the four studies reported on outcomes of patients treated with DEX700 one month prior to cataract surgery.[86, 87, 112] DEX700 decreased the DMO on the day of surgery, and was still effective at least 2-3 months after the surgery.[86, 87] This ensures

adequate control of postoperative inflammation and prevents deterioration of macular oedema.

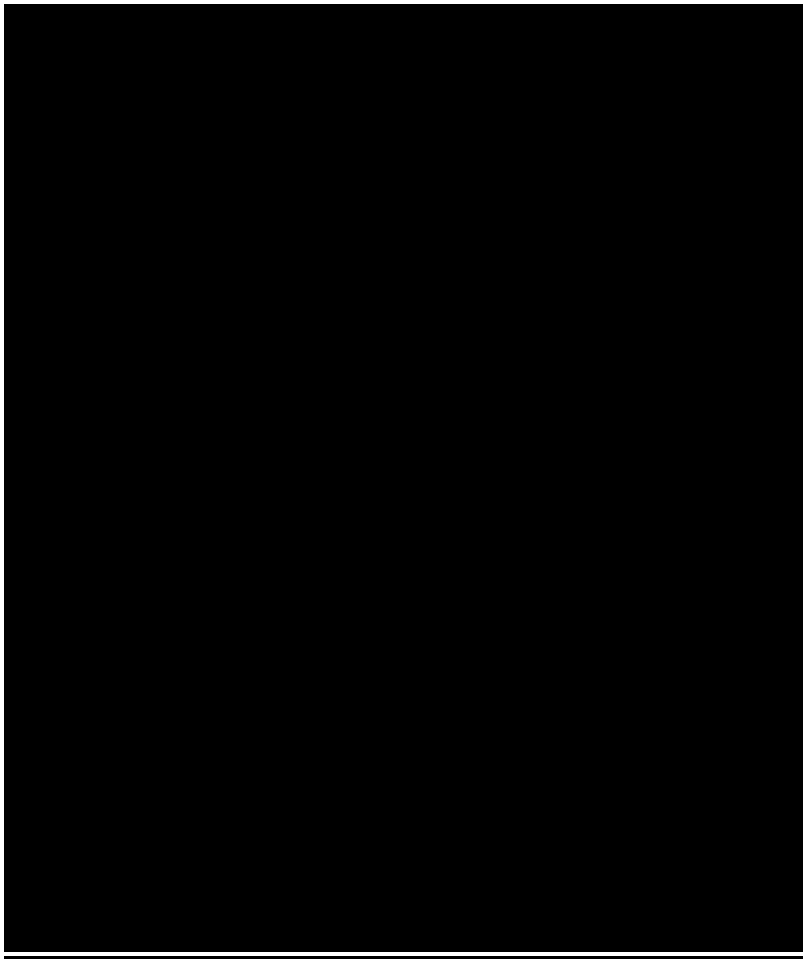
B.2.6.3 French RWD

The mean time to retreatment, reasons for discontinuation of DEX700 injections, and anatomical efficacy is presented in Appendix M.2.2. Safety analyses of the French RWD are presented in Section B.2.10.3.

B.2.6.3.1 Primary endpoint

In patients with phakic eyes, the mean gain in visual acuity was [redacted] letters at month 2, ([redacted]), [redacted] letters at month 6 ([redacted]), [redacted] letters at month 12 ([redacted]), [redacted] letters at month 24 ([redacted]) and [redacted] letters at month 36 ([redacted]). The mean change in BCVA was never significantly inferior in phakic DMO patients and was numerically superior at months [redacted] (Figure 9). When adjusting for visual acuity at baseline, age and sex in the multivariate model, no significant differences in the change in BCVA were observed between phakic and pseudophakic eyes (likelihood ratio test, [redacted]). The mean change in BCVA from baseline was never significantly inferior in both treatment-naïve and previously treated phakic eyes.

Figure 9: Difference in mean change in visual acuity between the study groups



Notes: Error bars indicate 2-sided 97.5% confidence intervals.

B.2.6.3.2 Number of injections/ healthcare resource use

During the follow-up, patients received a mean of [redacted] (SD [redacted]) DEX700 injections. A similar number of injections were administered in phakic and pseudophakic eyes ([redacted] [SD [redacted]] and [redacted] [SD [redacted]], respectively).

The mean number of monitoring visits was [redacted] (SD [redacted]) overall, [redacted] (SD [redacted]) in pseudophakic eyes and [redacted] (SD [redacted]) in phakic eyes. The number of vitrectomies during follow-up was [redacted] ([redacted]%) in pseudophakic eyes and [redacted] ([redacted]%) in phakic eyes ([redacted]). The number of focal lasers during follow-up was [redacted] ([redacted]%) in pseudophakic eyes and [redacted] ([redacted]%) in phakic eyes ([redacted]).

B.2.6.4 UK RWE audit

B.2.6.4.1 Primary endpoint

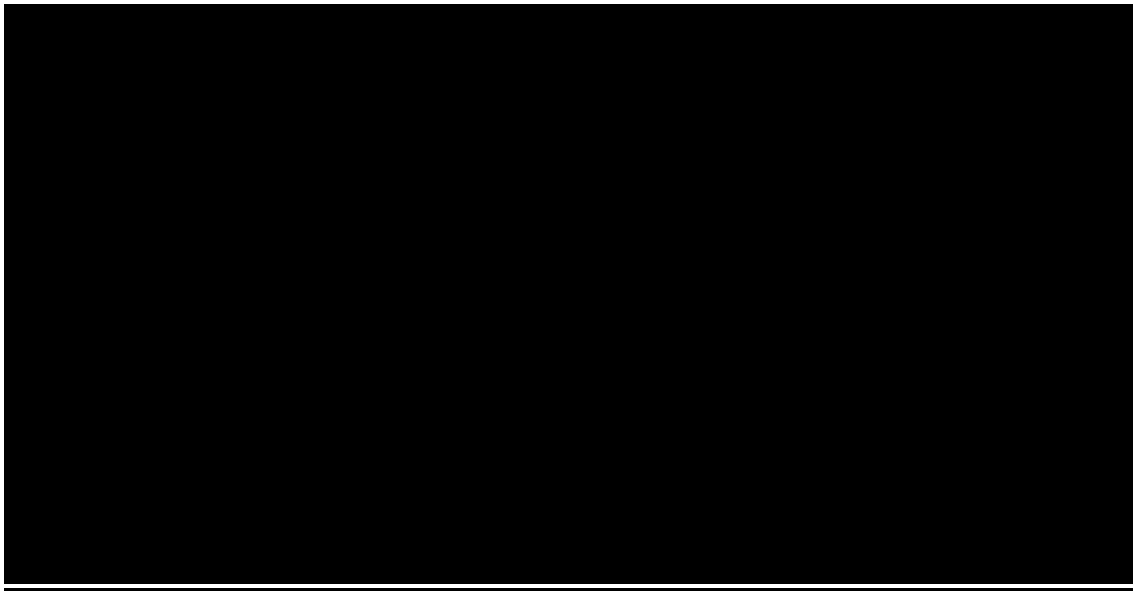
A total of [redacted] eligible eyes from [redacted] patients have undergone treatment for DMO with anti-VEGFs.[10] At [redacted] months, [redacted]% of eyes had a suboptimal response to treatment, defined as ≤ 5 letter gain at 6 months (this increased to [redacted]% of patients based on insufficient response defined as ≤ 5 letter gain at 6 months or < 20% reduction in central subfield thickness). For the [redacted] follow-up, data were missing for [redacted]% of eyes, with the majority ([redacted]%) due to a lack of recording of visual acuity within [redacted] weeks of the follow-up period.

No significant difference was observed between the proportion of suboptimal and optimal responders at 3 and 6 months, therefore results are presented based on suboptimal responders at 6 months, as this time-point resulted in a larger sample size. The available results for the 3-month follow-up are presented in Appendix M.3.2.

The proportion of suboptimal responders was higher than anticipated. The data available for (BRVA was reported in LogMAR which was later converted to ETDRS letters. In [redacted]% of cases, LogMAR was not reported to 2 decimal places. Therefore, 2 decimal places were used where available, otherwise 1 decimal place was used. As a result, some eyes will be needing to reach a 10 letter improvement (i.e. 2 lines) to make a > 5 letter gain. The proportion of patients classified as suboptimal responders may therefore be overestimated.

The mean BRVA at baseline was [redacted] ETDRS letters, or [redacted] LogMAR. There was a relatively high baseline visual acuity with [redacted]% of eyes having a BRVA of > [redacted] letters. In the optimal group, [redacted]% of eyes had a baseline BRVA of > [redacted] letters compared with [redacted]% of eyes in the suboptimal group ([redacted], 95% CI [redacted], [redacted]). As a significant number of eyes in the suboptimal group had a higher baseline BRVA, these patients were less likely to improve by > 5 letters than those in the optimal group. The mean change from baseline BRVA in the suboptimal and optimal groups is presented in Figure 10.

Figure 10: Comparison of mean change from baseline BRVA over time



Key: BRVA, best recorded visual acuity

Optical coherence tomography (OCT) data at 6 months was available for [redacted] eyes, of which [redacted]% were optimal, and [redacted]% were suboptimal (i.e. a change in OCT of < 20%) based on OCT alone (95% CI [redacted], [redacted]). When combining < 20% OCT improvements with a gain in BRVA of ≤ 5 letters, [redacted]% of patients were classified as suboptimal responders.

The mean change in OCT foveal thickness at 6 months was [redacted]% (SD [redacted]). Of note there are few eyes with very large changes in CRT which may skew the mean value. Results show that [redacted]% of eyes improved OCT thickness by ≥ 20%, [redacted]% improved 5 to < 20%, [redacted]% stay within ± 5% change and [redacted]% worsen by > 5% (up to >200%). Patients presenting with a marked increase in OCT thickness may be due to missed injections and/or delayed follow up, rather than lack of response to the anti-VEGF injections.

B.2.6.4.2 Treatment burden in insufficient responders

The mean number of clinic visits during the follow-up period were recorded, with the vast majority being face-to-face appointments. The mean number of visits was similar for the optimal and suboptimal groups. In the suboptimal patient cohort, the mean number of in-person clinic visits was [redacted] between 6 – 12 months, [redacted] between 12 – 24 months, [redacted] between 24 – 36 months and [redacted] between 36 – 48 months.

At 6 months, the overall mean number of anti-VEGF injections was [redacted] (SD [redacted]), and [redacted]% of patients received > 3 injections over 6 months. When patients received ≤ 3 anti-VEGF injections, [redacted]% of patients were classified as optimal responders and [redacted]% were classified as suboptimal responders. In patients who received > 3 anti-VEGF injections, the proportion of optimal responders increased to [redacted]%.

B.2.6.5 Post-hoc analysis of Protocol T

B.2.6.5.1 Insufficient responders

In total, [redacted] ([redacted]%) patients with phakic eyes were classified as having an insufficient response (i.e. <5 letter gain from baseline) to anti-VEGF treatment at week 12.[138] Patients with an insufficient response had a mean change in BCVA of [redacted] letters at week 12, and [redacted] letters at week 104, whereas patients who did achieve sufficient response (i.e. ≥ 5 letter gain from baseline) had a mean change in BCVA of [redacted] letters at week 12, and [redacted] letters at week 104.

B.2.6.5.2 Number of injections

Nearly all patients ([redacted]%) received a mean of [redacted] injections in the first 12 weeks, and an average of [redacted] injections at 52 weeks and [redacted] injections at 104 weeks. Although the patients enrolled in Protocol T were not treated in strict accordance with the EMA label, they could be considered to be intensively treated and monitored (monitoring every 4 weeks [± 1 week]), yielding potential best-case outcomes compared with routine clinical practice. The mean number of injections for phakic and pseudophakic eyes over the first 12, 52 and 104 weeks from randomization was similar (Table 11).

Table 11: Number of anti-VEGF injections administered in phakic and pseudophakic eyes

	All eyes (n = [redacted])	**Phakic (n = [redacted])**	**Pseudophakic (n = [redacted])**
Week 12	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]

Key: VEGF, vascular endothelial growth factor.
Source: Post-hoc analysis of Protocol T [138]

Figure 11 presents the mean number of anti-VEGF injections administered within 12 and 24 months in Protocol T and the UK RWE audit. Both studies highlight the high number of anti-VEGF injections administered over 2 years. It is to be noted that, unlike the UK RWE audit, Protocol T followed a strict RCT regimen which may explain the higher frequency of injections compared with what has been observed in UK clinical practice, and as such PROTOCOL T is not directly comparable to UK practice.

Figure 11: Mean number of anti-VEGF injections administered at month 12 and month 24

Key: RWE, real-world evidence; VEGF, vascular endothelial growth factor.
Source: Protocol T post-hoc analyses[138]; UK RWE audit.[10]

B.2.7. Subgroup analysis

The management of phakic DMO patients in the MEAD trials was not fully aligned with management of these patients in the UK clinical practice, as suggested through an advisory board conducted in 2021.[9] In patients where cataracts progress to impact vision, cataract surgery is performed earlier in UK clinical practice than was observed in the MEAD trials. Moreover, clinicians advised that in UK clinical practice DEX700 would be administered before or during cataract surgery to minimize inflammation and DMO progression post-cataract surgery. This also did not occur during the MEAD trials. Several exploratory post-hoc sub-analyses were therefore conducted of the

phakic-only population (mITT) from MEAD to investigate the impact of these known limitations of the MEAD study.

These analyses allow an assessment of the impact of DEX700 in phakic DMO patients who more closely resemble those treated in UK clinical practice. It should be noted that the post-hoc analyses presented in this section are intended as supportive data only and are not used within the economic analyses. The sample sizes of the mITT sub-populations are small and although no firm conclusions can be made (i.e. no claims of statistical significance are made), a directional change in the results of the sub-analysis is apparent.

B.2.7.1 Impact of patient baseline characteristics and patient management during MEAD

As previously discussed (Section B.2.3.1.1), patients with cataract that impairs their vision will likely receive cataract surgery earlier in clinical practice than they did in MEAD, and unlike MEAD, DEX700 would be administered prior to or during cataract surgery to minimize inflammation and DMO progression following surgery. This is also apparent in published RWE studies (Section B.2.6.2.4) which reported, when DEX700 was administered one month prior to cataract surgery, the extent of DMO was decreased on the day of surgery, and DEX700 was still effective at least 2–3 months after the surgery[9, 86, 87, 112, 113]. Furthermore, phakic DMO patients in clinical practice are more likely to present with lens opacity when initiating treatment with DEX700.

As such, the following exploratory sub-analyses were performed to explore the impact of these factors within MEAD:

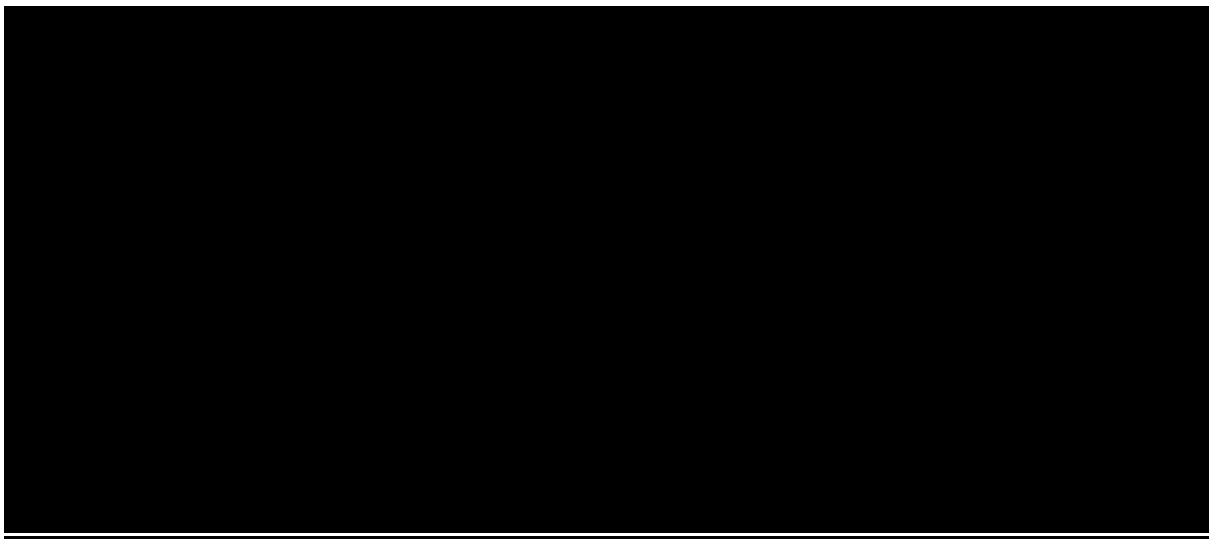
- Impact of lens opacity (SectionB.2.7.1.1)
- Timing of cataract surgery (SectionB.2.7.1.2)
- Timing of DEX700 injection prior to cataract surgery (Section B.2.7.1.3)

B.2.7.1.1 Impact of lens opacity

Figure 12 presents the impact of lens opacity on BCVA. Patients with a cortical or a posterior subscapular opacity at baseline had consistently worse outcomes than patients without lens opacity. Posterior subscapular lens opacity is known to progress rapidly, and therefore accounts for the rapid deterioration in vision loss.

Given that patients in clinical practice are more likely to present without lens opacity when initiating treatment with DEX700, this further reinforces that DEX700 outcomes observed in the MEAD mITT population can be considered pessimistic.

Figure 12: Impact of lens opacity on BCVA



Key: BCVA, best corrected visual acuity; DEX700, Dexamethasone 700 µg intravitreal implant.
Source: AbbVie, 2021 (MEAD post-hoc exploratory analyses).[83]

B.2.7.1.2 Timing of cataract surgery

In the mITT population, the mean time from cataract development until cataract surgery was [redacted] months. Figure 13 presents the impact of time to cataract surgery on BCVA. Patients who have a shorter gap between cataract development and surgery do not experience as much of a decline in their BCVA from baseline. Patients therefore have less vision loss to recover, leading to the better long term outcomes following surgery. This suggests that if the timing of cataract progression and treatment is more aligned with what is expected in clinical practice (i.e. shorter time to extraction), outcomes for DEX700 can be expected to be improved compared with that observed in the MEAD mITT population.

Figure 13: Impact of cataract surgery timing on BCVA

Key: BCVA, best corrected visual acuity; DEX700, Dexamethasone 700 µg intravitreal implant.
Source: AbbVie, 2021 (MEAD post-hoc exploratory analyses).[83]

B.2.7.1.3 Timing of DEX700 injection

Evidence from published RWE studies (Section B.2.6.2.4) has demonstrated positive visual outcomes in patients treated with DEX700 one month prior to cataract surgery.[86, 87, 112] In the mITT population, the mean time between the last DEX700 injection and cataract surgery was [redacted] months. Figure 14 presents the impact of DEX700 timing on BCVA. Patients who received DEX700 at their last visit before cataract surgery experienced better outcomes than patients who did not receive DEX700 at the last visit prior to surgery. This reinforces the expectation that in clinical practice, where DEX700 would be given prior to or during cataract surgery, outcomes for DEX700 would improve compared with those observed in the mITT population of MEAD.[86, 87, 112] It is however to be noted that phakic DMO patients without DEX700 in their last visit prior to cataract surgery had a greater BCVA loss prior to surgery, and therefore have more room to improve their BCVA following DEX700 injection.

Figure 14: Impact of DEX700 injection timing on BCVA

Key: BCVA, best corrected visual acuity; DEX700, Dexamethasone 700 µg intravitreal implant.
Source: AbbVie, 2021 (MEAD post-hoc exploratory analyses).[83]

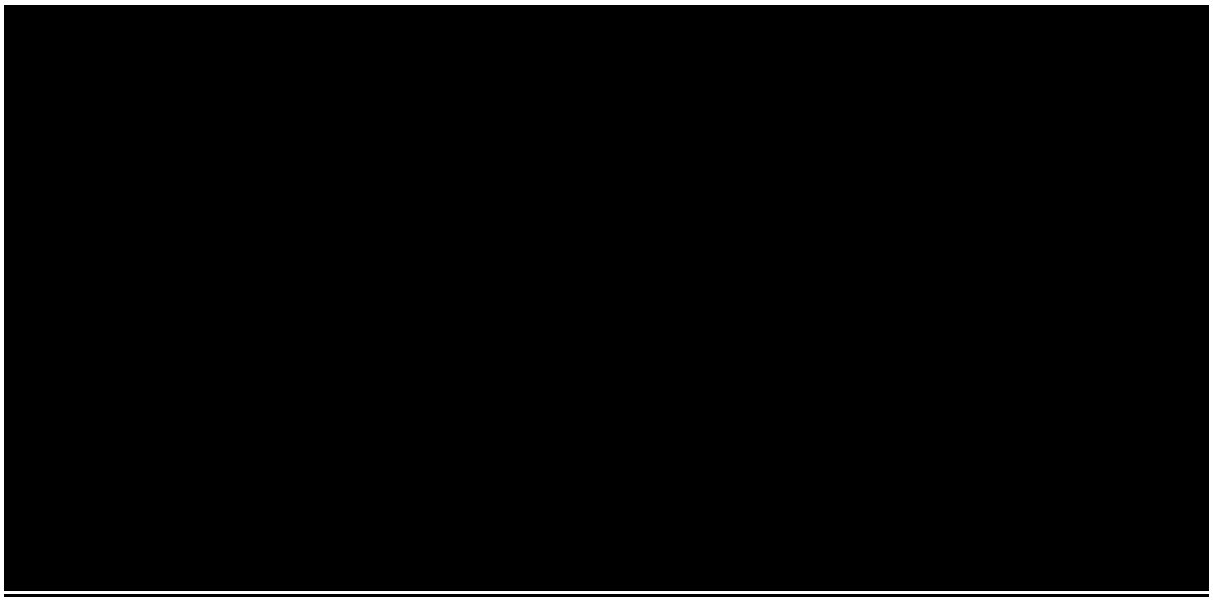
B.2.7.2 Impact of cataract development and cataract surgery

Additional post-hoc exploratory analyses were also conducted to investigate the impact of cataract development and cataract surgery on the visual outcomes of phakic DMO patients during MEAD. In the BCVA analysis of the mITT population (Section B.2.6.1.1), there was a [redacted] in mean visual acuity between 18–30 months. This [redacted] is believed to be attributed to the development and extraction of cataract during the study. To investigate the claim, a post-hoc analysis was conducted to investigate the visual outcomes of patients who developed cataract but did not receive surgery (Section B.2.7.2.1). The impact of cataract surgery on the visual outcomes of the phakic population was also assessed (Section B.2.7.2.2).

B.2.7.2.1 Impact of cataract on visual outcomes

Figure 15 presents the change in BCVA for patients who developed cataract but did not receive cataract surgery. The development of cataract appears to coincide with patients having poorer outcomes, with visual acuity scores decreasing as the number of patients with cataract increased.

Figure 15: Change in BCVA for patients who developed cataract but did not receive cataract surgery



Key: BCVA, best corrected visual acuity; DEX700, Dexamethasone 700 µg intravitreal implant.
Source: AbbVie, 2021 (MEAD post-hoc exploratory analyses).[83]

B.2.7.2.2 Impact of cataract surgery

Figure 16 presents the impact of cataract surgery on mean BCVA during MEAD. Patients who underwent cataract surgery during MEAD experienced a [redacted] in visual acuity between 18–30 months but had better outcomes by the end of the trial than those patients who did not receive surgery. This is likely due to the recovery of vision following the cataract surgery for those who underwent surgery during the study. Those who did not have cataract surgery during the study would have their visual outcomes impacted by the presence of cataract.

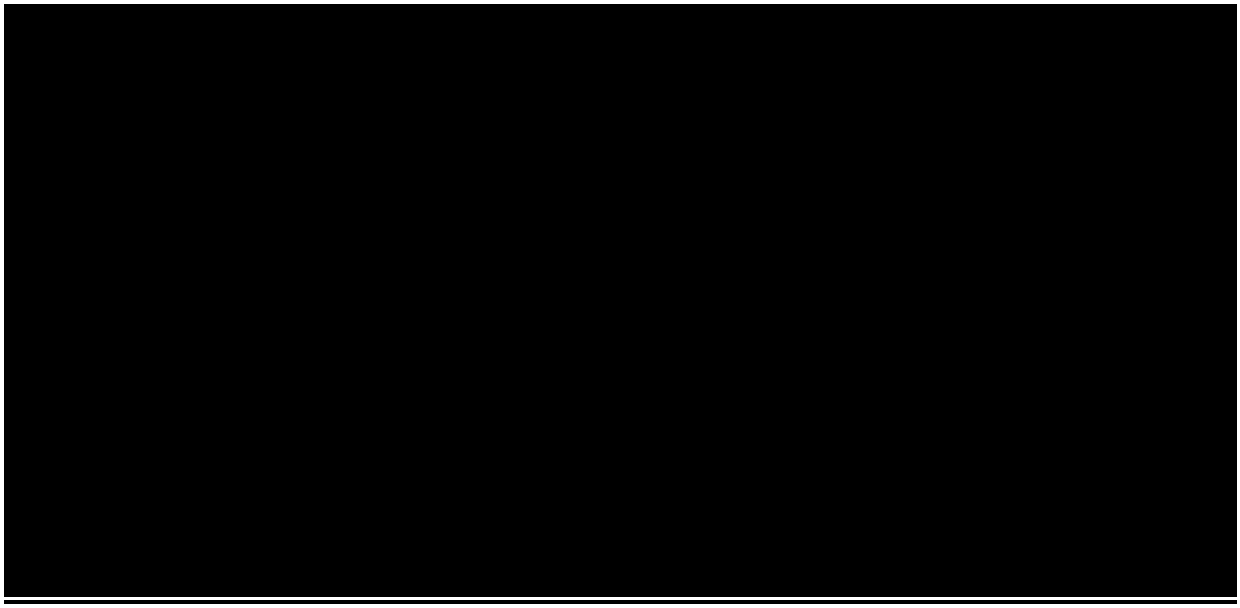
Figure 16: Impact of cataract surgery on BCVA

Key: BCVA, best corrected visual acuity; DEX700, Dexamethasone 700 µg intravitreal implant.
Source: AbbVie, 2021 (MEAD post-hoc exploratory analyses).

B.2.7.3 Impact of prior treatment

Evidence from published RWE studies (Section B.2.6.2) indicates favourable outcomes for DEX700 in both treatment-naïve patients, and patients who are insufficiently responsive to prior treatment.[81] To support these findings, a post-hoc exploratory analysis was conducted to investigate the impact of prior treatment on the visual outcomes of phakic DMO patients in MEAD. Figure 17 presents the impact of DEX700 on the BCVA outcome in previously treated patients. Overall, DEX700 appears to have similar outcomes in previously treated and treatment-naive patients. For this reason, to ensure as large a sample size as possible, we chose to have the full mITT population of phakic DMO patients in MEAD represent the population of phakic DMO patients who are either insufficiently responsive to prior non-corticosteroid therapy or are unsuitable for non-corticosteroid therapy (and therefore are treatment-naïve).

Figure 17: Impact of prior treatment on BCVA



Key: BCVA, best corrected visual acuity; DEX700, Dexamethasone 700 µg intravitreal implant.
Source: AbbVie, 2021 (MEAD post-hoc exploratory analyses).

B.2.8. Meta-analysis

Efficacy data supporting the use of DEX700 for the treatment of patients with phakic DMO who are unsuitable for or insufficiently responsive to prior treatment are provided by the pooled MEAD-010 and MEAD-011 studies; therefore, a meta-analysis was not needed. Given the different dosing regimens adopted for DEX700 treatment across studies and varying primary efficacy timepoints, additional pooling of clinical efficacy outcomes in the form of a meta-analysis was not considered appropriate.

Indirect treatment comparisons for DEX700 versus the relevant comparators were explored, as presented in B.2.9.

B.2.9. Indirect and mixed treatment comparisons

B.2.9.1 Data sources and outcomes for the analysis

The most robust data sources providing evidence for the use of DEX700 in phakic DMO patients who are unsuitable for or insufficiently responsive to non-corticosteroid therapies are MEAD-010 and MEAD-011 which investigated DEX700 versus Sham in an RCT setting.

No head-to-head data are available for DEX700 versus the comparators of interest in the relevant population (phakic DMO patients who are unsuitable for or are insufficiently responsive to non-corticosteroid treatment). ITCs were therefore explored with the objective to compare DEX700 versus laser photocoagulation alone or versus anti-VEGF treatment alone or in combination with laser photocoagulation for the population of interest. Evidence used to support the ITCs was sourced from:

- Published evidence identified from the SLR (Appendix D.1)
- Evidence from the UK RWE audit (Section B.2.2.2.1)

Data from the UK RWE audit were used to help address the paucity of published data for comparator treatments in the unsuitable for or are insufficiently responsive to non-corticosteroid treatment population and the data from this audit were considered the most relevant for ITC. Patient-level data for the [redacted] patients in the DEX700 arm of MEAD with a phakic lens and who had received prior treatment were compared with the UK RWE audit summary data for the [redacted] phakic eyes receiving anti-VEGF therapy (ranibizumab or aflibercept), classified as being insufficient responders (≤5 letter gain after 6 months of treatment).

Due to the paucity of data available to support the decision problem, two further decision problems were considered:

- How does the efficacy of Sham investigated in MEAD compare with continued anti-VEGF treatment in the real-world?
  - Data used to support this decision problem were:
    - Patient-level data for the [redacted] patients in the Sham arm of MEAD with a phakic lens and who had received prior treatment
    - Summary data for the [redacted] phakic eyes receiving anti-VEGF therapy (ranibizumab or aflibercept), classified as being insufficient responders (≤5 letter gain or <20% reduction in central subfield thickness after 6 months of treatment) from the UK RWE audit
- In eyes with a phakic lens, how does the efficacy of DEX700 investigated in MEAD compare with DEX700 in the real-world?
  - Data used to support this decision problem were:

- Patient-level data for the [redacted] patients in the DEX700 arm of MEAD with a phakic lens and who had received prior treatment
- Retrospective summary data for 30 phakic eyes treated with DEX700 in a single-centre in Tenerife, Spain, for whom laser or anti-VEGF therapy had not shown to improve retinal thickness or visual acuity after 3 months of treatment (Pareja-Ríos et al. 2018)

A summary of each study identified in the SLR and the reasons for inclusion/exclusion in the ITCs can be found in Appendix D.

Outcomes investigated were:

- Mean BCVA change from baseline to Year 1, Year 2 and Year 3
- ≥ 10 letter BCVA improvement from baseline to Year 1, Year 2 and Year 3
- ≥ 10 letter BCVA worsening from baseline to Year 1, Year 2 and Year 3
- ≥ 15 letter BCVA improvement from baseline to Year 1, Year 2 and Year 3
- ≥ 15 letter BCVA worsening from baseline to Year 1, Year 2 and Year 3

Mean BCVA was investigated as the primary endpoint in the MEAD studies and the 10 or 15 letter BCVA improvement or worsening endpoints were investigated to potentially input into the economic model.

B.2.9.2 Statistical methods

As both comparator evidence sources (Pareja-Ríos et al. 2018[93] and the UK RWE audit[10]) were non-comparative real-world retrospective studies, standard techniques such as Bucher ITC and network meta-analyses (NMA), which require a common comparator to estimate a relative treatment effect, could not be performed. We therefore explored using both unanchored matching-adjusted indirect comparison (MAIC) methods and unanchored simulated treatment comparison (STC) methods. Both methods can be used to adjust for between-study differences in baseline patient characteristics (considered to be treatment effect modifiers or prognostic factors) in the absence of randomization and are described in detail in the NICE DSU TSD 18.[139]

B.2.9.2.1 *Prognostic factors and treatment effect modifiers*

Prognostic factors and treatment effect modifiers used for population adjustment were identified through clinician input at an advisory board and desk research of publications reporting prognostic factors or treatment effect modifiers in DMO. Clinician input and desk research identified the following characteristics as prognostic factors or treatment effect modifiers:

- Percentage of patients with pre-existing cataracts at baseline
- Timing of cataract surgery
- Baseline BCVA
- Prior anti-VEGF treatments
- Duration of oedema before treatment

However, the final set of characteristics used for population adjustment was limited to those characteristics reported in the comparator evidence. At least two different sets of matching variables were therefore used:

1. Characteristics reported in the comparator evidence and identified as important via clinician input or desk research
2. All characteristics reported in the comparator evidence and available in MEAD

B.2.9.3 Results

B.2.9.3.1 DEX700 and Sham investigated in MEAD compared with suboptimal anti-VEGF treatment in the real-world (UK RWE audit)

In the UK RWE audit, outcome data were available for [redacted] eyes at Year 1, [redacted] eyes at Year 2 and [redacted] eyes at Year 3. Patient characteristics were available for the three different populations and were relatively comparable across the three populations – the main difference was in the percentage of patients with a pre-existing cataract which was [redacted]% for the Year 1 population, [redacted]% in the Year 2 population and [redacted]% in the Year 3 population.

Compared with patients in MEAD, patients in the UK RWE audit had a higher mean BCVA at baseline (mean baseline BCVA was [redacted], [redacted] and [redacted] in the three different UK RWE audit populations compared with [redacted] and [redacted] in the DEX700 and Sham arms of MEAD, respectively). Additionally, a noteworthy difference in the percentage

of patients with a pre-existing cataract was higher in the DEX700 arm of MEAD compared with patients in the UK RWE study. Finally, there was a higher percentage of patients in the Sham arm of MEAD with Type II diabetes compared with in the UK RWE audit. Baseline characteristics across MEAD and the UK RWE audit are summarized in more detail in Appendix D.2.

Adjusting for the difference in mean BCVA at baseline introduced high levels of uncertainty into both comparisons with a small number of patients in the DEX700 and Sham arms of MEAD contributing to the analyses (effective sample sizes [ESSs] ranged from 1 to 2.1 across the analyses performed comparing DEX700 with suboptimal anti-VEGF and ranged from 3.2 to 6 across the analyses performed comparing Sham with suboptimal anti-VEGF). Attempt was also made to match on mean baseline BCVA only, however, the ESS remained small (ESS was under 15). Further details on the matching variables included in the analyses can be found in Appendix D.2.

Endpoints compared were:

- Mean BCVA change from baseline to Year 1, Year 2 and Year 3
- ≥ 10 letter BCVA improvement from baseline to Year 1, Year 2 and Year 3
- ≥ 10 letter BCVA worsening from baseline to Year 1, Year 2 and Year 3
- ≥ 15 letter BCVA improvement from baseline to Year 1, Year 2 and Year 3
- ≥ 15 letter BCVA worsening from baseline to Year 1, Year 2 and Year 3

Across most endpoints compared, conflicting results between MAICs and STCs suggest these analyses are too uncertain to make any conclusions from and are therefore not reported here. The full set of results have been presented in Appendix D.2, for information.

B.2.9.3.2 DEX700 investigated in MEAD compared with DEX700 in the real-world (Pareja-Ríos et al. 2018)

Patient characteristics were relatively comparable across MEAD and Pareja-Ríos et al. 2018. The main difference in patient characteristics was mean baseline BCVA which was lower in Pareja-Ríos et al. 2018 compared with in the DEX 700 arm of MEAD (42.4 compared with [redacted]). The difference in mean BCVA lead to an extremely

small effective sample size (ESS) in the MAIC analyses, highlighting uncertainty in these analyses. Matching variables used in the analyses (and corresponding ESSs) were:

- Matching variables 1: mean BCVA and variance
  - ESS = 5.1
- Matching variables 2: mean BCVA and variance, mean age and variance, mean CMT and variance, mean MV and variance, mean IOP and variance
  - ESS = 4.9

The only relevant endpoint reported by Pareja-Ríos et al. 2018 was Mean BCVA average change from baseline at Year 1. ITC results for this endpoint can be found in Table 12. Despite the uncertainty associated with this analysis (further highlighted by the large confidence interval around the mean difference), the four different analyses resulted in relatively comparable results: after matching, mean change from baseline (CFB) in MEAD increased, tending towards the mean CFB reported in Pareja-Ríos et al. 2018.

Table 12: Results of DEX700 investigated in MEAD versus DEX700 in the real-world (Pareja-Ríos et al. 2018) for the endpoint of mean BCVA average change from baseline at Year 1

Matching variables	Method	MEAD, DEX700, N=[redacted]: Mean CFB (SD)	Adjusted MEAD, DEX700, N=[redacted]: Mean CFB (SD)	Pareja-Ríos et al., DEX700, N=30 : Mean CFB (SD)	Naïve ITC - DEX 700 (MEAD) versus DEX 700 (Pareja-Ríos et al. 2018) : MD (95% CI)	Adjusted ITC - DEX 700 (MEAD) versus DEX 700 (Pareja-Ríos et al. 2018) : MD (95% CI)
1*	MAIC	[redacted]	[redacted]	4.8 (19.99)	[redacted]	[redacted]
	STC		[redacted]			[redacted]
2	MAIC		[redacted]			[redacted]
	STC		[redacted]			[redacted]

Key: BCVA, best corrected visual acuity; CFB, change from baseline; CI, confidence interval; DEX700, Dexamethasone 700 µg intravitreal implant; MAIC, matching-adjusted indirect comparison; MD, mean difference; N, number of eyes; OR, odds ratio; STC, simulated treatment comparison.

Note: *Matching variables 1 included: mean BCVA and variance.

**Matching variables 2 included: mean BCVA and variance, mean age and variance, mean age and variance, mean CMT and variance, mean MV and variance, mean IOP and variance.

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

The population-adjusted indirect treatment comparisons performed were subject to high levels of uncertainty primarily due to differences in mean baseline BCVA across the studies (reflected in large confidence intervals around the mean differences and odds ratios, different results from MAICs and STCs and very low ESSs for the MAICs).

Baseline BCVA has been previously identified to be a treatment effect modifier and has an impact on a patient's ability to gain letters due to the ceiling effect already discussed.[81, 127, 140, 141] In MEAD, baseline BCVA was not identified as a treatment effect modifier for outcomes at Year 1. For example, ORs comparing DEX700 with Sham for ≥ 15 letter BCVA improvement from baseline to Year 1 for patients with baseline BCVA ≤ 60 and > 60 were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively. It is therefore likely that, if adjustment had been possible to match the MEAD data with the higher baseline BCVA in the UK RWE audit, little change would have been seen in the MEAD results. Whereas, at Year 2, ORs were [redacted] (95% CI: [redacted]) for patients with baseline BCVA ≤ 60 and [redacted] (95% CI: [redacted]) for patients with baseline BCVA > 60 and at Year 3 ORs were [redacted] (95% CI: [redacted]) for patients with baseline BCVA ≤ 60 and [redacted] (95% CI: [redacted]) for patients with baseline BCVA > 60. Increasing the baseline BCVA for the Year 2 and Year 3 outcomes may therefore have resulted in a decrease in the number of DEX700 patients achieving ≥ 15 letter BCVA improvement. However, it should also be noted that relative effects in MEAD are very likely to be conservative for reasons already discussed and there are RWE studies with mean baseline BCVA similar to that in the UK RWE audit which show improved efficacy outcomes for DEX700 compared with in MEAD.[81, 97, 100]

A key assumption for unanchored MAICs and STCs is that all treatment effect modifiers and prognostic variables are available and properly accounted for. However, for all three comparisons made, it was also not possible to adjust for all potential treatment effect modifiers and prognostic factors, identified to be important by clinicians at an advisory board, due to no data being available for those variables in

the comparator evidence. It was not possible to adjust for timing of cataract surgery, prior anti-VEGF treatments and duration of oedema before treatment in any of the analyses performed.

The comparability of data sources for these analyses is also uncertain due to limitations with comparing RCT data to RWE. Follow-up of patients is less regular in real-world practice and the UK RWE audit included less patients for the outcomes at Year 2 and Year 3 and the impact of this missing data is unknown.

Further, the comparison of DEX700 in MEAD and DEX700 in Pareja-Ríos et al. 2018 was limited by the small sample size in Pareja-Ríos et al. 2018 (which included only 30 eyes).

B.2.9.5 Conclusion

The evidence base for the decision problem is patient-level data from the DEX700 arm of MEAD and reported summary data from a UK RWE audit investigating suboptimal anti-VEGF treatment. Two further supportive ITCs were performed to understand how Sham in MEAD compared with suboptimal anti-VEGF in the real-world and how DEX700 in MEAD compared with DEX700 in the real-world. All comparisons were subject to high levels of uncertainty mainly driven by differences in baseline BCVA across evidence sources. Results from the ITCs were therefore inconclusive.

B.2.10. Adverse reactions

Cataract formation and increase in IOP are considered to be the main side effects of intravitreal corticosteroids.[81]

B.2.10.1 MEAD trials

B.2.10.1.1 Treatment exposure

Table 13 presents a summary of treatment injections received by phakic DMO patients during the MEAD clinical trials. The 3-year study was completed by [redacted] ([redacted]) patients. Study completion rates were higher in the DEX700 ([redacted]) group than in the sham group ([redacted]). There was a >3-fold higher rate of discontinuations owing to lack of efficacy in the sham group.

Table 13: Summary of treatment injections received by phakic DMO patients

	DEX700 (n = [redacted])	Sham (n = [redacted])
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Day 1, n (%)	[redacted]	[redacted]
Month 6, n (%)	[redacted]	[redacted]
Month 9, n (%)	[redacted]	[redacted]
Month 12, n (%)	[redacted]	[redacted]
Month 15, n (%)	[redacted]	[redacted]
Month 18, n (%)	[redacted]	[redacted]
Month 21, n (%)	[redacted]	[redacted]
Month 24, n (%)	[redacted]	[redacted]
Month 27, n (%)	[redacted]	[redacted]
Month 30, n (%)	[redacted]	[redacted]
Month 33, n (%)	[redacted]	[redacted]
Month 36, n (%)	[redacted]	[redacted]
Month 39, n (%)	[redacted]	[redacted]

Key: DEX700, Dexamethasone 700 µg intravitreal implant; DMO, diabetic macular oedema; SD, standard deviation.
Source: AbbVie, 2021 (MEAD post-hoc analyses – Tables).[135]

B.2.10.1.2 Summary of adverse events

Table 14 presents a summary of AEs observed in phakic DMO patients during the MEAD trials. As expected, a larger proportion of patients in the DEX700 arm experienced AEs compared with patients in the sham arm.[135] However, there was a similar trend in the rates of AEs between the DEX700 and sham treatment arms. In both treatment arms, there was a low level of serious treatment-related adverse events (TRAEs).[135]

Table 14: Summary of AEs observed in phakic DMO patients during the MEAD trials

Event Type	DEX700 (n = [redacted])		Sham (n = [redacted])	
	All AEs, n (%)	Serious AEs, n (%)	All AEs, n (%)	Serious AEs, n (%)
All events	[redacted]	[redacted]	[redacted]	[redacted]
Ocular	[redacted]	[redacted]	[redacted]	[redacted]
Study eye	[redacted]	[redacted]	[redacted]	[redacted]
Non-study eye	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
Ocular	[redacted]	[redacted]	[redacted]	[redacted]
Study eye	[redacted]	[redacted]	[redacted]	[redacted]
Applicator/Insertion	[redacted]	[redacted]	[redacted]	[redacted]
DEX PS DDS	[redacted]	[redacted]	[redacted]	[redacted]
Non-study eye	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; DEX700, Dexamethasone 700 µg intravitreal implant; DEX PS DDS, Dexamethasone Posterior Segment Drug Delivery System.
Source: AbbVie, 2021 (MEAD post-hoc analyses – Tables).[135]

B.2.10.1.3 Most common treatment-related ocular adverse events

Table 15 presents the most common treatment-related ocular AEs in the study eye occurring in ≥ 2% of phakic DMO patients in the MEAD trials. In the DEX700 treatment arm, the most common treatment-related ocular AEs were [redacted] [135] In the sham treatment arm, the most common treatment-related ocular AEs were [redacted].[135]

Table 15: Most common treatment-related ocular AEs in the study eye occurring in ≥ 2% of phakic DMO patients

Adverse event	DEX700 (n = [redacted])	Sham (n = [redacted])
N, (%)		
Total events	[redacted]	[redacted]
Cataract	[redacted]	[redacted]
Cataract cortical	[redacted]	[redacted]
Cataract nuclear	[redacted]	[redacted]
Cataract subcapsular	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]
Conjunctival hyperaemia	[redacted]	[redacted]
Conjunctival oedema	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]
Lenticular opacities	[redacted]	[redacted]
Ocular hypertension	[redacted]	[redacted]
Vitreous floaters	[redacted]	[redacted]
Vitreous haemorrhage	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]

Key: AEs, adverse events; DEX700, Dexamethasone 700 µg intravitreal implant; DMO, diabetic macular oedema.
Source: AbbVie, 2021 (MEAD post-hoc analyses – Tables).[135]

B.2.10.1.4 Adverse events leading to treatment discontinuation

Table 16 presents a summary of the TRAEs leading to discontinuation of DEX700. Note that there were no TRAEs leading to discontinuation of sham treatment.[135] In the DEX700 arm, [redacted] patients ([redacted]%) discontinued treatment due to TRAEs, and [redacted] patients ([redacted]%) discontinued due to eye-related TRAEs.[135]

Table 16: Treatment-related adverse events leading to discontinuation of treatment

Adverse event	DEX700 (n = [redacted])
N, (%)	
Total events	[redacted]
Eye-related	[redacted]
Cataract	[redacted]
Lens dislocation	[redacted]
Necrotizing retinitis	[redacted]
Open angle glaucoma	[redacted]
Retinal detachment	[redacted]
Infection-related (endophthalmitis)	[redacted]

Key: DEX700, Dexamethasone 700 µg intravitreal implant.
Source: AbbVie, 2021 (MEAD post-hoc analyses – Tables).[135]

B.2.10.2 DEX700 real-world evidence studies

Summaries of the AEs reported in relevant published RWE studies are presented in Appendix F.1.

B.2.10.2.1 Cataract progression and cataract surgery

Twelve studies reported on the proportion of phakic DMO patients with cataract or cataract progression during their respective study periods.[84, 94-96, 100, 103, 104, 114, 118, 120, 142] The rate of cataract was generally low, with the majority of studies reporting rates of below 15%. In total, 20 RWE studies reported on the proportion of phakic DMO patients who underwent cataract surgery, with the proportion ranging from 6% up to 87%. Although three of these studies reported on the concomitant use of DEX700 with other DMO treatments, the results reported aligned with the range reported in studies of DEX700 monotherapy.[89, 102, 123] As expected, the longer the study follow-up period, the higher the proportion of patients undergoing cataract surgery. A larger proportion of phakic DMO patients enrolled into these trials may already have advanced cataracts prior to administration of DEX700, and thus, cataracts is not necessarily described as an adverse event.

In the RELDEX trial, and unlike the MEAD trial, no visual impairment was experienced in the months after cataract surgery. This is most likely due to the timing of cataract surgery, in which patients were treated with DEX700 one month prior to their cataract

surgery (Section B.2.6.2.4). DEX700 therefore decreased the DMO on the day of the surgery, and was effective at least 2–3 months after the surgery.

Furthermore, recent data has demonstrated that anti-VEGFs may also drive cataract progression. In the RISE and RIDE studies, the risk of cataract AEs with ranibizumab was up to 42.7% at 2 years, and the risk of cataract AEs with DEX700 was up to 67.9% at 3 years.[54, 82]

B.2.10.2.2 IOP and IOP-lowering medication

In total, 36 studies reported on the proportion of DMO patients experiencing increased IOP following treatment with DEX700, of which two reported a sub-analysis of the MEAD trials. Of note, the majority of studies reported a pooled analysis of both phakic and pseudophakic DMO patients. Three studies reported that the effects of DEX700 on IOP were similar in phakic and pseudophakic eyes.[91, 111, 130]

Increase in IOP is considered one of the main side effects of treatment with intravitreal steroids including DEX700, although elevated IOP following DEX700 can typically be managed with medication. Many of the RWE studies reported the rise in IOP which peaked 2–3 months after DEX700 administration, but returned back to baseline 4–6 months after the injection.

IOP was successfully managed with IOP-lowering medication in the vast majority of DMO patients. Only three studies reported a small proportion of patients (0.5–3.2%) who required surgery.

Patients may experience recurrences of increases in IOP after sequential injections, but there is no evidence for a cumulative effect of multiple injections on IOP.[91] Furthermore, treatment with DEX700 has demonstrated a benefit in improving visual and anatomical outcomes in both patients who and do not have increases in IOP.[91]

In the MEAD trial, [redacted] of patients needed IOP-lowering treatment. When reported, the proportion of patients within the RWE studies treated with IOP-lowering treatment is lower. This may be explained by the high mean number of DEX700 injections given in MEAD during a longer study period. Furthermore, because MEAD was an RCT, treatments were given on a more regular bases, and follow-up examinations were more frequent.

B.2.10.3 French RWD

During the study period, cataract surgery was performed in [redacted] ([redacted]%) phakic eyes, of which, [redacted] ([redacted]%) patients had cataract surgery after the 1st DEX700 injection, [redacted] ([redacted]%) after the 2nd DEX700 injection, [redacted] ([redacted]%) after the 3rd and [redacted] ([redacted]%) after the 4th.

An increase of ≥ 10 mmHg from baseline IOP was seen in [redacted] ([redacted]%) eyes, of which [redacted] eyes were pseudophakic and [redacted] were phakic ([redacted]). In total, [redacted] ([redacted]%) patients had ocular hypertension (≥ 35 mmHg), of which [redacted] were pseudophakic, and [redacted] were phakic ([redacted]). Topical antiglaucoma medication was administered in [redacted] ([redacted]%) patients ([redacted]% pseudophakic and [redacted]% phakic eyes).

B.2.10.4 UK RWE audit

Of the [redacted] anti-VEGF injections administered, a total of [redacted] perioperative AEs were reported: IOP spike (n = [redacted]), pain (n = [redacted]) and other – not specified (n = [redacted]). The rate of perioperative AE was [redacted] per 1,000 injections.

Postoperative adverse events show that endophthalmitis was reported on [redacted] occasions for [redacted], and [redacted] identified as receiving ceftazidime. The further analysis of event per injection gives a rate for endophthalmitis of [redacted] per 1,000 injections given. Post operative uveitis was only recorded in [redacted]. The most frequently reported postoperative complication was raised IOP (>21 mmHg) with [redacted] reports in [redacted] eyes.

At baseline, [redacted] eyes ([redacted]%) had no cataract. At the last recorded visual acuity, [redacted] ([redacted]%) had undergone cataract surgery. For the suboptimal group, this was [redacted] eyes ([redacted]%) had no cataract and [redacted] eyes ([redacted]%) had cataract recorded at baseline.

Further detail on the AEs reported within the UK RWE audit are presented in Appendix F.2.

B.2.11. Ongoing studies

There are currently no ongoing studies relevant to the decision problem.

B.2.12. Innovation

There remains a substantial unmet clinical need for patients with phakic eyes and DMO who are insufficiently responsive to or unsuitable for non-corticosteroid treatment. DEX700 has the potential to address the unmet need in these patients. For phakic DMO patients who are insufficiently responsive to treatment with non-corticosteroids, DEX700 offers a treatment option that improves patient outcomes and decreases the burden on patients and healthcare systems. Phakic DMO patients who are unsuitable for treatment with non-corticosteroids, have no available pharmacotherapy treatment options and are treated with watch and wait; therefore, DEX700 provides a pharmacological treatment option for these patients.

While anti-VEGF agents only target a single component of the inflammatory pathway of DMO, DEX700 has a mechanism of action that targets the multifactorial pathophysiology of DMO. It works to improve visual acuity through resolution of macular oedema[1], which is the key to effective long-term management of this condition. DEX700 utilizes an innovative solid polymer drug delivery system to deliver dexamethasone, which overcomes the suboptimal durability of bolus intravitreal administration of dexamethasone (half-life of only ~3 hours).[143, 144] This innovative system is characterized by dual-phase pharmacokinetics; initially releasing a burst of dexamethasone to rapidly achieve a therapeutic concentration, then gradually releasing the remaining total dose (700 µg) over several months. This allows for up to 6 months of corticosteroid treatment through a single intravitreal application.[11] As such, DEX700 has a longer duration of action compared with the anti-VEGFs. In addition, DEX700 has a flexible retreatment criterion, allowing the optimization of treatment frequency based on the individual patient need.

DEX700 requires less frequent injections than current treatment options.[145] A therapy requiring less frequent injections reduces the treatment burden on patients, thereby improving patient compliance and patient quality of life.[6] A reduction in the number of injections also will also reduce the resource use burden.[6, 145] The Royal College of Ophthalmologists recently issued guidance for the management of ophthalmology services during the COVID-19 pandemic; the guidelines endorse the use of treatments that reduce the frequency of patient visits.[75] As such, DEX700 has the potential to free

up resources and reduce the burden on the healthcare system whilst providing clinical benefit.

B.2.13. Interpretation of clinical effectiveness and safety evidence

The results of the analysis of phakic-only patients from the MEAD clinical trials indicated superior outcomes for patients treated with DEX700 compared with sham. Overall, DEX700 resulted in a greater mean change in average BCVA (AUC approach) from baseline to 39 months compared with sham ([redacted] versus [redacted] ETDRS letters, respectively; [redacted]).[135] In addition, a significantly greater number of patients treated with DEX700 achieved a BCVA improvement of ≥ 10 and ≥ 15 letters from baseline compared with those receiving sham ([redacted]% versus [redacted]%; [redacted]; and [redacted]% versus [redacted]%; [redacted], respectively).[135] Patients treated with DEX700 also reported significantly greater reductions in CRT from baseline to 39 months compared with sham [redacted] versus [redacted]; [redacted]).[135]

Although the results of the post-hoc efficacy analysis of phakic DMO patients from MEAD indicate favourable outcomes for patients treated with DEX700, several of the patient baseline characteristics of the MEAD phakic population were unfavourable and likely contributed to poorer outcomes than may be expected in clinical practice (Section B.2.7.1). Furthermore, and in line with clinical opinion[9], the management of patients in MEAD was suboptimal and likely contributed to poorer outcomes than expected in practice (Section B.2.7.1). The development of cataract and lens opacity and relatively delayed cataract extraction is also thought to have contributed to poorer visual outcomes, particularly between 18–30 months (Section B.2.7.2.1). In support of this, the reduction in CRT was consistently greater in patients treated with DEX700, indicating that the decline in visual outcomes is likely to have been caused by cataract rather than a reduction in DEX700 effectiveness.

In real-world clinical practice, DEX700 demonstrated substantially greater improvements in vision in phakic DMO patients who are insufficiently responsive to (Section B.2.6.2.2) or unsuitable for (Section B.2.6.2.3) non-corticosteroid treatment than observed in MEAD. Conversely, the results of the pseudophakic-only population of MEAD (on which the recommendations in TA349 are based) align with those seen

in clinical practice for pseudophakic eyes. Given there are a number of RWE studies that indicate similar outcomes between patients with phakic and pseudophakic DMO treated with DEX in clinical practice (Section B.2.6.2.1), this suggests that the results of the MEAD post-hoc analysis of phakic DMO patients are not fully reflective of clinical practice.

Overall, the results of the MEAD phakic mITT analyses likely present a worst-case scenario for the effectiveness of phakic DMO patients treated with DEX700 and do not reflect the outcomes of patients treated in real-world clinical practice.

In the UK RWE audit, [redacted]% of insufficient responders (≤ 5 letter gain at month 6) continued to receive anti-VEGFs over a period of 42 months, and the patients that were on treatment received approximately [redacted] injections per year over the longer term without achieving gains in BRVA.[10] This large proportion of insufficient responders highlights the current lack of an effective treatment. Anti-VEGFs also require frequent monitoring and injections in an attempt to achieve a robust response. In the UK RWE audit, patients attended a high number of in-person clinic appointments (Section B.2.6.4.2). Clinicians have highlighted this as a current concern due to the prevalence of capacity issues in ophthalmology services in the UK, which are likely to have been intensified by COVID-19 and are expected to persist for some time after.[9] The high burden associated with anti-VEGFs will likely be reduced with the approval of DEX700.[6, 9, 145] PROTOCOL T illustrates that with significantly higher monitoring and injection burden, significant gains in BCVA can be achieved with anti-VEGFs (Section B.2.6.5), however it is clear that in UK clinical practice these numbers of injections are not being reached in the majority of patients.

Results presented from the French RWD study demonstrate no significant differences in the change in BCVA between phakic and pseudophakic DMO patients, and was numerically superior at months 2, 24 and 36 (Section B.2.6.3.1).[132] This study therefore provides positive evidence for long-term use of DEX700 in phakic DMO patients.

An ITC was conducted using patient-level data from the DEX700 arm of MEAD and reported summary data from the UK RWE audit. Two further supportive ITCs were performed to compare the sham arm of MEAD with suboptimal anti-VEGFs in the real-

world, and to assess how DEX700 in MEAD compared with DEX700 in real-world clinical practice. All comparisons were subject to high levels of uncertainty, mainly driven by differences in baseline BCVA across evidence sources. Results from the ITCs were therefore inconclusive.

In phakic DMO patients who are unsuitable for or insufficiently responsive to non-corticosteroid treatment, DEX700 has proven to be safe and well-tolerated in both a clinical trial and real-world setting. In MEAD, there were low levels of serious TRAEs and very few phakic DMO patients ([redacted]%) discontinued treatment due to TRAEs.[135] Furthermore, cataracts were the most frequently reported TRAE in both the clinical trial and real-world settings (Sections B.2.10.1.3 and B.2.10.2.1, respectively).

B.3. Cost-effectiveness

B.3.1. Published cost-effectiveness studies

A systematic review of the published literature was conducted to identify all relevant cost-effectiveness studies for the treatment of phakic DMO patients who are insufficiently responsive to or unsuitable for non-steroidal therapies. Full details of the methods and results are presented in Appendix G.

No economic studies that included DEX700 in the specific population of interest were identified. The most relevant studies identified in the SLR to inform model development assessed the cost-effectiveness of fluocinolone acetonide, including the previous NICE appraisal TA613, which was a part review of TA301, assessing the cost-effectiveness of treatment in phakic eyes after an inadequate response to previous therapy. Learnings from the identified studies have been incorporated in the development of the cost-effectiveness model and are presented in each of the subsequent sections.

B.3.2. Economic analysis

No relevant studies comparing DEX700 with the relevant comparators in the population of interest were identified in the SLR. Therefore, the economic model submitted and reviewed in the previous NICE appraisal of DEX700 in DMO (TA349) was adapted for this submission as it was considered the most relevant analysis for decision making. This is because the model was judged to be appropriate for decision making by both the evidence review group (ERG) and committee, with the ERG stating that *'the model structure appears to be consistent with the progression of the disease and reflective of patient presentation and treatment in clinical practice.'*

The use of the same model structure also ensures consistency, as it allows for the assumptions applied previously to be tested in the analysis to clearly demonstrate which assumptions and inputs have impacted the results. Additionally, the model structure is broadly consistent with those that have been submitted in previous DMO appraisals to NICE, each of which adopted a state transition model approach. The model adopts a Markov state transition approach, with multiple discrete and independent health states used to capture the progression of DMO over time. Vision

loss, potentially leading to blindness, is captured through the modelling of transitions between visual acuity states. There are six health states based on visual acuity (10-letter increments) and both eyes may transition between the six health states because BCVA changes in both eyes are modelled independently. Further details on the model structure are presented in Section B.3.2.2.

In TA346, which considered aflibercept for treating visual impairment caused by DMO, a state transition model including three distinct and separate phases was submitted. The model first included an efficacy phase that lasted for 1 year, during which time vision could improve. This was followed by a 4-year maintenance phase where vision remained stable, and then a rest-of-life phase where a long-term decline of vision occurs based on the assumption that patients' vision declines at a steady rate over the remainder of their life.

TA613 considered fluocinolone acetonide intravitreal implant in a similar but narrower population of patients with chronic DMO and eyes with phakic lenses considered insufficiently responsive to available therapies and affected by symptomatic cataracts. A similar state transition model was presented in this appraisal. The model considered both eyes, with BCVA modelled independently for each, and the health states were defined according to BCVA, DMO status, lens status and treatment phase. This approach is broadly consistent with the original DEX700 model from TA349 that has been adapted for this appraisal, but given the recency of the TA613, feedback from the appraisal committee for this appraisal has also been considered and incorporated in our model. Two key learnings from this appraisal were related to the relevant comparator that should be modelled and the appropriate assumptions regarding the efficacy of this comparator.

The committee accepted that, at the time of the appraisal, both laser treatment and anti-VEGFs were appropriate comparators for decision making in phakic eyes with DMO that are insufficiently responsive to non-corticosteroid treatment. The committee was aware that most people will initially have anti-VEGFs and that in phakic eyes they might be continued even if they do not work well given a lack of approved alternatives.

The committee also considered it appropriate to assume that the net effect between fluocinolone acetonide intravitreal implant and the sham arm of the FAME study

reflected the net effect between fluocinolone acetonide intravitreal implant and continued anti-VEGF/laser in the absence of alternative robust evidence.

In TA613 the committee concluded that the cost-effectiveness estimates were too uncertain because of the lack of clinical evidence, as only very few people received anti-VEGFs prior to the FAME trials, and few people in the trial had phakic eyes with symptomatic cataracts (the population for which reimbursement was sought). Also, non-comparative studies used to support the company's submission included few people with phakic eyes and symptomatic cataracts.

In this appraisal, attempts have been made to address these challenges through substantial RWE data collection, the presentation of published clinical evidence including patients with phakic eyes and the inclusion of a range of alternative plausible scenarios in the cost-effectiveness model.

B.3.2.1 Patient population

This economic evaluation includes analyses that cover the population within the marketing authorization for DEX700 (Section B.1.2) that have a phakic lens and DMO that does not respond sufficiently to non-corticosteroid treatment.

The phakic-only mITT population of the MEAD trial is the primary data source used to inform the model. However, as outlined in Section B.2.3.1.1, the MEAD trial may be considered to under-estimate the efficacy of DEX700 in phakic patients that can be achieved in clinical practice, and to over-estimate the efficacy of the sham arm, which may not be an ideal proxy to represent the efficacy of current UK clinical practice in the relevant patient population (see Section B.3.3.1 for further details). Therefore, additional supplementary RWE was gathered and presented to provide supportive evidence for the population of interest and to provide data that give a better representation of the efficacy of existing therapies in UK clinical practice.

As highlighted in Section B.1.3.4.3, first-line treatment with non-corticosteroid therapies is ineffective in approximately 40% of patients in clinical practice, with sources such as the UK RWE audit reporting proportions as high as [redacted]% (Section B.2.6.4). However, no alternative treatment option is currently recommended by NICE to prevent irreversible damage to the retina of patients with a phakic lens. UK clinical

experts have indicated that because there are currently no alternative treatment options available, they continue administering non-corticosteroid treatment even if it is ineffective, as they believe providing no treatment option is guaranteed to result in worsening patient outcomes. As a result, this patient group continues to receive expensive and ineffective anti-VEGF injections, which are frequently administered monthly given the lack of recommended alternatives, leading to the wasteful use of NHS resources. This was confirmed during the appraisal of fluocinolone acetonide (TA613) where it was noted in the final appraisal determination document: *'The committee was aware that most people will initially have anti-VEGFs and that in phakic eyes they might be continued even if they do not work well.'*

In addition, as noted in Section B.1.3.4.3, clinicians have highlighted the prevalence of capacity issues in ophthalmology services in the UK, which are likely to have been exacerbated by COVID-19 and are expected to persist for some time after. Continued use of anti-VEGFs is likely to add to the existing burden, as these regimens require frequent injections, with many patients receiving a significant number over a prolonged period in an attempt to achieve any level of response. Guidance from the Royal College of Ophthalmologists suggested that, in the context of COVID-19, ophthalmology clinics should use treatment changes that can reduce the frequency of required attendances. Therefore, there is clear unmet need in this patient group given the absence of a treatment option that is both effective and minimizes the need for frequent clinic visits.

B.3.2.2 Model structure

B.3.2.2.1 Overview

The model used for this appraisal is consistent with the model from the previous submission (TA349) that was reviewed and updated by the ERG and submitted prior to the final appraisal determination. Therefore, the model aligns with the Committee's stated preferred assumptions.

A Markov model approach has been adopted, with multiple discrete and independent health states used to capture the progression of DMO over time. Vision loss, potentially leading to blindness, is captured through the modelling of transitions between visual acuity states. There are six health states based on visual acuity (10-

letter increments). Both eyes may transition between the six health states because BCVA changes in both eyes are modelled independently. Treatment may be modelled in both eyes (bilateral DMO) or in either the better-seeing eye (BSE) or worse-seeing eye (WSE) (unilateral DMO). Patients who are affected unilaterally at baseline may develop DMO in their second eye, termed fellow eye involvement.

The model assumes a maximum duration of treatment of 5 years across all treatments. This assumption was based on feedback provided by UK clinical experts which noted that 5 years was sufficiently long enough to capture key differences in treatment costs. The clinicians noted that although there will be a proportion who remain on treatment beyond 5 years, this group will be likely be small across for both those receiving DEX700 or anti-VEGFs. This is supported by data from MEAD and the French RWE study, which demonstrate that a proportion of patients were still receiving DEX700 at the end of the 3-year follow-up period.[131, 132] Similarly, this assumption is supported for anti-VEGFs by the UK RWE audit and other published studies such as the RESTORE trial, which demonstrate that a sizeable proportion of patients were still receiving frequent anti-VEGFs after 3–4 years.[10, 146] Although a longer duration may be justified, capping the treatment duration at 5 years is only likely to underestimate the cost-savings of DEX700 given the higher long-term injection frequency for anti-VEGF patients.[129]

B.3.2.2.2 Health states

Both eyes may transition between six visual acuity states of 10-letter increments defined in Table 17. 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.[133] Severe vision loss (defined as BCVA ≤ 35 letters in the model) in both eyes is considered clinical blindness and is additionally associated with increased costs (section B.3.5.2).

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), allowing patients to move between visual acuity health state, with no restrictions on the health state they can transition to in each model cycle in the

model base case. The probability of moving between visual acuity states in each cycle is modelled using transition probability matrices.

Table 17: 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 6 m/20 ft	≤ 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[147]

B.3.2.2.3 Patient pathways

The patient pathways are intended to capture the treatment and disease status of the DMO cohort. The pathways capture the proportion of patients in the cohort who have unilateral DMO in the BSE or WSE or bilateral DMO over time. In addition, they capture whether the patients in the cohort remain on treatment or have discontinued from treatment, which is consistent with the original TA349 appraisal. Figure 18, Figure 19 and Figure 20 show the patient pathways for patients in the cohort who have unilateral DMO in the BSE, unilateral DMO in the WSE or bilateral DMO at baseline. Figure 21 shows all possible movements for all patients within the cohort.

On treatment

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 in 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 phakic population (see Section B.3.3.2 for further details). Patients in 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 consistent with what was assumed in TA349.

As patients who are affected unilaterally may, in practice, develop DMO in their fellow eye over time, the model accounts for patients in the cohort who are affected unilaterally at baseline but who 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 B.3.3.3.2.

The base case model assumes that the BSE and WSE are defined at baseline and fixed throughout the time as a simplifying assumption, which is consistent with previous modelling in DMO.

In terms of transitions between visual acuity states, eyes that are affected with DMO are assumed to receive treatment for up to 5 years and are assigned the efficacy associated with treatment for as long as they remain on treatment. During the initial 5-year treatment period, patients are at risk of discontinuation from treatment due to two explicit and independent reasons: either due to AEs and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment (see section B.3.3.3.1 for further details).

Off-treatment

Following discontinuation from treatment due to either AEs and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment, 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)[43] (see section B.3.3.2), in line with the preferred assumption by the ERG in TA349. 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 patients with phakic DMO who are insufficiently responsive to non-corticosteroid treatment. As patients will have exhausted all available treatment options available to them, it makes sense to assume no further treatment. 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.

Patients who experience fellow eye involvement and discontinuation in the same cycle are treated the same as a patient who was already bilaterally affected and experiences discontinuation. Both eyes are then assumed to receive no further treatment and as a result the vision in their affected eyes transitions through the visual acuity states at a rate consistent with the natural history of vision in patients with DMO.

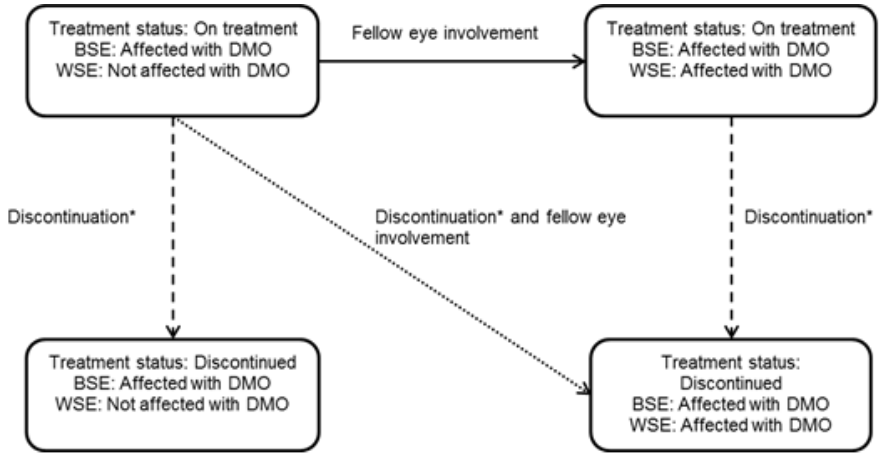
Eyes without DMO

Eyes without DMO are assumed to retain constant vision, as the focus of this submission is the treatment of visual impairment due to DMO.

Death

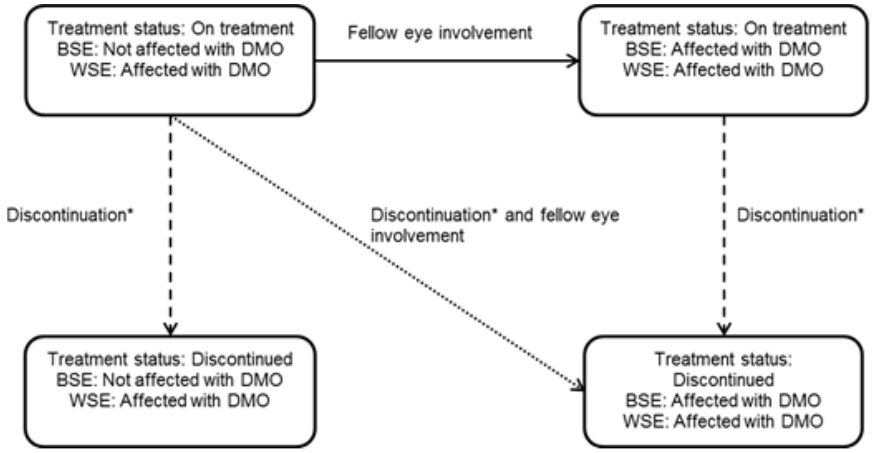
All patients within the cohort are at risk of death throughout the model time horizon. The risk of all-cause mortality is applied to all patients, adjusted for the additional mortality due to diabetes mellitus (relative to the general population) and due to DMO (relative to the diabetic population) and 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 (see Section B.3.3.3.3).

Figure 18: Patient pathway, patient with unilateral DMO in the BSE at baseline



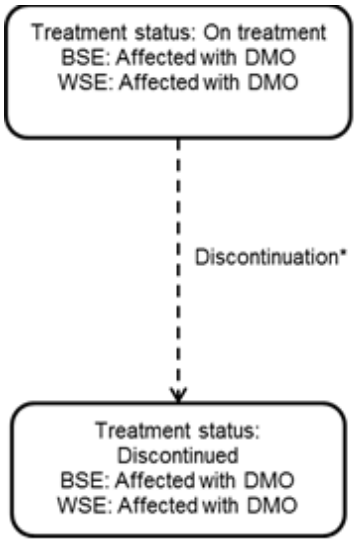
Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: * Discontinuation due to either adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment.

Figure 19: Patient pathway, patient with unilateral DMO in the WSE at baseline



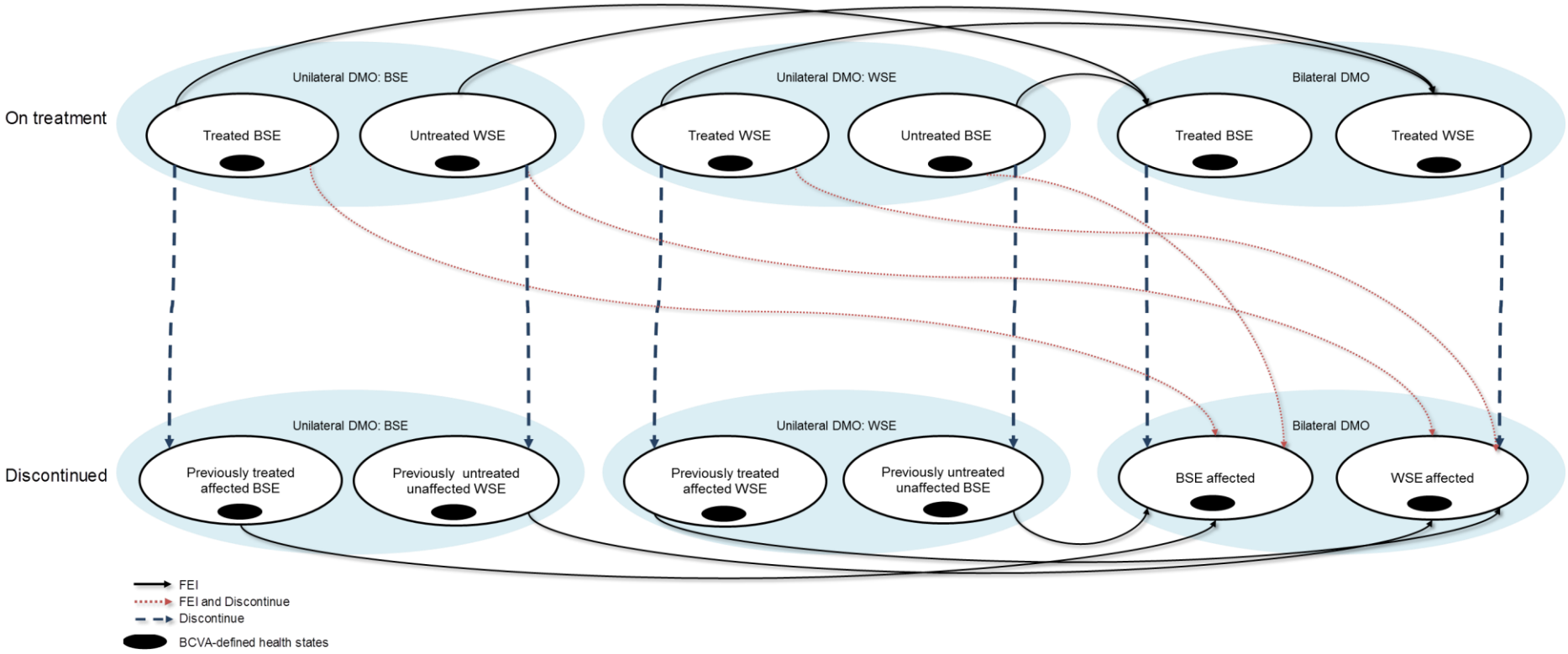
Key: BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: * Discontinuation due to either adverse events and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment.

Figure 20: 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 21: 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.

B.3.2.2.4 Features of the de novo analysis

The analysis was conducted from the perspective of the UK NHS and Personal Social Services in England across a lifetime time horizon consistent with NICE TA613 and TA346, assumed to be 40 years given the mean age of patients in MEAD ([redacted] years). A lifetime horizon is required to ensure all relevant downstream benefits and costs are captured following discontinuation from treatment.

The cycle length is set at 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. Half-cycle correction is applied to account for the fact that events can occur at any point during the cycle, not necessarily at the start or end of each cycle.

In the model, health effects are calculated in terms of both life years and quality-adjusted life years (QALYs). Both costs and effects were discounted at a rate of 3.5% per year, in line with the NICE reference case.

The main features of the model in comparison with previous appraisals are presented in Table 18.

Table 18: Key features of the model

Factor	Previous appraisals			Current appraisal	
	DEX700 (TA349)	Iluvien (TA613)	Aflibercept (TA346)	Chosen values	Justification
Model structure	Markov model	Markov model	Markov model	Markov model	Consistent with the model from the previous submission (TA349) that was reviewed and updated by the ERG.
Health states	By eye (i.e. study/fellow) By DMO status By treatment Six BCVA states Death	By eye (i.e. study/fellow) By lens status By DMO status By treatment Eight BCVA states Death	By eye By treatment Eight BCVA states Death	By eye (i.e. study/fellow) By DMO status By treatment Six BCVA states Death	Consistent with the model from the previous submission (TA349) that was reviewed and updated by the ERG.
Source of efficacy data	Dexamethasone: DEX700arm from pooled MEAD; Watch and wait: sham arm from pooled MEAD; NMA for dexamethasone compared with sham (though committee concluded that the focus should be on the head-to-head results from the MEAD trials)	Fluocinolone acetonide: FAc 0.2 µg/day arm from FAME; Usual care: sham arm from FAME; RWE: ICE-UK and Retro-IDEAL; NMA was not feasible because of the insufficient number of RCTs carried out. Consequently, indirect and mixed comparisons were also not feasible.	Laser: VISTA and VIVID trials; Aflibercept and ranibizumab: relative risk as calculated in NMA; Dexamethasone: relative risk from indirect comparison of aflibercept with dexamethasone; Fluocinolone: improvement rates from FAME, worsening rates assume same as laser	Dexamethasone: DEX700 arm from pooled MEAD trials (mITT population); Anti-VEGF: sham arm in from pooled MEAD trials (mITT population); Alternative sources are applied in scenario analysis (Section B.3.3.2.7)	As highlighted in Section B.2.3.1.1, some of the baseline characteristics from MEAD do not align with characteristics of patients expected to be treated in UK clinical practice or with the characteristics observed in the RWE studies. However, given the MEAD trials provide patient-level, head-to-head RCT evidence in a large sample of patients, this data is considered the most relevant data for the base-case comparison. Additionally, these imbalances in baseline characteristics are expected to underestimate the efficacy of dexamethasone, and over-estimate the efficacy of sham, resulting in a more conservative estimate of the relative treatment effect. Using the phakic population from MEAD to represent (patients insufficiently responsive to non-corticosteroid treatment is consistent with the approach adopted in TA349 where the full

Factor	Previous appraisals			Current appraisal	
	DEX700 (TA349)	Iluvien (TA613)	Aflibercept (TA346)	Chosen values	Justification
					pseudophakic population in MEAD was used to represent both patients who were insufficiently responsive for non-corticosteroid treatment As highlighted in Section B.3.3.1.2, the sham arm from MEAD is not considered a perfect proxy for continued anti-VEGF use as it is likely to overestimate the efficacy of the comparator arm as demonstrated by a naive comparison of this data to the UK RWE audit for continued use of anti-VEGF. However, the sham arm is used in the base-case as it allowed for a full set of transition probabilities to be estimated for this treatment arm which was a key advantage of the data from the sham arm from MEAD over other data sources. It also avoided the potential issues associated with indirect treatment comparisons such as imbalances between patient and study characteristics that add heterogeneity and, therefore, uncertainty. However, given the sham arm provides an overestimate of the efficacy of continued use of anti-VEGFs, the use of this data results in a conservative estimate of the treatment effect.
Long-term treatment effect	DMO natural history from Mitchell et al. (2012) after the treatment period	The company assumed that treatment effect is maintained for a lifetime even after treatment has stopped. The committee	During the maintenance phase, patient vision is assumed to remain stable for 4 years. During the rest of life phase, a long-	DMO natural history from Mitchell and al. (2012) after the 5-year treatment period	This assumption was based on feedback provided by UK clinical experts which noted that five years was sufficiently long enough to capture key differences in treatment costs. This is supported by data from MEAD and the French RWE study which demonstrate that a proportion of patients were still receiving DEX700 at the end of the three-year follow-up period. Similarly, this assumption is

Factor	Previous appraisals			Current appraisal	
	DEX700 (TA349)	Iluvien (TA613)	Aflibercept (TA346)	Chosen values	Justification
		concluded that it is implausible to assume the continued treatment effect would last for a lifetime	term decline of vision occurs.		supported for anti-VEGFs by the UK RWE audit and other published studies such as the RESTORE trial which demonstrate that a sizeable proportion of patients were still receiving frequent anti-VEGFs after three to four years.
Time horizon	15 years	30 years (lifetime)	35 years (lifetime)	40 years	A lifetime time horizon was applied consistent with NICE TA613 and TA346. This was assumed to be 40 years given the mean age of patients in MEAD (61 years).
Cycle length	3 months	3 months	4 weeks	3 months	Consistent with the model from the previous submission (TA349): a 3-month cycle length was chosen to enable the use of patient-level transition probability matrices from MEAD with a consistent cycle length.
Source of utilities	TTO scores literature (Czoski-Murray et al. 2009)	VFQ-UI utilities from FAME trials	TTO scores literature (Czoski-Murray et al. 2009)	TTO scores literature (Czoski-Murray et al. 2009)	Preferred by the ERG in the previous submission (TA349) and NICE TA346.
Source of costs	National tariff of drugs and National schedule of reference costs	British National Formulary of Drugs and National schedule of reference costs	National tariff of drugs and National schedule of reference costs	National tariff of drugs and National schedule of reference costs	Consistent with previous appraisals and the NICE reference case
Key: BCVA, best-corrected visual acuity; DMO, diabetic macular oedema; ERG, Evidence Review Group; ITC, indirect treatment comparison; mITT, modified intention-to-treat; NMA, network meta-analyses; RWE, real-world evidence; TA, technology appraisal; TTO, time trade off.					

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

Ozurdex 700 micrograms (DEX700 pro re nata [PRN]) intravitreal implant is the intervention of interest and is implemented in the model as per its marketing authorization, 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.

Consistent with the model from TA349 and based on clinician feedback, 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. In addition, 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 5 years starting from this point (see Section B.3.3.3.2 for further details).

Data from phakic DMO patients in the DEX700 arm of the pooled MEAD studies were used to inform the clinical outcomes for the DEX700 arm. See Section B.3.3 for further details.

Discontinuation from DEX700 has been explicitly modelled, based on rates observed in the MEAD studies (see section B.3.3.3.1 for further details). The average number of treatments with intravitreal injections per patient remaining 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

Given the follow-up time of 3 years in MEAD, the average number of injections in Years 1–3 are taken from MEAD, whereas the average in Years 4 and 5 were elicited from two practicing UK clinicians.[73] The average numbers of intravitreal injection treatments assumed in Years 1–5 are shown below in Table 19 (see Section B.3.5.1.1 for further details).

Table 19: Average numbers of intravitreal injection treatments per year; All phakic DMO patients

Treatment	Average number of intravitreal injection treatments					Reference
	Year 1	Year 2	Year 3	Year 4	Year 5	
DEX700	[redacted]	[redacted]	[redacted]	1.00	1.00	MEAD[148]
Key: DEX, dexamethasone; DMO, diabetic macular oedema.						

B.3.2.3.2 Comparators

As discussed in Section B.3.2, a key learning from TA613 is that the appraisal committee accepted continued use of non-corticosteroid treatments as appropriate comparators for decision making in patients with phakic eyes with DMO that are insufficiently responsive to non-corticosteroid treatment. The committee was aware that most people will initially receive anti-VEGFs and that in phakic eyes treatment will often continue even if it is found to be relatively ineffective. This assumption was also supported by clinical experts during an advisory board conducted for this appraisal which confirmed that patients who are insufficiently responsive to anti-VEGFs in UK clinical practice are continuing treatment due to a lack of alternative treatment options.

The appraisal committee for TA613 concluded that a composite comparator of anti-VEGF and laser therapies (28% laser, 63% ranibizumab and 9% bevacizumab), based on the proportion of patients using each treatment in the ICE-UK study was appropriate for decision making. However, in an advisory board conducted for this re-appraisal, clinical experts confirmed that anti-VEGFs are almost exclusively administered to patients in clinical practice, with laser treatment rarely used. This is consistent with a statement made in a study conducted by Kodjikian et al. (2018)[81] noting that since anti-VEGF and DEX-implants came onto the market, laser photocoagulation treatments have gradually been abandoned in favour of intravitreal injections. In addition, laser photocoagulation is only recommended in patients with non-centre involved DMO (estimated to be ~20% of the total DMO population) and/or patients with DMO with no associated visual impairment due to concerns of safety and long-term clinical efficacy. Therefore, laser is excluded from our base case analysis, but scenario analyses are presented where the percentage of patients assumed to receive laser photocoagulation is increased to 5% and 10%.

Ranibizumab and aflibercept are both approved for use in this indication; however, bevacizumab does not currently have a marketing authorization in the UK for this indication and the SmPC states that bevacizumab is not formulated for intravitreal use. Bevacizumab is also not recommended by NICE in this indication and therefore any use of bevacizumab is off-label.[19]

The base case for this economic evaluation includes a composite comparator based on the proportion of patients receiving ranibizumab and aflibercept treatment in the UK RWE audit. UK clinicians have flagged that the use of aflibercept has increased in recent years. This likely explains why the composite comparator of TA613 did not capture any aflibercept use, as it used data from an older study (ICE-UK) which did not include data after 2018 (given the date of the NICE submission). In the base case, the proportion of eyes using aflibercept and ranibizumab from the complete set of UK RWE has been used to maximize the sample of eyes, but in a scenario analysis the composition of treatments is estimated based on the latest 2 years of the UK RWE audit.

In addition, the ICE-UK market shares from TA613, which include off-label use of bevacizumab and no aflibercept are tested in a scenario analysis for completeness. In this scenario, the proportion of patients assumed to receive laser photocoagulation in TA613 has been re-allocated proportionally between the anti-VEGF treatments, as per feedback received from clinicians during the advisory board. Details of the calculation steps and assumptions that were made in this scenario analysis are presented in Appendix Q.

Table 20 presents the composition of the blended comparator in the base case and the scenario analyses explored.

Table 20: Composition of blended comparator

Comparator composition source	Ranibizumab	Bevacizumab	Aflibercept	Laser
Base case				
UK RWE audit (overall)	[redacted]	0.0%	[redacted]	0.0%
Scenario analyses				
UK RWE audit (latest 2 years)	[redacted]	0.0%	[redacted]	0.0%
UK RWE audit (overall) - including 5% laser	[redacted]	0.0%	[redacted]	5.0%
UK RWE audit (overall) - including 10% laser	[redacted]	0.0%	[redacted]	10%
NICE TA613 (excluding laser)	87.5%	12.5%	0.0%	0.0%

Key: RWE, real world evidence; TA, technology appraisal.

Ranibizumab and aflibercept are implemented in the model as per their marketing authorizations. Treatment in adults is initiated with one injection per month, with three or more consecutive monthly injections potentially required. Thereafter, monitoring and treatment intervals are determined by the physician and based on disease activity. However, as the analysis considers patients who are insufficiently responsive to anti-VEGF's, all patients are assumed to start in the physician-led phase as patients had received their loading dose prior to being classed as an insufficient responder. Given that treatment is not administered as a fixed regimen that is consistent across all patients, data on anti-VEGF use was required to provide estimates for the average number of injections patients receive over time.

The average number of ranibizumab and aflibercept administrations applied per model cycle were taken from the UK RWE audit. In the base case it is assumed, in line with TA613 and feedback from UK clinical experts from the advisory board, that patients cannot discontinue anti-VEGF treatment during the treatment period because it represents the last therapeutic option for these patients. Please see Section B.3.5.1.1 for further details.

Just as for the intervention arm, it is assumed that patients in the anti-VEGF arm who are affected bilaterally from baseline receive the same treatment at the same frequency and achieve the same level of efficacy in both eyes. 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 5 years starting from this point (see B.3.2.2.3 for further details).

B.3.3. Clinical parameters and variables

As noted in Section B.3.2.3 data from phakic DMO patients in the MEAD trial (mITT population) was used as the primary data source to inform long-term outcomes for DEX700 and anti-VEGFs. The phakic population from MEAD was used to represent the relevant sub-population of patients insufficiently responsive to non-corticosteroid treatment). This is consistent with the approach adopted in TA349 where the full pseudophakic population in MEAD was used to represent both patients who were insufficiently responsive or unsuitable for non-corticosteroid treatment.

The key baseline characteristics used in the model are summarized below in Table 21.

RWE investigating patients receiving either DEX700 (Section B.2.2.1.2) or continued use of anti-VEGF therapies (Section B.2.2.2.1) are used as supportive evidence to provide further evidence of the effectiveness of treatment in the relevant populations of interest. The RWE data are presented as supportive evidence and are used in scenario analyses only given the limitations in being able to use the data in a robust indirect treatment comparison which are highlighted in Section B.2.9. Additionally, given this the RWE data do not include sufficient information to model all possible transitions in the model, stringent assumptions are required to use aggregate data to populate the model, which limits the potential for this data to be robustly incorporated into the cost-effectiveness analysis base case.

Table 21: Key baseline characteristics

Characteristic	Value
Mean age, years	[redacted]
Proportion of males (%)	[redacted]

B.3.3.1 Treatment efficacy

B.3.3.1.1 DEX700

Data from the mITT population from the MEAD clinical trials were used to model treatment efficacy for the DEX700 arm. However, a range of RWE studies (Section B.2.6.2) and exploratory sub-group analyses from MEAD (Section B.2.7) have consistently demonstrated how the mITT data from MEAD under-estimates DEX700 outcomes in phakic DMO patients. A range of simplified scenarios have been explored in the model testing different plausible scenarios relating to the long-term effectiveness of DEX700 in this patient population (B.3.3.2.7).

B.3.3.1.2 Anti-VEGFs

There is limited evidence that directly compares the dexamethasone intravitreal implant with anti-VEGF treatments in the group of patients who are insufficiently responsive to anti-VEGF treatment. In addition, there is limited relevant RCT evidence on the use of anti-VEGF or laser in insufficient responders (Section B.2.6.5).

As noted in Section B.3.2.1, in the base-case analysis, the sham arm of the MEAD trial is used as a proxy for continued anti-VEGF use. The sham arm is not considered a perfect proxy for continued anti-VEGF; however, it is applied in the base-case given MEAD provides head-to-head RCT evidence, and as Section B.2.9 highlights, there were significant challenges in making a robust indirect treatment comparison between different DEX700 and anti-VEGF data sources. In addition, the availability of patient-level data allows for a full set of transition probabilities to be estimated for this treatment arm which was a key advantage of the data from the sham arm from MEAD over other data sources. Also, as noted in Section B.2.9, there are significant imbalances between the data for DEX700 from MEAD and the available anti-VEGF study data, which limit the ability to make a robust matched comparison which can address imbalances between patient and study characteristics that add heterogeneity and, therefore, uncertainty.

Using the MEAD sham arm as a proxy for continued anti-VEGF use is also consistent with the approach adopted in TA613, where the committee considered it appropriate, in the absence of suitable alternative evidence, to assume the net effect between fluocinolone acetonide intravitreal implant and the sham arm of the FAME study

reflected the net effect between fluocinolone acetonide intravitreal implant and continued anti-VEGF/laser.

Although this approach was pragmatically accepted in TA613, there are key differences between the sham arms in MEAD and FAME, as patients in FAME could receive rescue therapy if they were unresponsive to therapy and remain in the study, whereas in MEAD any patient who received rescue therapy was excluded from the study. This at least partially explains why there are differences in the efficacy outcomes between the MEAD and FAME sham arms, as shown in Figure 22. However, as Figure 22 also demonstrates, a naïve comparison of the mean BCVA change from baseline over time in the MEAD sham arm with UK RWE shows that using the MEAD sham arm as a proxy for continued anti-VEGF use likely overestimates the efficacy of this treatment arm and therefore likely results in a conservative estimate of the relative treatment effect. Therefore, use of the MEAD sham arm is considered a reasonable approach as any bias in using this data is likely to favour the comparator rather than DEX700.

Figure 22: Comparison of BCVA change from baseline in MEAD sham arm (phakic) vs FAME sham arm (phakic) vs UK RWE for continued anti-VEGF use (phakic and insufficiently responsive)

Key: BCVA, best corrected visual acuity; RWE, real world evidence; anti-VEGF, anti–vascular endothelial growth factor therapy.

B.3.3.2 Transition probabilities

The approach that was adopted to estimate transition probabilities between health states is consistent with the approach applied in TA349 that was considered acceptable by the appraisal committee. However, the only key difference is that data from the phakic sub-group from MEAD were used to inform the transition probabilities as opposed to the ITT or pseudophakic data. Section B.3.3.2 summarizes which transitions were applied in each health state and how these were estimated, with further details of the methods used presented in Appendix N.

B.3.3.2.1 Baseline visual acuity

The distribution of vision at baseline for a BSE or WSE with DMO was taken from the study eye data for phakic DMO patients 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 for phakic DMO patients 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 22. Due to the study inclusion criteria no study eyes (i.e. no treated eyes) fell into Health State 6 at baseline.

Table 22: Baseline distribution of vision across visual acuity states; All phakic 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[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE[c]	[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: [a] Based on data for study eyes which were the BSE. [b] Based on data for non-study eyes which were the BSE. [c] Based on data for study eyes which were the WSE. [d] Based on data for non-study eyes which were the WSE.
References: MEAD (2021)[148]

B.3.3.2.2 Visual acuity state transition probabilities

The model allows patients to move between visual acuity health states, with no restrictions on the health state they can transition to in each model cycle. This ensures that all small and large improvements or worsening of vision observed in the clinical trials are captured in the model. Different transition probabilities between visual acuity states are applied to eyes with different characteristics for different time-periods as described in Table 23.

Given the change in visual acuity was not reported for all patients in each cycle of the trial, assumptions were required to account for the potential unobserved movements between states that were not observed in the trial. One approach considered was to exclude any missing patients and estimate the transition probabilities based on the observed number of patients, with the denominator equalling the number of observations in each given cycle. However, this approach produced results which lacked face validity as the predicted outcomes were contradictory to the observed data from MEAD, given they predicted worse outcomes for patients on the DEX700 arm compared with sham. This was likely due to small event numbers in several model cycles having a large influence on the transition probability estimates.

Therefore, a last observation carried forward (LOCF) approach was adopted. This approach used the total number of patients on each trial arm fixed as the denominator in each cycle, and therefore assumed that patients with a missing observation did not move to a different health state in that cycle.

Table 23: Visual acuity state transition probabilities

DMO status	Treatment status	Time period (base case analysis)	Transition probabilities	Cross-reference
Eye with DMO	On treatment	Years 1–5 following initiation of treatment	Transition probabilities estimated from MEAD trial	B.3.3.2.3
	Off treatment	Years 6+ following initiation of treatment	Transition probabilities assumed to follow DMO natural history	B.3.3.2.4
	Discontinued from treatment	From the point of discontinuation	Transition probabilities assumed to follow DMO natural history	B.3.3.2.5
Eye without DMO	N/A*	From baseline	Constant vision	B.3.3.2.6

Key: DMO, diabetic macular oedema.
Notes: * No treatment assumed for eyes without DMO.

B.3.3.2.3 Eyes with DMO, on treatment, Years 1–5 following initiation of treatment

Changes in BCVA resulting from DEX700 and comparator treatments during the 5-year treatment period are modelled using 3-monthly transition probabilities derived from the DEX700 arm and the sham arm of the pooled MEAD studies, respectively. Transition probabilities for DEX700 and sham arms 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 from the DEX700 and sham arms of the pooled MEAD studies for each year, and an example of how the transition probabilities are calculated, are presented in Appendix N.

Given that MEAD provides us with 3 years of data, assumptions are required to model Years 4 and 5 where patients are still expected to receive treatment based on feedback from UK clinicians.[73] Therefore, throughout these years, the last transition probability matrix estimated from MEAD is applied in each of the subsequent model cycles until the end of Year 5. This approach is adopted as the last transition matrix provides the most relevant data available from MEAD as it allows for any recovery in

BCVA following the development and extraction of cataracts in a significant proportion of patients to be captured.

B.3.3.2.4 Eyes with DMO, Years 6+ following initiation of treatment

For all eyes with DMO, a single extrapolation is applied after the 5-year treatment period. 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)[43] used data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy adjusted to account for the improvement in diabetes mellitus 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 24. This transition probability matrix is applied to all eyes with DMO from Year 6 following the initiation of treatment, for the remainder of the model time horizon.

Table 24: Transition probability matrix: natural history of vision in patients with DMO

		To						Total
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**	
From	**Health State 1**	0.965	0.035	0.000	0.000	0.000	0.000	1.000
	Health State 2	0.045	0.920	0.035	0.000	0.000	0.000	1.000
	Health State 3	0.000	0.045	0.920	0.035	0.000	0.000	1.000
	Health State 4	0.000	0.000	0.045	0.920	0.035	0.000	1.000
	Health State 5	0.000	0.000	0.000	0.045	0.920	0.035	1.000
	Health State 6	0.000	0.000	0.000	0.000	0.045	0.955	1.000

Key: DMO, diabetic macular oedema.
Source: Mitchell et al. (2012)[43]

B.3.3.2.5 Eyes with DMO, discontinued from treatment

In the model, patients can discontinue from their initially assigned treatment during the initial 3-year treatment period for two distinct reasons (see Section B.3.3.3.1 for further details):

- AEs and other non-efficacy-related reasons
- Lack (or loss) of efficacy of treatment

In the economic model these two reasons have been modelled independently. This is in accordance with the way the data is reported due to the non-trivial proportion of discontinuations for each reason within the DEX700 treatment arm of the pooled MEAD studies. Considering these reasons for discontinuation independently in 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 B.3.2.2.3 to reflect that vision may still be affected by DMO following discontinuation. Consistent with TA349, this simplifying assumption has been made given that patients do not have access to any further effective treatment options.

B.3.3.2.6 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, 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.

B.3.3.2.7 Additional scenarios

As highlighted in Section B.3.3.1, the use of the MEAD data to model the long-term efficacy outcomes for each treatment arm is associated with limitations which are likely to underestimate the effectiveness of DEX700 and overestimate the effectiveness of anti-VEGF treatment. Therefore, a range of plausible scenarios related to the long-

term effectiveness of each treatment regimen have also been explored to assess the impact of each on the results.

Net-zero impact on vision

This scenario assumes that, on average, patients in the anti-VEGF arm maintain constant vision over time, as per the transition probability matrix presented Table 25. The scenario assumes 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%, consistent with the probability of gaining at least 10 letters from the natural history study data from Mitchell et al. (2012)[43]. This data is applied in order to capture some variation in vision over time given it is unlikely that vision would remain constant for each individual patient. The reason for exploring this scenario is that feedback from UK clinical experts indicated that the primary aim of treatment with anti-VEGFs in those who are insufficiently responsive to treatment is to stop the decline in outcomes and keep visual outcomes maintained at their current level.[73]

Table 25: Transition probability matrix: net-zero impact on vision

		To						Total
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**	
From	**Health State 1**	0.965	0.035	0.000	0.000	0.000	0.000	1.000
	Health State 2	0.035	0.930	0.035	0.000	0.000	0.000	1.000
	Health State 3	0.000	0.035	0.930	0.035	0.000	0.000	1.000
	Health State 4	0.000	0.000	0.035	0.930	0.035	0.000	1.000
	Health State 5	0.000	0.000	0.000	0.035	0.930	0.035	1.000
	Health State 6	0.000	0.000	0.000	0.000	0.035	0.965	1.000
Key: DMO, diabetic macular oedema.								

Natural history

This scenario assumes that patients in the anti-VEGF arm follow the natural history data from Mitchell et al. (2012)[43] that is applied in the base-case for those who

discontinue treatment (Section B.3.3.2.4). The reason for exploring this scenario is consistent with the rationale outlined for the net-zero impact on vision scenario and represents a more pessimistic yet plausible scenario of how patients may fare if they continue on an ineffective treatment regimen.

Pseudophakic transition probabilities

This scenario assumes the efficacy for DEX700 and comparators are modelled using the transition probabilities from the pseudophakic population of the pooled MEAD studies. The reason for exploring this scenario is that RWE studies have reported that visual outcomes with DEX700 are similar in both phakic and pseudophakic DMO patients (see Section B.2.6.2.1). In addition, Section B.2.7.1.1 noted that patients with a shorter gap between cataract development and cataract surgery, and patients who received a dose of DEX700 prior to surgery, experienced a quicker recovery of their vision and better long-term outcomes that are more akin to the outcomes of the pseudophakic DMO patients in MEAD. As feedback from UK clinicians has indicated that these treatment practices are likely to occur in UK clinical practice, the visual outcomes in the pseudophakic population may better reflect the recovery of vision following cataract surgery in the long-term than the phakic data.

UK RWE

This scenario assumes that the efficacy in the anti-VEGF treatment arm is based on UK RWE data. The reason for exploring this scenario is that the MEAD sham arm as a proxy for continued anti-VEGF use likely overestimates the efficacy of this treatment arm based on a naïve comparison of change in baseline BCVA outcomes of sham with the UK RWE data (see Section B.3.3.1.2). The UK RWE provides the strongest evidence available for the efficacy of anti-VEGFs in those that are insufficiently responsive to treatment, but this data has not been formally included in the base-case analysis due to the challenges of matching patient and study characteristics between MEAD and the UK RWE, and because the study does not provide the data required to model the full set of transition probabilities. However, in this scenario, a naïve comparison is made by using data on 10-letter improvement/worsening over time, which allows patients to improve/worsen by one health state in each cycle. This approach is consistent with the application of the network meta-analysis that was

presented in TA349. Given that the UK RWE report the proportion of patients experiencing improvement or worsening in vision from baseline to 12, 24 and 36 months, each of these estimates have been used in separate scenario analyses to estimate transition probabilities to ensure that there is consistency in the results regardless of the timepoint used (Table 26).

Table 26: >=10-letter improvement/worsening UK RWE

Scenario	Criteria	Proportion of patients			3-month probability		
		Baseline to Month 12	Baseline to Month 24	Baseline to Month 36	Baseline to Month 12	Baseline to Month 24	Baseline to Month 36
UK RWE	>=10-letter improving	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>=10-letter worsening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: RWE, real world evidence.							

French RWE

This scenario assumes that the efficacy in the DEX700 treatment arm is based on the French RWE data. The reason for exploring this scenario is that the MEAD DEX700 arm likely under-estimates efficacy outcomes in phakic DMO patients due to difference in patient characteristics and treatment practices between the MEAD trial and UK clinical practice (see Section B.3.3.1.1). The French RWE provides efficacy data for DEX700 in phakic DMO patients from a retrospective observational study in France. As this study does not provide the data required to model the full set of transition probabilities, a naïve comparison is made by using data on 10-letter improvement/worsening over time, which allows patients to improve/worsen by one health state in each cycle. Given that the French RWE report the proportion of patients experiencing improvement or worsening in vision from baseline to 12, 24 and 36 months, each of these estimates have been used in separate scenario analyses to estimate transition probabilities to ensure that there is consistency in the results regardless of the timepoint used (Table 27).

Table 27: >=10-letter improvement/worsening in French RWE

Scenario	Criteria	Proportion of patients			3-month probability		
		Baseline to Month 12	Baseline to Month 24	Baseline to Month 36	Baseline to Month 12	Baseline to Month 24	Baseline to Month 36
French RWE	>=10-letter improving	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>=10-letter worsening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: RWE, real world evidence.							

B.3.3.3 Event probabilities

B.3.3.3.1 Discontinuation from treatment and long-term treatment effect

DEX700

Within the MEAD studies, patients were censored upon receipt of non-study treatments. This accounts for a non-trivial proportion of the DEX700 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 AEs or other non-efficacy reasons within the MEAD studies also accounts for a non-trivial proportion of the DEX700 patient population ([redacted]). 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 to assume a pathway for these patients and, thus, include them within the economic modelling. 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 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 pooled MEAD studies and were entered into the model as a proportion per month. 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.

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.

Following discontinuation from DEX700, patients are assumed to receive no further treatment and receive visual acuity outcomes consistent with the natural history of vision in patients with DMO (see Section B.3.3.2).

Anti-VEGFs

UK RWE provides data on the proportion of patients receiving anti-VEGF treatment over time. However, there is no clear data on whether the patients that did not receive anti-VEGF treatment within a certain time period in fact permanently discontinued anti-VEGF treatment, or whether these patients simply did not receive an injection within that period of time but may have received injections at later time periods. Therefore, it assumed in the base case, in line with TA613, that patients do not discontinue during the anti-VEGF treatment period because it represents the last therapeutic option for these patients. However, scenario analyses are explored where it is assumed that those eyes included in UK RWE that did not receive any treatment within a certain time period have discontinued treatment.

The proportions of patients who discontinue from DEX700 and sham during each cycle of Years 1–5 for each reason are detailed in Appendix O; these are based on the proportions of phakic DMO patients who discontinued from the MEAD studies. Appendix O also shows the proportion of patients who are assumed to discontinue from anti-VEGF in the scenario analysis. The proportions of phakic DMO patients who remain on treatment at the start of each year are presented in Table 28. This is calculated in 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 28: Proportion of patients remaining on treatment; all phakic DMO

Treatment	Proportion remaining on treatment		
	Year 1	Year 2	Year 3
DEX700	[redacted]	[redacted]	[redacted]
Anti-VEGF	100.00%	100.00%	100.00%

Key: DEX, dexamethasone; DMO, diabetic macular oedema.
Source: MEAD (2021)[148]

B.3.3.3.2 Fellow eye involvement

As patients who are affected unilaterally may in practice develop DMO in their fellow eye over time, the model takes into account that 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.

To reflect the more intensive treatment expected in the first year compared with subsequent years when considering 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, which aligns with timeframe over which such data is available from MEAD. This simplifying assumption is essential given the memory-less property of the model and the additional complexity that is needed to capture potential fellow eye involvement at future time points. 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 and size 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 is consistent with TA349, where the 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 was previously validated with clinical experts during the TA349 appraisal, 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.

The proportion of fellow eyes that develop DMO in each year was estimated using data from the mITT population of the pooled MEAD studies, which indicated that approximately [redacted]% of DEX700 patients developed fellow eye involvement over the 3-year study duration. 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 probability 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 neovascularization”.

Appendix R explains in more detail how fellow eye involvement is applied within the economic model, which is consistent with the approach adopted in TA349.

B.3.3.3.3 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 diabetes mellitus (relative to the general population) and due to DMO (relative to the diabetes mellitus population), and assuming that mortality occurs equally across all visual acuity states in the base case. Consistent with the original appraisal, 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. The model does however include 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.[149] This is not presented as the impact is expected to be minimal.

All-cause mortality is taken from 2020 life tables for England 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 patients at baseline in the phakic population ([redacted] years of age) of the pooled MEAD studies.

The hazard ratio for the additional mortality due to diabetes mellitus relative to the general population is 1.93 and the hazard ratio for the additional mortality due to DMO relative to the diabetes mellitus population is 1.27.[53, 150] These two hazard ratios are multiplied together to give a hazard ratio for the additional mortality relative to diabetes mellitus and DMO of 2.45. Scenario analyses explore the hazard ratios used in TA613 of 1.95 (Preis et al. 2009)[151] and 1.23 (Christ et al. 2008)[149] for the additional mortality relative to the general population and the diabetes mellitus population, respectively.

There may be some double-counting in the application of these two hazard ratios, as it is possible that the diabetes mellitus population from which the hazard ratio for the additional mortality due to diabetes mellitus 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.

All-cause mortality is available for male and female patients. At baseline it is assumed that [redacted] of all phakic DMO patients are male, consistent with the baseline characteristics of DEX700 patients in the phakic population of the MEAD clinical trials. The proportion of male and female patients who remain is expected to change over time due to the different mortality experienced by each gender. Therefore, the model uses the annual risk of mortality for males and females, adjusted for diabetes mellitus 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.

B.3.3.3.4 Adverse events

Treatments for DMO are associated with five key AEs of interest that may require medical or surgical intervention. These are cataracts, raised IOP, retinal detachment, endophthalmitis and vitreous haemorrhage. These AEs were selected in the model, consistent with the AEs selected in TA349 and TA613.

The proportions of patients requiring treatment for each adverse event during each year of the 5-year treatment period are detailed here. Data were taken from the pooled MEAD trials for DEX700. For anti-VEGFs, data were taken from the ERG report from

TA613 (using data from RISE and RIDE trials) and the UK RWE audit. The UK RWE audit is used to estimate the cataract extraction rates for anti-VEGFs.

The UK RWE audit is not used for adverse event estimates related to anti-VEGFs as these were not reported well in this study. Instead, the adverse event estimates for anti-VEGFs are taken from the NICE TA613 ERG report. This report presents adverse event estimates for Year 1 and Year 2 combined, and for Year 3, based on the RISE and RIDE trials for ranibizumab in DMO. The data for Year 1 and 2 combined is used to calculate adverse event probability per year for Year 1 and Year 2 separately, using the exponential cumulative distribution function, assuming a constant risk over time.

Where necessary, the data were extrapolated using last observation carried forward. For fellow eyes it holds that resource requirements are assumed to be the weighted average of the resource use associated with the year of treatment each eye is receiving.

Cataracts

As discussed in Section B.1.3.3.1 , patients with DMO are at a higher risk of requiring cataract extraction compared with the general population due to their diabetes mellitus. Consistent with TA349, the model includes the cost of surgery for the proportion of phakic DMO patients experiencing cataracts requiring extraction (see Section B.3.5.3.1). Once eyes have undergone a cataract extraction, they become pseudophakic and are no longer at risk of cataracts.

Cataract extraction rates differ between treatments. For DEX700, the cataract extraction rates in Year 1, Year 2 and Year 3 are based on MEAD study clinical study reports (CSRs) with those who had a cataract operation in the previous year subtracted.

For anti-VEGFs, the cataract extraction rates applied in the base case are taken from the UK RWE audit. The UK RWE provides data on the number of eyes having cataract surgery in five time periods: 3–6 months, 6–12 months, 12–24 months, 24–36 months and 36–48 months. Data from months 12–24, 24–36 and 36–48 have been used in the model for Year 1, Year 2 and Year 3, respectively, given that data from months

12–24 provide the first full year of data following an assessment of insufficient response.

However, it is possible that the UK RWE audit underreports the true cataract extraction rates. In the RISE and RIDE study on ranibizumab in DMO, it appears that the risk of cataracts for ranibizumab could be as high as 42% after only 2 years when looking at all types of cataracts reported in the trial.[152] Indeed, feedback from UK clinical experts indicates that all patients with DMO with a phakic lens will eventually develop a cataract and therefore there is no reason for the cataract rates to differ between treatments in the long-term, but differences may be observed with regards to the timing of cataract development instead.[73] Therefore, a scenario is explored where it is assumed that the cataract extraction rates from DEX700 are applied in the anti-VEGF arm.

For eyes not receiving treatment to reflect the underlying risk of cataract in the diabetes mellitus population, the cataract extraction rate is assumed equal to the general population's risk of cataracts, i.e. 2.32% per year. This rate is consistent with what was assumed in TA349, calculated from the Blue Mountain Eye Study[39], which demonstrated a cumulative incidence of cataract surgery in a diabetes mellitus population of 20.9% over 10 years. Assuming that the risk is constant over time using the exponential cumulative distribution function, this gives a risk of 2.32% per year.

The proportions of phakic DMO patients in the cohort receiving treatment who experience a cataract that requires extraction are shown in Table 29.

It is assumed that a patient is phakic in both eyes where both eyes are affected with DMO. This is a further simplifying assumption of the economic model.

Table 29: Proportions of 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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	MEAD[148]
Anti-VEGFs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK RWE[10]

Key: DEX, dexamethasone; VEGF, vascular endothelial growth factor.

Raised intraocular pressure

The model includes the cost of treating raised IOP for the proportion of phakic DMO patients experiencing this AE. For DEX700, consistent with TA349, it has been assumed that IOP ≥ 30 mmHg would result in the initiation of treatment. For anti-VEGF treatments, the proportion of patients experiencing raised IOP is from the ERG report of TA613. The proportions of patients within the cohort who experience raised IOP that requires treatment are shown in Table 30.

Table 30: Proportion of patients with raised IOP

Treatment	Proportion with raised IOP			Reference
	Year 1	Year 2	Year 3	
DEX700	[redacted]	[redacted]	[redacted]	MEAD incidence of raised IOP ≥ 30 mmHg[148]
Anti-VEGFs	8.57%	8.57%	7.9%	ERG report TA613[3]
Key: DEX, dexamethasone; IOP, intraocular pressure; VEGF, vascular endothelial growth factor.				

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 31. Clinical expert opinion indicated that patients with IOP ≥ 30 mmHg would require treatment with medication, and patients with IOP ≥ 40 mmHg would require surgical intervention rather than medication.

Table 31: 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	[redacted]	[redacted]	MEAD incidence of raised IOP ≥ 40 mmHg divided by incidence of raised IOP ≥ 30 mmHg (i.e. number eligible for surgery divided by number eligible for any treatment); based on cumulative data over 3 years
Anti-VEGFs	[redacted]	[redacted]	Assumed consistent with DEX700
Key: DEX, dexamethasone; IOP, intraocular pressure; VEGF, vascular endothelial growth factor.			

Retinal detachment

Consistent with TA349, the model includes the cost of treating retinal detachment for the proportion of phakic DMO patients experiencing this AE. The proportions of patients within the cohort who experience retinal detachment are shown in Table 32.

Table 32: Proportions of patients with retinal detachment

Treatment	Proportion with retinal detachment			Reference
	Year 1	Year 2	Year 3	
DEX700	[redacted]	[redacted]	[redacted]	MEAD (note no incidences in Year 1)[148]
Anti-VEGFs	0.20%	0.20%	0.20%	ERG report TA613[3]
Key: DEX, dexamethasone; VEGF, vascular endothelial growth factor.				

Endophthalmitis

Consistent with TA349, the model includes the cost of treating endophthalmitis for the proportion of phakic DMO patients experiencing this AE. The proportions of patients within the cohort who experience endophthalmitis are shown in Table 33.

Table 33: Proportions of patients with endophthalmitis

Treatment	Proportion with endophthalmitis			Reference
	Year 1	Year 2	Year 3	
DEX700	[redacted]	[redacted]	[redacted]	MEAD (note no incidences in Year 3)[148]
Anti-VEGFs	0.40%	0.40%	0.40%	ERG report TA613[3]
Key: DEX, dexamethasone; VEGF, vascular endothelial growth factor; VEGF, vascular endothelial growth factor.				

Vitreous haemorrhage

Consistent with TA349, the model includes the cost of treating vitreous haemorrhage for the proportion of phakic DMO patients experiencing this AE. The proportions of patients within the cohort who experience vitreous haemorrhage are shown in Table 34.

Table 34: Proportions of patients with vitreous haemorrhage

Treatment	Proportion with vitreous haemorrhage			Reference
	Year 1	Year 2	Year 3	
DEX700	[redacted]	[redacted]	[redacted]	MEAD[148]
Anti-VEGFs	0.40%	0.40%	0.40%	ERG report TA613[3]

Key: DEX, dexamethasone; VEGF, vascular endothelial growth factor.

B.3.4. Measurement and valuation of health effects

Adults experiencing sight loss incur an associated loss in HRQL. As described in Section B.1.3.3.1, DMO is the leading cause of sight loss in the diabetes mellitus population. Visual impairment can negatively impact both the physical and emotional functioning of the diabetic patient. DMO can have a damaging effect on vision, which can limit patients' ability to perform everyday activities (see Section B.1.3.3.3 for examples). These factors are directly linked to patients' quality of life. Any improvement in clinical outcomes with DEX700 can therefore improve HRQL DEX700 not only has the potential to improve quality of life through improvements in clinical outcomes but can also enhance quality of life by reducing frequency of treatment administrations and therefore the burden of treatment on patients.

The approach adopted to model changes in HRQL over time in the cost-effectiveness analysis is consistent with the approach that was accepted by the appraisal committee in TA349.

B.3.4.1 Health-related quality-of-life data from clinical trials

Health-related quality of life and visual functioning were assessed at baseline for each study arm in the MEAD studies using two generic HRQL instruments – the short-form 36 question health survey version 1 (SF-36v1) and the EQ-5D questionnaire – and one instrument specific to visual functioning and vision-related quality of life, the National Eye Institute VFQ-25.

However, in TA349 the committee was not convinced that the utility values from the MEAD trial used in the model were a good fit to the data nor how the fit would compare with more complex models that allowed interaction between eyes. In addition, the committee noted that the bands of utility values from the regression equation derived from the MEAD trial data were too narrow.

In light of this, the committee accepted the ERG-preferred published utility values from Czoski-Murray et al.[153], which have a wider range than those derived from the MEAD

studies and have been preferred by the committee in other technology appraisals in DMO.[7] In the Czoski-Murray study, utility values were elicited from 108 healthy participants via a novel experimental method that helps participants experience health states similar to the condition of age-related macular degeneration using contact lenses to simulate the visual impairment.[153] Consistent with TA349, the utility values from Czoski-Murray are used in the base case (see Section B.3.4.5 for further details).

TA349 also included utility values from Brown[154] and Brown et al.[155] as scenario analyses. Brown (1999) and Brown et al. (2000) estimated quality of life among 80 and 325 patients with impaired vision, respectively, using both time trade-off and standard gamble. The utility values from these two studies are included as scenario analyses in this evaluation as well.

B.3.4.2 Mapping

No mapping of HRQL data was undertaken for the economic model.

B.3.4.3 Health-related quality-of-life studies

A systematic review of the published literature was conducted to identify all relevant studies reporting utility data and disutilities associated with treatments and TRAEs for the treatment of phakic patients with refractory DMO that are not responsive or insufficiently responsive or are unsuitable for non-steroidal therapies. Full details of the methods and results are presented in Appendix H.

The most relevant studies identified in the SLR to inform HRQL assessed the cost-effectiveness of fluocinolone acetonide, including the previous NICE appraisal TA613 and a study by Pochopien et al. 2019.[156]

TA613 used quality-of-life data using the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) during the FAME study. These data were mapped using a published mapping algorithm (Rentz et al. 2014)[157] to estimate quality of life for FAME data. While the ERG had some concerns around the HRQL data and noted that previous NICE appraisals in ocular diseases used the experimental lenses study by Czoski-Murray et al. (2009)[153], the committee concluded that the use of NEI-VFQ-25 and mapping algorithm was acceptable. In addition, the committee agreed that a disease-specific instrument might be more responsive to changes in

people's BCVA than the generic EQ 5D. The quality-of-life reduction due to retinal detachment and vitreous haemorrhage was accounted for in the model based on event-specific utility decrements obtained from the ERG report for NICE TA346 aflibercept submission. In addition, a utility decrement for anxiety associated with injections during treatment with anti-VEGFs was included. The reduction in quality of life for patients with reduced BCVA due to cataracts was captured in the utility decrement associated with BCVA levels. No long-term effect of the AEs was considered because they were expected to be captured by the utility associated with each BCVA level. The ERG concluded that the AE utility decrements had very little impact and do not affect the cost-effectiveness estimate.

Pochopien et al. 2019[156] used health state utilities linked to BCVA levels in both eyes based on a study by Czoski-Murray et al. 2009. The same utility decrements for AEs as in TA613 were used (retinal detachment repair, vitreous haemorrhage and anxiety associated with injections during treatment with anti-VEGFs), obtained from the ERG report for NICE TA346 aflibercept submission. The impact of long-term AEs of treatment that affects BCVA (e.g. cataracts, glaucoma) was assumed to be captured in BCVA levels modelled based on clinical trial data.

B.3.4.4 Adverse reactions

AEs associated with treatment for DMO are expected to have little effect on HRQL due to their nature. The main AEs 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. In TA349, the committee accepted that any disutility associated with the cataract extraction procedure is experienced for a very short period and was therefore not considered in the model. Consistent with TA349, AE disutilities are also not included in this model.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

As noted in Section B.3.4.1, utility values from Czoski-Murray et al.[153] were applied in the base-case analysis with estimates from Brown[154] and Brown et al.[155] applied in scenario analysis. Section B.3.4.3 did outline that additional studies were identified from a systematic review of the literature. However, estimates from these sources were not applied in the cost-effectiveness analysis given the estimated utility values did not align with the included health states, and also because of the acceptability of Czoski-Murray et al.[153] in prior appraisals.

Czoski-Murray et al.[153], Brown[154] and Brown et al.[155] report BSE utilities only; therefore the range of utility values in the WSE has been estimated. In line with the ERG preferred assumption in TA349, the contribution of WSE and BSE to the overall utility was 3/13 and 10/13, respectively, based on the assumption that the impact of WSE on overall utility equalled 30%. The utility values reported by Czoski-Murray et al.[153], Brown[154] and Brown et al.[155] used in the model are presented in Table 35. Appendix P presents the detailed calculations of these values.

Table 35: Utilities values used in the model

Publication	Eye	Health state 1	Health state 2	Health state 3	Health state 4	Health state 5	Health state 6
Czoski-Murray et al. utilities	**BSE**	0.57	0.71	0.83	0.94	1.05	1.24
	WSE	0.17	0.21	0.25	0.28	0.32	0.37
Brown utilities*	**BSE**	0.60	0.67	0.74	0.77	0.84	0.92
	WSE	0.78	0.80	0.82	0.83	0.85	0.90
Brown et al. utilities*	**BSE**	0.52	0.57	0.57	0.57	0.81	0.89
	WSE	0.75	0.77	0.77	0.77	0.84	0.88

Key: BSE, better-seeing eye; WSE, worse-seeing eye.
Notes: *Included in scenario analysis only.

The derived utilities for the BSE and WSE across the BCVA-defined health states have been applied within the model, consistent with the preference of the committee in TA349. The distribution of utilities in the BSE across the health states is applied to the distribution of vision across the health states in the baseline-defined BSE and the distribution of utilities in the WSE across the health states is applied to the distribution

of vision across the health states in the baseline-defined WSE for all patients. This includes those treated unilaterally in the BSE or WSE and those treated bilaterally. This, therefore, accounts for the utility associated with the level of vision in both eyes for all patients, which was preferred by the committee in TA349 as it was stated that '*modelling the transitions for each eye independently was a more realistic approach than that used in previous appraisals of eye conditions, which sometimes modelled the vision in only one eye*'.

In the base case analysis, utilities are not age-adjusted; however, a sensitivity analysis is included whereby utilities are adjusted due to patients' age. This is done using a coefficient of -0.00029 per year reported by Sullivan et al. (2011).[158] This paper reports an analysis that provides a UK-based catalogue of EQ-5D index scores including a coefficient for age. The coefficient is 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.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

A systematic review of the published literature was conducted to identify all relevant studies reporting cost and healthcare resource use associated with the treatment of phakic patients with refractory DMO that are not responsive or insufficiently responsive or are unsuitable for non-steroidal therapies. Full details of the methods and results are presented in Appendix I.

The most relevant study identified in the SLR to inform cost and healthcare resource use is the previous NICE appraisal TA613, which assessed the cost-effectiveness of fluocinolone acetonide. Learnings and relevant inputs from TA613 have been incorporated in the development of the cost-effectiveness model and are presented in each of the subsequent sections.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

DEX700 unit cost is obtained from the Monthly Index of Medical Specialties (MIMS) (2021) with a cost per intravitreal implant of £870. For unilateral treatment the cost of drug acquisition per round of treatment is equal to the cost of one 700 microgram intravitreal implant. For bilateral treatment, the cost of drug acquisition per round of treatment is equal to the cost of two 700 microgram intravitreal implants, as one unit is assumed to treat one eye.

The average number of injections administered per model cycle was calculated based on the DEX700 dosing schedule and the proportion of patients receiving treatment from the last observation to the current observation in MEAD (Appendix Q). The corresponding average annual injections are presented in Table 36. Given the absence of data beyond Year 3, a simplifying assumption was made where patients were assumed to receive an average of one injection per year in Years 4 and 5 which was based on feedback from two UK treating clinicians.[73]

As noted in Section B.3.3.3.2, upon fellow eye involvement, the newly affected eye is assumed to receive the same treatment as received in the initially affected eye for a period of up to 5 years starting from this point. The newly affected eye is assumed to receive treatment at the rate expected in Year 1 for the eye that was initially affected.

The French RWE study, summarized in Section B.2.3.3, also provided data on the average number of injections administered over a 4-year period in a group of phakic DMO patients. This data indicates that the dosing schedule in MEAD is broadly consistent with how patients are treated in clinical practice, but also that the average number of injections may be marginally lower in clinical practice, meaning that the application of the MEAD data in the base-case analysis may overestimate the true cost of treatment. Therefore, the average number of injections estimated over time from the French RWE (Table 36) are applied in scenario analysis. Given the absence of data beyond Year 4, a simplifying assumption was made where patients would receive the same average number of injections in Year 4 and Year 5.

Table 36: Average number of treatments per year: DEX700

Treatment	Average number of intravitreal injection treatments					Reference
	Year 1	Year 2	Year 3	Year 4	Year 5	

MEAD (base case)	[redacted]	[redacted]	[redacted]	1.00	1.00	MEAD[148]
French RWE (scenario)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	French RWE[132]
Key: DEX, dexamethasone; RWE, real-world evidence.						

Anti-VEGFs

As discussed in Section B.3.2.3.2, ranibizumab and aflibercept are included in the base case composite comparator of this economic evaluation. Bevacizumab and laser are included within the composite comparator in scenario analyses. The drug acquisition unit costs for all these treatments are presented in Table 37.

Ranibizumab and aflibercept are both subjected to a confidential patient access scheme (PAS) discount. As the information related to the size of the discount is not publicly available, the reported list price for each treatment was used.

Table 37: List price costs of anti-VEGF and laser treatments

Treatment	List price	Reference
Ranibizumab 0.5 mg	0.23 ml vial = £551.00	MIMS (2021)[159]
Aflibercept 2 mg	40 mg/ml vial = £816.00	MIMS (2021)[160]
Bevacizumab 1.25 mg*	Single pre-filled syringe = £50	NICE DSU report (Poku et al., 2012)[161]
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
Key: DSU, decision support unit; MIMS, Monthly Index of Medical Specialties; NICE, National Institute for Health and Care Excellence; VEGF, vascular endothelial growth factor. **Notes:** *Included in scenario analysis only.		

The average number of ranibizumab and aflibercept administered per model cycle is taken from UK RWE. This is considered to be the most relevant data source available to estimate long-term treatment costs for continued anti-VEGF use, as it is UK-based and in the relevant population of interest (phakic DMO patients who are insufficient responders to anti-VEGF treatment). Moreover, as the data have recently been collected, it provides an accurate reflection of UK clinical practice today, and it includes a large sample of eyes that have been observed over a time span of up to 4 years.

UK RWE provides data on the average number of ranibizumab and aflibercept injections administered over time and data on the proportion of patients receiving treatment in five time periods: 3–6 months, 6–12 months, 12–24 months, 24–36 months and 36–48 months. As insufficient response was determined at 6 months in this RWE study, the data from 6 months onwards is of interest for the model (see Table 38).

The UK RWE provides 42 months of data from the point at which the level of clinical response is defined. Therefore, assumptions are required to estimate the number of anti-VEGF injections from 42 to 60 months. Feedback from two UK clinicians noted that although there may be some reduction in the average number of injections over time, a simplifying assumption that the average from 36 to 48 months remained constant until 60 months was reasonable. Although this may lead to a slight overestimation of the number of anti-VEGF administrations this was considered a reasonable approach as capping the treatment duration at 5 years may lead to a slight underestimation of the true number of injections as the clinicians did note that a small proportion of patients would likely receive treatment beyond this time point.

Additionally, the estimated average number of injections obtained from the UK RWE is lower than values that are reported in alternative studies from the published literature. The RESTORE study provides data on the average number of anti-VEGF injections administered over a three-year time period.[146] The values from this study indicate that the base-case analysis may underestimate the true cost of anti-VEGFs in UK clinical practice, and therefore these values presented in Table 39 are applied in a scenario analysis. Given the absence of data beyond Year 3, a simplifying assumption was made where the average number of injections from Year 3 remained constant until the end of Year 5.

Taking the market shares for ranibizumab and aflibercept into account ([redacted] ranibizumab, [redacted] aflibercept), the weighted anti-VEGF dosing schedule and the proportion of patients receiving treatment is calculated per model cycle in Appendix Q. The corresponding average annual injections are presented in Table 39. However, as the RWE demonstrates that the use of aflibercept has increased substantially in recent years, a scenario is also presented where the market shares are estimated using just

the last 2 years of data from the RWE study. In this scenario 77.3% of patients are assumed to receive aflibercept and 22.7% ranibizumab.

Table 38: Ranibizumab and aflibercept injections from UK RWE

Time period UK RWE (months)	Time period within model (months)	Ranibizumab injections	Aflibercept injections	Proportion receiving anti-VEGF treatment
6–12	0–6	[redacted]	[redacted]	[redacted]
12–24	6–18	[redacted]	[redacted]	[redacted]
24–36	18–30	[redacted]	[redacted]	[redacted]
36–48	30–42	[redacted]	[redacted]	[redacted]
36-48	42-60	[redacted]	[redacted]	[redacted]

Key: RWE, real-world evidence; VEGF, vascular endothelial growth factor.
Notes: The number provided here represent the average number of treatments for those patients who remain on treatment.

Table 39: Average number of treatments per year: anti-VEGFs

Treatment	Average number of intravitreal injection treatments					Reference
	Year 1	Year 2	Year 3	Year 4	Year 5	
UK RWE (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK RWE
The RESTORE study (scenario)*	5.50	3.90	2.90	2.90	2.90	The RESTORE study[43, 134, 146]

Key: RWE, real-world evidence; VEGF, vascular endothelial growth factor.
Notes: *5.5 injections in year 1 was calculated from Mitchel et al. (2011)[134] which reported 4.1 injections between months 3 and 11 which is adjusted to an annual figure (4.1/0.75=5.5). The figures from years 2 and 3 are sourced from Schmidt-Erfurth (2014)[146] which reports data on the extension study.

An additional scenario is also presented which applies the anti-VEGF costing assumptions referenced in NICE TA613. This data is only considered in scenario analysis as this evidence has a number of significant limitations associated with it. The data only provides the number of injections patients received over a 1-year time period, which led to an arbitrary assumption being made in TA613 that patients discontinued treatment at a constant rate from the end of the first year. Additionally, the data is not captured in the specific patient population of interest (phakic DMO patients insufficiently responsive to anti-VEGFs) and includes data that is older than the evidence that has been presented in this submission from the UK RWE audit.

Details of the calculation steps and assumptions that were made in scenario analysis are presented in Appendix Q.

B.3.5.1.2 Drug administration costs

The unit costs associated with treatment administration are presented in Table 40. Consistent with TA349, the base case analysis assumes that all intravitreal injections are performed in the outpatient setting. Sensitivity analyses have been included, varying the proportion of day case and outpatient procedures assumed.

Table 40: Treatment administration unit costs

Type of administration	Unit cost	Reference
Day case intravitreal injection procedure	£668.31	NHS reference costs 2019/20: Day Case (DC) - BZ87A - Minor Vitreous Retinal Procedures, 19 years and over
Outpatient intravitreal injection procedure	£129.61	NHS reference costs 2019/20: Outpatient procedure - service code 130 Ophthalmology - BZ87A - Minor vitreous retinal procedures
Laser procedure*	£129.61	NHS reference costs 2019/20: Outpatient procedure - service code 130 Ophthalmology - BZ87A - Minor vitreous retinal procedures
Key: NHS, National Health Service. **Notes:** *The laser procedure cost is only applied in scenario analysis. **Source:** NHS (2021)[162]		

Also consistent with TA349, bilateral treatment with DEX700 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 DEX700. In contrast, due to the less complex injection procedure of an anti-VEGF, 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. This is also in line with NG82 (for wet AMD, clinical guideline).[163] Bilateral treatment with laser has been assumed to be administered in the same visit on 100% of occasions, also consistent

with TA349. An overview with the number of appointments for bilateral treatment per treatment is presented in Table 41.

Table 41: Number of appointments for bilateral treatment

Treatment	Number of appointments for bilateral treatment
DEX700	1.75
Anti-VEGF	1.5
Laser	1
Key: DEX, dexamethasone; VEGF, vascular endothelial growth factor.	

Additional feedback from two UK clinical experts has indicated that the approach to bilateral treatment varies in clinical practice, with some clinicians almost always administering bilateral treatment at the same appointment, and other almost always administering treatment at separate visits.[73] Therefore, to reflect this uncertainty, additional scenario analyses are presented testing the impact of assuming 10% or 90% of bilateral administrations are done at the same appointment.

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 Severe vision loss costs

If a patient's BCVA falls below 35 letters on the ETDRS chart they are classified as having severe vision loss. This definition is fixed in the model. Severe vision loss in the BSE is associated with a number of additional costs including community care, residential care, hip replacement and depression, in line with Meads and Hyde (2006) and Colquitt et al. (2008)[164] and consistent with what was assumed in TA349[7], TA613[3] and NG82.[163] Note that only patients with both eyes in Health State 1 are assigned a cost here.

The unit costs associated with severe vision loss are presented in Table 42. Regarding the cost of residential care, the ERG believed in TA349 that the cost of residential care should be the cost of private sector residential care instead of the cost of local authority residential care. The committee noted that whilst it recognized that provision is not likely to be 100% local authority residential care, it also believed it to be unlikely that provision will be 100% private sector residential care. The committee therefore preferred a weighted cost that is 95% of the cost of private sector residential care and

5% of the cost of local authority residential care. The committee's preferred approach has been adopted in the base case.

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. Consistent with TA349, 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.

Table 42: Severe vision loss unit costs

Resource	Unit costs	Cost type	% patients with severe vision loss requiring service (funded by NHS)*	Reference
Community care	£12,617.35	Annual	6.00%	Curtis (2014 - last version to report this cost); based on weekly cost of community care package for the elderly (excluding accommodation costs) of £219; uplifted to 2020 using Curtis (2020)[165, 166]
Private sector residential care	£37,151.14	Annual	30.00%	Curtis (2020); based on private sector residential care weekly cost of £712.[166]
Local authority residential care	£64,753.61	Annual	30.00%	Curtis (2020); based on weekly cost of local authority residential care of £1,241[166]
Weighted average residential care	**£38,531.27**	**Annual**	**30.00%**	**95% private sector; 5% local authority**
Hip replacement	£4,700.12	Event	5.00%	NHS reference costs 2019/20 HT14C, intermediate hip procedures for trauma, with CC Score 0–1 (weighted by non-elective short and long stay, elective inpatient and day case data submissions)
Depression	£2,513.92	Annual	39.00%	Colquitt et al. (2008); uplifted to 2013 in original submission; uplifted to 2020 using Curtis (2020)[164, 166]
Blind registration	£154.06	One-off	95.00%	Colquitt et al. (2008); uplifted to 2013 in original submission; uplifted to 2020 using Curtis (2020)[164, 166]
Low-vision aids	£200.95	One-off	33.00%	
Low-vision rehabilitation	£346.97	One-off	11.00%	
Notes: * Colquitt et al (2008)[164]; Meads and Hyde (2003)[167]				

B.3.5.3 Adverse reaction unit costs and resource use

B.3.5.3.1 Cataracts

Consistent with TA349 and TA613, the unit cost of cataract extraction is taken from the National Schedule of NHS Costs. Using the most recent version of the NHS reference costs, the unit cost is assumed to be £966.72 (BZ34C - Phacoemulsification cataract extraction and lens implant, with CC score 0-1 [day case]).

B.3.5.3.2 Raised intraocular pressure

Raised IOP may be treated by either medication or by surgical intervention (see Section B.3.3.3.4; Table 31).

The unit costs of medications included within the model for the treatment of raised IOP are shown in Table 43. 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.

A mean cost of £67.67 was calculated for patients receiving medication for raised IOP, consistent with the ERG-preferred assumptions in TA349 that medication for raised IOP comprises 70% generic prostaglandins, 10% generic beta-blockers, and 20% equal use of remaining treatments.[168, 169]

In addition, six extra IOP visits were added to patients with DMO who were treated for raised IOP, consistent with the preferred ERG assumption in TA349.[168, 169] The unit costs of each IOP visit is assumed to be £101.95 (NHS reference costs 2019/20 - WF01A code 130 Ophthalmology; consultant-led non-admitted, face-to-face attendance, follow-up).[162] As a result, total average costs for patients treated with medications for raised IOP are £679.36.

Table 43: Unit cost of medications for the treatment of raised intraocular pressure

Resource	Unit cost	Mean number of days required*	Maximum number of days per bottle†	Average cost per patient	Reference
Beta-blockers	£0.60	1096	28	£24.00	eMIT (Accessed June 2021); Timolol 0.25% eye drops 5 ml/Pack size 1[170]
Prostaglandins	£1.75	1096	28	£70.00	eMIT (Accessed August 2021); Latanoprost 50micrograms/ml eye drops 2.5 ml/Pack size 1[170]
CA inhibitors	£1.64	1096	28	£65.60	eMIT (Accessed August 2021); Brinzolamide 10mg/ml eye drops 5 ml/Pack size 1[170]
Combination	£2.60	1096	28	£104.00	eMIT (Accessed August 2021); Dorzolamide 20mg/ml/Timolol 5mg/ml eye drops 5 ml (2%/0.5% e.g. Cosopt, tidomat)/Pack size 1[170]
Brimonidine	£1.86	1096	28	£74.40	eMIT (Accessed August 2021); Brimonidine 0.2% eye drops 5 ml/Pack size 1[170]
Total average cost per patient				£67.67	Assuming that medication for raised IOP comprises 70% generic prostaglandins; 10% generic beta-blockers; and 20% equal use of remaining treatments

Key: CA, carbonic anhydrase; eMIT, electronic Market Information Tool; IOP, intraocular pressure.
Notes: * Assumption; patients who have raised IOP will receive up to 5 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 44. The total average cost per patient is calculated based on ERG preferred assumptions in TA349, which assumed trabeculectomy was the only surgical procedure considered for the management of raised IOP. 50% of procedures were assumed to be intermediate and 50% major glaucoma day-case procedures.

In addition, six extra IOP visits were added to patients with DMO who were treated for raised IOP, consistent with the preferred ERG assumption in TA349.[168, 169] The unit costs of each IOP visit is assumed to be £101.95 (NHS reference costs 2019/20 - WF01A code 130 Ophthalmology; consultant led non-admitted, face-to-face attendance, follow-up).[162] As a result, total average costs for patients treated with surgery for raised IOP are £1,239.70.

Table 44: Cost of surgical procedures for the treatment of raised IOP

Resource	Unit cost	Reference
Trabeculectomy	£881.58	NHS reference costs 2019/20 - BZ93B - Major, Glaucoma or Iris Procedures, with CC Score 0–1 (day case)[162]
	£374.45	NHS reference costs 2019/20 - BZ94B - Intermediate, Glaucoma or Iris Procedures, with CC Score 0 (day case[162]
Total average cost per patient	£628.01	Assuming 50% of procedures were assumed to be intermediate and 50% major glaucoma day case procedures[168, 169]
Key: CC, complication and comorbidity; IOP, intraocular pressure; NHS, National Health Service.		

B.3.5.3.3 Retinal detachment

Resource use for a procedure for the re-attachment of the retina following retinal detachment is consistent with what was assumed in TA349 and TA613. The unit cost of a procedure for the re-attachment of the retina following retinal detachment is assumed to be £483.22, taken from the most recent version of the National Schedule of NHS Costs (Table 45).

Table 45: Retinal detachment procedure unit costs

Resource	Unit cost	Number of examinations	Reference
Intermediate procedure for attachment of retina	£3,964.60	45	NHS reference costs 2019/20 - BZ86B - Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0–1 (Non-elective long stay)
	£344.46	1129	NHS reference costs 2019/20 - BZ86B - Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0–1 (Non-elective short stay)
	£483.22		**Weighted average**
Major procedure for attachment of retina	£8,665.71	12	NHS reference costs 2019/20 – BZ84B - Major Vitreous Retinal Procedures, 19 years and over, with CC Score 0–1 (Non-elective long stay)
	£1,518.60	176	NHS reference costs 2019/20 – BZ84B - Major Vitreous Retinal Procedures, 19 years and over, with CC Score 0–1 (Non-elective short stay)
	£1974.80		**Weighted average**
Total average cost per patient	**£781.54**		**The management of retinal detachment was estimated to be an intermediate/major vitreous day case procedure in 80% and 20% of cases, as per ERG preferred assumptions in TA349[168, 169]**

Key: CC, complication and comorbidity; ERG, Evidence Review Group; NHS, National Health Service; TA, technology appraisal.

B.3.5.3.4 Endophthalmitis

Resource use for a vitreous biopsy procedure for endophthalmitis is consistent with what was assumed in TA349 and TA613. The unit cost of a vitreous biopsy procedure for endophthalmitis is assumed to be £925.26, taken from the most recent version of the National Schedule of NHS Costs (Table 46).

Table 46: Endophthalmitis procedures unit costs

Resource	Unit cost	Number of examinations	Reference
Vitreous biopsy	£1,501.68	17	NHS reference costs 2019/20 - BZ87A - Minor Vitreous Retinal Procedures, 19 years and over - (Elective inpatient)[162]
	£653.06	36	NHS reference costs 2019/20 - BZ87A - Minor Vitreous Retinal Procedures, 19 years and over - (Non-elective short stay)[162]
Total average cost per patient			**£925.26**
Key: NHS, National Health Service.			

B.3.5.3.5 Vitreous haemorrhage

Resource use for a vitrectomy procedure for vitreous haemorrhage is consistent with what was assumed in TA349 and TA613. The unit cost of a vitrectomy procedure for vitreous haemorrhage is assumed to be £483.22, taken from the most recent version of the National Schedule of NHS Costs (Table 47).

Table 47: Vitreous haemorrhage procedure unit costs

Resource	Unit cost	Number of examinations	Reference
Vitrectomy	£3,964.60	45	NHS reference costs 2019/20 - BZ86B - Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0–1 (Non-elective long stay)
	£344.46	1129	NHS reference costs 2019/20 - BZ86B - Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0–1 (Non-elective short stay)
Total average cost per patient			**£483.22**
Key: NHS, National Health Service.			

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Costs 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 48.

Table 48: Medical resource unit costs

Resource	Unit cost	Number of examinations	Reference
Routine monitoring visit	£101.95	Not relevant	NHS reference costs 2019/20 - WF01A code 130 Ophthalmology; consultant led non-admitted, face-to-face attendance, follow-up[162]
OCT	£52.42	1934917	NHS reference costs 2019/20 - RD40Z, diagnostic imaging - direct access: ultrasound scan less than 20 minutes (without contrast)
	£59.07	14618	NHS reference costs 2019/20 - RD41Z, diagnostic imaging - direct access: ultrasound scan less than 20 minutes (with contrast)[162]
		£52.47	**Weighted average of RD40Z and RD41Z**
Fluorescein angiography	£129.61	Not relevant	NHS reference costs 2019/20: Outpatient procedure - service code 130 Ophthalmology - BZ87A - Minor vitreous retinal procedures[162]
Intraocular pressure check	£101.95	Not relevant	NHS reference costs 2019/20 - WF01A code 130 Ophthalmology; consultant led non-admitted, face-to-face attendance, follow-up[162]
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 5 onwards and the resulting total cost of resource use in each year for each treatment are shown in Table 49 to Table 52. For fellow eyes it holds that resource requirements are assumed to be the weighted average of the resource use associated with the year of treatment each eye is receiving.

Consistent with the assumptions made in TA349 and TA613, all patients are assumed to receive a fluorescein angiography at baseline, except for non-treated patients who are assumed to receive one per year. All patients are assumed to require routine

monitoring visits including OCT. IOP checks are assumed to be included in the routine monitoring visit costs, which is in line with the ERG-preferred assumption in TA349 and in line with what was assumed in TA613. The number of routine monitoring visits for non-treated patients this is in line with the assumptions made in TA349 (whose estimates were based on the SPC and/or relevant guidelines) and has been further validated with clinicians. The number of monitoring visits for DEX700 regimen is in line with the ERG preferred assumptions in NICE TA349.

For anti-VEGF treatments, the number of routine monitoring visits for anti-VEGF are obtained from UK RWE. The UK RWE provides data on the number of clinic visits in five time periods: 3–6 months, 6–12 months, 12–24 months, 24–36 months and 36–48 months. Data from months 12–24, 24–36 and 36–48 have been used in this scenario for Year 1, Year 2 and Year 3, respectively, given that the data from months 12–24 provide the first full year of data following an assessment of insufficient response. The corresponding number of routine monitoring visits for anti-VEGF in this scenario are 4.0, 3.8 and 3.4 in Year 1, Year 2 and Year 3, respectively. Data from Year 3 has been used for Year 4 and Year 5 as well.

The number of routine monitoring visits recorded in the UK RWE is markedly lower than the ERG preferred assumptions relating to routine monitoring visits from TA613. Therefore, a scenario analysis is conducted to assess the impact that applying these estimates has on the results. An additional scenario is explored where it is assumed that both DEX700 and anti-VEGF treatments require 4 routine monitoring visits per year to assess the impact on the results of assuming no differences between treatments.

Table 49: Medical resource requirements, non-treated patients

Resource	Number required in				
	Year 1	Year 2	Year 3	Year 4	Year 5
Routine monitoring visit	4	4	4	4	4
OCT	4	4	4	4	4
Fluorescein angiography	1	1	1	1	1
Intraocular pressure check	0	0	0	0	0
Total cost per patient	**£747.29**	**£747.29**	**£747.29**	**£747.29**	**£747.29**

Key: NICE, National Institute of Health and Care Excellence; OCT, optical coherence tomography.
Reference: Fluocinolone acetonide NICE submission (TA271)

Table 50: Medical resource requirements, DEX700

Resource	Number required in				
	Year 1	Year 2	Year 3	Year 4	Year 5
Routine monitoring visit	3	3	3	3	3
OCT	3	3	3	3	3
Fluorescein angiography	1	0	0	0	0
Intraocular pressure check	0	0	0	0	0
Total cost per patient	**£622.59**	**£393.84**	**£413.82**	**£463.26**	**£463.26**

Key: NICE, National Institute of Health and Care Excellence; OCT, optical coherence tomography.
Reference: ERG preferred assumptions in TA349

Table 51: Medical resource requirements, anti-VEGF treatment

Resource	Number required in				
	Year 1	Year 2	Year 3	Year 4	Year 5
Routine monitoring visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fluorescein angiography	1.0	0.0	0.0	0.0	0.0
Intraocular pressure check	0.0	0.0	0.0	0.0	0.0
Total cost per patient	**£747.29**	**£586.79**	**£525.03**	**£525.03**	**£525.03**

Key: NICE, National Institute of Health and Care Excellence; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor.
Reference: UK RWE

Table 52: Medical resource requirements, laser treatment (included in scenario analysis only)

Resource	Number required in				
	Year 1	Year 2	Year 3	Year 4	Year 5
Routine monitoring visit	2.6	2.6	2.6	2.6	2.6
OCT	2.6	2.6	2.6	2.6	2.6
Fluorescein angiography	1.0	0.0	0.0	0.0	0.0
Intraocular pressure check	0.0	0.0	0.0	0.0	0.0
Total cost per patient	**£531.10**	**£401.49**	**£401.49**	**£401.49**	**£401.49**

Key: NICE, National Institute of Health and Care Excellence; OCT, optical coherence tomography.
Reference: TA613 Supplement to Company Submission

The tables above 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 patients with DMO. 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 for clinicians who would need to see patients less frequently for both treatment and monitoring, increasing the capacity of the clinic.

B.3.6. Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of the variables and distributions applied in the economic model can be found in Appendix S, including references to the corresponding sections in the submission where each is explained in more detail.

B.3.6.2 Assumptions

Table 53 outlines the key assumptions made in the economic model and provides a justification for each.

Table 53: Base case assumptions

Assumption	Justification	Reference in submission
A maximum of 5 years of treatment has been assumed in the base case	This assumption was based on feedback provided by UK clinical experts which noted that five years was sufficiently long enough to capture key differences in treatment costs. This is supported by data from MEAD and the French RWE study which demonstrate that a proportion of patients were still receiving DEX700 at the end of the three-year follow-up period. Similarly, this assumption is supported for anti-VEGFs by the UK RWE audit and other published studies such as the RESTORE trial which demonstrate that a sizeable proportion of patients were still receiving frequent anti-VEGFs after three to four years.	B.3.2.2.1
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	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 patients with phakic DMO who are insufficiently responsive to non-corticosteroid treatment. As there are no other treatment options for this population, it makes sense to assume no further treatment. 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.	B.3.2.2.3
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.	B.3.3.3.2
Fellow eyes receive the same treatment as the study eye	As per TA349 and validated with clinical experts during advisory board	B.3.3.3.2
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.	B.3.3.3.3
Natural progression of vision in eyes with DMO assumed constant over time	Lack of evidence to inform an alternative assumption	B.3.3.2.5
Eyes without DMO are assumed to have stable vision	The model only considers vision loss due to DMO.	B.3.3.2.6

Assumption	Justification	Reference in submission
BSE and WSE defined at baseline and assumed fixed throughout the model time horizon	Simplifying assumption consistent with previous economic modelling in DMO.	B.3.2.2.3
A blended comparator consisting of multiple anti-VEGF therapies is the most relevant for the population who are insufficiently responsive to non-corticosteroid therapy	This is consistent with the approach that was accepted by the appraisal committee in TA613, and is consistent with the idea that each anti-VEGF therapy is considered to be equally efficacious	B.3.2.3.2
MEAD sham treatment arm has been used as a proxy for the efficacy of continued use of anti-VEGFs	The sham arm from MEAD is not considered a perfect proxy for continued anti-VEGF use as it is likely to overestimate the efficacy of the comparator arm when naively comparing this data to the UK RWE. However, the sham arm is used in the base case as it allowed for a full set of transition probabilities to be estimated for this treatment arm which was a key advantage of the data from the sham arm from MEAD over other data sources. It also avoided the potential issues associated with indirect treatment comparisons such as imbalances between patient and study characteristics that add heterogeneity and, therefore, uncertainty.	B.3.3.1.2
Key: anti-VEGF, anti-vascular endothelial growth factors; BSE, best-seeing eye; WSE, worse-seeing eye; DMO, diabetic macular oedema; TA, technology appraisal.		

B.3.7. Base case results

As noted in Section B.3.5.1.1, ranibizumab and aflibercept are both subjected to a confidential patient access scheme (PAS) discount. As the information related to the size of the discount is not publicly available, the results presented are based on the reported list price for each treatment.

B.3.7.1 Base case incremental cost-effectiveness analysis results

Table 54 presents the base case results in the population of patients with phakic eyes and DMO that are insufficiently responsive to non-corticosteroid treatment. It is shown that DEX700 dominates treatment with anti-VEGFs, as DEX700 is associated with lower total costs and higher QALYs compared with anti-VEGFs. Therefore, DEX700 is considered a highly cost-effective use of NHS resources in this population.

These results likely represent an underestimate of the true cost-effectiveness of DEX700. As highlighted in Section B.3.3.1, the use of MEAD to model the efficacy of DEX700 and anti-VEGFs was a pragmatic decision, and evidence from the published literature, RWE studies, and UK clinical feedback have consistently demonstrated that the efficacy of DEX700 is underestimated in MEAD and that the use of the sham arm in MEAD results in an overestimate of the effect of anti-VEGFs in this patient group. Scenario analyses (described in Section B.3.3.2.7) consistently demonstrate that the use of alternative clinical data sources for DEX700 and anti-VEGFs results in incremental QALY gains that are significantly higher than those estimated in the base-case. Additionally, scenario analysis (described in Section B.3.5.1) highlight that the use of alternative sources to inform the average number of DEX700 or anti-VEGF injections patients receive also lead to results that indicate that DEX700 is more cost-saving than predicted in the base-case.

Table 54: Base case results; patients with phakic eyes and DMO that are insufficiently responsive to non-corticosteroid treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£38,695	16.8245	7.4815					
DEX700	£31,728	16.8245	7.5853	-£6,968	0.0000	0.1038	Dominant	£10,080
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years.								

B.3.8. Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

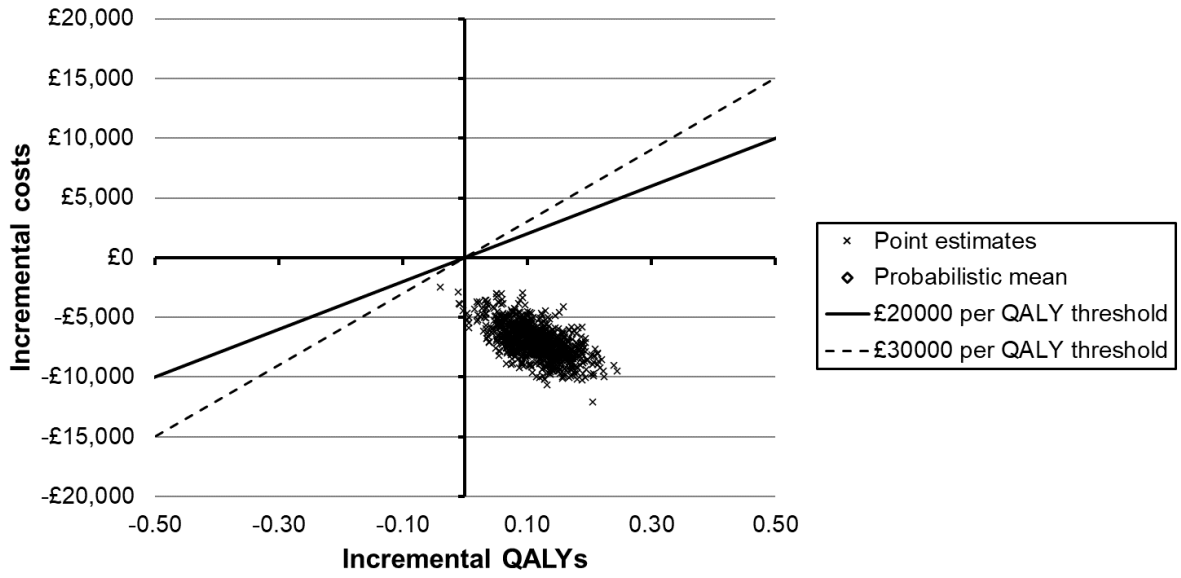
A probabilistic sensitivity analysis (PSA) was conducted where all inputs were varied simultaneously over 1,000 iterations, based on their distributional information (reported in Appendix S). In general, costs were varied using a gamma distribution, probabilities using a beta-distribution and continuous variables using a normal distribution. In addition to the parameters listed in Appendix S, transition probability matrices were also varied in PSA using the Dirichlet probability distribution.

The PSA results are summarized below in Table 55 and are also presented on a cost-effectiveness plane in Figure 23. The results demonstrate there is consistency between the deterministic base-case incremental cost-effectiveness ratio (ICER) and the probabilistic ICER and also indicate that there remains a 100% probability that DEX700 is a cost-effective treatment option as the willingness-to-pay threshold is varied between £0 and £100,000 (which is well above what NICE would usually consider acceptable) per QALY.

Table 55: Probabilistic sensitivity analysis results; patients with phakic eyes and DMO that are insufficiently responsive to non-corticosteroid treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incr. (£/QALY)	Incr NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£39,457	16.9590	7.4029					
DEX700	£32,446	16.9590	7.5157	-£7,011	0.0000	0.1128	Dominant	£10,396
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; WTP, willingness-to-pay.								

Figure 23: Cost-effectiveness plane; patients with phakic eyes and DMO that are insufficiently responsive to non-corticosteroid treatment



Key: DMO, diabetic macular oedema; QALY, quality-adjusted life year.

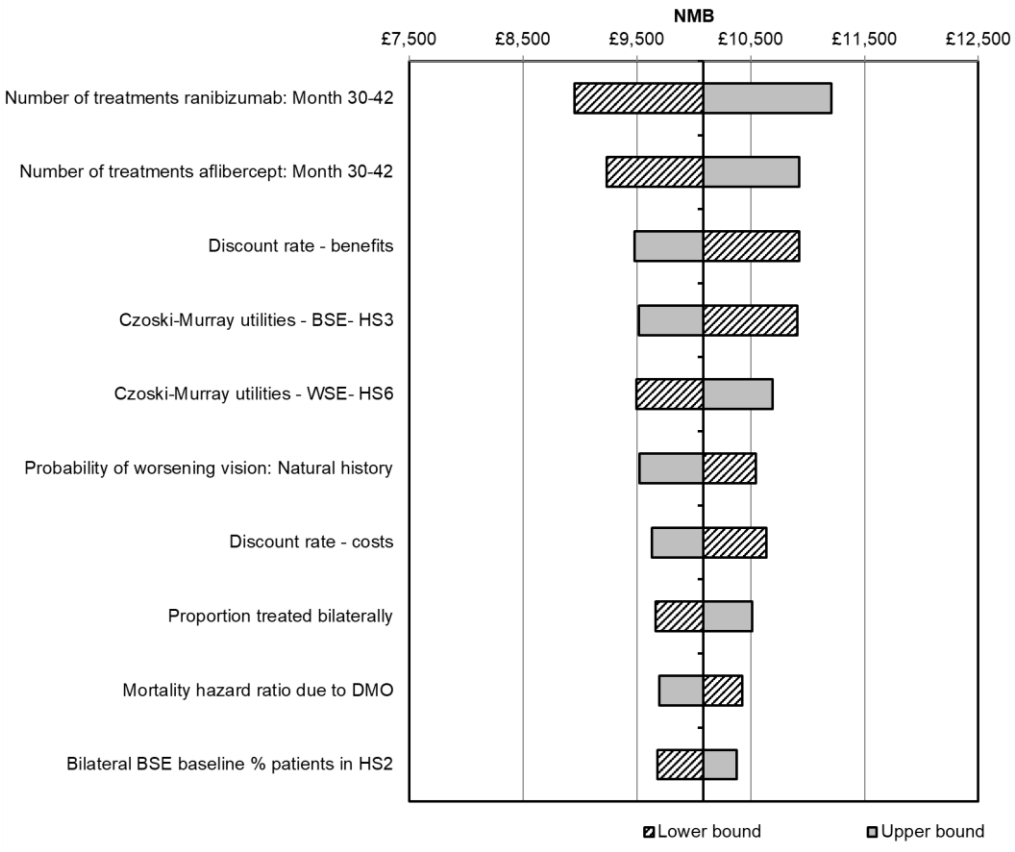
B.3.8.2 Deterministic sensitivity analysis

A series of deterministic sensitivity analyses were performed to evaluate the sensitivity of the model's ICER to individual inputs, holding all else constant. The lower and upper bounds of a parameter were set to their upper and lower limits of the confidence intervals reported in Appendix S. Where confidence intervals were not reported, upper and lower bounds were calculated from the mean, standard error and assumed distribution of each parameter. A tornado diagram providing a visual representation of the results of the deterministic sensitivity analyses is presented in Figure 24. As the

results are in the South-East quadrant, the incremental NMB has been presented to ensure ease of interpretation of the figure.

The results of the deterministic sensitivity analysis demonstrate that the model is relatively insensitive to most parameters, with DEX700 remaining dominant for variations in all parameters tested. The parameters with the greatest impact on the ICER are the average number of aflibercept and ranibizumab injections patients are assumed to receive in later timepoints, where DEX700 remains dominant even if the pessimistic lower bound estimates are applied. However, the average number of injections applied in the base-case are sourced from a large UK RWE audit, are consistent with other alternative data sources e.g. the RESTORE trial[146], and have been validated by two UK clinical experts.[73]

Figure 24: Results of one-way sensitivity analysis; patients with phakic eyes and DMO that are insufficiently responsive to non-corticosteroid treatment (NMB based on £30,000 per QALY threshold)



Key: BSE, better-seeing eye; DMO, diabetic macular oedema; HS, health state; NMB, net monetary benefit.

B.3.8.3 Scenario analysis

There are a number of parameters and assumptions that have been varied in scenario analysis. The results of these scenarios are outlined in Table 56, with the results demonstrating that DEX700 remains dominant consistently across all scenarios tested.

The scenario with the most significant change in the results is the use of the anti-VEGF costing assumptions applied NICE TA613 rather than the application of data from the UK RWE audit. This scenario is presented to have consistency with the approach adopted in NICE TA613, but the UK RWE audit data is used in the base-case analysis as it is considered a superior source. As noted in Section B.3.5.1, there are a number of significant limitations associated with this scenario given the ICE-UK data used to estimate the average number of injections only provides data over a 1-year time period which requires the use of arbitrary assumptions to model the long-term cost of treatment. Additionally, the data are not captured in the specific patient population of interest (phakic DMO patients insufficiently responsive to anti-VEGFs) and includes data that is older than the evidence that has been presented from the UK RWE audit.

Scenarios that also have a meaningful impact on the results include the use of data from the French RWE study and the RESTORE trial to estimate the average number of DEX700 and anti-VEGF injections respectively over time. Both these scenarios highlight that the use of alternative data sources to inform the frequency of injections leads to results that are consistent with the base-case and could also lead to improvements in the cost-effectiveness of DEX700.

Finally, scenarios relating to the number of routine monitoring visits patients have over time and the setting in which intravitreal injection procedures take place also have a notable impact on the results. The committee's preferred base-case analysis from NICE TA613 assumed that anti-VEGF patients had a higher frequency of monitoring visits than are being assumed in the base-case analysis for this appraisal, and therefore this scenario leads to an improvement in the results for DEX700. The results also demonstrate that even a small increase in the proportion of patients treated in a day-case setting can lead to meaningful changes in the results that favour DEX700 given anti-VEGFs are administered more frequently.

Table 56: Scenario analyses results

Model assumption	Base case	Scenario	ICER (DEX700 vs anti-VEGFs)	Incremental NMB (WTP threshold £30,000)
Base case			Dominant	£10,080
Time horizon	40 years	15 years	Dominant	£9,294
		30 years	Dominant	£10,074
Baseline characteristics	[redacted] unilateral DMO in the BSE	100% unilateral DMO in the BSE	Dominant	£11,913
	[redacted] unilateral DMO in the WSE	100% unilateral DMO in the WSE	Dominant	£9,581
	[redacted] bilateral DMO	100% bilateral DMO	Dominant	£14,782
Comparator composition	UK RWE (overall) ([redacted] ranibizumab; [redacted] aflibercept)	UK RWE (latest 2 years)	Dominant	£10,886
		UK RWE (overall) - including 5% laser	Dominant	£8,656
		UK RWE (overall) - including 10% laser	Dominant	£7,296
		NICE TA613 (excl laser) (aligned with NICE TA613 anti-VEGF dosing)	Dominant	£4,170
Dosing DEX700	MEAD	French RWE	Dominant	£10,285
Dosing anti-VEGF	UK RWE	The RESTORE study	Dominant	£14,929
Discontinuation anti-VEGF	Assume no discontinuation	Assume eyes included in UK RWE that did not receive any treatment within a certain time period have permanently discontinued treatment	Dominant	£10,472
Cataract extraction rate anti-VEGF	UK RWE	Assume equal to DEX700	Dominant	£10,502
Mortality hazard ratio diabetes	Mulnier et al. (2006)	Preis et al. 2009	Dominant	£10,064

Model assumption	Base case	Scenario	ICER (DEX700 vs anti-VEGFs)	Incremental NMB (WTP threshold £30,000)
Mortality hazard ratio DMO	Hirai et al. (2008)	Christ et al. 2008	Dominant	£10,130
Fellow eye involvement	From MEAD ITT population	From MEAD phakic population	Dominant	£10,074
Routine monitoring visits	DEX700 as per ERG preferred assumptions in TA349; Anti-VEGF from UK RWE	Anti-VEGF routine monitoring visits as per ERG preferred assumptions in TA613	Dominant	£11,088
		Assume equal number of routine monitoring visits for DEX700 and anti-VEGF	Dominant	£9,674
Optical coherence tomography costs	Exclude OCT cost at each administration visits; Include OCT cost at each routine monitoring visit	Include OCT cost at each administration visit; Exclude OCT cost at each routine monitoring visit	Dominant	£10,253
Administration costs	All intravitreal injection procedures 100% outpatient	All intravitreal injection procedures 50% day case and 50% outpatient	Dominant	£12,541
Number of appointments for bilateral injection	DEX700: 1.75; anti-VEGF: 1.5	DEX700 and anti-VEGF: 1.1	Dominant	£10,389
		DEX700 and anti-VEGF: 1.9	Dominant	£9,944
Severe vision loss costs	Exclude one-off severe vision loss direct medical costs	Include one-off severe vision loss direct medical costs	Dominant	£10,080
Utilities	Czoski-Murray et al.	Brown (1999)	Dominant	£8,549
		Brown et al. (2000)	Dominant	£9,469

Key: anti-VEGF, anti-VEGF, anti-vascular endothelial growth factors; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; RWE, real world evidence; TA, technology appraisal.

Table 57 presents the results of scenario analyses which use alternative sources of efficacy data to inform the transition probabilities for either the DEX700 or anti-VEGF treatment arms (see Section B.3.3.2.7 for further details). Given the absence of patient-level data for each of these sources it was not possible to estimate the full set of transition probabilities for these scenarios, with the one exception being the MEAD pseudophakic scenario. Therefore, the scenarios utilize data on the proportion of patients who experience 10 letter improvement or worsening from baseline to calculate a restricted set of transition probabilities where patients can only move up or down one health state at each time point. To ensure a consistent approach is taken to estimate transition probabilities in each treatment arm, a restricted set of MEAD transition probabilities is also applied MEAD is selected as the data source to model either DEX700 or anti-VEGFs. Given both the French and UK RWE report the proportion of patients experiencing improvement or worsening in vision from baseline to 12, 24 and 36 months, each of these estimates have been used to estimate transition probabilities to ensure that there is consistency in the results regardless of the timepoint used.

The results demonstrate that not only does DEX700 remain dominant in each scenario but that both the incremental costs and QALYs improve in favour DEX700. These improvements in costs and QALYs are driven by an increase in the relative effect between DEX700 and anti-VEGFs which results in both improvements in HRQL and reductions in costs associated with severe vision loss. Incremental QALYs consistently improve, with the one exception being the scenario which assumes a net-zero change in vision over time for the anti-VEGF arm. This result does lack some face validity given patients in the sham arm in MEAD experienced an overall net gain in BCVA, and therefore assuming a net-zero gain should increase the incremental QALY gain. However, this result is likely driven by the simple application of this scenario given it assumes a 3.5% improvement/worsening over time, and therefore it may not capture the full distribution of visual acuity outcomes expected to occur over time.

Table 57: Efficacy scenario analyses results

Model assumption	Base case	Scenario	ICER (DEX700 PRN vs anti-VEGFs)	Incremental NMB (WTP threshold £30,000)
Base case			Dominant	£10,080
Efficacy DEX700	MEAD DEX700 - phakic population	MEAD pseudophakic population	Dominant	£20,920
		French RWE (baseline to Month 12 probabilities recalculated into 3-month probabilities)	Dominant	£24,988
		French RWE (baseline to Month 24 probabilities recalculated into 3-month probabilities)	Dominant	£22,507
		French RWE (baseline to Month 36 probabilities recalculated into 3-month probabilities)	Dominant	£25,825
Efficacy anti-VEGF	MEAD sham - phakic population	UK RWE (baseline to Month 12 probabilities recalculated into 3-month probabilities)	Dominant	£19,417
		UK RWE (baseline to Month 24 probabilities recalculated into 3-month probabilities)	Dominant	£12,393
		UK RWE (baseline to Month 36 probabilities recalculated into 3-month probabilities)	Dominant	£10,071
		DMO natural history	Dominant	£12,258
		Net-zero impact on vision	Dominant	£8,076
DMO natural history	DMO natural history from Mitchell et al. (2012) (3.5% improving/4.5% worsening per cycle)	DMO natural history as per TA613 (0% improving/3.5% worsening per cycle)	Dominant	£8,725

Key: anti-VEGF, anti-VEGF, anti-vascular endothelial growth factors; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; RWE, real world evidence; TA, technology appraisal.

B.3.8.4 Summary of sensitivity analyses results

The sensitivity analyses that have been conducted consistently demonstrate that the results are robust to changes in parameters and key assumptions. There is consistency between the deterministic base-case and probabilistic results, with a difference in incremental net monetary benefit of just £316 between them, and DEX700 remaining cost-effective even at thresholds that are higher than what is considered acceptable by NICE. The deterministic sensitivity and scenario analysis results also demonstrate that DEX700 remains consistently dominant when changes are made to parameters and key assumptions, including changes to the frequency of DEX700 and anti-VEGF administrations, the frequency of monitoring visits and the use of alternative sources of efficacy data.

B.3.9. Subgroup analysis

No specific subgroups are considered in the cost-effectiveness model.

B.3.10. Validation

The model was finalized before being validated by internal and external modellers. A programmer (other than the one who built the model) reviewed all formulae and labelling in the model. Following this first validation step, an extreme value analysis was conducted. This involved inputting sensible upper and lower bounds (e.g. £0 for costs, but not negative costs) into the model, one parameter at a time, and observing the corresponding changes in the results. Where it was not sensible to vary only one parameter or the expected effect on the results was not straightforward, a related group of parameters was varied simultaneously. The results were checked against their expected impact or the predicted direction of change for the varied parameter(s). For example, setting all AE costs to zero would result in £0 for AE management across all treatment arms. An academic health economist also validated the model and critiqued the modelling strategy and methodology.

A number of the parameters and assumptions included in the model were validated by UK clinical experts. First, an advisory board was conducted involving six UK-based clinical experts to validate key assumptions; subsequently, interviews were conducted with two UK treating clinicians to validate parameters and assumptions applied in the model.

B.3.11. Interpretation and conclusions of economic evidence

The results of the economic analysis consistently demonstrate that DEX700 is a cost-effective use of NHS resources that results in both incremental QALY gains and reductions in costs to the health service. The base-case results are also considered to be underestimates of the true cost-effectiveness of DEX700, which is supported by a series of scenario analyses which explore plausible alternative assumptions for to estimate the QALYs and costs associated with DEX700 and anti-VEGF therapies.

The results of the economic analysis are consistent with the published literature, RWE studies, and UK clinical opinion which consistently highlight the potential for DEX700 to improve outcomes in patients with phakic eyes and DMO that are insufficiently responsive to non-corticosteroid treatment. DEX700 not only has the potential to improve clinical outcomes in a patient group who fail to experience any meaningful improvement with existing anti-VEGF therapies, but also reduce the burden of treatment administration given the lower injection frequency that is required, resulting in both improvements in the quality of life of patients, and the resource burden that is placed on the NHS.

The results are largely insensitive to parameters and assumptions tested in deterministic sensitivity analyses and scenario analysis, with DEX700 remaining the dominant treatment option in all instances. The assumptions implemented in the base-case analysis have been extensively validated by both the clinical trial data, the published literature, extensive RWE data collection and UK clinical expert opinion.

A key limitation of the evaluation includes the inability to conduct a robust indirect treatment comparison between DEX700 and anti-VEGFs in the relevant population of interest given the significant heterogeneity that exists between the available studies. However, the use of the MEAD data to model the efficacy of both treatment options is expected to result in a conservative estimate of the true treatment effect between DEX700 and anti-VEGFs whilst retaining trial randomization. A naïve comparison of data sources and clinical expert opinion has consistently stated that the outcomes for DEX700 in MEAD are overly pessimistic and the sham arm from MEAD results in outcomes for anti-VEGF patients that are superior to what is observed in the UK RWE data. Another limitation is the reliance on RWE to inform key modelling assumptions.

However, the UK RWE audit is the most relevant and robust data source available provides comprehensive data from a large sample of patients recently treated in UK clinical practice who align with the population of interest. Additionally, the estimates used from this study have been validated by two UK clinical experts and scenario analyses have demonstrated that using alternative data sources to inform assumptions such as the frequency of anti-VEGF injections results in results that are consistent with the base-case analysis.

DEX700 provides clear benefit in patients with phakic eyes and DMO that are insufficiently responsive to non-corticosteroid treatment, by offering a highly effective, cost-saving treatment option to patients who currently receive ineffective, and expensive treatments which place a significant burden on both patients and the NHS.

B.4. References

1. European Medicines Agency. Dexamethasone intravitreal implant 700 micrograms (Ozurdex®). *Summary of Product Characteristics*. 2015.
2. American Society of Aerospace Medicine Specialists. Clinical Practice Guideline for Cataracts. (Updated: 26 September 2010) Available at: http://www.asams.org/guidelines/Completed/NEW%20Cataract.htm. Accessed: 22 June 2021.
3. National Institute for Health and Care Excellence. Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy. 2019. (Updated: 20 November 2019) Available at: https://www.nice.org.uk/guidance/ta613/resources/fluocinolone-acetonide-intravitreal-implant-for-treating-chronic-diabetic-macular-oedema-in-phakic-eyes-after-an-inadequate-response-to-previous-therapy-pdf-82608955110853.
4. Sun JK and Jampol LM. The Diabetic Retinopathy Clinical Research Network (DRCR.net) and Its Contributions to the Treatment of Diabetic Retinopathy. *Ophthalmic Res*. 2019; 62(4):225-30.
5. Writing Committee for the Diabetic Retinopathy Clinical Research Network. Comparison of the Modified Early Treatment Diabetic Retinopathy Study and Mild Macular Grid Laser Photocoagulation Strategies for Diabetic Macular Edema. *Arch Ophthalmol*. 2007; 125(4):469-80.
6. Mourtzoukos S. The treatment of diabetic macular oedema (DMO) in UK real-life clinical practice with ILUVIEN® (fluocinolone acetonide) – its impact on current clinical practice. *Expert Rev Ophthalmol*. 2017; 12(2):95-7.
7. National Institute for Health and Care Excellence. Dexamethasone intravitreal implant for treating diabetic macular oedema (final appraisal determination). 2015. Available at: https://www.nice.org.uk/guidance/ta349/resources/macular-oedema-diabetic-dexamethasone-intravitreal-implant-final-appraisal-determination-document2. Accessed: 11 October.
8. National institute for Health and Care Excellence. Review of TA349; Dexamethasone intravitreal implant for treating diabetic macular oedema. 2021. Available at: https://www.nice.org.uk/guidance/ta349/evidence/review-decision-may-2021-9130585645?tab=evidence.
9. AbbVie. Virtual Advisory Board for Ozurdex® in Phakic Patients with Diabetic Macular Oedema – Report. 1 March 2021.
10. AbbVie. Long-term Follow Up of anti-VEGF use in Phakic Patients with Diabetic Macular Oedema: Real World Outcomes (Data on file). 2021.
11. Dutra Medeiros M, Alkabes M and Nucci P. Effectiveness of the Dexamethasone Intravitreal Implant for Treatment of Patients with Diabetic Macular Oedema. *Eur Endocrinol*. 2014; 10(2):111-6.
12. Diabetes UK. State of the Nation. 2015. (Updated: 2015) Available at: https://www.diabetes.org.uk/resources-s3/2017-11/state%20of%20the%20nation%202014.pdf. Accessed: 10 June 2021.
13. Diabetes.co.uk. Diabetes Prevalence. 2019. (Updated: 15 January 2019) Available at: https://www.diabetes.co.uk/diabetes-prevalence.html. Accessed: 22 June 2021.
14. National Health Sevice. Diabetes. 2019. (Updated: 11 July 2019) Available at: https://www.nhs.uk/conditions/diabetes/. Accessed: 22 June 2021.

15. Macular Society. Diabetic macular oedema. 2021. (Updated: 2021) Available at: https://www.macularsociety.org/macular-disease/macular-conditions/diabetic-macular-oedema/. Accessed: 22 June 2021.
16. American Optometric Association. Diabetic retinopathy. 2021. Available at: https://www.aoa.org/healthy-eyes/eye-and-vision-conditions/diabetic-retinopathy?sso=y. Accessed: 22 June 2021.
17. Ciulla TA, Amador AG and Zinman B. Diabetic Retinopathy and Diabetic Macular Edema. *Diabetes Care*. 2003; 26(9):2653-64.
18. Ciulla TA, Harris A, McIntyre N and Jonescu-Cuypers C. Treatment of diabetic macular edema with sustained-release glucocorticoids: intravitreal triamcinolone acetonide, dexamethasone implant, and fluocinolone acetonide implant. *Expert Opin Pharmacother*. 2014; 15(7):953-9.
19. Amoaku WM, Ghanchi F, Bailey C, et al. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. *Eye (Lond)*. 2020; 34(Suppl 1):1-51.
20. Chung Y-R, Kim YH, Ha SJ, et al. Role of Inflammation in Classification of Diabetic Macular Edema by Optical Coherence Tomography. *J Diabetes Res*. 2019.
21. National Health Sevice. Record high two million people at risk of Type 2 Diabetes. 2020. (Updated: 24 February 2020) Available at: https://www.england.nhs.uk/2020/02/record-high-two-million-people-at-risk-of-type-2-diabetes/. Accessed: 22 June 2021.
22. Kollias AN and Ulbig MW. Diabetic retinopathy: Early diagnosis and effective treatment. *Dtsch Arztebl Int*. 2010; 107(5):75-83; quiz 4.
23. American Diabetes Association. Introduction. *Diabetes Care*. 2002; 25(Suppl 1):S1–S2.
24. National Health Sevice. Patient information: Laser treatment for diabetic macular oedema. 2013. (Updated: June 2013) Available at: https://www.moorfields.nhs.uk/sites/default/files/uploads/documents/Patient%20information%20-%20laser%20for%20diabetic%20macula%20oedema.pdf. Accessed: 22 June 2021.
25. International Diabetes Federation. Diabetes & blindness due to DME: Blindness in Europe. 2016. (Updated: 2016) Available at: https://docplayer.net/20732436-Diabetes-blindness-due-to-dme-blindness-in-europe.html. Accessed: 22 June 2021.
26. Minassian DC, Owens DR and Reidy A. Prevalence of diabetic macular oedema and related health and social care resource use in England. *Br J Ophthalmol*. 2012; 96(3):345-9.
27. Gale R, Scanlon PH, Evans M, et al. Action on diabetic macular oedema: achieving optimal patient management in treating visual impairment due to diabetic eye disease. *Eye (Lond)*. 2017; 31(S1):S1-S20.
28. Yau IW, Rogers SL, Kawasaki R, et al. Global Prevalence and Major Risk Factors of Diabetic Retinopathy. *Diabetes Care*. 2012; 35(3).
29. The International Diabetes Federation. International Diabetes Federation Diabetes Atlas (9th edition). 2019. (Updated: 2019) Available at: https://www.diabetesatlas.org/en/sections/individual-social-and-economic-impact.html. Accessed: 22 June 2021.
30. American Diabetes Association. Eye Complications. 2021. Available at: https://www.diabetes.org/diabetes/complications/eye-complications?loc=footer/. Accessed: 22 June 2021.

31. Becker C, Schneider C, Aballéa S, et al. Cataract in patients with diabetes mellitus-incidence rates in the UK and risk factors. *Eye (Lond)*. 2018; 32(6):1028-35.
32. Olafsdottir E, Andersson DK and Stefánsson E. The prevalence of cataract in a population with and without type 2 diabetes mellitus. *Acta Ophthalmol*. 2012; 90(4):334-40.
33. Jeganathan VS, Wang JJ and Wong TY. Ocular associations of diabetes other than diabetic retinopathy. *Diabetes Care*. 2008; 31(9):1905-12.
34. Pollreisz A and Schmidt-Erfurth U. Diabetic cataract-pathogenesis, epidemiology and treatment. *J Ophthalmol*. 2010; 2010:608751.
35. Williams AS. Making diabetes education accessible for people with visual impairment. *Diabetes Educ*. 2009; 35(4):612-21.
36. Williams R, Airey M, Baxter H, et al. Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye (Lond)*. 2004; 18(10):963-83.
37. Klein K, Moss SE, Klein BE, et al. The NEI-VFQ-25 in people with long-term type 1 diabetes mellitus: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Arch Ophthalmol*. 2001; 119(5):733–40.
38. Janghorbani M, Jones RB and Allison SP. Incidence of and risk factors for cataract among diabetes clinic attenders. *Ophthalmic Epidemiol*. 2000; 7(1):13-25.
39. Tan JS, Wang JJ and Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. *Ophthalmic Epidemiol*. 2008; 15(5):317-27.
40. Wallick CJ. The Economic Burden of Diabetic Macular Edema in a Working Age and Commercially Insured Population. 2013. Available at: https://digital.lib.washington.edu/researchworks/bitstream/handle/1773/23543/Wallick_washington_0250O_11859.pdf?seque%20nce=1. Accessed: 22 June 2021.
41. Shea AM, Curtis LH, Hammill BG, et al. Resource use and costs associated with diabetic macular edema in elderly persons. *Arch Ophthalmol*. 2008; 126(12):1748-54.
42. Wallick CJ, Hansen RN, Campbell J, et al. Comorbidity and Health Care Resource Use Among Commercially Insured Non-Elderly Patients With Diabetic Macular Edema. *Ophthalmic Surg Lasers Imaging Retina*. 2015; 46(7):744-51.
43. Mitchell P, Annemans L, Gallagher M, et al. Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial. *Br J Ophthalmol*. 2012; 96(5):688-93.
44. Zhang X, Zeng H, Bao S, et al. Diabetic macular edema: new concepts in patho-physiology and treatment. *Cell Biosci*. 2014; 4(27).
45. Colenbrander A. Measuring Vision and Vision Loss 2001; 5.
46. Vermeire E, Wens J, Van Royen P, et al. Interventions for improving adherence to treatment recommendations in people with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2005; (2):CD003638.
47. Watkins JD, Williams TF, Martin DA, et al. A study of diabetic patients at home. *Am J Public Health Nations Health*. 1967; 57(3):452-9.
48. Hulka BS, Cassel JC, Kupper LL and Burdette JA. Communication, compliance, and concordance between physicians and patients with prescribed medications. *Am J Public Health*. 1976; 66(9).
49. Chatterjee JS. From compliance to concordance in diabetes. *J Med Ethics*. 2006; 32(9):507-10.
50. Wing RR, Lamparski DM, Zaslow S, et al. Frequency and accuracy of self-monitoring of blood glucose in children: relationship to glycemic control. *Diabetes Care*. 1985; 8(3):214-8.

51. Diabetes.co.uk. Diabetes Life Expectancy. 2019. (Updated: 15th January 2019) Available at: https://www.diabetes.co.uk/diabetes-life-expectancy.html. Accessed: 22 June 2021.
52. Heald AH, Stedman M, Davies M, et al. Estimating life years lost to diabetes: outcomes from analysis of National Diabetes Audit and Office of National Statistics data. *Cardiovasc Endocrinol Metab*. 2020; 9(4):183-5.
53. Hirai FE, Knudtson MD, Klein BE and Klein R. Clinically Significant Macular Edema and Survival in Type 1 and Type 2 Diabetes. *Am J Ophthalmol*. 2008; 145(4):700-6.
54. Nguyen-Khoa B-A, Goehring Jr EL, Werther W, et al. Hospitalized cardiovascular events in patients with diabetic macular edema. *BMC Ophthalmol*. 2012; 12(11).
55. Cusick M, Meleth AD, Agrón E, et al. Associations of Mortality and Diabetes Complications in Patients With Type 1 and Type 2 Diabetes. *Diabetes Care*. 2005; 28(3):617–25.
56. Barbeau M, Gonder J, Walker V, et al. PSS12 C-Reality (Canadian Burden of Diabetic Macular Edema Observational Study): Three-Month Findings. *Value in Health*. 2011; 14(7).
57. Hariprasad SM, Mieler WF, Grassi M, et al. Vision-related quality of life in patients with diabetic macular oedema. *Br J Ophthalmol*. 2008; 92(1):89-92.
58. Coyne KS, Margolis MK, Kennedy-Martin T, et al. The impact of diabetic retinopathy: perspectives from patient focus groups. *Fram Pract*. 2004; 21(4):447-53.
59. Hirai FE, Tielsch JM, Klein BE and Klein R. Ten-year change in vision-related quality of life in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. *Ophthalmology*. 2011; 118(2):353-8.
60. Fenwick EK, Xie J, Ratcliffe J, et al. The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in type 1 and type 2 diabetes. *Invest Ophthalmol Vis Sci*. 2012; 53(2):677-84.
61. Peters CM, James AI, Tran I, et al. The Impact of Diabetic Macular Edema on the Daily Lives of Diabetic Adults: A Qualitative Study. *Investig Ophthalmol Vis Sci*. 2012; 53(14).
62. Brose LS and Bradley C. Psychometric development of the individualized Retinopathy-Dependent Quality of Life Questionnaire (RetDQoL). *Value Health*. 2010; 13(1):119-27.
63. Diabetes UK. The cost of diabetes. 2014. Available at: https://www.diabetes.org.uk/resources-s3/2017-11/diabetes%20uk%20cost%20of%20diabetes%20report.pdf. Accessed: 22 June 2021.
64. Wallick CJ, Hansen RN, Campbell J, et al. Increased health care utilization among patients with diabetic macular edema compared with diabetic patients without edema. *Investig Ophthalmol Vis Sci*. 2014; 55.
65. Happich M, Reitberger U, Breitscheidel L, et al. The economic burden of diabetic retinopathy in Germany in 2002. *Graefes Arch Clin Exp Ophthalmol*. 2008; 246(1):151-9.
66. Javitt JC, Zhou Z and Willke RJ. Association between vision loss and higher medical care costs in Medicare beneficiaries costs are greater for those with progressive vision loss. *Ophthalmology*. 2007; 114(2):238-45.
67. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management (NG17). 2021. (Updated: 16 December 2020) Available

at: https://www.nice.org.uk/guidance/ng17/resources/type-1-diabetes-in-adults-diagnosis-and-management-pdf-1837276469701. Accessed: 29 June 2021.
68. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management (NG28). 2015. (Updated: 16 December 2020) Available at: https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-pdf-1837338615493. Accessed: 29 June 2021.
69. The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines. 2012. Available at: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-301-FINAL-DR-GUIDELINES-DEC-2012-updated-July-2013.pdf. Accessed: 29 June 2021.
70. National Institute for Health and Care Excellence. Ranibizumab for treating diabetic macular oedema. 2013. (Updated: 27 February 2013) Available at: https://www.nice.org.uk/guidance/ta274/resources/ranibizumab-for-treating-diabetic-macular-oedema-pdf-82600612458181.
71. National Institute for Health and Care Excellence. Aflibercept for treating diabetic macular oedema. 2015. (Updated: 22 July 2015) Available at: https://www.nice.org.uk/guidance/ta346/resources/aflibercept-for-treating-diabetic-macular-oedema-pdf-82602611201221.
72. National Institute for Health and Care Excellence. Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy. 2013. (Updated: 27 November 2017) Available at: https://www.nice.org.uk/guidance/ta301/resources/fluocinolone-acetonide-intravitreal-implant-for-treating-chronic-diabetic-macular-oedema-after-an-inadequate-response-to-prior-therapy-pdf-82602360938437.
73. AbbVie. Clinical Interview: Model Assumptions and Inputs (Data on file). 25 November 2021.
74. Korobelnik J-F, Loewenstein A, Eldem B, et al. Anti-VEGF intravitreal injections in the era of COVID-19: responding to different levels of epidemic pressure. *Graefes Arch Clin Exp Ophthalmol*. 2021; 259(3):567-74.
75. The Royal College of Ophthalmologists. RCOphth: Management of Ophthalmology Services during the Covid pandemic. 2020. Available at: https://www.iapb.org/wp-content/uploads/2020/11/RCOphth-Management-of-Ophthalmology-Services-during-the-Covid-pandemic-280320.pdf. Accessed: 17 December.
76. Busch C, Fraser-Bell S, Iglicki M, et al. Real-world outcomes of non-responding diabetic macular edema treated with continued anti-VEGF therapy versus early switch to dexamethasone implant: 2-year results. *Acta Diabetol*. 2019; 56(12):1341-50.
77. Aiello L, Edwards AR, Beck RW, et al. Factors Associated with Improvement and Worsening of Visual Acuity 2 Years after Focal/Grid Photocoagulation for Diabetic Macular Edema. *Ophthalmology*. 2010; 117(5):946-53.
78. Diabetic Retinopathy Clinical Research Network. A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Focal/Grid Photocoagulation for Diabetic Macular Edema. *Ophthalmology*. 2008; 115(9):1447-59.e10.
79. Early Treatment Diabetic Retinopathy Study Research Group. Treatment Techniques and Clinical Guidelines for Photocoagulation of Diabetic Macular Edema: Early Treatment Diabetic Retinopathy Study Report Number 2. *Ophthalmology*. 1987; 94(7):761-74.

80. Kodjikian L, Bellocq D, Bandello F, et al. First-line treatment algorithm and guidelines in center-involving diabetic macular edema. *Eur J Ophthalmol*. 2019; 29(6):573-84.
81. Kodjikian L, Bellocq D and Mathis T. Pharmacological Management of Diabetic Macular Edema in Real-Life Observational Studies. *BioMed Research International*. 2018; 2018:8289253.
82. Boyer DS, Yoon YH, Belfort R, Jr., et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014; 121(10):1904-14.
83. AbbVie. MEAD Post-hoc Exploratory Analyses. 14 July 2021.
84. Guigou S, Pommier S, Meyer F, et al. Efficacy and Safety of Intravitreal Dexamethasone Implant in Patients with Diabetic Macular Edema. *Ophthalmologica*. 2015; 233(3-4):169-75.
85. Kaldırım H, Savur F, Kırgız A and Atalay K. Comparison of Anatomical and Functional Outcomes of Intravitreal Dexamethasone Implant between Phakic and Pseudophakic Eyes with Diabetic Macular Edema. *Korean J Ophthalmol*. 2020; 34(5):383-91.
86. Malclès A, Dot C, Voirin N, et al. Real-life Study in Diabetic Macular Edema Treated with Dexamethasone Implant: The Reldex Study. *RETINA*. 2017; 37(4).
87. Mathis T, Lereuil T, Abukashabah A, et al. Long-term follow-up of diabetic macular edema treated with dexamethasone implant: a real-life study. *Acta Diabetol*. 2020; 57(12):1413-21.
88. Mello Filho P, Andrade G, Maia A, et al. Effectiveness and Safety of Intravitreal Dexamethasone Implant (Ozurdex) in Patients with Diabetic Macular Edema: A Real-World Experience. *Ophthalmologica*. 2019; 241(1):9-16.
89. Singer MA, Dugel PU, Fine HF, et al. Real-World Assessment of Dexamethasone Intravitreal Implant in DME: Findings of the Prospective, Multicenter REINFORCE Study. *Ophthalmic Surg Lasers Imaging Retina*. 2018; 49(6):425-35.
90. Wallsh J, Luths C, Kil H and Gallemore R. Initial Ten Years of Experience with the Intravitreal Dexamethasone Implant: A Retrospective Chart Review. *Clin Ophthalmol*. 2020; 14:3097-108.
91. Maturi RK, Pollack A, Uy HS, et al. Intraocular Pressure in Patients with Diabetic Macular Edema Treated with Dexamethasone Intravitreal Implant in the 3-year MEAD study. *RETINA*. 2016; 36(6):1143-52.
92. Cornish EET, K Y C. Gillies, M C. Lim, L L. Nguyen, V. Wickremasinghe, S. Mehta, H. McAllister, I L. Fraser-Bell, S. Five-year outcomes of eyes initially enrolled in the 2-year BEVORDEX trial of bevacizumab or dexamethasone implants for diabetic macular oedema. *Br J Ophthalmol*. 2021:bjophthalmol-2021-319839.
93. Pareja-Ríos A, Ruiz-de la Fuente-Rodríguez P, Bonaque-González S, et al. Intravitreal dexamethasone implants for diabetic macular edema. *Int J Ophthalmol*. 2018; 11(1):77-82.
94. Chatziralli I, Theodossiadis P, Parikakis E, et al. Dexamethasone Intravitreal Implant in Diabetic Macular Edema: Real-Life Data from a Prospective Study and Predictive Factors for Visual Outcome. *Diabetes Ther*. 2017; 8(6):1393-404.
95. Aydin E, Aygun Karaboga N, Deniz Egrilmez E and Kazanci L. Efficacy of Dexamethasone Implant versus Intravitreal Ranibizumab Treatment for Chronic Diabetic Macular Edema in Patients with Type 2 Diabetes Mellitus. 2019.
96. Zhioua IS, O. Lalloum, F. Souied, E. H. Intravitreal Dexamethasone Implant in Patients with Ranibizumab Persistent Diabetic Macular Edema. *RETINA*. 2015; 35(7):1429-35.

97. Cavalleri M, Cicinelli MV, Parravano M, et al. Prognostic role of optical coherence tomography after switch to dexamethasone in diabetic macular edema. *Acta Diabetol*. 2020; 57(2):163-71.
98. Al-khersan H, Hariprasad S, Singh S and Chhablani J. Long-term outcomes after intravitreal dexamethasone treatment in steroid responders. *Acta Diabetologica*. 2019; 56(6):675-80.
99. Al-Khersan H, Hariprasad SM and Chhablani J. Early Response to Intravitreal Dexamethasone Implant Therapy in Diabetic Macular Edema May Predict Visual Outcome. *Am J Ophthalmol*. 2017; 184:121-8.
100. Cicinelli M, Cavalleri M, Querques L, et al. Early response to ranibizumab predictive of functional outcome after dexamethasone for unresponsive diabetic macular oedema. *British Journal of Ophthalmology*. 2017; 101(12):1689.
101. Park YG and Park Y-H. Quantitative Analysis of Retinal Microvascular Perfusion and Novel Biomarkers of the Treatment Response in Diabetic Macular Edema. *J Diabetes Res*. 2020; 2132037.
102. Iglicki M, Busch C, Zur D, et al. Dexamethasone Implant for Diabetic Macular Edema in Naive Compared with Refractory Eyes: The International Retina Group Real-Life 24-Month Multicenter Study. The IRGREL-DEX Study. *RETINA*. 2019; 39(1):44-51.
103. Akıncıoğlu D, Küçükevcilioğlu M, Durukan A, et al. Outcomes of Intravitreal Dexamethasone Implant in the Treatment of Recalcitrant Diabetic Macular Edema. *Turk J Ophthalmol*. 2017; 47(5):274-8.
104. Scaramuzzi M, Querques G, Spina CL, et al. Repeated intravitreal dexamethasone implant (Ozurdex) for diabetic macular edema. *RETINA*. 2015; 35(6):1216-22.
105. De Geronimo D, Giorno P, Scarinci F, et al. Treatment of Diabetic Macular Edema with Multiple Dexamethasone Intravitreal Implants: Evidence from Real-Life Experience. *Ophthalmologica*. 2020; 243(6):413-9.
106. Bansal P, Gupta V, Gupta A, et al. Efficacy of Ozurdex implant in recalcitrant diabetic macular edema--a single-center experience. *Int Ophthalmol*. 2016; 36(2):207-16.
107. Augustin AJ, Kuppermann BD, Lanzetta P, et al. Dexamethasone intravitreal implant in previously treated patients with diabetic macular edema: subgroup analysis of the MEAD study. *BMC Ophthalmology*. 2015; 15(1):150.
108. Hsia NY, Lin CJ, Chen HS, et al. Short-Term Outcomes of Refractory Diabetic Macular Edema Switch From Ranibizumab to Dexamethasone Implant and the Influential Factors: A Retrospective Real World Experience. *Front Med (Lausanne)*. 2021; 8:649979.
109. Al-Latayfeh M, Abdel Rahman M and Shatnawi R. Outcome of Single Dexamethasone Implant Injection in the Treatment of Persistent Diabetic Macular Edema After Anti-VEGF Treatment: Real-Life Data from a Tertiary Hospital in Jordan. *Clin Ophthalmol*. 2021; 15:1285-91.
110. Bux AVF, F. Barone, A. Russo, V. Delle Noci, N. Iaculli, C. Early treatment with dexamethasone intravitreal implants in diabetic macular edema: Naïve versus refractory patients. *Eur J Ophthalmol*. 2021:1120-6721.
111. Sharma A, Kuppermann BD, Bandello F, et al. Intraocular pressure (IOP) after intravitreal dexamethasone implant (Ozurdex) amongst different geographic populations-GEODEX-IOP study. *Eye (Lond)*. 2020; 34(6):1063-8.

112. Kabanarou SA, Xirou T, Boutouri E, et al. Pre-operative intravitreal dexamethasone implant in patients with refractory diabetic macular edema undergoing cataract surgery. *Sci Rep*. 2020; 10(1):5534.
113. García Layana A, Adán A, Ascaso FJ, et al. Use of intravitreal dexamethasone implants in the treatment of diabetic macular edema: Expert recommendations using a Delphi approach. *Eur J Ophthalmol*. 2020; 30(5):1042-52.
114. Bilgic A, Sudhalkar A, Kodjikian L, et al. Pro Re Nata Dexamethasone Implant for Treatment-Naive Phakic Eyes with Diabetic Macular Edema: A Prospective Study. *Ophthalmol Retina*. 2019; 3(11):929-37.
115. Unsal E, Eltutar K, Sultan P, et al. Efficacy and Safety of Intravitreal Dexamethasone Implants for Treatment of Refractory Diabetic Macular Edema. *Korean J Ophthalmol*. 2017; 31(2):115-22.
116. Hernández Martínez A, Pereira Delgado E, Silva Silva G, et al. Early versus late switch: How long should we extend the anti-vascular endothelial growth factor therapy in unresponsive diabetic macular edema patients? *Eur J Ophthalmol*. 2020; 30(5):1091-8.
117. Demir G, Ozkaya A, Yuksel E, et al. Early and Late Switch from Ranibizumab to an Intravitreal Dexamethasone Implant in Patients with Diabetic Macular Edema in the Event of a Poor Anatomical Response. *Clin Drug Investig*. 2020; 40(2):119-28.
118. Ozsaygili C and Duru N. Comparison of Intravitreal Dexamethasone Implant and Aflibercept in Patients with Treatment-Naive Diabetic Macular Edema with Serious Retinal Detachment. *RETINA*. 2020; 40(6):1044-52.
119. Menezo M, Roca M, Menezo V and Pascual I. Intravitreal dexamethasone implant Ozurdex in the treatment of diabetic macular edema in patients not previously treated with any intravitreal drug: a prospective 12-month follow-up study. *Curr Med Res Opin*. 2019; 35(12):2111-6.
120. Rajesh B, Zarranz-Ventura J, Fung AT, et al. Safety of 6000 intravitreal dexamethasone implants. *Br J Ophthalmol*. 2020; 104(1):39-46.
121. Rezkallah A, Mathis T, Abukhashabah A, et al. Long-term Incidence and Risk Factors of Ocular Hypertension Following Dexamethasone-Implant Injections: The SAFODEX-2 Study. *RETINA*. 2021; 41(7):1438-45.
122. Pinto M, Mathis T, Massin P, et al. Visual Acuity Gain Profiles and Anatomical Prognosis Factors in Patients with Drug-Naive Diabetic Macular Edema Treated with Dexamethasone Implant: The NAVEDEX Study. *Pharmaceutics*. 2021; 13(2).
123. Goldberg R, Keyloun K, Campbell J, et al. Real-World Impact of Early Treatment With Intravitreal Dexamethasone Implant in DME in US Clinical Practice: Outcomes From the Vestrum Database. *American Society of Retina Specialists*. Texas, USA. 2021.
124. Modi Y, Keyloun K, Campbell J, et al. Real World Outcomes after Dexamethasone in DME Eyes with Suboptimal Response to Anti VEGF Therapy. *Retina Society 54th Annual Meeting*. Chicago. USA. 2021.
125. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology*. 2016; 123(6):1351-9.
126. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *N Engl J Med*. 2015; 372(13):1193-203.
127. Bressler NM, Beaulieu WT, Maguire MG, et al. Early Response to Anti-Vascular Endothelial Growth Factor and Two-Year Outcomes Among Eyes With Diabetic Macular Edema in Protocol T. *Am J Ophthalmol*. 2018; 195:93-100.

128. Allergan. A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema (MEAD-010). (Clinical Study Report) 2012.
129. Allergan. A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema (MEAD-011). (Clinical Study Report) 2012.
130. Malclès A, Dot C, Voirin N, et al. Safety of Intravitreal Dexamethasone Implant (Ozurdex): The SAFODEX Study. Incidence and Risk Factors of Ocular Hypertension. *RETINA*. 2017; 37(7):1352-9.
131. AbbVie. MEAD Studies: Demographics and Baseline Characteristics of Phakic Patients. 19 May 2021.
132. AbbVie. French RWD. Real World Study in Diabetic Macular Oedema Treated with Dexamethasone Implant: phakic vs pseudophakic (Data on file). 2021.
133. Csaky KG, Richman EA and Ferris FL, 3rd. Report from the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium. *Invest Ophthalmol Vis Sci*. 2008; 49(2):479-89.
134. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011; 118(4):615-25.
135. AbbVie. MEAD Post-hoc analysis: Tables for Phakic Input. 10 June 2021.
136. AbbVie. MEAD Post-hoc Analysis: Figures for Phakic Inputs. 25 May 2021.
137. The National Eye Institue. 25-Item Visual Function Questionnaire (VFQ-25). 2000. (Updated: August 2020) Available at: https://www.nei.nih.gov/sites/default/files/2019-06/manual_cm2000.pdf.
138. AbbVie. Outcomes Following Initial Insufficient Response to anti-VEGF Therapy: A Post-hoc Analysis of Protocol T (Data on file). 21 Nov 2021.
139. National Institute for Health and Care Excellence. NICE DSU Technical support document 18: Methods for Population-adjusted Indirect Comparisons in Submissions to NICE. 2016.
140. Muston D, Korobelnik JF, Reason T, et al. An efficacy comparison of anti-vascular growth factor agents and laser photocoagulation in diabetic macular edema: a network meta-analysis incorporating individual patient-level data. *BMC Ophthalmol*. 2018; 18(1):340.
141. Régnier S, Malcolm W, Allen F, et al. Efficacy of anti-VEGF and laser photocoagulation in the treatment of visual impairment due to diabetic macular edema: a systematic review and network meta-analysis. *PLoS One*. 2014; 9(7):e102309.
142. Rosenblatt A, Udaondo P, Cunha-Vaz J, et al. A Collaborative Retrospective Study on the Efficacy and Safety of Intravitreal Dexamethasone Implant (Ozurdex) in Patients with Diabetic Macular Edema: The European DME Registry Study. *Ophthalmology*. 2020; 127(3):377-93.
143. Graham RO and Peyman GA. Intravitreal Injection of Dexamethasone: Treatment of Experimentally Induced Endophthalmitis. *Arch Ophthalmol*. 1974; 92(2):149-54.
144. Kwak HW and D'Amico DJ. Evaluation of the Retinal Toxicity and Pharmacokinetics of Dexamethasone After Intravitreal Injection. *Arch Ophthalmol*. 1992; 110(2):259-66.

145. Sivaprasad S and Oyetunde S. Impact of injection therapy on retinal patients with diabetic macular edema or retinal vein occlusion. *Clin Ophthalmol*. 2016; 10:939-46.
146. Schmidt-Erfurth U, Lang GE, Holz FG, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology*. 2014; 121(5):1045-53.
147. Gregori NZ, Feuer W and Rosenfeld PJ. Novel method for analyzing snellen visual acuity measurements. *RETINA*. 2010; 30(7):1046-50.
148. AbbVie. MEAD Post-Hoc Analysis: Tables for Phakic Inputs (model) (Data on file). 24 May 2021.
149. Christ SL, Lee DJ, Lam BL, et al. Assessment of the effect of visual impairment on mortality through multiple health pathways: structural equation modeling. *Invest Ophthalmol Vis Sci*. 2008; 49(8):3318-23.
150. Mulnier HE, Seaman HE, Raleigh VS, et al. Mortality in people with type 2 diabetes in the UK. *Diabet Med*. 2006; 23(5):516-21.
151. Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation*. 2009; 119(13):1728-35.
152. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012; 119(4):789-801.
153. Czoski-Murray C, Carlton J, Brazier J, et al. Valuing condition-specific health states using simulation contact lenses. *Value Health*. 2009; 12(5):793-9.
154. Brown GC. Vision and quality-of-life. *Trans Am Ophthalmol Soc*. 1999; 97:173-511.
155. Brown GC, Sharma S, Brown MM and Kistler J. Utility values and age-related macular degeneration. *Arch Ophthalmol*. 2000; 118(1):47-51.
156. Pochopien M, Beiderbeck A, McEwan P, et al. Cost-effectiveness of fluocinolone acetonide implant (ILUVIEN®) in UK patients with chronic diabetic macular oedema considered insufficiently responsive to available therapies. *BMC Health Serv Res*. 2019; 19(1):22.
157. Rentz AM, Kowalski JW, Walt JG, et al. Development of a preference-based index from the National Eye Institute Visual Function Questionnaire-25. *JAMA Ophthalmol*. 2014; 132(3):310-8.
158. Sullivan PW, Slejko JF, Sculpher MJ and Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making*. 2011; 31(6):800-4.
159. MIMS UK. Ranibizumab NHS list price. 2021. Available at: https://www.mims.co.uk/drugs/eye/diagnostic-and-surgical/lucentis. Accessed: 29 September 2021.
160. MIMS UK. Aflibercept NHS list price. 2021. Available at: https://www.mims.co.uk/drugs/eye/diagnostic-and-surgical/eylea. Accessed: 29 September 2021.
161. Poku E, Rathbone J, Everson-Hock E, et al. Bevacizumab in eye conditions: Issues related to quality, use, efficacy and safety. 2012. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/Bevacizumab-report-NICE-published-version-11.04.13.pdf. Accessed: 29 September 2021.
162. National Health Service. 2019/20 National Cost Collection data. 2021. Available at: https://www.england.nhs.uk/national-cost-collection/. Accessed: 1 July 2021.

163. National Institute for Health and Care Excellence. Age-related macular degeneration (NG82). 2018. Available at: https://www.nice.org.uk/guidance/ng82/evidence/appendix-j-health-economics-pdf-170036251093. Accessed: 29 September 2021.
164. Colquitt JL, Jones J, Tan SC, et al. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess*. 2008; 12(16):iii-iv, ix-201.
165. Curtis L. Unit costs of health and social care. 2013. Available at: https://www.pssru.ac.uk/pub/uc/uc2013/full-with-covers.pdf. Accessed: 29 September 2021.
166. Curtis L and Burns A. Unit Costs of Health and Social Care. 2020. Available at: https://kar.kent.ac.uk/84818/13/Unit_Costs_of_Health_and_Social_Care_2020%20%281%29.pdf. Accessed: 29 September 2021.
167. Meads C and Hyde C. What is the cost of blindness? *Br J Ophthalmol*. 2003; 87(10):1201-4.
168. BMJ Technology Assessment Group. Dexamethasone intravitreal implant for diabetic macular oedema: A Single Technology Appraisal. 2014. (Updated: 20 February 2015) Available at: https://www.nice.org.uk/guidance/ta349/documents/macular-oedema-diabetic-dexamethasone-intravitreal-implant-committee-papers-part-2. Accessed: 29 September 2019.
169. BMJ Technology Assessment Group. ERG's critique of the Company's additional evidence submitted at the Appraisal Consultation stage - Addendum to ERG Report. 2015. (Updated: 2 June 2015) Available at: https://www.nice.org.uk/guidance/ta349/documents/macular-oedema-diabetic-dexamethasone-intravitreal-implant-committee-papers. Accessed: 29 September 2021.
170. Government UK. Drugs and pharmaceutical electronic market information tool (eMIT). 2021. (Updated: 28 September 2021) Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed: 1 July 2021.

B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Measuring vision and vision loss

Appendix M: Supportive information for Section B.2

Appendix N: Supporting efficacy data

Appendix O: Disaggregated discontinuation data

Appendix P: Utilities calculations

Appendix Q: Average number of treatments calculations

Appendix R: Application of fellow eye involvement in the model

Appendix S: Parameters from the cost-effectiveness model

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

Clarification questions

February 2022

File name	Version	Contains confidential information	Date
		Yes/no	

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Missing data

A1. Priority Question. Please use multiple imputation instead of last observation carried forward (LOCF) to account for the missing data in the pooled analysis of the MEAD studies (MEAD-010 and MEAD-011) and provide the results for the Dex 700 arm and the Sham arm for the following outcomes in the mITT subgroup of phakic study eyes at baseline:

a) **please provide a table with the results for ≥ 10 letter improvement in BCVA from baseline to months 12, 24, 36 and 39, and the equivalent of Figure 7 in the company submission;**
b) **please provide a table with the results for ≥ 10 letter worsening in BCVA from baseline to months 12, 24, 36 and 39, and the equivalent of Figure 7 in the company submission;**
c) **please provide a table with the mean change in BCVA for each 3 month time period from baseline to month 39 and the equivalent of Figure 6 in the company submission.**

Given the primary reasons for missing observations in MEAD are linked to patients either discontinuing the study treatment (due to a lack or loss of efficacy or adverse events) or due to censoring of patients receiving of rescue therapy, missing observations do not occur at random. There is therefore a high risk of informative

censoring as participants are lost to follow-up due to reasons related to the study. Table 1 summarizes the reasons for missing observations across both treatment arms.

Table 1: Reasons for MEAD study exclusion

DEX700	Definition[1]	DEX700[2]	Sham[2]
Receipt of rescue therapy	Patients who received escape therapy[a] in the study eye were considered treatment failures and were no longer be eligible to receive study medication, and were withdrawn from the study based on when they last received study treatment.	[redacted]	[redacted]
Discontinuation due to lack (or loss) of efficacy	A patient with confirmed[b] 15 or more letter decrease in BCVA from baseline in the study eye, attributable to macular oedema, could be exited from the study at the investigator's discretion.	[redacted]	[redacted]
Discontinuation due to AE or other non-efficacy related reasons	All other non-efficacy related reasons for withdrawal from the study.	[redacted]	[redacted]

Key: AE, adverse event
Notes: [a]Escape therapy could have included intravitreal steroids other than the study medication in the study eye, periocular steroids in the study eye, laser and/ or surgical treatments for macular edema in the study eye, intravitreal anti-vascular endothelial growth factor (VEGF) therapy in the study eye, systemic anti-VEGF therapy or other pharmacologic therapies for macular edema in the study eye. [b]15 or more letter decrease confirmed and documented at 2 consecutive visits at least 4 weeks apart. The patient did not receive any study treatment between these two visits.

All available methods that seek to overcome the issues of missing data involve numerous assumptions to be made, with each introducing the risk of different levels of bias. The LOCF approach has been selected in the submitted base case as it potentially reduces the overall risk of bias relative to methods such as the multiple imputation approach given the qualities of the MEAD data. When the multiple imputation approach is utilised, missing values are informed based on the distribution of non-missing data. As this approach makes use of the non-missing data to inform outcomes for patients with missing observations, there is a high risk of bias if the reasons for their exclusion are non-random. This is because the assumption that the outcomes of the observed participants can be used to inform the outcomes of the non-observed participants may not hold.

The primary analysis of change in visual acuity outcomes over time from MEAD was conducted using the LOCF approach to account for missing observations. Therefore, the data that have been presented in the company submission and that have fed through into the cost-effectiveness model have consistently adopted this approach throughout TA349 and into the ongoing appraisal.

As Table 1 summarises, a far larger number of sham patients went on to receive rescue therapy, or were discontinued due to lack (or loss) of efficacy, compared with DEX700 patients. Rescue therapy is typically offered to patients who experience poor outcomes on their existing treatment regimen, and by definition patients who discontinued due to lack (or loss) of efficacy had lost more than 15 letters from baseline. Therefore, the multiple imputation approach is highly likely to overestimate the longer-term outcomes of these patients because it makes use of information on the remaining observed patients. By definition, the remaining patients were experiencing superior vision-related outcomes to those who were censored or discontinued due to lack (or loss) of efficacy. Given the far greater proportion of sham patients with missing data due to receipt of rescue therapy or lack (or loss) of efficacy, analysis using multiple imputation will be biased more heavily in favour of the sham arm.

A2. Please use multiple imputation instead of last observation carried forward (LOCF) to account for the missing data in the pooled analysis of the MEAD studies and provide the results for the Dex 700 arm and the Sham arm for the following outcomes in the mITT subgroup of phakic study eyes at baseline:

a) please provide the equivalent of Figure 8 in the company submission for change in CRT from baseline;
b) please provide a table with change in CRT from baseline to months 12, 24, 36 and 39.

As noted in the response to question A1, the multiple imputation approach is not considered to be appropriate in this instance, and therefore the data from MEAD that have been generated utilising this approach have not been presented.

Indirect comparison using RWE

A3-A6.

It is not feasible for us to conduct the analyses requested in questions A3-A6 using the French and UK RWE studies as the company does not have access to the data for either of these two studies. The RWE were intended to provide supportive evidence to validate the clinical data presented in the base case.

A3. Priority Question: Please conduct an adjusted indirect comparison using the appropriate methods, according to the DSU guidance (TSD 17 and 18) and IPD availability, using the phakic cohort from the French RWE to inform dexamethasone, and the suboptimal responder cohort from the UK RWE to inform the comparator (continued treatment with anti-VEGFs) for the following outcomes:

a) **≥ 10 letter improvement in BCVA from baseline to month 12, 24 and 36;**
b) **≥ 10 letter worsening in BCVA from baseline to month 12, 24 and 36;**
c) **mean change in BCVA from baseline to month 12, 24 and 36.**

A4. Priority Question: Please conduct an adjusted indirect comparison using the appropriate methods, according to the DSU guidance (TSD 17 and 18) and IPD availability, using the phakic cohort from the French RWE to inform dexamethasone, and the suboptimal responder cohort from the UK RWE to inform the comparator (continued treatment with anti-VEGFs) for the following outcomes:

a) **Discontinuations due to any reason from baseline to 12, 24 and 36 months;**
b) **Proportion of patients who develop fellow eye involvement over 36 months;**
c) **Proportion of patients who undergo cataract surgery over 36 months;**
d) **Proportion of patients who experience adverse events over 36 months: raised IOP, retinal detachment, endophthalmitis, and vitreous haemorrhage;**
e) **Number of injections at 12, 24 and 36 months.**

A5. Priority question. Please conduct an adjusted indirect comparison using the appropriate methods, according to the DSU guidance (TSD 17 and 18) and

IPD availability, using the phakic cohort from the French RWE to inform dexamethasone, and the suboptimal responder cohort who received ranibizumab from the UK RWE to inform the comparator (continued treatment with ranibizumab) for the outcomes detailed in questions A3 and A4.

A6. Priority question. Please conduct an adjusted indirect comparison using the appropriate methods, according to the DSU guidance (TSD 17 and 18) and IPD availability, using the phakic cohort from the French RWE to inform dexamethasone, and the suboptimal responder cohort who received aflibercept from the UK RWE to inform the comparator (continued treatment with aflibercept) for the outcomes detailed in questions A3 and A4.

Comparators

A7. Priority Question: Please provide the rationale for only including watch and wait as a comparator for patients who are unsuitable for non-corticosteroids and not also as a treatment option for patients with an insufficient response to non-corticosteroids in Figure 4 of the company submission document B.

Subsequent to feedback from the ERG in question B2, the company has consulted additional UK clinicians who have confirmed that, as was accepted in TA613,[3] due to the lack of alternative treatments, phakic DMO patients who have an insufficient response to non-corticosteroids will continue to receive anti-VEGF/laser therapy in an attempt to achieve a response and/or with the aim of maintaining the retinal architechture.[4-6] Clinicians also stated that there will be some patients with high baseline BCVA who do not show any obvious signs of improvement, but who sustain their vision and will therefore continue with anti-VEGF treatment.[6] Furthermore, there will be a very small proportion (~5%) of complete non-responders who may discontinue anti-VEGF treatment, but these patients will be monitored and treatment will be tried again as they deteriorate. This is in alignment with the EURETINA guidelines that state in relation to ranibizumab "*If no more functional or anatomical benefit occurs, the treatment must be stopped, and extended monitoring intervals can be evaluated for each patient individually*".[7] Therefore, aligning with the recent TA613 appraisal, watch and wait is only considered a comparator in patients who are

unsuitable for non-corticosteroid treatment as no alternative treatment is currently available.[3]

This is also confirmed by the retrospective cohort study of two ophthalmology centres in the UK between 2015 and 2020.[8] This UK RWE audit has indicated that the [redacted]% of patients who were insufficient responders (≤ 5 letter gain at month 6) continued to receive anti-VEGFs over a period of 42 months. These patients received approximately [redacted] anti-VEGF injections per year over the long term with most not achieving clinically meaningful gains in BRVA.

Of note, TA613 suggested that laser therapies were used in 28% of DMO patients; recent reviews of the treatment landscape have suggested a decrease in the use of laser therapy in UK clinical practice, aligning with clinical opinion at the ad-board conducted in 2021.[9, 10]

Subgroup results

A8. Priority Question. Please provide baseline characteristics for the phakic patients from the pooled MEAD studies, separately for the Dex 700 arm and the sham arm for the following subgroups:

a) **baseline CRT ≥ 400µm; and**
b) **baseline CRT < 400µm**

Table 2 presents the baseline characteristics for the phakic DMO patients for the pooled MEAD trial (mITT population), stratified by CRT ≥ 400 µm and CRT < 400 µm. Baseline characteristics are relatively similar for the CRT ≥ 400 µm and CRT < 400 µm populations, although patients with CRT ≥ 400 µm were more likely to have received prior laser therapy, and less likely to be treatment naïve at baseline than the CRT < 400 µm population.

As there are no CRT restrictions on the use of DEX700 in either the marketing authorisation or the existing NICE guidance (TA349), baseline characteristics are pooled for the phakic-only mITT population and can therefore be assessed as a whole. Furthermore, according to NICE technical appraisals, treatment with anti-VEGFs is restricted to patients with a CRT ≥ 400 µm, although this restriction only applies at the point of treatment initiation.

Table 2: Baseline characteristics, stratified by baseline CRT ≥ 400 µm and CRT < 400 µm

A8	a) CRT ≥ 400 µm		b) CRT < 400 µm	
	DEX700 (n = [redacted])	Sham (n = [redacted])	DEX700 (n = [redacted])	Sham (n = [redacted])
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Treated eye, n (%)				
Better seeing eye	[redacted]	[redacted]	[redacted]	[redacted]
Worse seeing eye	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Prior laser, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-VEGF, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
BCVA < 50 letters, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-naïve at baseline, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
DMO duration > 1.3 years[a], n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
DMO duration ≥ 3 years, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Cataract, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, best-corrected visual acuity; CRT, central retinal thickness; DMO, diabetic macular oedema; SD, standard deviation; VEGF, vascular endothelial growth factor.
Notes: [a] DMO duration of 1.3 years was based on the median of the intention-to-treat population of the MEAD clinical trials.
Source: MEAD (2022)[11].

A9. Priority Question. Please provide subgroup results for the phakic patients with a baseline CRT ≥ 400µm from the pooled MEAD studies, separately for the Dex 700 arm and the sham arm for the following outcomes:

a) **≥ 10 letter improvement in BCVA from baseline to month 12, 24, 36 and 39;**
b) **≥ 10 letter worsening from baseline in BCVA to month 12, 24, 36 and 39;**
c) **mean change in BCVA for each 3 month time period from baseline to month 39 and the equivalent of Figure 6 in the company submission.**
d) **discontinuations due to AEs and other non-efficacy-related reasons at 12, 24 and 36 months;**
e) **discontinuations due to lack (or loss) of efficacy of treatment at 12, 24 and 36 months;**
f) **proportion who develop fellow eye involvement;**
g) **cataract surgery rates;**
h) **the following adverse event rates: raised IOP, retinal detachment, endophthalmitis, and vitreous haemorrhage;**
i) **number of injections at 12, 24, 36 and 39 months.**

Table 3 presents the requested subgroup results from the pooled MEAD trial for the phakic-only mITT population with a baseline CRT of ≥ 400 µm.

Table 3: Requested subgroup results from the pooled MEAD trial for the phakic-only mITT population patients with a baseline CRT ≥ 400 µm (LOCF analysis)

A9		DEX700 (n=[redacted])	Sham (n=[redacted])
a)	**≥ 10 letter improvement in BCVA from baseline, n (%)**		
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]
b)	**≥ 10 letter worsening in BCVA from baseline, n (%)**		
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]
c)	**Mean change in BCVA from baseline**		
	Month 3	[redacted]	[redacted]
	Month 6	[redacted]	[redacted]
	Month 9	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]
	Month 15	[redacted]	[redacted]
	Month 18	[redacted]	[redacted]
	Month 21	[redacted]	[redacted]

	Month 24	[redacted]	[redacted]
	Month 27	[redacted]	[redacted]
	Month 30	[redacted]	[redacted]
	Month 33	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]
d)	**Discontinuations due to AEs and other non-efficacy related reasons[a]**		
	At Month 12 visit	[redacted]	[redacted]
	At Month 24 visit	[redacted]	[redacted]
	At Month 36 visit	[redacted]	[redacted]
e)	**Discontinuations due to lack (or loss) of efficacy of treatment[a]**		
	At Month 12 visit	[redacted]	[redacted]
	At Month 24 visit	[redacted]	[redacted]
	At Month 36 visit	[redacted]	[redacted]
f)	**Proportion who developed fellow eye involvement, n (%)**		
	Patients with unilateral DMO at baseline	[redacted]	[redacted]
	During Year 1[b]	[redacted]	[redacted]
	During Year 2[b]	[redacted]	[redacted]
	During Year 3[b]	[redacted]	[redacted]
g)	**Proportion who had cataract surgery, n (%)**		
	Year 1	[redacted]	[redacted]
	Year 2	[redacted]	[redacted]
	Year 3	[redacted]	[redacted]
h)	**AE rates, n (%)**		
	Raised IOP (change from baseline ≥ 10 mmHg)		
	Year 1	[redacted]	[redacted]
	Year 2	[redacted]	[redacted]
	Year 3	[redacted]	[redacted]
	Retinal detachment		
	Year 1	[redacted]	[redacted]
	Year 2	[redacted]	[redacted]
	Year 3	[redacted]	[redacted]
	Endophthalmitis		
	Year 1	[redacted]	[redacted]
	Year 2	[redacted]	[redacted]
	Year 3	[redacted]	[redacted]
	Vitreous haemorrhage		
	Year 1	[redacted]	[redacted]
	Year 2	[redacted]	[redacted]
	Year 3	[redacted]	[redacted]

i)	**Number of injections, n (%)[a]**			
	Month 12	Patients remaining in the study, n (%)	[redacted]	[redacted]
		Receiving treatment/re-treatment, n (%)	[redacted]	[redacted]
	Month 24	Patients remaining in the study, n (%)	[redacted]	[redacted]
		Receiving treatment/re-treatment, n (%)	[redacted]	[redacted]
	Month 36	Patients remaining in the study, n (%)	[redacted]	[redacted]
		Receiving treatment/re-treatment, n (%)	[redacted]	[redacted]
	Month 39	Patients remaining in the study, n (%)	[redacted]	[redacted]
		Receiving treatment/re-treatment, n (%)	[redacted]	[redacted]

Key: AE, adverse event; BCVA, best-corrected visual acuity; CRT, central retinal thickness; IOP, intraocular pressure; LOCF, last observation carried forward; mITT, modified intention-to-treat.
Notes: [a] Percentages were calculated based on the number of patients remaining in the study at each visit as a denominator; [b] Percentages were calculated based on the number of patients with unilateral DMO at baseline as a denominator.
Source: MEAD (2022).[11]

A10. Priority Question. Please provide subgroup results for the phakic patients with a baseline CRT < 400µm from the pooled MEAD studies, separately for the Dex 700 arm and the sham arm for the following outcomes:

a) **≥ 10 letter improvement in BCVA from baseline to month 12, 24, 36 and 39;**
b) **≥ 10 letter worsening from baseline in BCVA to month 12, 24, 36 and 39;**
c) **mean change in BCVA for each 3 month time period from baseline to month 39 and the equivalent of Figure 6 in the company submission.**
d) **discontinuations due to AEs and other non-efficacy-related reasons at 12, 24 and 36 months;**
e) **discontinuations due to lack (or loss) of efficacy of treatment at 12, 24 and 36 months;**
f) **proportion who develop fellow eye involvement;**
g) **cataract surgery rates;**
h) **the following adverse event rates: raised IOP, retinal detachment, endophthalmitis, and vitreous haemorrhage;**
i) **number of injections at 12, 24, 36 and 39 months.**

Table 4 presents the requested subgroup results from the pooled MEAD trial for the phakic-only mITT population with a baseline CRT of < 400 µm.

Table 4: Requested subgroup results from the pooled MEAD trial for the phakic-only mITT population with a baseline CRT < 400 µm (LOCF analysis)

A10		**DEX700 (n=[redacted])**	**Sham (n=[redacted])**
a)	**≥ 10 letter improvement in BCVA from baseline, n (%)**		
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]

	Month 36	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]
b)	**≥ 10 letter worsening in BCVA from baseline, n (%)**		
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]
c)	**Mean change in BCVA from baseline**		
	Month 3	[redacted]	[redacted]
	Month 6	[redacted]	[redacted]
	Month 9	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]
	Month 15	[redacted]	[redacted]
	Month 18	[redacted]	[redacted]
	Month 21	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 27	[redacted]	[redacted]
	Month 30	[redacted]	[redacted]
	Month 33	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]
d)	**Discontinuations due to AEs and other non-efficacy related reasons[a]**		
	At Month 12 visit	[redacted]	[redacted]
	At Month 24 visit	[redacted]	[redacted]
	At Month 36 visit	[redacted]	[redacted]
e)	**Discontinuations due to lack (or loss) of efficacy of treatment[a]**		
	At Month 12 visit	[redacted]	[redacted]
	At Month 24 visit	[redacted]	[redacted]
	At Month 36 visit	[redacted]	[redacted]
f)	**Proportion who developed fellow eye involvement, n (%)**		
	Patients with unilateral DMO at baseline	[redacted]	[redacted]
	During Year 1[a]	[redacted]	[redacted]
	During Year 2[a]	[redacted]	[redacted]
	During Year 3[a]	[redacted]	[redacted]
g)	**Proportion who had cataract surgery**		
	Year 1	[redacted]	[redacted]
	Year 2	[redacted]	[redacted]
	Year 3	[redacted]	[redacted]
h)	**AE rates, n (%)**		
	Raised IOP (change from baseline ≥ 10 mmHg)		

	Year 1		[redacted]	[redacted]
	Year 2		[redacted]	[redacted]
	Year 3		[redacted]	[redacted]
	Retinal detachment			
	Year 1		[redacted]	[redacted]
	Year 2		[redacted]	[redacted]
	Year 3		[redacted]	[redacted]
	Endophthalmitis			
	Year 1		[redacted]	[redacted]
	Year 2		[redacted]	[redacted]
	Year 3		[redacted]	[redacted]
	Vitreous haemorrhage			
	Year 1		[redacted]	[redacted]
	Year 2		[redacted]	[redacted]
	Year 3		[redacted]	[redacted]
i)	**Number of injections, n (%)[b]**			
	Month 12	Patients remaining in the study, n (%)	[redacted]	[redacted]
		Receiving treatment/re-treatment, n (%)	[redacted]	[redacted]
	Month 24	Patients remaining in the study, n (%)	[redacted]	[redacted]
		Receiving treatment/re-treatment, n (%)	[redacted]	[redacted]
	Month 36	Patients remaining in the study, n (%)	[redacted]	[redacted]
		Receiving treatment/re-treatment, n (%)	[redacted]	[redacted]
	Month 39	Patients remaining in the study, n (%)	[redacted]	[redacted]
		Receiving treatment/re-treatment, n (%)	[redacted]	[redacted]

Key: AE, adverse event; BCVA, best-corrected visual acuity; CRT, central retinal thickness; IOP, intraocular pressure; LOCF, last observation carried forward; mITT, modified intention-to-treat.
Notes: [a] Percentages were calculated based on the number of patients remaining in the study at each visit as a denominator; [b] Percentages were calculated based on the number of patients with unilateral DMO at baseline as a denominator.
Source: MEAD (2022).[11]

mITT and ITT populations

A11. Priority question. Please define the mITT population for the pooled MEAD study analyses and explain why the mITT population is used for the efficacy outcomes from the phakic subgroup of the MEAD studies and not the ITT population.

The mITT population of the pooled MEAD trial is defined as all DMO patients enrolled into the study who had attended at least 1 follow-up visit. The efficacy outcomes are therefore presented for the phakic-only mITT population to align with the patient population of interest for this submission. The mITT population was used

for all efficacy analyses to ensure that the model was based on data from patients with at least one follow-up observation so that there was at least some evidence of treatment effect. Use of the mITT population is consistent with the MEAD data presented in TA349; the main difference between the submissions is that in TA349 the full mITT population was used (i.e. including patients who were both phakic and pseudophakic at baseline), whereas for this appraisal only the phakic population at baseline are of interest.

A12. Please provide the following for the phakic subgroup of the pooled MEAD study analyses:

a) the number of patients in the mITT and ITT populations;
b) the results for the ITT population for the primary outcome (BCVA improvement of 15 or More Letters from Baseline);
c) the results for the ITT population for BCVA improvement of 15 or More Letters from Baseline;
d) the results for the ITT population for mean change in BCVA from baseline.

The phakic-only ITT population consists of [redacted] phakic DMO patients, [redacted] of which were enrolled into the DEX700 arm, and [redacted] into the Sham arm. The phakic-only mITT population consists of [redacted] phakic DMO patients, [redacted] in the DEX700 arm, and [redacted] into the Sham arm. There was therefore only [redacted] patients who did not attend at least 1 follow-up visit. We therefore do not expect the outcomes to differ from the mITT population. Due to the high volume of additional data requests, and as this is not a priority question, we have been unable to provide the requested additional tables by the requested deadline. If the ERG would still like to see these data, we will be able to follow-up with these by 24 February 2022.

A13. Priority Question. Please provide the pooled MEAD study results for the phakic population for the dex 700 and sharm arms for following outcomes:

a) ≥ 10 letter improvement in BCVA from baseline to month 12, 24, 36 and 39 in the mITT population;
b) ≥ 10 letter worsening from baseline in BCVA to months 12, 24, 36 and 39 in the mITT population;
c) total discontinuations;
d) discontinuations due to lack (or loss) of efficacy of treatment;
e) proportion who developed fellow eye involvement;

f) proportion who had cataract surgery;
g) retinal detachment;
h) endopthalmitis;
i) number of injections at 12, 24, 36 and 39 months.

Table 6 presents all requested results for the phakic population (mITT population) of the pooled MEAD trial for the DEX700 and Sham arms. Of note, the number of injections at 12, 24, 36 and 39 months was presented in Table 13 of Document B.

Table 6: Requested outcomes for the pooled MEAD trial (phakic-only mITT population; LOCF analysis)

A13		DEX700 (n=[redacted])	Sham (n=[redacted])
a)[1]	**≥ 10 letter improvement in BCVA from baseline, n (%)**		
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]
b)[1]	**≥ 10 letter worsening in BCVA from baseline, n (%)**		
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]
c)[2]	**Total discontinuations**	[redacted]	[redacted]
d)[2]	**Discontinuations due to lack (or loss) of efficacy of treatment**	[redacted]	[redacted]
e)[2]	**Proportion who developed fellow eye involvement**		
	Patients with unilateral DMO at baseline	[redacted]	[redacted]
	During Year 1[a]	[redacted]	[redacted]
	During Year 2[a]	[redacted]	[redacted]
	During Year 3[a]	[redacted]	[redacted]
f)[2]	**Proportion who had cataract surgery**	[redacted]	[redacted]
g)[2]	**Retinal detachment, n (%)**	[redacted]	[redacted]
h)[2]	**Endophthalmitis n (%)**	[redacted]	[redacted]
i)[1]	**Number of injections, n (%)**		
	Month 12	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]
Key: BCVA, best-corrected visual acuity; mITT, modified intention-to-treat.			

Notes: [a] Percentages were calculated based on the number of patients remaining in the study at each visit as a denominator.
Source: [1]MEAD (2022)[11]; [2]MEAD (2021)[2].

A14. The ERG notes that the company considers the sham arm from the pooled MEAD studies to overestimate the efficacy of continued anti-VEGF. Please can the company provide further explanation why they consider the use of the sham arm from the pooled MEAD studies to be an overestimate of the efficacy of continued anti-VEGF use in patients deemed to be insufficiently responsive to anti-VEGFs, in particular for the subgroup who are partial responders to anti-VEGFs.

As presented in Document B (Figure 22), the use of the MEAD sham arm as a proxy for continued anti-VEGF use likely overestimates the efficacy of continued anti-VEGF use in patients deemed to be insufficiently responsive to anti-VEGF treatment. The BCVA change from baseline was consistently higher in the MEAD sham arm than the UK RWE audit.

When comparing the proportion of phakic DMO patients with an improvement of ≥ 15 letters at months 12 and 24, the MEAD Sham arm was considerably higher (Figure 1). The proportion of phakic DMO patients with a loss of ≥ 15 letters was similar in the sham arm of MEAD and UK RWE audit at 12 and 24 months. These therefore show that compared with the UK RWE audit, the MEAD sham arm experienced similar a proportion of patients with worsening vision but a much greater proportion of patients experiencing significant gains in vision, meaning that on average the sham arm performs better than continued use of anti-VEGF per the UK RWE audit.

Figure 1: Proportion of phakic DMO patients with an improvement or loss of ≥ 15 letters in MEAD and the UK RWE audit at a) 12 months and b) 24 months

Of note, using the MEAD sham arm as a proxy for continued anti-VEGF use is comparable with the approach taken in TA613 whereby the incremental difference between the fluocinolone and sham arms of FAME was accepted as an appropriate proxy for the incremental difference between fluocinolone and continued use of anti-VEGF or laser.

Section B: Clarification on cost-effectiveness data

B1. Priority question. If as a result of the responses to the clarification questions the company base case is revised, please indicate what assumptions are considered for the revised base case and provide updated results including updated probabilistic sensitivity analyses and deterministic sensitivity analyses. Please provide all requested scenario analyses as options in the economic model and on top of any revised assumptions.

A significant number of additional scenario analyses have been presented in response to the clarification questions on the cost-effectiveness data. The vast majority of scenarios had minimal impact on the results, leading to INMB estimates which were consistent with the results of the base-case analysis. The most impactful scenarios were those utilising data from the French and UK RWE studies to model efficacy across both treatment arms, which (consistent with the scenario analyses using RWE presented in the company submission) significantly increased the

incremental QALY gains, and further demonstrates that the base-case results may underestimate the true treatment effect of DEX700. Given the limited impact the majority of scenarios have on the results and given the methodological limitations with a number of the requested scenarios, the base-case assumptions have not been revised at this stage.

Comparator

B2. Priority question. Clinical experts have advised the ERG that there are two types of insufficient responders to non-corticosteroid treatment: those that have a partial response and maintain vision and those that have no response and receive no further treatment. The comparator depends on which type of insufficient responder is being treated.

a) **Please provide cost-effectiveness results for the four subgroups outlined in the table.**

   The ERG would urge the company to revise their base case analysis in line with these four subgroups as the treatment options and outcomes vary between them. The ERG also considers that the comparators in the composite anti-VEGF comparator should also be considered separately as their costs vary.

b) **Please provide scenarios using your responses to questions A8, A9 and A10 to populate the different subgroups. Please include baseline characteristics and baseline BCVA distributions from the dexamethasone 700 and sham arms of the pooled MEAD trials according to the CRT thresholds in these scenarios.**

Response	CRT	Comparison	Source of efficacy data	
			DEX700	Comparator
Partial response to non-corticosteroid treatment	=>400 micrometers	DEX700 vs ranibizumab	DEX700 arm in the pooled MEAD studies	Sham arm in the pooled MEAD studies
		DEX700 vs aflibercept	DEX700 arm in the pooled MEAD studies	Sham arm in the pooled MEAD studies

	<400 micrometers	DEX700 vs watch and wait	DEX700 arm in the pooled MEAD studies	Sham arm in the pooled MEAD studies
No response to non-corticosteroid treatment	=>400 or <400 micrometers	DEX700 vs watch and wait	DEX700 arm in the pooled MEAD studies	Sham arm in the pooled MEAD studies

Subsequent to the feedback from the ERG, the company has consulted additional clinicians who have indicated that in UK clinical practice almost all patients continue to receive anti-VEGF treatment.[6] Clinicians will treat to obtain treatment-related benefits with the aim of obtaining improvement in vision, and/or with the aim of maintaining the retinal architecture and preventing irreversible loss of photoreceptors due to prolonged oedema.[5] Only a countable few patients will be disregarded as complete non-responders in whom even the retinal prevention is unlikely to be achieved. Therefore, we do not believe this patient group is sufficiently large enough to justify the inclusion of watch and wait as an additional comparator in complete non-responders.

The ERG also requests a comparison with watch and wait in patients with a partial response to non-corticosteroid treatment and a CRT < 400 micrometers. Feedback received by UK clinicians confirmed that a fall in CRT levels below 400 micrometres would not in isolation be considered a reason to discontinue treatment. Further, the assertion that patients would discontinue treatment with anti-VEGFs if they later have a CRT of <400 contradicts the NICE guidance. The guidance for aflibercept (TA346)[12] states:

*"Aflibercept solution for injection is recommended as an option for treating visual impairment caused by diabetic macular oedema only if: the eye has a central retinal thickness of 400 micrometres or more at the **start** of treatment"*

Therefore, given this appraisal covers a population of patients with a phakic lens and DMO that does not respond sufficiently to non-corticosteroid treatment, then all patients would have needed to have had a CRT of ≥ 400 micrometres to initiate treatment on non-corticosteroids, but if their CRT then fell below this specified level then the guidance does not state that a patient must discontinue therapy at this time point.

The ERG has also requested separate comparisons with aflibercept and ranibizumab rather than including these treatments within one composite comparator. However, this also contradicts the committee's preferred assumptions in NICE TA613, where a composite comparator which represented "usual care" was accepted. The inclusion of aflibercept and ranibizumab within a composite comparator is also considered appropriate because the data from clinical trials for both treatments and feedback from clinicians highlights that there is no evidence to suggest a difference in the efficacy of these treatment options. Indeed, it is noted in the Final Appraisal Determination Document for TA346[12] that: *"The Committee concluded that aflibercept is likely to have similar clinical effectiveness to ranibizumab, based on the results of the network meta-analysis and clinical expert opinion."* Clinical experts noted in that appraisal that given aflibercept and ranibizumab are the same class of drug, there is no reason to suggest there would be differences in efficacy between the treatments, which was supported by clinicians consulted for this appraisal. This is further supported by the findings of the DRCR.net PROTOCOL T study which found no difference between aflibercept and ranibizumab in mean change in visual acuity from baseline among eyes with baseline visual acuity of 20/50 to 20/40.[13] Given the use of a composite comparator has been accepted across numerous NICE appraisals (for example the use of composite salvage chemotherapy regimens in oncology appraisals) for the same reasons stated here, then this approach is considered most appropriate for the base-case analysis in this appraisal.

However, as per the ERG's request, scenarios are presented comparing DEX700 to aflibercept and ranibizumab separately, where the efficacy remains based on the MEAD sham arm for both aflibercept and ranibizumab (i.e. only costs are changed).

Table 7: Scenario results: 100% ranibizumab comparator

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£34,906	7.4815				
DEX700	£31,728	7.5853	-£3,179	0.1038	Dominant	£6,291
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

Table 8: Scenario results: 100% aflibercept comparator

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£40,922	7.4815				
DEX700	£31,728	7.5853	-£9,194	0.1038	Dominant	£12,307
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

Model structure

B3. Priority question. Please clarify why health states for patients undergoing cataract surgery and health states according to the lens status of a patient (phakic or pseudophakic) were not included in the model. The ERG is concerned that the model structure is inconsistent with the model structure accepted in TA613.

The model structure that has been utilised is consistent with the structure which was considered appropriate for decision making by the appraisal committee in TA349. The final appraisal document for TA349 notes: *"The ERG stated that the model structure appears to be consistent with the progression of the disease and reflective of patient presentation and treatment in clinical practice."* During that appraisal, which included both phakic and pseudophakic patients, there were no criticisms or concerns raised regarding the lack of health states specifically linked to cataract surgery status and little has changed to now justify such an structural change to the

model. Additionally, the model structure is also broadly consistent with other models submitted in ophthalmology and specifically DMO, including the aflibercept NICE appraisal (TA346)[12].

As a result, we saw no reason to deviate from the original approach. An added benefit of keeping a consistent approach with the previous appraisal is that we can clearly demonstrate that the differences in the results from the previous appraisal to this one are driven by changes in key parameters and assumptions, and not due to a fundamental change in the model structure, which we believe aids decision making.

Although the Iluvien appraisal (TA613)[3] did consider the phakic population, the appraisal was focussed on a narrower sub-group of patients who had both phakic eyes and symptomatic cataract at the point of treatment initiation. Therefore, given the differences in the population of interest, there was greater justification for including formal health states to capture the outcomes explicitly of those undergoing cataract surgery given all patients will have potentially been eligible for cataract extraction at baseline.

Although cataract surgery is not explicitly captured within a distinct health state, the costs associated with cataract surgery, and the impact cataract surgery has on visual acuity outcomes are captured within the transition probabilities that are estimated from the MEAD data and applied in the model. Similarly, given visual acuity outcomes of patients following cataract surgery are captured in MEAD, the outcomes for patients who have a cataract extraction and subsequently become pseudophakic are also implicitly captured in the model. Adding additional distinct health states for cataract surgery and lens status would risk adding additional complexity to a model that already includes a significant number of health states, and the additional benefit these changes would likely to be minimal.

The inclusion of additional health states would have resulted in greater uncertainty for each transition as each probability would have been informed by a smaller sample of patients. Critically, the addition of these health states would further pose challenges in attempting to incorporate the efficacy data from the UK and French RWE studies. The inclusion of these distinct health states would require an explicit relationship between visual acuity outcomes and cataract surgery/lens status to be

modelled, but there is insufficient data available from the UK or French RWE to allow for this. Therefore, we believe the current model structure provides greater flexibility to utilize these RWE data sources.

Treatment effectiveness (BCVA transition probabilities)

B4. Priority question. For all subgroups, please provide a scenario (if this does not form part of the revised base case) based on your response to question A1 (using multiple imputation instead of LOCF to account for the missing data).

As noted in the response to question A1, the multiple imputation approach is not considered to be appropriate in this instance, and therefore the data from MEAD that have been generated utilising this approach have not been included in the cost-effectiveness model.

B5. Priority question. For the two subgroups that include anti-VEGFs as the comparator (partial responders to non-corticosteroid treatment and CRT =>400 micrometers: DEX700 vs ranibizumab and DEX700 vs abilfercept) please provide scenarios where the anti-VEGFs maintain vision for the duration of treatment (that is, no movements up or down health states).

A net-zero impact on vision scenario has been provided in the company submission where it is assumed that, on average, patients in the anti-VEGF arm maintain constant vision. This scenario assumes 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%, consistent with the probability of gaining at least 10 letters from the natural history study data from Mitchell et al. (2012)[14]. We believe that this scenario is more realistic than assuming no movement up or down health states, as it is unlikely that vision would remain constant for each individual patient over time. In addition, the scenario requested by the ERG is associated with a bias against DEX700 related to severe vision loss costs. As DEX700 patients can transition between any of the health states, some patients will move into the worst health state and incur the costs associated with severe vision loss. However, if patients on the anti-VEGF arm do not transition between any of the health states, no patients can move into the worst

health state and incur these costs. In reality, even if BCVA is maintained on average over time, some anti-VEGF patients would fall into the most severe health states and others could move into the better health states at different timepoints. The scenario requested by the ERG does not take this into account and therefore biases against DEX700. To account for this, we have presented a scenario assuming no movement up or down health states within the anti-VEGF arm, but excluding severe vision loss costs in both treatment arms to avoid bias. In this scenario DEX700 remains dominant (Table 9).

Moreover, we would like to re-iterate that company base case analysis uses the MEAD sham arm as a proxy of the efficacy of continued anti-VEGF use. The availability of patient-level data from MEAD allows for a full set of transition probabilities to be estimated for the anti-VEGF treatment arm which is a key advantage over other data sources or assumptions. In addition, because the MEAD sham arm likely overestimates the efficacy of continued anti-VEGF use, the company submission base case analyses produces conservative estimates of the relative treatment effect.

Table 9: Scenario results: Anti-VEGF maintain vision (excluding severe vision loss costs)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£25,869	7.5674				
DEX700	£17,546	7.5853	-£8,323	0.0179	Dominant	£8,861
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

B6. Priority question. For the two subgroups that include watch and wait as the comparator (non-responders to non-corticosteroid treatment and partial responders to non-corticosteroid treatment with CRT <400 micrometers) please provide scenarios where vision in the watch and watch arm follows the natural history of vision in eyes with DMO.

As discussed in the response to question B2:

- The population of patients who would not achieve any level of response to non-corticosteroid treatment and who may therefore discontinue treatment following their loading dose is expected to be extremely small
  - We therefore do not believe this patient group is sufficiently large enough to justify the inclusion of watch and wait as an additional comparator in this group of patients
- The assertion that patients would discontinue treatment with anti-VEGFs if they later have a CRT of <400 contradicts the NICE guidance which stipulates a restriction to anti-VEGF use based on CRT only at the start of treatment
  - Therefore in patients that are partial responders to non-corticosteroid treatment with CRT < 400 micrometers, continued use of anti-VEGF treatment is the appropriate comparator for these patients

B7. Priority question. For all subgroups, please provide a scenario where dexamethasone treatment in years 4 and 5 maintains vision (that is, no movements up or down health states).

Scenario results have been provided assuming net-zero impact on vision for DEX700 in years 4 and 5. This scenario assumes 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%, consistent with the probability of gaining at least 10 letters from the natural history study data from Mitchell et al. (2012)[14]. We believe that this scenario is more realistic than assuming no movement up or down health states, as it is unlikely that vision would remain constant for each individual patient over time. As the net-zero impact on vision scenario assumes that patients can only move up or down one health state at each time point, a restricted set of MEAD transition probabilities should also be applied to the anti-VEGF treatment arm in year 4 and 5 to ensure a consistent approach. However, as the last transition probability matrix from the MEAD sham arm that is used for each model cycle in year 4 and 5 is already limited to movements up or down one health state it was not necessary to apply a restricted set of MEAD transition probabilities. Under this scenario, DEX700 remains dominant (Table 10).

Table 10: Scenario results: DEX700 PRN net-zero impact on vision in years 4 and 5

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£38,695	7.4815				
DEX700	£32,153	7.5061	-£6,542	0.0246	Dominant	£7,280
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

B8. Priority question. Please provide a clinical rationale as to why the mean BCVA in the dexamethasone arm is above the anti-VEGF arm during the "off-treatment period" and throughout the model time horizon.

The cost-effectiveness model applies transition probabilities estimated from MEAD for the DEX700 and sham arms to estimate the efficacy of patients who are on-treatment in each cycle, for up to the maximum treatment duration of five years. Therefore, within this five-year period, the visual acuity outcomes between the two treatment arms differ, and the mean visual acuity outcomes for patients on the DEX700 arm are superior to the anti-VEGF at the five-year mark. From five years, till the end of the modelled time horizon, the outcomes of patients on both treatments are modelled based on the same natural history data source. The source of the natural history data is Mitchell et al. (2012)[14] which used data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy adjusted to account for the improvement in diabetes mellitus 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%.

Therefore, any treatment effect is only being captured for the time during which patients are actively receiving treatment, so no off-treatment benefit is assumed. However, because treatment with DEX700 results in superior mean BCVA outcomes by the end of the treatment period, patients on the DEX700 arm begin the off-treatment period with better visual acuity outcomes and therefore, given the same natural history transition probabilities are applied to both arms, those relative improvements in vision achieved by the end of the treatment period are maintained during the off-treatment period.

The approach adopted is consistent with both the approach that was accepted in previous appraisal (TA349), but also the approach adopted in other NICE appraisals in ophthalmology (for example the appraisal of aflibercept, TA346[12]). Feedback received from UK clinical experts has highlighted that the long-term treatment effect for both treatment arms is uncertain, but they confirmed that this approach was reasonable in the absence of data to inform these outcomes. Clinicians also highlighted that patients who achieve a good response to treatment have a good chance of maintaining the effects of treatment for a pro-longed period of time after completing their course of therapy, and patients with a higher baseline are more likely to achieve and maintain an optimal outcome. As a result, there is no indication that the difference in visual acuity outcomes between the two arms would converge over time and given the potential for DEX700 to result in a strong treatment response in patients who are currently insufficiently responsive to anti-VEGFs, the difference in outcomes even has the potential to become greater over time.

RWE

B9. Priority question. Scenarios including RWE data (Tables 26, 27 and 57 of the company submission) are based on the proportion of patients experiencing improvement or worsening in vision from baseline to 12, 24 and 36 months; each of these estimates have been used in separate scenario analyses. Please clarify if the proportion of patients experiencing improvement or worsening in vision between these timepoints (from 12 to 24 months and from 24 to 36 months) could be estimated so that different 3-monthly transition probabilities can be applied in years 1, 2 and 3. If this is possible, please provide this analysis.

We would like to confirm that our preferred base case uses unrestricted MEAD transition probability matrices for both DEX700 and continued use of anti-VEGFs (represented by the sham arm), and that the scenarios provided using RWE were intended to provide supportive evidence to validate the clinical data presented in the base case.

We agree with the ERG that estimating the proportion of patients experiencing improvement or worsening of vision between time-points would be the preferred

approach to applying the data from the UK RWE audit and the French RWE, however, based on the data that were made available to us from these studies, which were based on the change from baseline to different time-points, it was not possible to back-calculate the required probabilities.

In response to your question, we have been able to obtain the data required to perform the requested analysis for the UK RWE audit, these data are provided in Table 11. A scenario analysis is presented in Table 12 using the 3-month probabilities in year 1, 2 and 3 from the UK RWE audit to estimate the efficacy of anti-VEGFs, and using the restricted set of transition probabilities from MEAD (whereby patients can only move up or down one health state at each time point) for DEX700. As can be expected, the incremental NMB is between that obtained using the baseline to Month 24 and baseline to Month 36 probabilities as presented in Table 57 of Document B.

Table 11 >=10-letter improvement/worsening over time UK RWE

Criteria	Proportion of patients			3-month probability		
	Baseline to Month 12	Month 12 to Month 24	Month 24 to Month 36	Baseline to Month 12	Month 12 to Month 24	Month 24 to Month 36
>=10-letter improving	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=10-letter worsening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 12 Scenario analysis results; Anti-VEGF efficacy based on UK RWE using >=10-letter improvement/worsening over time

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£37,628	7.3577				
DEX700	£27,756	7.5855	-£9,872	0.2278	Dominant	£16,706
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

It has not been possible for us to obtain the same data for the French RWE study, and therefore we are unable to present additional scenario analyses using these data.

B10. Priority question. For the two subgroups that include anti-VEGFs as the comparator (partial responders to non-corticosteroid treatment and CRT =>400 micrometers: DEX700 vs ranibizumab and DEX700 vs aflibercept) please provide scenarios using RWE data and considering ranibizumab and aflibercept separately:

a) **Please provide naive comparisons using the phakic cohort from the French RWE for dexamethasone with the suboptimal responder cohort from the UK RWE for ranibizumab and aflibercept (please note that RWE comparisons are disabled in 'Inp_Efficacy'J74).**

   Please provide results ensuring treatment-specific data in the model is taken from the French RWE for dexamethasone and the UK RWE for ranibizumab and aflibercept, when available. Baseline characteristics can be taken from the UK RWE audit.

As highlighted in the company submission, a naïve comparison of the French and UK RWE data on DEX700 and anti-VEGFs respectively highlight the potential for DEX700 to result in significantly improved outcomes relative to anti-VEGFs in those who are insufficiently responsive to non-corticosteroid treatment. However, given the MEAD trials provided patient-level, head-to-head RCT evidence in a large sample of patients, this data was considered more relevant for the base-case comparison than a naive comparison of different RWE datasets, despite the fact that the data from MEAD result in an conservative estimate of the treatment effect .

We have provided the requested naïve comparison using the phakic cohort from the French RWE for DEX700 and the UK RWE for anti-VEGF in Table 13, Table 14 and Table 15 below, using data for proportion of patients experiencing improvement or worsening of vision from baseline to month 12, month 24 and month 36 respectively. Key baseline characteristics of the mean age ([redacted] years) and proportion males ([redacted]%) are taken from the UK RWE audit.[8] The baseline distribution of vision across the modelled visual acuity states was not available from the UK RWE and is therefore taken from the DEX700 treatment arm of the pooled MEAD clinical studies as per the company base case. Using the baseline distributions from MEAD is consistent with the approach taken for the final base case analysis in TA349 in which

these data were chosen to reflect the patients that were actually treated with DEX700 in the MEAD trials. The same distribution is applied to all treatments, therefore we assume that the dexamethasone patients are representative of a general phakic DMO population.

These scenarios consider the basket of anti-VEGFs as the comparator, and use data for the full anti-VEGF population of the UK RWE audit, consistent with the scenario analyses presented in the company submission. Per our response to question B2, there is clinical consensus that ranibizumab and aflibercept can be considered to be equivalent in terms of their efficacy, supported by the DRCR.net study PROTOCOL T.[13] This approach is also consistent with that accepted in TA613 where the comparator was a basket of treatments. Consistent with the RWE scenarios presented in the company submission, these scenarios significantly improve the incremental costs, QALYs and NMB in favour of DEX700.

Table 13: Scenario results: French RWE vs UK RWE (baseline to 12 months probabilities)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£36,380	6.7806				
DEX700	£21,150	7.3695	-£15,230	0.5889	Dominant	£32,898
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

Table 14: Scenario results: French RWE vs UK RWE (baseline to 24 months probabilities)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£33,369	6.8969				
DEX700	£21,231	7.2958	-£12,138	0.3989	Dominant	£24,103
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

Table 15: Scenario results: French RWE vs UK RWE (baseline to 36 months probabilities)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£32,440	6.9375				
DEX700	£20,202	7.3635	-£12,238	0.4260	Dominant	£25,019

Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.

b) Please provide a scenario based on your response to question A5 (indirect comparison of dexamethasone from the French RWE and ranibizumab from the UK RWE).

Per our response to question A5, it has not been feasible for us to conduct indirect comparison using the RWE studies.

c) Please provide a scenario based on your response to question A6 (indirect comparison of dexamethasone from the French RWE and aflibercept from the UK RWE).

Per our response to question A6, it has not been feasible for us to conduct indirect comparison using the RWE studies.

d) In the company submission (Tables 26, 27 and 57), changes in vision from baseline to 12, 24 and 36 months are considered separately in scenario analysis. If alternative timepoints are chosen to inform parts A, B and C, please explain why. Please consider your response to question B9 when choosing which timepoints to model and present.

As per our response to question B9, it has not been possible for us to obtain data to calculate 3-months probabilities in year 1, 2 and 3 for the French RWE study. To ensure a consistent approach, we have provided the requested naïve comparison in part A using data on the proportion of patients experiencing >=10-letter improvement or worsening from baseline to month 12, month 24 and month 36 respectively for both the French RWE for DEX700 and the UK RWE for anti-VEGF. All three

timepoints are assessed in separate scenarios to ensure that there is consistency in the results regardless of the timepoint used.

Per our response to question B9, we would like to confirm that our preferred base case uses unrestricted MEAD transition probability matrices for both DEX700 and continued use of anti-VEGFs (represented by the sham arm), and that the scenarios provided using RWE were intended to provide supportive evidence to validate the clinical data presented in the base case.

Adverse events

B11. Priority question. For the two subgroups that include anti-VEGFs as the comparator (partial responders to non-corticosteroid treatment and CRT =>400 micrometers: DEX700 vs ranibizumab and DEX700 vs aflibercept), please provide scenarios (if this does not form part of the revised base case) using the cataract extraction rates and other adverse event rates in the sham arm of MEAD to inform the rates in anti-VEGF-treated patients.

In the company submission we took the rates of cataract extraction from the UK RWE audit as we believe this is the most appropriate data to use given that it represents the observed rate of cataract extractions in patients receiving anti-VEGFs despite initial insufficient response in UK clinical practice in recent years. Given that patients in the sham arm of MEAD did not receive active treatment, we believe the rate of cataract extraction observed in the sham arm of MEAD will underestimate the true rate of cataracts in patients receiving anti-VEGFs as clinical advice indicates that even the act of receiving repeat injections can increase the rate of cataract development and therefore extraction. In the RISE and RIDE study on ranibizumab in DMO for example, it appears that the risk of cataracts for ranibizumab could be as high as 42% after only 2 years when looking at all types of cataracts reported in the trial.[15] In the company submission the rates of other adverse events for anti-VEGF were taken from RISE/RIDE, based on the data presented in TA613.[3, 15]

We have provided the requested scenario, using data from the MEAD sham arm for all adverse event rates for anti-VEGF in Table 16, where the comparator is a basket of ranibizumab or aflibercept (labelled anti-VEGF) per our original base case and response to question B2. Given the points noted above we believe that our base

case assumption remains most appropriate, however this scenario does not have a large impact on the incremental costs, QALYs or NMB and DEX700 remains dominant.

Table 16: Scenario results: Anti-VEGF cataract surgery and AE rates as per MEAD sham arm

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£37,829	7.4815				
DEX700	£31,728	7.5853	-£6,101	0.1038	Dominant	£9,214
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

B12. Priority question. Clinical experts advised the ERG that steroids increase the risk of cataracts. Please provide a clinical rationale as to why the cataract extraction rates in the UK RWE audit are substantially higher than the rates obtained from the Blue Mountains study (1). Also clarify why the source used to inform the model depends on whether a patient is on or off anti-VEGF treatment.

The feedback the ERG have received on the potential for steroids to increase the risk of cataract is consistent with the clinical feedback received prior to the submission and the data used in the model, which assumes a higher risk for patients receiving DEX700 compared to those receiving anti-VEGFs. However, feedback from UK clinical experts also indicates that all patients with DMO with a phakic lens will eventually develop a cataract at some stage and therefore there is no reason for the cataract rates to differ between treatments in the long-term, but differences may be observed with regards to the timing of cataract development instead.[15] Therefore, the company base-case approach, which involves attributing greater cataract surgery costs to the DEX700 arm is considered to be a conservative approach, as the total undiscounted cataract related costs are likely to be equal between the arms over a lifetime horizon.

The rates of cataract extraction observed in the UK RWE are higher than those from the Blue Mountain study, and this difference is driven by a number of factors. Firstly,

both clinical feedback and clinical data indicate the potential for anti-VEGFs to increase the risk of cataract development. Although DEX700 will lead to a greater rate of cataract development, and therefore surgery relative to anti-VEGFs, there is still the expectation that patients receiving anti-VEGFs will experience a higher risk relative to those who are not receiving any treatment. In the RISE and RIDE study on ranibizumab in DMO for example, it appears that the risk of cataracts for ranibizumab could be as high as 42% after only 2 years when looking at all types of cataracts reported in the trial.[15]

Secondly, feedback from UK clinical experts has highlighted that the Blue Mountain study is not an appropriate proxy for the cataract extraction rate in UK clinical practice. This is because the Blue Mountain study, which is not a UK-based study, considers a broader and less clinically severe population compared to the UK RWE. Further, the data were published in 2008 and assessed patients from as early as 1997. Therefore, this study does not capture the evolution in clinical practice over time including advanced patient management. UK clinical experts have highlighted that they are now far more proactive in extracting cataracts as soon as they develop than they were historically. Given the age of the Blue Mountain study, no patients will have received treatment with anti-VEGFs which limits its potential to represent an appropriate proxy for cataract extraction rates on the anti-VEGF arm. The UK RWE audit provides current data for cataract extraction rates in the relevant population of interest, for patients receiving anti-VEGFs in UK clinical practice, and is therefore considered to provide the most relevant source of data to estimate the rate of cataract extraction for the anti-VEGF comparator arm.

a) **Please use the cumulative incidence of cataract extractions from the UK RWE audit over 48 months (including months 0-12) to calculate the probability of cataract extraction per year in phakic eyes (assuming that the risk is constant over time using the exponential cumulative distribution function, as per the methods applied to the Blue Mountains study). For all subgroups, please provide scenarios which apply these rates to patients on anti-VEGF treatment, on watch and wait, and**

patients who discontinue treatment (including those who discontinue dexamethasone).

The risk of cataract derived from the Blue Mountains study and used in the economic model to represent natural history of cataract extraction was a constant risk over time based on the exponential cumulative distribution function because the study reported a 10-year cumulative incidence and data were not available by year. It is our belief that where data are available by year that it is most appropriate to use these data, hence the approach taken using data by year from the UK RWE audit for anti-VEGF and from MEAD for DEX700.

Table 17 presents a scenario in which a constant cataract extraction rate per year for patients receiving anti-VEGFs and patients who have discontinued treatment on either arm is based on the exponential cumulative distribution function, using the cumulative data from month 0 to month 48 in the UK RWE audit. In this scenario, to ensure consistency in methods between the anti-VEGF arm and the DEX700 arm, we have also used the same method to adjust the cataract extraction rate for DEX700 from MEAD to be a constant risk over time, using the cumulative data from month 0 to month 36 in MEAD and the exponential cumulative distribution function. This does not have a large impact on the incremental costs, QALYs or NMB and DEX700 remains dominant.

Table 17: Scenario results: Anti-VEGF and discontinued patients cataract surgery rates as per UK RWE using exponential cumulative distribution function

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£38,502	7.4815				
DEX700	£31,793	7.5853	-£6,710	0.1038	Dominant	£9,822
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

b) For all subgroups, please provide scenarios where cataract extraction rates in the Blue Mountains study (2.32% per year in phakic eyes) are applied to patients on anti-VEGF treatment, on watch and wait, and

patients who discontinue treatment (including those who discontinue dexamethasone).

In the company submitted base case, the cataract extraction rate from the Blue Mountains study is applied to patients who have discontinued treatment on either arm. As previously discussed, the UK RWE study provides current data for cataract extraction rates in the relevant population of interest, for patients receiving anti-VEGFs in UK clinical practice, and is therefore considered to provide the most relevant source of data to estimate the rate of cataract extraction for the anti-VEGF comparator arm. Table 18 presents the requested scenario whereby the cataract extraction rate from the Blue Mountains Study is applied to patients receiving anti-VEGFs and to patients who have discontinued treatment on either arm. This does not have a large impact on the incremental costs, QALYs or NMB and DEX700 remains dominant.

Table 18: Scenario results: Anti-VEGF and discontinued patients cataract surgery rates as per Blue Mountains study

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£38,257	7.4815				
DEX700	£31,728	7.5853	-£6,530	0.1038	Dominant	£9,642

Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.

B13. When the UK RWE audit is used to inform annual cataract extraction probabilities in patients treated with anti-VEGFs, please provide a scenario using data from month 0-12, 12–24, 24–36 and 36–48 to inform years 1, 2, 3 and 4, respectively.

Table 19 presents a scenario using data from month 0-12, 12-24, 24-36 and 36-48 to inform the cataract extraction rate for anti-VEGFs in years 1, 2, 3 and 4. The cataract extraction rates for DEX700 are as per the submitted base case. This scenario does not have a large impact on the incremental costs, QALYs or NMB and DEX700 remains dominant.

Table 19: Scenario results: Anti-VEGF cataract surgery rates from UK RWE (including 0-12 months)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£38,570	7.4815				
DEX700	£31,728	7.5853	-£6,842	0.1038	Dominant	£9,955

Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.

B14. Please clarify why cataract extractions are not modelled according to a patient's visual acuity, as per TA613 (Table B3.13 in the company submission for TA613).

As noted in response to question B3, the modelling approach that has been adopted is consistent with the previous appraisal (TA349), and all feedback that was received by the ERG and appraisal committee for that appraisal has been captured in the model. Therefore, given the existing approach used to capture the cataract extraction rate in the analysis was considered appropriate, there was considered to be little additional benefit gained by deviating from this approach. Additionally, although a formal link between cataract extraction and visual acuity is not captured in the model, the visual acuity outcomes of patients in the MEAD trial who underwent cataract surgery are captured within the transition probabilities applied in the model, and therefore are accounted for. It was considered that the inclusion of additional health states to explicitly capture the link between cataract extractions and visual acuity would add additional complexity without providing a clear and significant benefit.

The cataract extraction rate for the anti-VEGF arm was calculated from the UK RWE audit given this was considered to be the most appropriate source that was most reflective of UK clinical practice. However, the UK RWE audit did not provide the level of data required to estimate a formal relationship between visual acuity levels and cataract extraction.

In theory, a formal relationship between visual acuity and cataract extraction rates could be established using the MEAD data. However, a key driver of cataract

extraction rates is the treatment that patients receive, but using the MEAD data does not allow for the impact that anti-VEGFs have on cataract extraction rates to be captured given this was not a treatment option that patients received in MEAD. Therefore, it was considered more appropriate to use data from MEAD for DEX700, and data from the UK RWE audit for anti-VEGFs to estimate the cataract extraction rate and the impact that this has on costs.

Discontinuation

B15. Priority question. For the two subgroups that include anti-VEGFs as the comparator (partial responders to non-corticosteroid treatment and CRT =>400 micrometers: DEX700 vs ranibizumab and DEX700 vs aflibercept), please provide scenarios (if this does not form part of the revised base case) using data from the sham arm of MEAD to inform the proportion of patients who discontinue anti-VEGF treatment due to an adverse event and other non-efficacy-related reasons or a lack (or loss) of efficacy of treatment.

UK clinicians have indicated that patients are kept on anti-VEGF treatment as long as possible, with the aim to improve vision and/or to prevent further (irreversible) damage due to the build-up of oedema that disrupts the retinal architecture causing photoreceptor loss.[5]

The company submission therefore assumes, in line with TA613, that patients do not discontinue during the anti-VEGF treatment period and the model does not explicitly include treatment discontinuation in the anti-VEGF treatment arm. However, although the company submission does not explicitly capture treatment discontinuation, it does capture it indirectly in the way the average number of anti-VEGF injections is calculated. This is because the average number of ranibizumab or aflibercept injections from UK RWE represent the average number of injections amongst patients who have received at least 1 injection. For example, Document B Table 38 shows that among those who had at least one aflibercept injection in the 24-36 months time period, the average number of injections was [redacted] but only [redacted]% of those who where receiving anti-VEGF treatment at the start of the study had at least one injection. This means that [redacted]% either had a gap between doses which was

longer than a year or had discontinued treatment. Applying an additional discontinuation rate from the MEAD sham arm to inform the proportion of patients who discontinue anti-VEGF treatment could therefore result in double counting discontinuation in the anti-VEGF arm.

In addition, UK clinicians have indicated that it is not appropriate to assume that discontinuation data from a placebo arm of an RCT is an appropriate proxy for anti-VEGF discontinuation in insufficient responders in UK clinical practice. We therefore think that on balance it is more appropriate to indirectly capture discontinuation in the anti-VEGF treatment arm from the UK RWE than applying discontinuation rates from the sham arm in MEAD.

Nevertheless, Table 20 presents the scenario results using data from the MEAD sham arm to inform the proportion of patients who discontinue anti-VEGF treatment due to an adverse event and other non-efficacy related reasons or a lack (or loss) of efficacy of treatment. DEX700 remains dominant in this scenario.

Table 20: Scenario results: Anti-VEGF discontinuation as per MEAD sham arm

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£33,684	7.5019				
DEX700	£31,728	7.5853	-£1,956	0.0834	Dominant	£4,459
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

B16. Priority question. For all subgroups, please provide a scenario using a 3-year treatment duration for dexamethasone and the comparator.

The results of the requested scenario analysis are presented in Table 21.

As noted in Section B.3.2.2.1, a maximum treatment duration of 5 years was considered the most appropriate approach for the base-case analysis. This assumption was based on feedback provided by UK clinical experts which noted that 5 years was sufficiently long enough to capture key differences in treatment costs. The clinicians noted that although there will be a proportion who remain on treatment

beyond 5 years, this group will be likely be small for both those receiving DEX700 or anti-VEGFs. This is supported by data from MEAD and the French RWE study, which demonstrate that a proportion of patients were still receiving DEX700 at the end of the 3-year follow-up period.[16, 17] Similarly, this assumption is supported for anti-VEGFs by the UK RWE audit and other published studies such as the RESTORE trial, which demonstrate that a sizeable proportion of patients were still receiving frequent anti-VEGFs after 3–4 years.[8, 18] Although a longer duration may be justified, capping the treatment duration at 5 years is only likely to underestimate the cost-savings of DEX700 given the higher long-term injection frequency for anti-VEGF patients.[19]

Additional feedback from UK clinical experts has highlighted that the duration of treatment, and the number of injections patients receive, is largely driven by the level of treatment response that is achieved. Patients who experience a strong level of response to treatment in most cases only require a small number of injections over a short duration of time, but those with a sub-optimal response are often treated more intensively in an attempt to improve the level of response to treatment, and to prevent the decline in visual acuity. Therefore, if patients who are insufficiently responsive to anti-VEGFs, are switched to DEX700, and therefore have the opportunity to receive a new effective treatment, then has the potential to reduce the number of injections required and therefore the overall burden of treatment.

Table 21: Scenario results: 3 year treatment duration

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£33,222	7.4647				
DEX700	£30,975	7.4884	-£2,247	0.0237	Dominant	£2,957
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

B17. Priority question. For all subgroups, please provide a scenario where there is no maximum treatment duration for dexamethasone or the comparator

(patients only discontinue treatment due to an adverse event and other non-efficacy-related reasons or a lack (or loss) of efficacy of treatment).

As noted in response to question B16, capping the treatment duration at 5 years was both an assumption that was consistent with UK clinical feedback, but also a pragmatic assumption based on the availability of data. MEAD provides 3 years of data, while the UK RWE audit provides 4 years and, although clinicians have been able to inform assumptions for the number of injections patients will receive at slightly later timepoints, there was considered to be too much uncertainty in expanding these predictions out beyond year 5.

Although clinical feedback has highlighted that an extremely small proportion of patients may still receive treatment beyond year 5, we have no data or feedback to make informed assumptions in order to sensibly model the requested scenario. As noted in response to question B16, clinicians have stated that the treatment duration is linked to the level of response patients achieve, and therefore given the potential for DEX700 to increase the proportion of patients achieving a treatment response, the comparative duration of treatment required is expected to be lower. Therefore, any capping of treatment duration is expected to disproportionately lower the treatment costs on the comparator arm, meaning this approach is likely to result in conservative estimates of the potential cost-savings of DEX700.

Given the aforementioned limitations, and the practical considerations relating to such a significant structural change to the model, it was not practical to provide this scenario without risk of introducing error.

B18. Priority question. For the two subgroups that include anti-VEGFs as the comparator (partial responders to non-corticosteroid treatment and CRT =>400 micrometers: DEX700 vs ranibizumab and DEX700 vs aflibercept), please provide two scenarios where patients receive anti-VEGF treatment when they

discontinue dexamethasone due to an adverse event and other non-efficacy-related reasons or a lack (or loss) of efficacy of treatment.

a) **Please provide a scenario assuming anti-VEGF treatment is given for 1 year and vision follows the natural history of vision in eyes with DMO during and after this 1-year period.**

Table 22 presents the scenario where patients receive 1 year of anti-VEGF treatment after discontinuing DEX700. The average cost of 1 year of anti-VEGF treatment (£3,538.69) is applied as an one-off cost to patients who discontinue DEX700 PRN due to an adverse event or other non-efficacy related reason or due to lack (or loss) of efficacy of treatment. This average one-off cost consists of drug acquisition and drug administration costs based on the ranibizumab and aflibercept market shares and number of injections in year 1 as observed UK RWE (as per company base case). The adverse events costs associated with subsequent anti-VEGF treatment are not taken into account for simplicity, which is in line with the ERG's advice in part c). Monitoring costs associated with subsequent anti-VEGF treatment are also not taken into account. This is a reasonable simplification as off treatment monitoring costs are already taken into account for patients who have discontinued. The model already assumes that vision follows the DMO natural history for patients who have discontinued treatment in both treatment arms. Therefore, no changes were made to the efficacy in the DEX700 PRN treatment arm for this scenario. DEX700 PRN remains dominant in this scenario.

Table 22: Scenario results: 1 year next line anti-VEGF after DEX700 PRN

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£38,695	7.4815				
DEX700	£33,435	7.5853	-£5,260	0.1038	Dominant	£8,373
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

b) **Please provide a scenario assuming anti-VEGF treatment is given for 5 years and vision is maintained during this 5-year period, followed by the natural history of vision in eyes with DMO.**

UK clinicians consulted subsequent to feedback from the ERG have indicated that very few patients will receive anti-VEGF treatment upon discontinuing DEX700 and that these patients will only receive anti-VEGF treatment for a short period of time because this treatment is unlikely to be effective in this population. In addition, it is not feasible within the current model structure to assume that vision is maintained for 5 years upon treatment discontinuation followed by DMO natural history without making significant structural changes to the model. Therefore, based on the clinical feedback and the practically of programming, we have presented the scenario requested in part a) but not the scenario requested in part b).

c) **Subsequent anti-VEGF treatment in these scenarios can be costed using the market share (ranibizumab [redacted] and aflibercept [redacted]) and number of injections observed in the UK RWE audit (as per the original base case). The adverse events associated with subsequent anti-VEGF treatment do not need to be modelled in these exploratory scenarios. The ERG will accept these simplifications as anti-VEGF treatments are being modelled as subsequent treatments rather than comparators.**

No answer needed. Please see part a) and b).

Health-related quality of life

B19. Priority question. Please provide a scenario using the utility values accepted in TA613, these can be found in Table B3.22 of the company submission for TA613. To estimate utility values for health state 6, please average the utility estimates over the 86-100 and 76-85 ETDRS utility estimates. To estimate utility values for health state 1, please average over the 26-35 and 0-25 ETDRS utility estimates.

Consistent with the original TA349 submission, the utility values from Czoski-Murray et al.[20] are used in the base case analysis. Given the limitations with the utility values from MEAD, the appraisal the committee for TA349 accepted the ERG-preferred

published utility values from Czoski-Murray et al.[20], which have a wider range than those derived from the MEAD studies and have been preferred by the committee in other technology appraisals in DMO.[21]

Given the differences in the model structure utilised for this appraisal, and the model presented in TA613, significant methodological challenges arise when attempting to apply the utility values sourced TA613 in a scenario analysis. Firstly, the utility values from TA613 have been estimated based on eight groupings of BCVA scores, whereas the model structure presented in this appraisal includes six BCVA health states. This means that to incorporate these data within the model, some of the utility estimates from TA613 need to be averaged to reduce the total number of values and force these estimates into the cost-effectiveness model.

More critically, the utility values reported in TA613 represent the average utility per patient, given different possible combinations of BCVA scores in the BSE and WSE. In contrast, the utility values applied in the base-case analysis from Czoski-Murray et al.[20] represent utility estimates by eye. In contrast, the model structure utilised for this appraisal, which was previously deemed appropriate and highly relevant for decision making by the ERG and appraisal committee in TA349, does not allow for the estimation of the proportion of patients who fall into each possible combination of BCVA grouping across both the best and worse seeing eye, rather it estimates the distribution of vision in each of the BSE and WSE across the health states for a cohort of patients. Given this, the utility values from TA613 cannot simply be included in the submitted model without adjustment. Any adjustment that is made to force these utility estimates to fit within the existing model structure requires major simplifying assumptions and is thus subject to significant limitations. Using the TA613 utilities is therefore not considered to be appropriate in this instance, and these utility values have not been included in the cost-effectiveness model.

B20. Priority question. The ERG has several concerns with the implementation of utility values using Czoski-Murray *et al.* 2009 (2):

a) **Please explain why the utility values in health states 5 and 6 for the BSE exceed 1 ('Inp_Utility'T42:U42), these lack face validity**
b) **Please provide a clinical rationale as to why the BSE has a higher utility than the WSE in health state 1 (blindness) (utility values of 0.57 and 0.17, respectively), these also lack face validity**
c) **The ERG has identified a discrepancy between the BSE and WSE utility values applied in the model ('Inp_Utility'P42:U43) with the utility calculations in the Appendix (Table 55 of Appendix P). Please provide a scenario (if this does not form part of the revised base case) using the values outlined in the Appendix (also given in 'Inp_Utility'K42:M47 of the model). Do not apply any further adjustments (such as 3/13 or 10/13) to these values.**

Part a) and b):

The utility weights reported for health states 5 and 6 for the BSE exceed 1 so that when averaged with the WSE utility weights they give the utility value for the whole person as per the values reported by Czoski-Murray *et al*. 2009.[20] The values reported should not be considered as utility values in their own right, more as the contribution of each of the BSE and WSE to the overall utility.

The BSE utility weights are higher than the WSE values (including in health state 1) due to the weighting of 10/13 given to the BSE as preferred by the committee in previous appraisals and as implemented by the ERG during TA349.[22] The ERG noted that in previous appraisals it was accepted that treating the WSE had 30% of the HRQL impact for the same change in vision from treating the BSE. In their critique of the company submission in TA349, the ERG implemented the utility data from Czoski-Murray et al. 2009[20] in their exploratory analyses (C13 and C14). The approach taken by the ERG was then adopted in the committee preferred base case, and has been brought forward into this appraisal without amendment.[23]

To apply the utility data reported by Czoski-Murray *et al*. 2009[20] separately to each eye, the ERG in TA349 assumed that the WSE and BSE contributed 3/13 and 10/13

to the overall utility (based on the assumption that treating the WSE had 30% of the impact of the BSE as preferred in previous appraisals). The calculations in the submitted model are fully aligned with the calculations implemented by the ERG during TA349, and are as follows:

Utility in BSE in Health State n = (10/13)*(Czoski-Murray utility in Health State n)*2

Utility in WSE in Health State n = (3/13)*(Czoski-Murray utility in Health State n)*2

The resulting utilities are then used to generate the cohort utility based on the distribution of BSE and WSE across the vision-related health states. For all patients the BSE and the WSE each contributes 50% of the whole vision. Therefore, if we take a simple example of a single patient with both the BSE and WSE falling into health state 6, the utility contribution of each eye would be:

Utility in BSE in Health State 6 = (10/13)*0.804*2 = 1.2369

Utility in WSE in Health State 6 = (3/13)*0.804*2 = 0.3711

Then the whole person utility would be:

(Utility in BSE)*0.5 + (Utility in WSE)*0.5 = 1.2369*0.5 + 0.3711*0.5 = 0.804

This is aligned with the utility reported by Czoski-Murray *et al*. 2009 for health state 6, as expected.

In our model, given that we model the distribution of the BSE and WSE across all health states for a cohort of patients, this scales up to the following:

(Utility in BSE across health states)*(Distribution of BSE across health states)

+

(Utility in WSE across health states)*(Distribution of WSE across health states)

Where the distribution of BSE and WSE across all of the health states each sums to 0.5 in cycle 1, and then remains equal in both eyes whilst decreasing over time due to mortality (see calculations in columns AOJ to APA of the ‘Markov_Calcs’ sheet).

Part c)

The utility values in 'Inp_Utility'P42:U43 are applied in the model as noted. As described above, this method of application was implemented first by the ERG in TA349, and was the preferred method adopted by the committee in the final base case analysis.

The utility values presented in Table 55 of Appendix P (shown below in Table 23) do not align with this approach, and were erroneously included in this appendix. The utility values in Table 23 were used by the company in additional analyses submitted following receipt of the ACD in TA349 as an alternative application of the utilities reported by Czoski-Murray *et al*. 2009[20]. This approach generated WSE utilities assuming that the same change in vision from the 86-100 ETDRS letters state in the WSE would result in 30% of the incremental change in utility as reported in the BSE, and anchoring on the health state with the best vision. The ERG however heavily criticized this implementation, stating that this application was flawed as it resulted in the WSE contributing a higher utility value than the BSE.[24] The ERG concluded that the approach they used (and as has been implemented in our submitted model) to be more appropriate, and as noted above, this approach was taken forward to the final base case preferred by the TA349 appraisal committee. Given that the approach to considering the Czoski-Murray *et al*. 2009[20] utilities per Table 23 was previously considered inappropriate, we do not believe it is appropriate to consider this approach to inform the final base case for this appraisal and hence have not included a scenario using these values.

Table 23: Czoski-Murray *et al*. 2009[20] utilities (Table 55 of Appendix P)

ETDRS letters	Health state in model	BSE utilities reported by Czoski-Murray *et al*. (2009)†	BSE utilities applied in the model	WSE utilities calculated assuming 30% of the change in the BSE	WSE utilities applied in the model
86–100		0.8500		0.8500	
76–85	Health State 6	0.7580	0.8040[a]	0.8224	0.8362[a]
66–75	Health State 5	0.6850	0.6850	0.8005	0.8005
56–65	Health State 4	0.6110	0.6110	0.7783	0.7783
46–55	Health State 3	0.5370	0.5370	0.7561	0.7561
36–45	Health State 2	0.4640	0.4640	0.7342	0.7342
26–35	Health State 1	0.3900	0.3715[a]	0.7120	0.7065[a]
0–25		0.3530		0.7009	

Key: BSE, better-seeing eye; ETDRS, Early Treatment Diabetic Retinopathy Study Research Group; WSE, worse-seeing eye.
Notes: [a]Average of two health states.

B21. Please provide a scenario analysis where adverse event related disutility and duration estimates used in TA613 (details may be found on pages 165 and 166 of the committee papers document and table B3.23) are applied using adverse event occurrence data from MEAD.

The model structure utilised for this appraisal does not take adverse event related disutilities into account. As indicated in the company submission, it is expected that the AEs associated with treatment for DMO have little effect on HRQL due to their nature. In addition, the detrimental effect of cataracts is already expected to be captured implicitly within the BCVA outcomes of the clinical trials. In TA349, the committee accepted that any disutility associated with the cataract extraction procedure is experienced for a very short period and was therefore not considered in the model.

It is not feasible to incorporate the adverse event disutilities formally within the model without making significant structural changes. As a pragmatic solution we have calculated one-off QALY decrements based on the proportion of the population having an adverse event over 5 years (see Table 24) multiplied with the disutility estimate for each adverse event from TA613 (see Table 25) and assuming that each

utility decrement last for a duration of 3 months. The one-off QALY decrement (-0.0018 versus -0.0008 for DEX700 PRN and anti-VEGF or laser, respectively) will over-estimate the true decrement as these calculations do not account for discounting and mortality.

This scenario considers the adverse event and cataract surgery rates from MEAD for DEX700 PRN. Cataract surgery rates for the anti-VEGF or laser treatment arm are taken from the UK RWE audit as we believe these are the most appropriate data to use given that it represents the observed rate of cataract extractions in patients receiving anti-VEGFs despite initial insufficient response in UK clinical practice in recent years. Adverse event rates for the anti-VEGF or laser treatment arm are taken from the NICE TA613 ERG report (using data from RISE and RIDE trials) as per the company submission base case, which is considered a more appropriate proxy for anti-VEGF adverse events in UK clinical practice than using adverse event data from the sham arm of an RCT.

The results of the scenario including the one-off QALY decrements are presented in Table 26. This scenario does not have a large impact on the incremental costs, QALYs or NMB and DEX700 remains dominant.

Table 24: Proportion of patients experiencing each adverse event

	DEX700 PRN					Anti-VEGF or laser				
	Y1	**Y2**	**Y3**	**Y4**	**Y5**	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
Raised IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.6%	8.6%	7.9%	7.9%	7.9%
Retinal detachment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.2%	0.2%	0.2%	0.2%	0.2%
Endophthalmitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.4%	0.4%	0.4%	0.4%	0.4%
Vitreous haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.4%	0.4%	0.4%	0.4%	0.4%
Cataract surgery*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: *Calculated as % phakic patients with cataract extraction multiplied by % phakic

Notes: DEX700 PRN adverse event and cataract surgery rates from MEAD DEX700 PRN arm; anti-VEGF or laser cataract surgery rate from UK RWE; anti-VEGF or laser adverse event rates from NICE TA613 ERG report.

Table 25: Disutility due to adverse events and cataract surgery

Adverse event	Disutility
Raised IOP	0
Retinal detachment	-0.13
Endophthalmitis	0
Vitreous haemorrhage	-0.02
Cataract surgery	-0.0034
Key: IOP, intraocular pressure **Reference:** Committee papers NICE TA613[3]	

Table 26: Scenario results: Include QALY decrement due to adverse events

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£38,695	7.4807				
DEX700	£31,728	7.5835	-£6,968	0.1028	Dominant	£10,050
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

B22. Please provide a scenario analysis where the multiplicative approach described in Ara *et al.* 2010 (3) is used to age-adjust the utility values for each health state in line with the overall age-related decline in quality of life experienced by the general population.

The requested scenario is provided in Table 27. This does not have a large impact on incremental costs, QALYs or NMB and DEX700 remains dominant.

Table 27: Scenario results: Ara et al. 2010 age adjustment of utility values

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£38,695	7.1282				
DEX700	£31,728	7.2265	-£6,968	0.0983	Dominant	£9,916
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

Resource use

B23. Please provide a scenario where the mean number of dexamethasone injections in years 4 and 5 matches the mean number of injections in year 3.

Table 28 presents a scenario where the mean number of DEX700 injections in years 4 and 5 is equal to the number in year 3. This does not have a large impact on incremental costs, QALYs or NMB and DEX700 remains dominant.

Table 28: Scenario results: Equal number of DEX700 PRN injections in Year 3, 4 and 5

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£38,695	7.4815				
DEX700	£32,243	7.5853	-£6,452	0.1038	Dominant	£9,565
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

B24. The ERG's clinical experts agreed that the majority of patients bilaterally treated with anti-VEGF therapies would have both eyes treated on the same day to reduce the number of appointments. One expert estimated that administration in both eyes would occur in a single appointment on 75% of occasions (the reverse of the assumption made for dexamethasone).

a) Please provide a scenario analysis applying this assumption (that is, 1.25 appointments per bilateral administration).

The ERG's clinical experts have provided a conflicting opinion to the clinical advice the company received during the development of the submission which indicated that bilateral administration would occur on 50% of occasions, however we recognise that this is uncertain. Subsequent to the ERG feedback, the company sought further clinical opinion which has indicated similar to the ERG feedback, however it is challenging to draw conclusive findings and the approach does appear to be dependent on the hospital and the patient.[6] Further, the clinical advice received following the ERG feedback indicated that the assumption used for DEX700 in the

company submission (an average of 1.75 appointments) may also be over-estimated.

Table 29 presents the results of a scenario analysis assuming 1.25 appointments per bilateral administration of anti-VEGFs, with assumptions for DEX700 remaining as per the submitted base case. This scenario does not have a large impact on the incremental costs, QALYs or NMB and DEX700 remains dominant.

Table 29: Scenario results: 1.25 number of appointments needed for anti-VEGF bilateral injection

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£38,470	7.4815				
DEX700	£31,728	7.5853	-£6,742	0.1038	Dominant	£9,855
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

B25. The ERG's clinical experts disagreed with some of the resource use assumptions in Tables 49-52 of the company submission. The experts agreed that fluorescein angiography was rarely used in clinical practice. One expert estimated that this would be done in a minority of patients, once every 5 years. The ERG's clinical experts also indicated that intraocular pressure checks would be performed at each visit (monitoring and administration).

a) **Please provide a scenario analysis where the annual number of intraocular pressure checks equals the sum of the annual monitoring and administration visits for each treatment. Please also set the annual number of fluorescein angiograms to zero.**

Within the submitted model, the cost of a monitoring visit is assumed to include an intraocular pressure check as standard, therefore for this scenario we have assumed an additional cost of £101.95[25] for an IOP check is applied at each treatment administration visit for both DEX700 and anti-VEGFs.

Table 30 provides the results of the requested scenario, assuming no fluorescein angiograms and assuming an intraocular pressure check applies at all visits (monitoring and administration). This scenario does not have a large impact on the incremental costs, QALYs or NMB and DEX700 remains dominant.

Table 30: Scenario results: IOP checks added to administration visits; no fluorescein angiograms

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER incr. (£/QALY)	Incr. NMB (WTP threshold of £30,000 per QALY)
Anti-VEGFs	£39,246	7.4815				
DEX700	£31,247	7.5853	-£7,999	0.1038	Dominant	£11,112
Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years.						

Section C: Textual clarification and additional points

C1. Priority question. Please clarify if data from cycle 12 of MEAD (months 36-39) has been used to inform any model inputs, and explain why this was considered appropriate for some inputs and not others.

The MEAD study was originally designed as a 36-month trial. Patients were assessed for retreatment every 3 months starting from month 6 to month 33. The final treatment was to occur at month 33. However, an amendment to the trial design was made in May 2010 which allowed an additional treatment at month 36 and an additional visit (month 39/exit) was added to accommodate the new treatment addition and associated procedures. Thus some patients would have had their final treatment at month 33 whereas others were eligible for an additional treatment at month 36. Patients were considered exited from the study upon completion of month 36 or 39 or upon early study discontinuation.

Re-treatment data including month 36 have been used as this provides us with useful information about the proportion of patients who were eligible for re-treatment at month 36 and who received a re-treatment. Treatment discontinuation data including month 36 and month 39 have been used as this provides additional useful information that is not dependent on whether patients had a re-treatment at month

36. Transition probability matrices from months 36-39 are not used in the model, as these are dependent on whether patients received a re-treatment at month 36 and event numbers in this cycle were particularly small (39 versus 28 patients observed in the DEX700 versus sham arm, respectively). Adverse event inputs were available per whole year and therefore do not include month 36-39 data.

C2. Please clarify why the following data were taken from the dexamethasone 700 µg arm of the pooled MEAD trials, and not from the dexamethasone 700 and sham arms of the pooled MEAD trials:

a) The proportions of patients within the cohort who have unilateral DMO in the BSE or the WSE, or bilateral DMO at baseline (company submission, Table 22);
b) The proportion of patients within the cohort who develop FEI.

The approach taken, to use data from the DEX700 µg arm of the pooled MEAD trials, was selected for consistency with the approach taken for the final base case analysis in TA349 in which these data were chosen to reflect the patients that were actually treated with DEX700 in the MEAD trials. The same distribution is applied to all treatments, therefore we assume that the dexamethasone patients are representative of a general phakic DMO population. We are conscious that the company were requested to provide data for the DEX700 and sham arms of the pooled MEAD trials in TA349 clarification questions, however as the ERG did not request these be incorporated into the modelling, we chose to remain consistent with the previous base case.

For completeness, the data for DEX700, sham and the pooled DEX700 and sham arms for the proportions of patients with unilateral DMO in the BSE or the WSE, or bilateral DMO at baseline, and who develop FEI are presented in Table 31.

The baseline proportions of patients treated bilaterally, and unilaterally in the BSE or WSE are very similar between the arms and therefore this choice is unlikely to have affected the results of the analysis. Of note, the question refers to Table 22 of the company submission which presents the distribution of vision across the health states by eye status (unilateral or bilateral BSE and WSE), and not the data that are referred to in the question. These data were also based on the DEX700 arm in the

company submission. Further details regarding these parameters are provided in response to question C3 below.

The proportion of patients with unilateral DMO at baseline and who develop FEI during the study is slightly more varied but still remains reasonably consistent between the arms. The data used in the submitted model for FEI were the data for DEX700 in the full mITT population of MEAD for consistency with TA349. We have therefore provided the FEI data for both the phakic only mITT population and the full mITT population of MEAD by treatment arm in Table 31 for completeness. Table 32 shows the resulting annual probabilities if alternative FEI values are used, and the resulting incremental net monetary benefit (at a willingness to pay of £30,000 per QALY gained), and demonstrates that changing the value of this parameter does not impact the results of the analysis. We therefore do not intend to update our base case assumption for FEI.

Table 31: Requested data by treatment arm in the pooled MEAD trials

Parameter	DEX700	Sham	Pooled DEX700 and sham
Proportion treated bilaterally at baseline	[redacted]	[redacted]	[redacted]
Proportion treated in their BSE at baseline[1]	[redacted]	[redacted]	[redacted]
Proportion treated in their WSE at baseline[1]	[redacted]	[redacted]	[redacted]
Proportion of patients who develop FEI[2] (full mITT population of MEAD)	[redacted]	[redacted]	[redacted]
Proportion of patients who develop FEI[2] (phakic only mITT population)	[redacted]	[redacted]	[redacted]

[1]Used to represent the proportion of unilateral patients treated in the BSE or WSE.
[2]Proportion of those who were unilateral at baseline

Table 32: Alternative probabilities of fellow eye involvement

Input source	Annual probability	Incremental net monetary benefit at WTP = £30,000 per QALY gained
Full mITT; DEX700 arm ([redacted]%): Base case[a]	[redacted]%	£10,080
Full mITT; pooled DEX700 and sham arms ([redacted]%)	[redacted]%	£10,087
Phakic mITT; DEX700 arm ([redacted]%)	[redacted]%	£10,074
Phakic mITT; pooled DEX700 and sham arms ([redacted]%)	[redacted]%	£10,082

Key: QALY, quality-adjusted life year; WTP, willingness to pay.
Notes: [a]As per TA349.

C3. Please clarify if the baseline distribution of BSE and WSE in bilateral DMO was taken from respective DMO eyes in unilateral DMO or from the sub-group of patients with bilateral DMO (company submission, Table 22).

a) Please provide the baseline distribution of BSE and WSE in bilateral DMO from the sub-group of patients with bilateral DMO if this is not the case.

The data for baseline distribution of BSE and WSE across the health states in the company submitted model were as described in Table 33. All data were taken from the DEX700 arm, and were taken from study eyes for treated eyes, and non-study eyes for untreated eyes. This approach is consistent with the data used and accepted in TA349 and has been retained in our base case. The corresponding distributions are provided in

Table 34. For comparison, we provide the same data, but for the sham arm, and for the pooled DEX700 and sham arms in Table 35 and Table 36.

Table 33: Summary of data used to describe baseline distribution of vision by eye in the company submitted model (phakic only mITT population)

DMO status	Eye	Data used
Unilateral DMO in the BSE	BSE (treated)	Study eyes that were BSE; DEX700 arm
	WSE (untreated)	Non-study eyes that were WSE; DEX700 arm
Unilateral DMO in the WSE	WSE (treated)	Study eyes that were WSE; DEX700 arm
	BSE (untreated)	Non-study eyes that were BSE; DEX700 arm
Bilateral DMO	BSE (treated)	Study eyes that were BSE; DEX700 arm
	WSE (treated)	Study eyes that were WSE; DEX700 arm
Key: BSE, better seeing eye; DMO, diabetic macular oedema; WSE, worse seeing eye		

Table 34: Baseline distribution of vision across visual acuity states; phakic only DEX700 patients (as per Table 22 of document B)

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[a]	[redacted]					
	WSE[b]						
Unilateral DMO in the WSE	WSE[c]						
	BSE[d]						
Bilateral DMO	BSE[a]						
	WSE[c]						

Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.
Notes: [a] Based on data for study eyes which were the BSE. [b] Based on data for non-study eyes which were the WSE. [c] Based on data for study eyes which were the WSE. [d] Based on data for non-study eyes which were the BSE.
References: MEAD (2021)[2]

Table 35: Baseline distribution of vision across visual acuity states; phakic only sham 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[a]	[redacted]					
	WSE[b]						
Unilateral DMO in the WSE	WSE[c]						
	BSE[d]						
Bilateral DMO	BSE[a]						
	WSE[c]						
Key: BCVA, Best-corrected visual acuity; BSE, better-seeing eye; DMO, diabetic macular oedema; WSE, worse-seeing eye.							

Notes: [a] Based on data for study eyes which were the BSE. [b] Based on data for non-study eyes which were the WSE. [c] Based on data for study eyes which were the WSE. [d] Based on data for non-study eyes which were the BSE.
References: MEAD (2022)[11]

Table 36: Baseline distribution of vision across visual acuity states; phakic only pooled DEX700 and sham 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[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE[c]	[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: [a] Based on data for study eyes which were the BSE. [b] Based on data for non-study eyes which were the WSE. [c] Based on data for study eyes which were the WSE. [d] Based on data for non-study eyes which were the BSE.
References: MEAD (2022)[11]

The use of study eyes to represent all treated eyes and non-study eyes to represent all non-treated eyes was selected to maximise the sample size for each of the treated and untreated BSE and WSE. To further cut the data by whether a patient is unilateral or bilateral would lead to reduced sample sizes for each relevant category of patients, for whom we then want to estimate the distribution of vision across the 6 vision-related health states. As the submitted data are aligned with the data accepted as appropriate in TA349, we believe that it is appropriate to retain this approach in order to maximise the available sample size. Due to the high volume of additional data requests, and as this is not a priority question, we have been unable to provide the requested additional tables by the requested deadline. If the ERG would still like to see these data, we will be able to follow-up with these by 24 February 2022.

C4. Please clarify if the UK RWE data in Table 26 of the company submission includes suboptimal responders or all types of responders.

Table 26 of the company submission includes suboptimal responders.

C5. Please provide the page, table or figure numbers in the UK RWE audit used to inform the values in Table 26 of the company submission.

The values in Table 26 of the company submission were taken from statistical outputs provided to us by the RWE vendor and that were used to inform the UK RWE audit report. We have provided the table used to inform Table 26 in the references to this response.[26]

C6. The visual acuity outcomes in the UK RWE audit are based on the best-recorded visual acuity (BRVA) measure. Please explain how this measure compares to the BCVA measure used in MEAD and the BCVA measure used in the French RWE audit.

BCVA is best corrected vision acuity which is the vision allowing the patient to wear corrective eyewear (glasses or lenses). BCVA is a measure more commonly used in clinical trials than in clinical practice.

BRVA is best recorded visual acuity, which is the most stringent measure that can be obtained in the clinic. This will be one of: best corrected visual acuity (aided), unaided visual acuity or pinhole recorded visual acuity (i.e. patients may or may not have used corrective eyewear for this measure). Therefore, BRVA gives the best vision taking out refractive error.

BCVA could therefore result in a higher score than BRVA, however both use the same letter scales and so when considering improvements or worsening in vision as measured by gains or losses of letters (which is the relevant outcome when considering the incremental efficacy of treatments), the two measures can be considered comparable.

C7. Please clarify which analysis population the baseline characteristics in Table 8 of the company submission correspond to, e.g. ITT population.

Table 8 of the company submission corresponds to the phakic-only mITT population.

References

(1) Tan JS, Wang JJ and Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. *Ophthalmic Epidemiol*. 2008; 15(5):317-27.
(2) Czoski-Murray C, Carlton J, Brazier J, et al. Valuing condition-specific health states using simulation contact lenses. Value Health. 2009; 12(5):793-9.
(3) Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010; 13: 509-18.

References used in answers

1. Allergan. Clinical summary report: Allergan Study 206207-010/011. 2021.
2. AbbVie. MEAD Post-Hoc Analysis: Tables for Phakic Inputs (model) (Data on file). 24 May 2021.
3. National Institute for Health and Care Excellence. Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy. 2019. (Updated: 20 November 2019) Available at: https://www.nice.org.uk/guidance/ta613/resources/fluocinolone-acetonide-intravitreal-implant-for-treating-chronic-diabetic-macular-oedema-in-phakic-eyes-after-an-inadequate-response-to-previous-therapy-pdf-82608955110853.
4. AbbVie. Virtual Advisory Board for Ozurdex® in Phakic Patients with Diabetic Macular Oedema – Report. 1 March 2021.
5. Shah SU and Maturi RK. Therapeutic Options in Refractory Diabetic Macular Oedema. *Drugs*. 2017; 77(5):481-92.
6. AbbVie. Allergan Ozurdex HTA Digital Advisory Board Interim Report. 15 February 2022.
7. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica*. 2017; 237(4):185-222.
8. AbbVie. Long-term Follow Up of anti-VEGF use in Phakic Patients with Diabetic Macular Oedema: Real World Outcomes (Data on file). 2021.
9. Kodjikian L, Bellocq D, Bandello F, et al. First-line treatment algorithm and guidelines in center-involving diabetic macular edema. *Eur J Ophthalmol*. 2019; 29(6):573-84.
10. Kodjikian L, Bellocq D and Mathis T. Pharmacological Management of Diabetic Macular Edema in Real-Life Observational Studies. *BioMed Research International*. 2018; 2018:8289253.
11. AbbVie. MEAD ERG Questions Analyses. 16 February 2022.
12. National Institute for Health and Care Excellence. Aflibercept for treating diabetic macular oedema. 2015. (Updated: 22 July 2015) Available at: https://www.nice.org.uk/guidance/ta346/resources/aflibercept-for-treating-diabetic-macular-oedema-pdf-82602611201221.
13. Cai S and Bressler NM. Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: recent clinically relevant findings from DRCR.net Protocol T. *Curr Opin Ophthalmol*. 2017; 28(6):636-43.

14. Mitchell P, Annemans L, Gallagher M, et al. Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial. *Br J Ophthalmol*. 2012; 96(5):688-93.
15. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012; 119(4):789-801.
16. AbbVie. MEAD Studies: Demographics and Baseline Characteristics of Phakic Patients. 19 May 2021.
17. AbbVie. French RWD. Real World Study in Diabetic Macular Oedema Treated with Dexamethasone Implant: phakic vs pseudophakic (Data on file). 2021.
18. Schmidt-Erfurth U, Lang GE, Holz FG, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology*. 2014; 121(5):1045-53.
19. Allergan. A 3-Year, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema (MEAD-011). (Clinical Study Report) 2012.
20. Czoski-Murray C, Carlton J, Brazier J, et al. Valuing condition-specific health states using simulation contact lenses. *Value Health*. 2009; 12(5):793-9.
21. National Institute for Health and Care Excellence. Dexamethasone intravitreal implant for treating diabetic macular oedematreating diabetic macular oedema (final appraisal determination). 2015. Available at: https://www.nice.org.uk/guidance/ta349/resources/macular-oedema-diabetic-dexamethasone-intravitreal-implant-final-appraisal-determination-document2.
22. BMJ Technology Assessment Group. Dexamethasone intravitreal implant for diabetic macular oedema: A Single Technology Appraisal. 2014. (Updated: 20 February 2015) Available at: https://www.nice.org.uk/guidance/ta349/documents/macular-oedema-diabetic-dexamethasone-intravitreal-implant-committee-papers-part-2. Accessed: 29 September 2019.
23. National Institute for Health and Care Excellence. Dexamethasone intravitreal implant for treating diabetic macular oedema (final appraisal determination). 2015. Available at: https://www.nice.org.uk/guidance/ta349/resources/macular-oedema-diabetic-dexamethasone-intravitreal-implant-final-appraisal-determination-document2. Accessed: 11 October.
24. BMJ Technology Assessment Group. ERG's critique of the Company's additional evidence submitted at the Appraisal Consultation stage - Addendum to ERG Report. 2015. (Updated: 2 June 2015) Available at: https://www.nice.org.uk/guidance/ta349/documents/macular-oedema-diabetic-dexamethasone-intravitreal-implant-committee-papers. Accessed: 29 September 2021.
25. National Health Service. 2019/20 National Cost Collection data. 2021. Available at: https://www.england.nhs.uk/national-cost-collection/. Accessed: 1 July 2021.
26. AbbVie. Long-term Follow Up of anti-VEGF use in Phakic Patients with Diabetic Macular Oedema: Real World Outcomes: Functional Categorical Outcomes (Data on file). 2021.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Macular Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Macular Society is the leading national charity fighting to end sight loss caused by macular disease. Every day over 300 people in the UK face the shock of a diagnosis of macular disease. This sight loss can rob people of their independence, leaving them unable to drive, read or recognise their family. Our members tell us what a profoundly isolating condition it is. People with macular disease are seven times more likely to feel distressed or depressed. We help people adapt to life with sight loss, regain their confidence and independence and take back control of their lives. We are one of the few sight loss charities that actively fund and support medical research into macular disease. With the exception of the details in the answer to 4b, all our income is fundraised from legacies, grants, donations from individuals and fundraising activities such as our lottery, raffle, appeals and community and challenge events. We have 15,000 members who we communicate with on a regular basis, an e-newsletter that is sent monthly to 40,000 people, 370,000 website visitors a year and our Advice & Information (A&I) Service responds to over 16,000 queries a year.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12	Alimera (fluocinolone acetonide intravitreal implant) - NA Bayer (aflibercept) - £8,100 (contribution to support activities around information, support and education) Genus Pharmaceuticals (bevacizumab) - NA Novartis Pharmaceuticals (ranibizumab) - NA Organon Pharma (bevacizumab) - NA

months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Pfizer (bevacizumab) - NA Roche (bevacizumab) - £30,000 (contribution to support activities around information, support and education) Sanofi (aflibercept) - NA Zentiva (bevacizumab) - NA
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**DMO patient survey** We carried out a survey and published a report highlighting patient experience of DMO in June 2021. A total of 41 patients with DMO were surveyed about their experiences and their perceptions of the management and support they have received for their diabetes and DMO. This work aimed to understand how the information and support for diabetes compares to that for DMO. **Wet AMD survey** A survey was conducted by the Macular Society in early 2020 to understand the burden that frequent anti-VEGF injections and ophthalmology appointments has on wet AMD patients and their carers or family. A total of 449 responses were received from across the UK. A full report was published August 2020. **Service users**

	Users of the charities services, such as our Befriending service and Advice and Information service are surveyed every other year. The last survey was completed in April 2020 and had 300 respondents. We also survey our volunteers every other year, most of our volunteers are also affected by macular disease. **Local peer support groups** Our Regional Managers who manage our network of over 400 local groups across the UK feedback regularly. They are our 'frontline', having face to face (or phone to phone) interaction every day with people affected by macular disease. We gather case studies which record the experiences of individuals living with macular disease and the impact on their families and carers. We use our social media channels to interact with people with macular disease and provide information and advice. It is also an important way for people to find others with the same condition where they have a rare form of macular disease and to share experiences.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Diabetic macular oedema (DMO) is a complication of diabetes that can lead to irreversible sight loss. It is a build-up of fluid in the macula due to leaky blood vessels damaged by high blood sugar due to diabetes. It is one of the most common causes of sight loss in the working age group. There are currently around 300,000 people living with the condition in the UK. However, the effects of DMO are still not well known, with recent research from Australia showing only a quarter (26 per cent) of people aged 50-70 are aware of DMO. Less is known about the levels of understanding in the UK. Several treatments are available for DMO. Earlier treatment usually means better outcomes for the patient, including maintaining better sight or stable sight for longer. To address early diagnosis and referral for timely treatment, the UK has set up the Diabetic Eye Screening Programme, where those who have been diagnosed with diabetes aged 12 and over are invited to get an eye screen every year. This

	programme has been very successful in getting patients diagnosed earlier and referring patients to treatment if needed. The lack of information for those newly diagnosed with DMO can lead to higher levels of anxiety, as patients aren't sure of what their diagnosis means for their future. This anxiety can be worsened when patients aren't aware of the support available to help them. Diabetes management is vital for maintaining a healthy life and reducing the risk of developing or accelerating complications such as DMO. However, tasks needed to help manage diabetes, such as reading blood glucose levels and injecting insulin, can become much more difficult after losing central vision. Nearly three-quarters of responders to our survey said they felt anxious about their DMO and the sight loss it might cause, compared to only one person who said they rarely felt anxious. No responders said they never felt anxious about their DMO and possible sight loss **"It makes me worry what my future may look like. I also would love children and I worry about the impact this would have on my eyes loss."** **"Straight lines look wavy and blurry. It feels very scary and I'm frightened of losing more of my vision in both eyes."** Loss of central vision through DMO can be very frustrating and can greatly affect everyday life as well as financial impact due to changes in employment and able to drive. Vision loss can make daily tasks more difficult, including tasks needed to monitor and manage diabetes. This can risk further vision loss as poor management of diabetes is a risk factor for DMO progression. This highlights the need for more support and guidance for those newly diagnosed with DMO. Some people with DMO experience visual hallucinations called Charles Bonnet syndrome which adds another level of impact on health and mental well being.

	In addition to living with and managing sight loss patients still need to manage their diabetes and the other morbidities and complications related to this. **Family and carers** There is a significant burden on family and carers supporting a patient with DMO. A patient with DMO needs to adapt and change to the emotional and practical impacts of the condition and will often rely on family and carers to provide additional support. **"Very difficult to carry out my office work for the small business that I run and also driving issues."** **"Travel to clinic is difficult my daughter has to take time off work for me."** **"Unable to get anyone to take me. I live alone and I am 82 years old."** It can be hard attending appointments, as people with diabetes have to attend multiple check-ups for their condition and other complications. Difficulties might include taking time off work or arranging friends or family to take them to these clinics.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**Treatments** Two-thirds of responders (65 per cent) were receiving anti-VEGF injections to treat their DMO. Another 7.5 per cent (those who responded "other") had stable DMO and were under observation, receiving injections when needed. One in ten (10 per cent) were receiving steroid injection as treatment and one in eight (12.5 per cent) had laser treatment. One responder was not receiving any treatment due to their sight loss being 'too bad to treat'. Anti-vascular endothelial growth factor (anti-VEGF) injections are the first line of treatment for DMO, and involve injecting these drugs into the eye at repeated intervals. These drugs work to stop the growth and leaking of blood vessels which leads to the damage and vision loss

	seen in DMO. Some patients do not respond well to these anti-VEGF drugs, or respond better to steroid injections. However, currently there are more restrictions on the use of steroids for DMO due to the increased risk of developing cataracts after steroid use in the eye. Almost four in five participants (78 per cent) feel anxious at least sometimes about their DMO treatment. Often this anxiety is due to having injections, which can be painful. Planning their life around injections can also be stressful, including taking time off work or finding someone to take them to the clinic. **“Regular trips to the hospital for check-ups, having to arrange holidays etc around treatment. Painful treatment.”** The remaining 22 per cent do not feel anxious about their treatment, and see injections as a positive step to maintaining their vision. **“Only positively. It has given me reassurance that my sight is being preserved as well as it can be for as long as possible.”** **Care** There is significant pressure on NHS eye care services. Patients regularly feedback personal experiences of cancelled appointments, frustration over communication with clinics, and many hours spent waiting around in clinic. Injections are not available in local health care settings, meaning many patients travel a good distance to attend injection clinics and need a driver to accompany them. There is also a challenge between the management of diabetes and eye condition. Around one in five (22 per cent) responded that they feel like they weren’t managing their eye health well, compared to only one in 20 (5 per cent) who felt they weren’t managing their diabetes well.

	Overall responders felt less able to manage their eye health and DMO compared to their diabetes. This lack of control may be a reason why responders felt anxious about their eye condition and the sight loss it can cause. It is important that patients feel that they are able to manage their condition and have all the necessary information and support. **"I think it's hard to manage how unpredictable sugar levels can be. Also to calculate the amount of insulin and correction doses are required takes a lot of hard work and concentration."** **"[It can be hard] keeping it [blood sugar] under control some difficulty reading syringes."** **"Fear of the unknown is difficult with my eye condition. I have been given great care once it was discovered DMO but there did not appear to be anybody on hand to explain things properly or talk from experience."** **"Just struggling with understanding it all re HBA1C time in target blood pressure exercise etc."** More than two in five responders (42.5 per cent) were not given any information about managing their DMO, while only a quarter (24 per cent) were not given any information about managing their diabetes. The importance of managing diabetes is well established, with poor blood sugar management being a major risk factor for developing complications such as diabetic macular oedema. Better management of diabetes through lifestyle changes and monitoring blood sugar levels help maintain good vision. **"I was told blood sugar too high and to bring it down quickly. I did bring it down within three months from 116 to 58. Shortly after this I started a range of treatments for retinopathy and DMO."** Only one in four (25 per cent) of those who took the survey felt they were given all the information about DMO that they needed when they were diagnosed. On the other hand, a similar proportion (28 per cent) were given no information at all. It can be difficult for patients to receive a diagnosis of DMO and learn that they could lose their vision. Understanding more about the condition and what treatments are available can be reassuring, and help patients feel more in control of the situation.

8. Is there an unmet need for patients with this condition?	There is no current cure for the condition and treatments can only manage and stabilise the sight loss. There is a need for longer acting treatments to reduce the time between treatment and injections. Nearly 75% of DMO patients are phakic, and are currently treated with anti-VEGF or laser therapy. Around 40% of patients on anti-VEGF treatment do not respond well and there is no improvement in their DMO. Those who are phakic currently have no alternative treatment option, compared to those who are pseudophakic who can be switched to dexamethasone. Phakic patients continue to be treated with anti-VEGF injections because there is a tendency is to carry on regardless, in the hope of maintaining vision. However this does have a continued impact and risk for the patient. So to have dexamethasone available for phakic patients who do not respond well to anti-VEGF would bring treatment options into line and relieve the treatment burden.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Real world evidence shows that the Dexamethasone intravitreal implant gives comparable outcomes for phakic and pseudophakic patients. <u>References</u> Guigou S, Pommier S, Meyer F, et al. Efficacy and Safety of Intravitreal Dexamethasone Implant in Patients with Diabetic Macular Edema. Ophthalmologica. 2015; 233(3-4):169-75. Malclès A, Dot C, Voirin N, et al. Real-life Study in Diabetic Macular Edema Treated with Dexamethasone Implant: The Reldex Study. RETINA. 2017; 37(4).

	Mello Filho P, Andrade G, Maia A, et al. Effectiveness and Safety of Intravitreal Dexamethasone Implant (Ozurdex) in Patients with Diabetic Macular Edema: A Real-World Experience. Ophthalmologica. 2019; 241(1):9-16. Singer MA, Dugel PU, Fine HF, et al. Real-World Assessment of Dexamethasone Intravitreal Implant in DME: Findings of the Prospective, Multicenter REINFORCE Study. Ophthalmic Surg Lasers Imaging Retina. 2018; 49(6):425-35 Patients will welcome an alternative treatment in the situation where they are continuing with anti-VEGF with no alternatives. Patients will also welcome the need for fewer injections compared to the current anti-VEGF drugs, due to the potential for longer intervals between injections with Dexamethasone intravitreal implant. Each appointment where there may be an injection can cause anxiety. In our survey of patients with wet AMD, 31% of patients reported always feeling anxious about injection appointments and 24% reported that they were sometimes anxious. When asked to say which of 4 statements on appointments was most important to them, 39% said that 'Keeping the same level of vision with fewer injections' was most important. Some people also experience pain and discomfort following eye injections and a very small minority can suffer serious complications, such as an infection. Fewer eye clinic appointments will mean less disruption to day to day life, particularly where patients need to be accompanied to appointments by family or friends, who may need to take time off work. There will also be less cost to the patient of attending the eye clinic, such as taxi or bus fares and parking fees. In our survey 62% of patients said that they are driven to hospital by family or friends and 28% take public transport.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage is that it will be an intravitreal injection which will need to be given regularly, sometimes for years. Appointments at an eye clinic, with all the attendant difficulties of travelling, needing someone to accompany them, costs of transport and hours at the hospital, will still be required, if at a reduced rate. Intravitreal injections carry a very small but serious risk of sight loss due to complications, such as endophthalmitis. There is an increased risk factor for cataracts (diabetes and having injections in the eye are also risk factors) Some patients can also experience significant pain for a short time afterwards due to corneal abrasion or drying of the cornea, which can be alleviated with lubricating gel.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who already struggle to attend all their eye clinic appointments, for the reasons given above, will benefit if they have to attend less often. Many patients also suffer from other health conditions associated with diabetes and advancing age, which can leave them unable to maintain their treatment regime. For some just leaving home can be extremely difficult. Only patients who are well enough, have the right transport means and the ability to make arrangements to attend can benefit.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes, age and disability are issues that need to be considered. As the drugs currently available are not a cure and do not work effectively in everyone, a proportion of patients will still experience significant sight loss such that they will be registered as sight impaired or severely sight impaired. There are also specific groups that may need to be taken into consideration: Pregnancy is a major risk factor for the progression of retinopathy and DMO and is associated with increased prevalence and severity of retinopathy compared to non-pregnant diabetic women. Women with type I diabetes are particularly vulnerable to ocular changes during pregnancy. People with learning disabilities - Type 1 and Type 2 diabetes are more common in people with learning disabilities, this group is likely to have more difficulty managing their diabetes. Reports suggest they are 10 times more likely to experience serious sight loss than other people in the general population. There are possible barriers that may affect those with learning disabilities such as a general lack of awareness of the importance of eye screening, problems understanding and processing instructions, fear that the procedures will hurt, memory of previous poor experiences and needing to interact with strangers. Ethnicity is considered a complex risk factor of diabetes. Type 2 diabetes is estimated to be three to four times more common in people of Asian and African–Caribbean origin compared to white Europeans. A UK study found that minority ethnic groups (both South Asians and African/Afro-Caribbeans) had increased odds of having retinopathy compared to their white counterparts. People from lower socio-economic backgrounds tend to have worse DMO outcomes. There is also wider evidence that outcomes are worse in white males who are socio-economically deprived.

Other issues	
13. Are there any other issues that you would like the committee to consider?	In line with the previous guidance for Dexamethasone intravitreal implant for treating diabetic macular oedema – this group of people are at a disadvantage and this real world evidence suggests that there is no longer a need to exclude them from treatment.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The numbers of people with DMO is increasing and over burdening hospital eye clinics
- The treatment burden on patients and carers is significant and longer acting drugs can alleviate the problem.
- Any measures that reduce the need or frequency of travelling to eye clinics for an invasive, distressing and sometimes painful treatment is a step in the right direction.
- Phakic patients with a natural lens who do not respond to anti-VEGF now have the opportunity for effective treatment
- The COVID-19 pandemic has significantly reduced eye clinic capacity due to the infection control measures now required. Any measures that might help to alleviate the pressure on eye clinics, such as longer acting drugs, are therefore even more important.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Professional organisation submission

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.
You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.
To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	1. [redacted] 2. [redacted]
2. Name of organisation	The Royal College of Ophthalmologists
3. Job title or position	1 [redacted] 2. [redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The RCOphth is the professional body for ophthalmologists in the UK. It sets standards and assures the excellence in the science and practice of ophthalmology, achieved by working with national health system organisations in both primary and secondary care, and in collaboration with the UK NHS and government.

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes. • The new RCOphth National Ophthalmology Database Age-Related Macular Degeneration (AMD) Audit is currently funded by the Macular Society, Novartis, Roche and Bayer. • AMD Audit Roche £65,000; AMD Audit Bayer £65,000; and ST1 web-based animated education resource £4,000; AMD Audit Novartis £130,000 https://www.nodaudit.org.uk/news • The RCOphth National Cataract Audit is currently has received funding from Alcon (£90,520) and Bausch + Lomb (£10,000). • Sponsorship for the RCOphth Annual Congress May 2021: Novartis £7950; Bayer £750; Thea £9750; Alcon £6200. • We also work with Bausch and Lomb to equip our surgical skills training centre
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment with dexamethasone implant is to reduce the macular oedema and stop progression of visual loss in DMO. NICE TA 349 recommends dexamethasone intravitreal implants as an option for treating DMO that is insufficiently responsive to available therapies in pseudophakic eyes because progression of cataracts and subsequent surgery was deemed 'not cost-effective', despite its clinical effectiveness. The aim of treatment in this particular indication in DMO eyes that are not pseudophakic (i.e. phakic eyes) (for this TA), but insufficiently responsive to or unsuitable for non-steroid therapies.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response in DMO is the maintenance of vision (visual acuity [VA]) change +/- 5 letters and achieving resolution or reduction of macular oedema, Amoaku et al, 2020. Full response will result in complete resolution of DMO and/or VA gain of >5 letters. Partial response is considered as (VA change of <5 letter gain and/or >20% reduction in central retina thickness). A poor or 'non-response' to treatment is defined as VA loss of 5 letters and/or <20% reduction in central retina thickness.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a significant unmet need for the treatment of DMO in phakic eyes, especially in eyes: i) unsuitable for anti-VEGF – i.e. 1st line. This is a rare occurrence and is anticipated in only those who are contraindicated (e.g. recent cardiovascular event, pregnant women), or they do not satisfy the requirements for treatment with ranibizumab (NICE TA 274), or aflibercept (NICE TA 346); ii) patients who

	do not like frequent intravitreal injections; iii) insufficiently responsive to anti-VEGF – i.e. 2nd/3rd line; this is more common than those unsuitable. It is anticipated that patients will normally be started on ranibizumab or aflibercept. Approximately 25% these patients are poor responders (Protocol I, VIVID/VISTA 100 weeks). If a poor response is demonstrated (<5 letter gain and/or <20% reduction in central retina thickness) then they will be switched to the other anti-VEGF, if deemed appropriate by the treating consultant ophthalmologist. If they continue to show a poor response to the second anti-VEGF then dexamethasone implant will be considered. A recent systematic review reported a variable adherence to intravitreal injection schedules in DMO patients receiving anti-VEGF therapies. (Rose MA et al. Adherence of patients with DMO to intravitreal injections: A systematic review. Clin Exp Ophthalmol 2020;48(9):1286-1298. Some situations are highlighted below: • Eyes demonstrating Insufficient or sub-optimal response to NICE recommended IVT anti-VEGF treatments (Ranibizumab or Aflibercept). • Eyes / Patients – unsuitable for first-line anti-VEGF treatments such as in pregnancy, in patients with recent ATEs (Arterial thrombo-embolic events such as ischaemic heart disease and cerebrovascular events) or not meeting the treatment recommendations as specified by NICE TA 246 Ranibizumab and TA 346 Aflibercept.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Laser photocoagulation- laser is still recommended in eyes with non-centre involving leakage. However, where laser photocoagulation is considered detrimental or not beneficial (leakage too close to the fovea, centre involving, or too diffuse), alternative therapies are indicated. Ranibizumab as per NICE TA 274, and aflibercept (NICE TA 346), are recommended by NICE specifically to treating DMO but excludes eyes with foveal thickness <400 microns on OCT, whilst Fluocinolone implant (NICE TA 301) is recommended in eyes with DMO that are pseudophakic, and where ranibizumab or aflibercept are not indicated, or after other therapies have failed, or are not indicated. There is no reference to chronicity in this guidance. The treatment regimens for the anti-VEGF agents are: i) ranibizumab, 3 monthly initiating doses followed by a PRN/Treat & Extend regime; ii) aflibercept, 5 monthly initiating doses followed by 2 monthly

	treatments. In year 2 onwards this treatment interval can be extended. Ranibizumab and aflibercept are the only agents recommended for the treatment of phakic patients with centre-involving DMO. However, anti-VEGF drugs are not the best treatment option in some patients e.g. pregnant women, recent cardiovascular events, or where patient does not like frequent injections, or cannot attend at monthly intervals (as required with anti-VEGF therapies) resulting in suboptimal treatment. Furthermore, it is known that some eyes with DMO do not respond completely to treatment with anti-VEGFs especially in cases of chronic DMO (Amoaku et al, 2015, 2020). In summary: • DMO phakic eyes with CRT < 400 microns or non-CI DMO – the current treatment options are observation or laser. • DMO Pseudophakic eyes insufficiently responsive or unsuitable for current first-line anti-VEGF agents may be offered DEX implant or Fluocinolone Iluvien implant as per NICE recommendations.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The RCOphth DMO Guidelines (2012) currency has been updated by the UK Consensus document. (Amoaku WM et al. Diabetic retinopathy and DMO pathways and management: UK Consensus Working Group. Eye 34, 1–51 (2020). https://doi.org/10.1038/s41433-020-0961-6* Eye (2020) 34:1–51 and Corrigendum https://doi.org/10.1038/s41433-020-1087-6. Other guidelines exist elsewhere, e.g. EURETINA: Schmidt-Erfurth U et al. Guidelines for the management of DME. Ophthalmologica 2017; 237:185–222. Figueira J et al. Guidelines for the management of center-involving DME. Clin Ophthalmol 2021;15:3221-3230.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The clinical pathway is well defined. Only a modification of usage of the technology (already in use) is being evaluated in this TA. Some clinicians are, however, less willing to use intravitreal corticosteroid injections because of the perceived adverse event profile, especially as it is not currently recommended by NICE. Furthermore, local funding requests are considered cumbersome and/or over-burdening for some clinicians.
• What impact would the technology have on the current pathway of care?	The technology will allow the inclusion of dexamethasone implant as a treatment option in eyes insufficiently responsive to non-corticosteroid therapies in DMO. E.g. Offering alternative treatment option in Phakic DMO eyes where anti-VEGF treatments cannot be used due to any reason, as noted in

	previous sections. The recommended dose is 1 implant (700 µg) into the affected phakic eye with DMO who are unsuitable for non-corticosteroid therapy (i.e. 1st line, rarely), or who are considered insufficiently responsive to alternative non-corticosteroid therapy e.g. those who have failed to respond to laser photocoagulation and anti- VEGF treatments or do not meet the requirements for treatment with ranibizumab (NICE TA 274), or aflibercept (NICE TA 346) (2nd/3rd line, less rarely). The second eye may receive similar treatment if the first treated eye shows good response, and there are no safety concerns. Retreatment at 4-6 month intervals (see NICE TA 349). These patients will be reviewed at 2 monthly intervals. No significant issues expected with logistics for implementation as the ophthalmologists are used to offer DEX implant in NHS for a number of years.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Dexamethasone implant is already used in the treatment of DMO in pseudophakic eyes (and in other indications of retinal vein occlusion, and non-infectious intraocular inflammation, irrespective of lens status). The use in phakic eyes will be similar.
• How does healthcare resource use differ between the technology and current care?	The proposed use will include treatment of eyes that are phakic, but unresponsive, or unsuitable for other (non-corticosteroid) DMO treatments. Access to the technology in phakic DMO will provide physicians with an opportunity at an early stage to switch non/sub-optimal responding patients from anti-VEGF treatment to dexamethasone implant hence likely avoid any damage to the retina and improve patient outcomes: more cost-effective of the technology. Capacity sparing: Use of intravitreal dexamethasone implant results in a reduced burden of injections when compared to intravitreal anti-VEGF injections and, therefore, capacity sparing. It is expected that patients treated with the technology will attend fewer appointments due to longer injection intervals resulting in reduction in clinic visits. This is even more important during current COVID pandemic. Adoption of the expanded technology indication can further “free-up” clinic slots and staff resources which can potentially be made available for other conditions and services. Proposed use of DEX implant in Phakic DMO eyes is expected to offer an alternative treatment option for eyes not sufficiently responsive or unsuitable for IVT anti-VEGF treatments.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be used by retinal specialists with expertise in the treatment of patients with diabetic retinopathy, including DMO. This would normally occur in secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No further investment is required in introducing the technology, as it is already used in other indications in the NHS. The injection room facilities, equipment, and expertise already exist, and are in use in the NHS. No additional logistics for equipment or training are expected as the technology is already in use in NHS settings for several years by retina specialists.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Phakic eyes that are insufficiently unresponsive to non-corticosteriod intravitreal therapies will benefit meaningfully from this technology. Non-response or very suboptimal response to anti-VEGF in DMO is well characterised (summarised in section 7). This often leads to frequent treatments with anti-VEGFs in an attempt to dry up the macula (e.g. 9-12 treatments in 12 months). Such eyes eventually have poor outcomes unless treatment is changed to a suitable alternative. Converting treatment of such eyes to intravitreal dexamethasone implant will require 2.4 treatments per annum (c.f. anti-VEGF), with significant cost saving, as well as better vision outcomes. Economically, there will be cost saving. A recent meta-analysis indicates that response to DMO treatments are similar for anti-VEGFs and dexamethasone implants. (He Y, Ren XJ, Hu BJ et al. A meta-analysis of the effect of a dexamethasone intravitreal implant versus intravitreal anti-VEGF treatment for DME. BMC Ophthalmol 2018;18(1):121. Furthermore, the use of dexamethasone implant pre-cataract surgery may be beneficial in eyes with DMO (Barone A et al, Eur J Ophthalmol. 2021 Mar 23:11206721211004395. Since the NICE TA 349 (2015) for DEX implant use in pseudophakic eyes insufficiently responsive or not suitable for anti-VEGF treatments, retina specialists in UK have gained more experience in treating DMO patients and understand the need for more flexible treatment options for Phakic DMO eyes (not limited to anti-VEGF agents). There is considerably more published evidence base, since 2015, to support DEX implant use in phakic DMO eyes including Cochrane reviews, meta-analysis, RCTs (small numbers), Real-world prospective and

	retrospective studies (with at least 12-month outcomes reported), Expert consensus guidelines, safety data and reviews on the topic.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. The new treatment will lead to better resolution of DMO, and visual acuity improvements, less frequent hospital visits, and patient satisfaction compared current care.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No. However, this technology will be available to groups did not have access previously, including pregnant diabetic women, and persons with recent cardiovascular events.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology is already in use in the NHS for other indications. The only change is an expansion of number of patients eligible for, and who will benefit from the technology. No further tests are required (compared to current care), and monitoring will be similar including clinical examination, intraocular pressure measurements, and optical coherence tomography imaging. There will be likely more patients requiring cataract surgery (usually between 12 to 24 months) based on current published literature.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Response to treatment is important. Eyes that are not sufficiently responsive to treatment (i.e. insufficient response to treatment) will have discontinued, and considered for alternative therapies. The rules will be similar to that used for eyes that are pseudophakic.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to	Yes. This should be supported by health economic assessments

be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. QoL - Management of patients with Retinal disease during COVID pandemic: • RCOphth guidance on Management of Ophthalmology Services during the COVID pandemic recommends treatment changes that can reduce the frequency of required attendances for the next few months e.g. changes in intravitreal treatment regime or longer-acting drug or procedure that would result in a lower number of hospital visits (RCOphth 2020, COVID-19 Clinical Guidance and National Information. RCOphth Management of Ophthalmology Services during the Covid pandemic dated 28th March 2020. https://www.rcophth.ac.uk/about/rcophth-covid-19-response/on 3rd August 2020). • During this unprecedented time of COVID-19, there is a stronger need for a therapy in phakic DMO with a predictable, extended treatment duration that would result in fewer hospital visits versus Anti-VEGF thus minimizing the risk of exposure to COVID for both the patients and healthcare worker. • Diabetes is strongly associated with COVID-19 mortality. A nationwide analysis in England demonstrated that a ⅓ of all in-hospital deaths with COVID-19 in England occurred in people with diabetes (Barron E et al. Lancet Diabetes Endocrinol 2020; 8:813-822).
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes: the unmet need as described above. The use of the technology addresses the unmet need for non-eligible patients and sub-optimal / non-responders to current intravitreal injection treatments. It addresses a patients' right to treatment. It is known that up to 50% patients do not respond optimally to anti-VEGF treatments. Clinical trials: RESTORE, VIVID and VISTA have shown that 50% eyes (pseudophakic or phakic) still have fluid, requiring other interventions. If patients are insufficiently responsive to anti-VEGF then dexamethasone implant will be recommended as per licence. Access to dexamethasone implant in phakic DMO will provide physicians the opportunity to switch non/sub-optimal responding patients from anti-VEGF treatment to dexamethasone implant earlier, and hence likely avoid irreversible damage to the retina and improve patient outcomes.
17. How do any side effects or adverse effects of the technology affect the	The two main concerns for phakic DMO eyes treated with DEX implant is new onset cataract development or cataract progression requiring cataract surgery AND Intraocular pressure (IOP) rise which may require

management of the condition and the patient's quality of life?	additional monitoring and / or treatment with drops, laser or surgery. Patients with cataract progression will, however, benefit from cataract surgery such that effects on patient's quality of life are limited. The clinical trials of the technology included eyes that are phakic and pseudophakic. Current UK use is restricted because of the recommendations of NICE TA 349, which this current appraisal is aimed to address. Data are summarised below. The MEAD Study (Boyer DS et al. Ophthalmology 2014; 121(10):1904-14). Three-year, pooled data from 2 randomised, multicentre, masked, sham controlled phase III clinical trials with identical protocols MEAD) showed that 22.2% of Ozurdex treated patients gain ≥15 letters over three years from an average of 4.1 injections. However, these VA results were significantly skewed by cataract progression amongst the phakic cohort in the study (75.5%). Cataract typically developed at 18+ months after initiation of Ozurdex (i.e. after the third implant). Prior to cataract development the visual improvements matched the pseudophakic cohort. For patients who underwent cataract surgery, visual improvements were typically re-gained by the end of the study (available @ http://dx.doi.org/10.1016/j.ophtha.2014.04.024) Other reports include: i)The BEVORDEX Study. http://dx.doi.org/10.1016/j.ophtha.2014.07.002 ii) Pacella E. Clin Ophthalmol 2013: 7 1423-1428; iii) NICE TA 349 • Dexamethasone implant is an intraocular steroid for which there is a class effect of an increased intraocular pressure (IOP) in some patients. Increased IOP is a risk factor for glaucoma. The clinical safety of dexamethasone implant has shown incidence of elevated IOP and cataract (Bilgic A et al. Ophthalmology Retina 2019;3: 929-937; Rajesh B et al. Br J Ophthalmol 2020; 104:39-46). • The SAFODEX studies (Malclès A et al. Retina 2017; 37:1352–9; Rezkallah A et al. Retina 2021; 41:1438-1445) reported that DMO patients were least likely to develop ocular hypertension (ONT) compared with RVO or uveitis patients. Approximately 90% of eyes with raised IOP were managed medically with topical drops (Rajesh et al, 2020); Malclès et al, 2017), while 0.5% eyes required filtering surgery. Endophthalmitis (0.07%), retinal detachment (0.03%) and vitreous haemorrhage (0.03%) were rare. Phakic status of the eye did not affect the risk of OHT compared to pseudophakic patients (Rajesh et al, 2020).

	• Rajesh et al (2020), reported 31% required cataract surgery while 14.3% saw a progression in their cataract requiring surgery. However, 25% of these patients had cataract at baseline (Rajesh et al, 2020). Similarly, in Bilgic et al (2019), at 24 months, 29/153 patients (19%) underwent cataract surgery, however, 26/29 (90%) of these patients had pre-existing cataract. (Bilgic A et al, 2019).
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials on the technology included eyes that are phakic and pseudophakic. Current UK use of the technology is restricted to largely pseudophakic eyes because of NICE TA 349. The UK Consensus Working Group (Amoaku et al, 2020), recommendations if implemented would reflect clinical trials data. The current appraisal is aimed to address this situation. As such, current UK practice does not currently reflect the clinical trial data.These clinical trial data are summarised in Section 17. In addition, the technology is used in phakic eyes elsewhere, as supported by the literature, including*: 1. Rosenblatt A et al. A collaborative retrospective study on the efficacy and safety of intravitreal dexamethasone implant (Ozurdex) in patients with DME: The European DME Registry Study. Ophthalmology 2020;127:377-393; 2. Mishra SK et al. Intravitreal dexamethasone implant versus intravitreal ranibizumab injection for treatment of non-proliferative DME. Curr Drug Deliv 2021;18:825-832. 3. Udaondo P et al. Impact of different clinical baseline characteristics on intravitreal dexamethasone implant (Ozurdex) outcomes. Clin Ophthalmol 2021;15:4153-4162. 4. Wei W et al. Multicenter, prospective, randomized study of dexamethasone intravitreal implant in patients with center-involved diabetic macular edema in the Asia-Pacific Region. Clin Ophthalmol 2021;15:4097-4108. 5. Ehlers JP et al. Intravitreal pharmacotherapies for DME: A Report by the AAO. Ophthalmology 2022;129(1):88-99. 6. Pacella E et al. Effects of repeated intravitreal injections of dexamethasone implants on intraocular pressure: A 4-Year Study. Clin Ophthalmol 2020;14:3611-3617. 7. Kaldırım H et al. Comparison of anatomical and functional outcomes of intravitreal dexamethasone implant between phakic and pseudophakic eyes with DME. Korean J Ophthalmol 2020;34:383-391. 8. Nair U et al. Postmarketing safety surveillance of dexamethasone intravitreal implant in the treatment of visual impairment due to DME in India. BMC Ophthalmol 2020;20:405. 9. Furino C et al. DME and cataract surgery: Phacoemulsification combined with dexamethasone intravitreal implant compared with standard phacoemulsification. Retina 2021;41(5):1102-1109. 10. Ratra D, Sharma U, Dalan D. Efficacy and safety of intravitreal dexamethasone implant in treatment naive eyes with DME: Real world experience. Eur J Ophthalmol 2021;31(4):1899-1906.*

• If not, how could the results be extrapolated to the UK setting?	Historical published pharmacoeconomic evaluations for Ozurdex use in phakic DMO eyes are available (NICE TA349), but outdated due to evolving DMO treatment landscape, and available real-world evidence. The NICE TA 349 did not account for an active comparator, but rather considered "watch and wait" as standard of care in patients with DMO that do not respond to non-corticosteroid treatment, or when such treatment is unsuitable (TA 349 - https://www.nice.org.uk/guidance/ta349). This approach has evolved and discussed during NICE TA 613. The NICE committee stated: *"The clinical expert explained that NHS clinical practice for treating diabetic macular oedema has changed since anti VEGFs were introduced. The committee was aware that most people will initially have anti VEGFs and that in phakic eyes they might be continued even if they do not work well".* The NICE committee also concluded people with DMO in phakic eyes would welcome a new treatment option. In the recent NICE review (TA 613) fluocinolone was not recommended as the evidence base was small. However, NICE concluded that people with DMO in phakic eyes would welcome a new treatment option. https://www.nice.org.uk/guidance/ta613/resources/fluocinolone-acetonide-intravitreal-implant-for-treating-chronic-diabetic-macular-oedema-in-phakic-eyes-after-an-inadequate-response-to-previous-therapy-pdf-82608955110853. Additionally, The RCOphth response to the TA 613 ACD (page 13-14/27), confirmed that *"patients who are on anti-VEGF treatment with inadequate response will continue to have treatment" and "their vision would not be expected to improve with this ongoing anti-VEGF treatment" and also physicians "would not stop treatment as that would risk vision worsening"*- (NICE TA 613- https://www.nice.org.uk/guidance/ta613/evidence/final-appraisal-determination-committee-papers-pdf-6965695405) Additionally, The RCOphth response to the ACD of TA 613 (page 13-14/27), also confirms that *"patients who are on anti-VEGF treatment with inadequate response will continue to have treatment" and "their vision would not be expected to improve with this ongoing anti-VEGF treatment" and also physicians "would not stop treatment as that would risk vision worsening"* - (Technology appraisal guidance [TA613] - https://www.nice.org.uk/guidance/ta613/evidence/final-appraisal-determination-committee-papers-pdf-6965695405)

• What, in your view, are the most important outcomes, and were they measured in the trials?	Dexamethasone implant is clinically effective as treatment of centre involving DMO, irrespective of lens status.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Long term clinical outcomes are clear and reflected by the clinical trial data, as well as routine clinical use in eyes that are pseudophakic.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes: some of the real-world data.
20. How do data on real-world experience compare with the trial data?	Real world data outcomes are comparable, and reported less frequent adverse events compared to clinical trial data. Since the NICE Technology appraisal guidance for Ozurdex (NICE TA 349) there is evolving evidence including real-world data (RWD) demonstrating similar outcomes between phakic and pseudophakic eyes with DMO (Macles et al, 2017; Singer et al, 2018), with as few injections as possible (Table 1). There is comparable mean improvement in BCVA in phakic eyes having undergone cataract surgery vs pseudophakic eyes, with no reduction in treatment benefit observed because of cataract surgery (Bilgic A et al. Br J Ophthalmol 2019; doi:10.1136/bjophthalmol-2019-313991; Malclès A et al. Retina 2017;37(4):753-760; Singer MA et al. Ophthalmic Surg Lasers Imaging Retina 2018;49(6):425-435. Menezo M et al. Current Med Res Opinion 35;12: 2111-2116). Existing practice positions intravitreal injections of anti-VEGF drugs before dexamethasone implant in phakic patients. However, recent real-world data have shown broadly equivalent outcomes (Callanan DG et al, Graefes Arch Clin Exp Ophthalmol 2017;255:463-473; Comet A et al, INVICTUS. Eur J Ophthalmol 2021;31(2):754-758). Patients who had a sub-optimal response to anti-VEGF when switched to dexamethasone implant (Ozurdex) had better visual and anatomical outcomes (Busch C et al. Acta Diabetol 2018;55(8):789-796; Ruiz-Medrano J et al. Eur J Ophthalmol 2021;31(3):1135-1145; Busch C et al. Acta Diabetol 2019;56(12):1341-1350. *Table 1: RWD with Ozurdex in phakic DMO vs. pseudophakic DMO*

Study	Follow-up (months)	BCVA from baseline (letters)		Mean number of injections
Reldex	36	Phakic +9.5	Pseudophakic +9.5	3.6
REINFORCE	12	Phakic +12.2	Pseudophakic +11.5	2.0

Guidelines for the management of DME by EURETINA. Recommendation for Steroids: *'In non-responders who have already been treated with anti-VEGF (after 3–6 injections, depending on the specific response of each patient), it is reasonable to switch to a steroid. First-line considered in patients who have a history of a major cardiovascular event, patients who are not willing to come for monthly injections (and/or monitoring) in the first 6 months of therapy, Dexamethasone shall be the first steroid used. Phakic patients have to be informed about the high risk for cataract surgery. The IOP has to be monitored frequently in all cases.'*

- UK Consensus Pathway (Amoaku et al, 2020) describes the pathway
- Summary from RCOphth response to NICE TA349. *"The NICE guidance, which covers NHS England and Wales, contrasts with guidance for NHS Scotland by the Scottish Medicines Consortium which recommends Ozurdex® not only for pseudophakic patients but also for phakic patients who are considered insufficiently responsive to, or unsuitable for non-cortico-steroid therapy (published April 2015). Ophthalmologists responsible for patients in NHS England and Wales will have to apply to their local Clinical Commissioning Group (CCG) or Local Health Board (LHB) respectively as an individual funding request if they wish to use Ozurdex® in a phakic patient with DMO. Alternatively, they could work closely with their CCG or LHB to develop local funding arrangements for selected groups of individuals meeting certain predefined criteria"*.
- Scottish - Scottish Medicines Consortium No.1046/15 – which allows for Ozurdex in phakic eyes.

Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes: pregnant women with DMO

21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- There is an unmet need for use of this technology in eyes that are phakic and unresponsive to intravitreal anti-VEGF therapies, and in patients where intravitreal injections of anti-VEGF therapies as treatment for DMO are unsuitable.
- The efficacy of dexamethasone implants in DMO is not affected by the lens status (i.e. pseudophakic or phakic).
- A significant proportion of eyes in diabetics have cataracts at baseline (pre-treatment with the technology); this is reflected in the clinical trial data.
- Intraocular pressure increases after dexamethasone implants in diabetics are less frequent than in non-diabetic eyes.
- Outcomes of cataract surgery in phakic eyes treated with dexamethasone implants are excellent and comparable eyes that have not been treated with the technology.

Thank you for your time.
Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens (part review of TA349)

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/50/19.

Title:	Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens (part review of TA349)
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Victoria Wakefield, Principal Clinical Evidence Analyst, BMJ-TAG, London Gemma Marceniuk, Senior Health Economist, BMJ-TAG, London Conor Hickey, Health Economist, BMJ-TAG, London Ben Mayer, Senior Clinical Evidence Analyst, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	15/03/2022
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/50/19.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The ERG would like to thank Dr Christine Kiire (consultant ophthalmologist, Oxford University Hospitals NHS Foundation Trust), Mr Ajay Kotagiri (consultant ophthalmologist, Sunderland Eye Infirmary), Dr Clare Bailey (consultant ophthalmologist, University Hospitals Bristol and Weston NHS Foundation Trust) and Mr Craig Goldsmith (consultant ophthalmologist, James Paget University Hospital NHS Trust) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Wakefield V, Marceniuk G, Hickey C, Mayer B. Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens (part review of TA349): A Single Technology Appraisal. BMJ Technology Assessment Group, 2022.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Vicky Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Ben Mayer	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and assisted with drafting the clinical results sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Conor Hickey	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; and assisted with drafting the economic sections

All authors read and commented on draft versions of the ERG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse event
AUC	Area under the curve
BCVA	Best-corrected visual acuity
BNF	British National Formulary
BRVA	Best-reported visual acuity
BSE	Best-seeing eye
CC	Complications and comorbidities
CDF	Cumulative distribution function
CI	Confidence interval
CRT	Central retinal thickness
CS	Company submission
CSR	Clinical study report
DRCR	Diabetic Retinopathy Clinical Research
DEX700	Dexamethasone 700 µg intravitreal implant in applicator (Ozurdex®)
DEX PS DDS	Dexamethasone posterior segment drug delivery system
DM	Diabetes mellitus
DMO	Diabetic macular oedema
DSU	Decision Support Unit
eMIT	Drugs and pharmaceutical electronic marketing tool
EQ-5D	EuroQol- 5 Dimension
ERG	Evidence Review Group
ESS	Effective sample size
ETDRS	Early Treatment Diabetic Retinopathy Study
FEI	Fellow eye involvement
HR	Hazard ratio
HS	Health state
HRQoL	Health-related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
IOP	Intraocular pressure
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LOCF	Last observation carried forward
LY	Life year
mITT	Modified intention-to-treat
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire-25
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analyses

NMB	Net monetary benefit
MAIC	Matching-adjusted indirect comparison
MD	Mean difference
MIMS	Monthly Index of Medical Specialities
µg/mg	Microgram
mmHg	millimetres of mercury
OCT	Optical coherence tomography
OR	Odds ratio
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PRN	Pro re nata
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALYs	Quality-adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
RWD	Real-world data
RWE	Real-world evidence
SD	Standard deviation
SE	Standard error
SLR	Systemic literature review
SmPC	Summary of product characteristics
STC	Simulated treatment comparison
SVL	Severe vision loss
SW	South-west
TA	Technology appraisal
TRAE	Treatment-related adverse event
TTO	Time trade-off
VEGF	Vascular endothelial growth factor
VFQ-25	Visual Functioning Questionaire-25
vs	Versus
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WSE	Worst-seeing eye
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

For an overview of the ERG's key issues, see Table 1.

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Uncertainty around the generalisability of the results from the MEAD trials	2.3 and 3
2	Time horizon considered for the economic analysis	4.2.5.1
3	Changes in BCVA resulting from DEX700 treatment in Years 4 and 5	4.2.6.1.1
4	Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5	4.2.6.2.1
5	Subsequent treatment following discontinuation of DEX700	4.2.7.1
6	The natural history of vision in eyes with DMO	4.2.8

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema.

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are around the time horizon, the assumptions used to model dexamethasone 700 µg intravitreal implant in applicator treatment (hereinafter referred to as DEX700, [Ozurdex®; AbbVie]) in Years 4 and 5, the changes in best-corrected visual acuity (BCVA) resulting from anti–vascular endothelial growth factor (anti-VEGF) treatment, the subsequent treatment following discontinuation of DEX700, the natural history of vision in eyes with diabetic macular oedema (DMO), the cataract extraction rates applied to patients on and off anti-VEGF treatment, the approach used to model the additional mortality due to diabetes mellitus (DM) and DMO, and the inclusion of disutilities due to adverse events (AEs).

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Improving BCVA.

Overall, the technology is modelled to affect costs by:

- Its higher unit price than anti-VEGF treatment;
- Increasing the number of cataract extractions compared to anti-VEGF treatment;
- Lowering the number of medical resource use requirements (routine monitoring visits and optical coherence tomography tests) compared to anti-VEGF treatment.

The modelling assumptions that have the greatest effect on the ICER are:

- The treatments and market shares assumed for the composite comparator;
- The time horizon;
- The assumed changes in BCVA resulting from DEX700 treatment in Years 4 and 5;
- The assumed changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5; and
- The natural history of vision in eyes with DMO.

1.3 Summary of the ERG's key issues

The ERG's key issues on the clinical cost-effectiveness evidence are given in Table 2 to Table 7.

Table 2. Issue 1: Uncertainty around the generalisability of the results from the MEAD trials

Report section	2.3 and 3
Description of issue and why the ERG has identified it as important	The primary evidence base in the CS to address the decision problem is from *post hoc* analyses of the subgroup of phakic patients from the DEX700 and sham arms of the MEAD trials. The ERG notes that the [redacted] in the MEAD trials does not reflect current UK clinical practice. In particular, clinical experts considered there to be [redacted] in the MEAD trials and [redacted]. Additionally, the population of the MEAD trials comprised of a [redacted] compared to a UK RWE audit and this was supported by the ERG's clinical experts. The ERG is therefore concerned that the DEX700 data from the MEAD trials does not reflect patients with an insufficient response to [redacted] and that the population has [redacted] than expected in UK clinical practice. Additionally, data from a UK RWE audit investigating suboptimal anti-VEGF treatment is used to provide supportive evidence for the insufficiently responsive to non-corticosteroid

	population but the ERG is concerned that these data are non-comparative and unsuitable for combining in an ITC with the DEX700 evidence from the MEAD trials due to [redacted]. The ERG notes that the sham arm in the MEAD trials comprises no treatment and patients requiring rescue therapy were required to discontinue from the studies. Additionally, there is a [redacted] discontinuations for the DEX700 and sham arms of the MEAD trials ([redacted] versus [redacted]; respectively) and the company has used a LOCF approach to account for missing data. The ERG notes that the natural history of DMO suggests that vision deteriorates over time and therefore the LOCF approach may be optimistic for both the DEX700 and sham arms as vision in patients with missing data cannot worsen. The ERG is, therefore, concerned that results for both the sham and DEX700 arms are likely to be biased and considers it difficult to predict the likely direction of the resulting bias for the comparison of DEX700 versus sham from using a LOCF approach to account for missing data. The ERG does not consider clinical evidence for the efficacy of laser alone compared with DEX700 has been provided in the CS and notes that the anti-VEGFs, ranibizumab and aflibercept, are considered [redacted] in the economic model. The ERG notes that the company considers watch and wait to only be a comparator for the unsuitable for non-corticosteroid population, although the populations are not considered separately in the model and cost-effectiveness of DEX700 versus watch and wait is not reported in the CS.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The ERG considers the uncertainties are generally unresolvable because of limitations in the availability of clinical evidence in the correct population for the required comparators.

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; CS, company submission; DEX700, dexamethasone 700 µg intravitreal implant in applicator (Ozurdex®); DMO, diabetic macular oedema; ESS, effective sample size; LOCF, last observation carried forward; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; RWE, real-world evidence; UK, United Kingdom.

Table 3. Issue 2: Time horizon considered for the economic analysis

Report section	4.2.5.1
Description of issue and why the ERG has identified it as important	The time horizon of the model is 40 years, which was considered to cover a lifetime. The ERG considers the company's long-term modelling assumptions to be too simplistic to accurately capture the costs and consequences over a lifetime time horizon. This is because more treatment options may become available to patients when they become pseudophakic and no treatment waning assumptions have been modelled, which means DEX700 maintains a benefit in visual acuity above anti-VEGFs beyond the 5-year treatment period and throughout the remaining time horizon. Shorter time horizons (10 and 15 years) have also been adopted in other DMO appraisals.
What alternative approach has the ERG suggested?	In the absence of data on treatment waning the ERG suggests reducing the time horizon to 5 or 10 years. The company's clinical experts noted that 5 years was sufficiently long enough to capture key differences in treatment costs and 10 years is consistent with the approach adopted by the company for the ranibizumab appraisal (TA274) to reduce the uncertainty about the projected effects of treatment.
What is the expected effect on the cost-effectiveness estimates?	Reducing the time horizon from 40 years to 10 or 5 years favours the comparator (inc. NMB reduced from £10,080 to £8,466 or £7,595, respectively). Nevertheless, the ICER remains dominant.
What additional evidence or analyses might help to resolve this key issue?	The ERG's clinical experts fed back that they would expect visual acuity across all treatments to converge during the off-treatment period, but were unable to suggest how long this might take. The ERG is also unaware of any longitudinal data that could resolve this issue.

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; DEX700, dexamethasone 700 µg intravitreal implant in applicator (Ozurdex®); DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year; WTP, willingness-to-pay

Note: the inc. NMB at a WTP threshold of £30,000 per QALY is reported.

Table 4. Issue 3: Changes in BCVA resulting from DEX700 treatment in Years 4 and 5

Report section	4.2.6.1.1
Description of issue and why the ERG has identified it as important	The economic analysis assumes a maximum duration of treatment of 5 years. Given the follow-up time of 3 years in MEAD, the 3-monthly transition probabilities in Years 1 to 3 were taken from MEAD, whereas the 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. The ERG and its clinical experts consider that in the absence of any evidence to substantiate improvements in vision in Years 4 and 5, assuming vision is maintained is more appropriate, if, conservative.
What alternative approach has the ERG suggested?	During the clarification stage, the company provided a scenario assuming vision is maintained in Years 4 and 5. To align with TA349 and reduce the number of assumptions required to model Years 4 and 5, the company also provided a scenario using a 3-year treatment duration for all treatments.
What is the expected effect on the cost-effectiveness estimates?	In the company's scenario which assumed a net-zero impact on vision for DEX700 in Years 4 and 5, the company also assumed that a net-zero impact on vision would be best represented using a 3-month probability of gaining or losing at least 10 letters of BCVA (that is, moving up or down one health state) of 3.5% as it is unlikely that vision would remain constant for each individual patient over time. Under this scenario, DEX700 continued to dominate anti-VEGFs and the inc. NMB reduced from £10,080 to £7,280. The ERG amended the company's scenario so that the probability of gaining

	or losing at least 10 letters of BCVA was set to 0% and produced a similar result (inc. NMB £7,383). Reducing the treatment duration to 3 years had a much larger impact in favour of the comparator (inc. NMB reduced from £10,080 to £2,957).
What additional evidence or analyses might help to resolve this key issue?	Given the large assumptions needed to model DEX700 treatment in Years 4 and 5, the ERG considers that Committee may want to account for this uncertainty by using the lower threshold for cost-effectiveness (that is, an ICER below £20,000 per QALY gained). Additional clinical expert input would also be helpful to verify the company's assumptions that 5 years is sufficiently long enough to capture key differences in treatment costs and that the last transition matrix provides the most relevant data available from MEAD as it allows for any recovery in BCVA following the development and extraction of cataracts in a significant proportion of patients to be captured.

Abbreviations: BCVA, best-corrected visual acuity; DEX700, dexamethasone 700 µg intravitreal implant in applicator (Ozurdex®); DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year; WTP, willingness-to-pay

Note: the inc. NMB at a WTP threshold of £30,000 per QALY is reported.

Table 5. Issue 4: Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5

Report section	4.2.6.2.1
Description of issue and why the ERG has identified it as important	The company used the sham arm of the MEAD trials as a proxy for continued anti-VEGF use. To support this, the company presented a naïve comparison of the mean BCVA change from baseline over time in the MEAD sham arm with UK RWE. However, the ERG is concerned that the baseline for the UK RWE study is the start of anti-VEGF treatment and thus does not reflect the insufficiently responsive to non-corticosteroid treatment population that the company is modelling. In addition, there are difference in study designs and the differences in baseline characteristics between the studies. For these reasons, the ERG does not agree with the company's argument that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF. In the CS, the company provided a scenario where anti-VEGF treatment has zero net impact on vision. This scenario favoured anti-VEGF treatment which is counterintuitive to the company's argument that the sham arm of MEAD results in a conservative estimate of the relative treatment effect (inc. NMB reduced from £10,080 to £8,076).
What alternative approach has the ERG suggested?	The company made additional assumptions in their scenario which assumed a zero net impact on vision. These include a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.5% and using a restricted set of transition probabilities to inform DEX700, i.e. patients can only move up or down one health state in each model cycle. A 3-monthly probability of 0% would be more transparent and restricted transition probabilities have been heavily criticised in TA349. The ERG's preferred approach is therefore to assume that anti-VEGF treatment maintains vision (a 3-month probability of gaining or losing at least 10 letters of BCVA of 0%) as it is transparent in terms of the likely biases that exist, and to remove the restrictions on DEX700 to reflect the trial evidence.
What is the expected effect on the cost-effectiveness estimates?	Adjusting the changes in BCVA resulting from anti-VEGF treatment in the manner described above has a large impact on the cost-effectiveness results in favour of anti-VEGF treatment. The changes in the inc. NMB are

	as follows: • Base case: £10,080; • Scenario in CS (3.5% 3-month probability of improving/worsening and restricted transition probability matrices for DEX700): £8,076; • ERG scenario 1 (0% 3-month probability of improving/worsening and restricted transition probability matrices for DEX700) £4,592; • ERG scenario 2 (0% 3-month probability of improving/worsening and unrestricted transition probability matrices for DEX700): £615.
What additional evidence or analyses might help to resolve this key issue?	Given the large assumptions needed to model continued anti-VEGF treatment, the ERG considers that Committee may want to account for this uncertainty by using the lower threshold for cost-effectiveness (that is, an ICER below £20,000 per QALY gained). The ERG would also urge the company to explain how utilising the sham arm of MEAD in the model does not lead to an overall net gain in BCVA.

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; BCVA, best-corrected visual acuity; CS, company submission; DEX700, dexamethasone 700 µg intravitreal implant in applicator (Ozurdex®); NMB, net monetary benefit; QALY, quality-adjusted life year; RWE, real world evidence UK, United Kingdom; WTP, willingness-to-pay

Note: the inc. NMB at a WTP threshold of £30,000 per QALY is reported.

Table 6. Issue 5: Subsequent treatment following discontinuation of DEX700

Report section	4.2.7.1
Description of issue and why the ERG has identified it as important	The ERG's clinical experts disagreed with the company's assumption that patients receive no treatment following discontinuation of DEX700 as these patients would be offered re-treatment with an anti-VEGF in clinical practice. It was noted that subsequent anti-VEGF treatment would be given for a relatively short period of time, and it would be unlikely to be effective.
What alternative approach has the ERG suggested?	During the clarification stage, the company provided a simplistic scenario which included a one-off cost to represent 1 year of subsequent treatment with anti-VEGFs. Including this cost in the model had a noteworthy impact on the results in favour of the comparator (inc. NMB reduced from £10,080 to £8,373).
What is the expected effect on the cost-effectiveness estimates?	Excluding subsequent treatment costs introduces bias in favour of DEX700 as there are no subsequent treatments available for the comparator.
What additional evidence or analyses might help to resolve this key issue?	The ERG is unaware of any evidence that could inform the efficacy of subsequent treatment in patients who have received prior DEX700 to resolve the uncertainty surrounding subsequent treatment. Additional clinical expert input would be helpful to determine if the simplistic scenario provided by the company resolves this uncertainty.

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; DEX700, dexamethasone 700 µg intravitreal implant in applicator (Ozurdex®); NMB, net monetary benefit; QALY, quality-adjusted life year; WTP, willingness-to-pay

Note: the inc. NMB at a WTP threshold of £30,000 per QALY is reported.

Table 7. Issue 6: The natural history of vision in eyes with DMO

Report section	4.2.8
Description of issue and why the ERG has identified it as important	After the 5-year treatment period or because of discontinuation within the 5-year treatment period, it is assumed that patients receive no further treatment. As a result, the vision in their DMO-affected eye(s) transitions through the BCVA states at a rate consistent with the natural history of vision in patients with DMO. As per TA349, the company estimated a 3-

	month probability of gaining or losing at least 10 letters of BCVA (moving up or down one health state) of 3.5% and 4.5%, respectively. The WESDR data (reported in Mitchell *et al*. 2012) used to inform these estimates were based on a population of patients with diabetic retinopathy who may not have had DMO which means WESDR could represent a less severe set of patients than the population for this appraisal. The ERG's clinical experts also considered the 3-month probability of gaining at least 10 letters of BCVA of 3.5% to be too high. Additionally, the data from WESDR are likely to reflect outdated practice as the publications suggest it was analysed and adjusted between 1998 and 2004.
What alternative approach has the ERG suggested?	The company explored a scenario in which the natural history of vision was as per TA613: a 3-month probability of gaining or losing at least 10 letters of BCVA of 0% and 3.5%, respectively. These estimates appear to be taken from the ranibizumab appraisal (TA274). The ERG consulted with its clinical experts who fed back that their expectations would align more closely with the natural history reported in TA613 than Mitchell *et al.* 2012.
What is the expected effect on the cost-effectiveness estimates?	Utilising the natural history data from TA613 favoured the comparator (inc. NMB reduced from £10,080 to £8,725). Nevertheless, the ICER remained dominant.
What additional evidence or analyses might help to resolve this key issue?	Additional clinical expert input would be helpful to determine the most appropriate source of natural history data.

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; DEX700, dexamethasone 700 µg intravitreal implant in applicator (Ozurdex®); DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; WTP, willingness-to-pay

Note: the inc. NMB at a WTP threshold of £30,000 per QALY is reported.

1.4 Other key issues: summary of the ERG's view

Other cost-effectiveness issues raised by the ERG include:

- the assumption that patients cannot discontinue anti-VEGF treatment during the treatment period (see Section 4.2.7.1);
- the different cataract extraction rates applied to patients on and off anti-VEGF treatment (see Section 4.2.10.1);
- the company's approach to model additional mortality due to DM and severe vision loss (see Section 4.2.12.1)
- the raised IOP rates applied to anti-VEGFs (see Section 4.2.11.1);
- the omission of disutilities due to AEs (see Section 4.2.13.1); and
- the number of DEX700 injections assumed in Years 4 and 5 (see Section 4.2.14.6).

However, exploratory and sensitivity undertaken by the company and ERG suggest these issues have a minimal impact on the cost-effectiveness results.

1.5 Summary of ERG's preferred assumptions and resulting ICER

A summary of the ERG's preferred assumptions is provided in Table 8. For detailed deterministic results and probabilistic results, see Section 6.4. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.2.

Table 8. ERG's preferred model assumptions (cumulative deterministic results, DEX700 vs comparator)

Preferred assumption	Section in ERG report	Inc. cost	Inc. QALY	Cumulative ICER (£/QALY)	Inc. NMB (£30,000/QALY)
Composite comparator					
Company base case	5.1.1.1	-£6,968	0.104	DEX700 dominant	£10,080
10-year time horizon	4.2.5.1	-£6,609	0.062	DEX700 dominant	£8,466
Average number of DEX700 injections from Year 3 remained constant until the end of Year 5 (as per company's assumption for anti-VEGFs)	4.2.14.6	-£6,093	0.062	DEX700 dominant	£7,950
Patients who continue DEX700 receive anti-VEGF treatment for 1 year[§] and vision follows the natural history of vision in eyes with DMO during and after this 1-year period (as per clinical expert opinion*)	4.2.7.1	-£4,385	0.062	DEX700 dominant	£6,242
Cataract extraction rates for patients on and off anti-VEGF treatment based on the sham arm of MEAD (as per TA613 using the sham arm of FAME)	4.2.10.1	-£3,885	0.062	DEX700 dominant	£5,742
Mortality as per TA613: a HR of 1.95 the additional mortality due to DM and a HR of 1.54[†] for the additional mortality due to blindness	4.2.12.1	-£3,916	0.060	DEX700 dominant	£5,709
Utility decrements due to AEs included as per TA613	4.2.13.1	-£3,916	0.058	DEX700 dominant	£5,670
Natural history of vision in eyes with DMO as per TA613: a 3-month probability of gaining or losing at least 10 letters of BCVA of 0% and 3.5%, respectively.	4.2.8.1	-£3,463	0.038	DEX700 dominant	£4,616
DEX700 has a net-zero impact on vision in Years 4 and 5, with a probability of gaining or losing at least 10 letters of BCVA of 0%	4.2.6.1.1	-£3,573	-0.007	£481,583 (SW quadrant[‡])	£3,351

Anti-VEGFs have a net-zero impact on vision in Years 1 to 5, with a probability of gaining or losing at least 10 letters of BCVA of 0% (unrestricted DEX700 transitions)	4.2.6.2.1	£1,713	-0.063	DEX700 dominated	-£3,597
Ranibizumab comparator					
Base case using 100% ranibizumab use	4.2.3.2.1	-£3,179	0.104	DEX700 dominant	£6,291
All preferred assumptions	-	£5,530	-0.063	DEX700 dominated	-£7,415
Aflibercept comparator					
Base case using 100% aflibercept use	4.2.3.2.1	-£9,194	0.104	DEX700 dominant	£12,307
All preferred assumptions	-	-£530	-0.063	£8,436 (SW quadrant‡)	-£1,355

Abbreviations: AE, adverse event; anti-VEGF, anti-vascular endothelial growth factor; BCVA, best-corrected visual acuity; DEX700, dexamethasone 700 µg intravitreal implant in applicator (Ozurdex®); DM, diabetes mellitus; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality adjusted life year; SW, south-west.

*most patients will receive anti-VEGF re-treatment for a short period of time and it is unlikely to be effective

†the ERG considers the multiplier associated with "severe visual impairment" (1.54) to be of more relevance than the multiplier applied in TA613 associated with "some visual impairment" (1.23) for patients whose BSE falls into BCVA state 1

‡DEX700 less costly and less effective than the comparator

§One-off cost of £3,539 based on the ranibizumab and aflibercept market shares and number of injections in year 1 as observed UK RWE (as per company scenario).

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost effectiveness of dexamethasone 700 µg intravitreal implant in applicator (hereinafter referred to as DEX700, [Ozurdex®; AbbVie]) as a regimen for treating diabetic macular oedema (DMO) in people without a pseudophakic lens. The population of interest for this STA is thus phakic patients with DMO; i.e. those with an intact natural lens in their eye.[1]

This appraisal comprises a part review of technology appraisal (TA) guidance TA349, which was published in July 2015 and included both pseudophakic and phakic patients with DMO.[2] In TA349, one of the potential uses of DEX700 in clinical practice that was considered was DEX700 compared with watch and wait in people who do not have a pseudophakic lens and with DMO that does not respond to non-corticosteroid treatment or for whom such treatment is unsuitable. DEX700 was not recommended by the National Institute for Health and Care Excellence (NICE) for use in these populations in TA349. The company reports that there is now a change in the most appropriate comparator for part of this population due to changes in clinical practice, and additionally, that there is new real world evidence (RWE) for dexamethasone. The current treatment pathway is discussed in 2.2.1 and the sources of new clinical effectiveness data are described in Section 2.2.2.

2.2 Background

Within Section B.1 of the CS, the company provides an overview of:

- DEX700, including its mode of action, dose and method of administration (Section B.1.2);
- DMO including risk factors, pathophysiology, prevalence and its impact on health-related quality of life (Section B.1.3).

The ERG considers the company to have provided a reasonable summary of DMO and notes that a key feature of the condition is that it can lead to loss of vision over time.

2.2.1 Clinical care pathway and proposed positioning of the technology

The ERG's clinical experts reported that there is no specific NICE guideline covering all available treatments for diabetic retinopathy and DMO (although there is guidance for individual pharmacological therapies such as dexamethasone [TA349][2]) and that the 2012 Royal College of Ophthalmologists guidelines for the management of diabetic retinopathy[3] do not fully reflect the current clinical management of patients with DMO in the UK. As reported in the CS, the ERG notes

that in 2020 a UK Consensus Working Group was formed to address the perceived variations and lack of uniformity in DMO management in the UK, and has published guidance for the management of diabetic retinopathy.[4] The 2020 UK Consensus Working Group defined the current UK treatment pathway for DMO and considers that for phakic centre involving and vision affecting DMO patients with a CRT < 400 µm, the treatment options comprise watch and wait, bevacizumab (Avastin® [note: off-label use]) and dexamethasone intravitreal implant (note: not routinely commissioned so would require an individual funding request).[4] For patients with a CRT > 400 µm, first-line therapy is an intravitreal anti-VEGF, although intravitreal steroids (including dexamethasone intravitreal implant) are suggested for patients unsuitable for, or insufficiently responsive to anti-VEGF therapy, or patients who can't tolerate the injection burden of anti-VEGF therapy.[4]

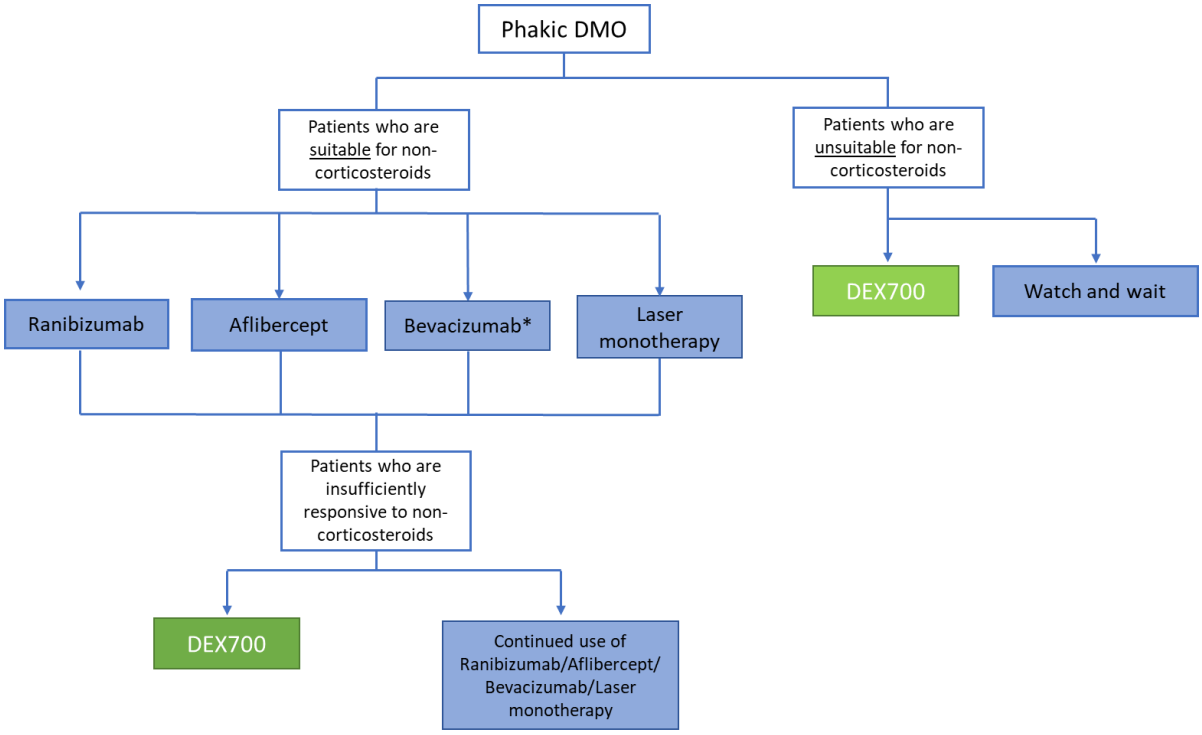
Figure 1 presents the company's proposed placement of DEX700 in the treatment pathway of phakic DMO patients and is reported to use treatment guidelines for patients with phakic DMO in England to inform the current treatment pathway. The ERG's clinical experts broadly agree with the company's treatment pathway and agree with the company's positioning of DEX700 in the pathway.

The ERG notes that in TA349 watch and wait was the comparator for DMO patients with phakic eyes after an insufficient response to non-corticosteroid therapy, whereas in the current treatment pathway continued use of anti-VEGFs and/or laser is used (

Figure 1). The ERG's experts reported that watch and wait could still be a potential comparator for a small proportion of the patients who are insufficiently responsive to non-corticosteroid treatment and the ERG notes watch and wait was not considered a comparator in the recent NICE appraisal of fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic

eyes after an inadequate response to previous therapy (TA613[5]). Additionally, the ERG's clinical experts were in agreement with the company that relevance of bevacizumab use in the phakic DMO patient populations is minimal due to the absence of a UK marketing authorisation for bevacizumab in DMO and so any use of bevacizumab is off-label. The UK RWE audit reported in the CS [redacted] bevacizumab for DMO treatment in phakic DMO patients ([redacted]%).

Figure 1. Clinical pathway of care for phakic DMO patients and proposed placement for DEX700 (Reproduced from CS, Figure 4)



Key: DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema.

Notes: * Bevacizumab does not currently have a marketing authorization in the UK and is not recommended by NICE; any use of bevacizumab is therefore deemed off-label.[4] In light of this, bevacizumab is not considered a relevant comparator to DEX700 and is not discussed in this submission.

The ERG's clinical experts reported that in phakic DMO patients who are insufficiently responsive to non-corticosteroid treatment, continued use of anti-VEGF (ranibizumab or aflibercept) would be the main treatment option and that laser would be given as necessary either in addition to anti-VEGF or

as monotherapy but laser would not usually be given routinely for centre-involving diabetic macular oedema. The ERG notes that anti-VEGFs (ranibizumab or aflibercept, or off-label use of bevacizumab), and laser monotherapy were also the agreed comparators for the fluocinolone (Iluvien®) NICE technology appraisal (TA613)[5] and that in TA613 it was suggested that laser therapies were used in 28% of patients with DMO. The company conducted an advisory board in 2021 with UK clinicians that suggests the percentage of DMO patients treated with laser is now much lower with estimates of 15-20%.[6, 7] The company reports that due to the reduced use and limited efficacy, they do not consider laser therapy a relevant comparator to DEX700, although some limited use of laser is explored in the company's economic scenario analyses. The ERG's clinical experts also consider that laser use in patients with DMO is now likely to be lower than 28%.

Additionally, the ERG's clinical experts agree with the company that in phakic DMO patients who are unsuitable for non-corticosteroid treatment, watch and wait is the only available treatment option at present.

2.2.2 New clinical effectiveness evidence sources for DEX700

The main sources of clinical evidence for the use of DEX700 in patients with either pseudophakic or phakic DMO in NICE TA349 were the Phase III randomised, sham-controlled trials MEAD-010 and MEAD-011. Analyses of the intention-to-treat (ITT) populations were used to provide evidence for DEX700 in patients with phakic DMO in TA349, whereas for this part review of TA349 a *post-hoc* pooled analysis of the phakic-only modified ITT (mITT) populations of the MEAD trials (hereafter, the pooled analysis is referred to as 'the MEAD trials') is the primary focus of the CS and used to inform the efficacy of DEX700 in the company's base case in their economic model.

The company reported that since the publication of TA349 in July 2015, several RWE studies have been published that further support the efficacy and safety of DEX700 in DMO. The company consider that visual outcomes reported for phakic DMO patients in the RWE studies are consistently better than those reported in the MEAD trials, and conclude that the MEAD trials underestimate the efficacy of DEX700. Additionally, the company state that the RWE studies suggest that the treatment outcomes with DEX700 are consistent between pseudophakic and phakic DMO patients. The RWE studies and their results are critiqued by the ERG in Section 3 and the ERG's conclusions on the clinical effectiveness evidence supplied in the CS are reported in Section 3.7.

2.3 Critique of the company's definition of the decision problem

Table 9. Summary of decision problem (Adapted from CS, Table 2)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Population	Phakic DMO patients who are insufficiently responsive to or unsuitable for the non-corticosteroid treatment	As per final scope	Although the submission does consider the full population outlined in the final scope, the economic analysis only considers insufficient responders because there is no relevant additional evidence available to model this specific population beyond the data that was presented in TA349. However, given the high unmet need in this population, the clinical benefit of DEX700 and the limited size of this population (and therefore the small contribution this population would make to the overall cost-effectiveness in the broad population), consideration is given to this sub-population throughout the clinical evidence section.	The primary evidence base in the CS to address the decision problem is from post hoc analyses of the MEAD trials (DEX700 and sham). Additionally, data from a UK RWE audit investigating suboptimal anti-VEGF treatment is used to inform the insufficiently responsive to non-corticosteroid population. The ERG notes that the prior treatments in the MEAD trials [redacted]. The ERG also notes that a history of use of intravitreal bevacizumab or ranibizumab in the 3 months prior to study entry was an exclusion criterion in the MEAD trials. Additionally, the population of the MEAD trials comprised of [redacted] compared to the UK RWE audit and this was supported by the ERG's clinical experts. The ERG is therefore concerned that the DEX700 data from the MEAD trials does not reflect patients with [redacted]

				[redacted] (Section 2.3.1).
Intervention	Dexamethasone intravitreal implant	As per final scope	N/A	The intervention in the DEX700 arms of the MEAD trials is in line with the scope and the EU marketing authorisation for DEX700. The ERG notes that the company conducted an ITC to compare DEX700 in the MEAD trials with DEX700 in the real-world. However, the ERG considers this ITC to be of little relevance to the decision problem given that [redacted]. Additionally, the resulting effective sample size for the ITC after matching was extremely low and thus the results are subject to high levels of uncertainty.
Comparator(s)	• Laser photocoagulation alone • Wait-and-wait (for people who are unsuitable for treatment with both anti-VEGFs and laser photocoagulation) The following technologies alone or in combination with laser photocoagulation: • Aflibercept (only if the eye has	Phakic DMO patients who are insufficiently responsive to non-corticosteroid treatment are: • Laser photocoagulation alone The following technologies alone or in combination with laser photocoagulation: • Aflibercept (only if the eye has a central retinal thickness of	Given the change in treatment pathway accepted in TA613, the economic analysis only considers anti-VEGF therapies. UK clinical feedback also confirms this is the only relevant comparator in the insufficiently responsive population, which is	The ERG notes that the sham arm in the MEAD trials comprises no treatment and patients requiring rescue therapy were required to discontinue from the studies. The ERG does not consider clinical evidence for the efficacy of laser alone compared with DEX700 has been

	a central retinal thickness of 400 micrometres or more) • Bevacizumab (does not currently have a marketing authorization in the UK for this indication) • Ranibizumab (only if the eye has a central retinal thickness of 400 micrometres or more) Comparators for phakic DMO patients who are unsuitable for the available therapies: • Watch and wait	400 micrometres or more) • Bevacizumab (does not currently have a marketing authorization in the UK for this indication) • Ranibizumab (only if the eye has a central retinal thickness of 400 micrometres or more)	the only population that is formally considered in the economic analysis	provided in the CS. The ERG also notes that the data provided for the anti-VEGFs (aflibercept, bevacizumab and ranibizumab) are from a single arm UK RWE audit and the results of the MAICs/STCs conducted by the company are subject to uncertainty. The ERG notes that the company does not include bevacizumab in the economic model and that the anti-VEGFs, ranibizumab and aflibercept, are [redacted] in the economic model. The ERG considers this to be reasonable based on its experts' advice. The ERG notes that the company considers watch and wait to only be a comparator for the unsuitable for non-corticosteroid population, although the populations are not considered separately in the model and cost-effectiveness of DEX700 versus watch and wait is not reported in the CS. The ERG notes that the company conducted an ITC to compare sham in the MEAD trials with suboptimal anti-VEGF in the UK RWE audit but is concerned about the reliability of the results of this analysis.
Outcomes	• Best corrected visual acuity (the affected eye) • Best corrected visual acuity (both eyes)	As per final scope	N/A	The ERG notes that no data from the phakic DMO subgroup of the MEAD trials are reported in the clinical

	• Central foveal subfield thickness • Central retinal thickness • Contrast sensitivity • Mortality • Need for cataract surgery • Adverse effects of treatment (including cataract formation and glaucoma) • Health-related quality of life, including the effects of changes in visual acuity			effectiveness sections of the CS for the outcomes of: • Best corrected visual acuity (both eyes); • Central foveal subfield thickness; • Contrast sensitivity; • Mortality; and • Glaucoma adverse events. However, the ERG's clinical experts have confirmed that the outcomes covered in the CS represent the key clinical outcomes of relevance to clinical practice. The ERG also notes that in terms of mortality, there were just 9 deaths in the DEX700 group of the full trial population across the two MEAD trials, and none of the deaths were due to ocular adverse events or considered by investigators to be related to treatment assignment. Additionally, the ERG notes that glaucoma does not feature in the Table of treatment-related ocular AE's that occurred in ≥ 2% of patients in the MEAD trials (Table 17) and thus the ERG considers the incidence of glaucoma related to DEX700 use in the MEAD trials is likely to be low.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in	The cost-effectiveness of treatments will be expressed in terms of incremental cost per quality-adjusted life year.	N/A	The economic analysis is in line with the NICE reference case. The company provided a cost-utility analysis, the time horizon was set to

	terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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 commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. Cost-effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.	The time horizon for estimating clinical- and cost-effectiveness is lifetime (40 years) and is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Longer time horizons are explored in scenario analyses.* Costs are considered from an NHS and Personal Social Services perspective. There is no commercial arrangement for DEX700. Aflibercept and ranibizumab are subject to confidential patient access scheme discounts, these have therefore not been applied in this submission as the value of discount is not known. The presented cost-effectiveness analysis considers treatment in either the best or worst seeing eye, or in both eyes.		lifetime, the perspective of the analysis was based on the UK NHS and costs and benefits were discounted using an annual rate of 3.5%. The ERG also notes that the modelling approach and model structure is consistent with that used in the previous NICE appraisal of DEX700 in DMO (TA349). However, the ERG considers the company's long-term modelling assumptions to be too simplistic to accurately capture the costs and consequences over a lifetime time horizon.
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include:	Several exploratory sub-analyses of the phakic-only population from	Exploratory post-hoc analysis of the MEAD data was performed to investigate the impact of	In addition to the subgroup analyses already mentioned by the company, the company conducted post hoc

	• 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, aflibercept, ranibizumab or bevacizumab)	MEAD were conducted (CS Section B.2.6.4.1) to explore: • Timing of cataract surgery • Timing of DEX700 implant prior to cataract surgery • Impact of lens opacity • Impact of diabetes duration • Impact of DMO duration • Impact of cataract surgery • Impact of prior treatment	some of the known limitations of the MEAD study. The sample size of the sub-populations is too small to draw firm conclusions from the results, and while a test of statistical significance was performed, no claims for statistical significance are made.	subgroup analyses of the MEAD trials for patients with baseline CRT ≥ 400 µm, and CRT < 400 µm in their response to clarification questions. These CRT thresholds align with those in the NICE TA guidance for the ant-VEGFs ranibizumab and aflibercept. The ERG notes that the company did not provide subgroup analyses by baseline visual acuity and considers this may have been useful given the potential discrepancy in visual acuity between the MEAD trials and the UK RWE.

* The ERG considers that the company explored shorter time horizons (30 and 15 years) in scenario analyses.

Abbreviations: CS, company submission; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ERG, evidence review group; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; VEGF, vascular endothelial growth factor; MAIC, matching-adjusted indirect comparison; STC, simulated treatment comparison; ITC, indirect treatment comparison; RWE, real world evidence; CRT, central retinal thickness.

2.3.1 Population

The ERG notes that the population of interest for this STA is phakic DMO patients who are insufficiently responsive to, or unsuitable for non-corticosteroid treatment. The clinical data from the MEAD trials comprises combined data for both of these two subpopulations (insufficient responders to non-corticosteroid treatment and unsuitable for non-corticosteroid treatments) with the exception of a subgroup analysis to assess the impact of prior therapy on mean BCVA change from baseline. The ERG does not consider the MEAD trials subgroup analysis of prior therapy versus no prior therapy to provide robust evidence that there would be no difference in effectiveness with DEX700 in patients deemed insufficiently responsive to non-corticosteroid treatments compared to patients who are unsuitable for non-corticosteroid treatment. Additionally, the ERG's clinical experts highlighted that a small proportion of the phakic unsuitable for non-corticosteroid treatment population may have had prior therapy and therefore not be treatment naïve. However, based on clinical advice, the ERG also acknowledges that the unsuitable for non-corticosteroid population is likely to comprise a much smaller population compared to the insufficiently responsive to non-corticosteroid population (ERG experts estimate approximately 20 to 40% of phakic DMO patients).

The ERG's clinical experts reported that there is no standard definition of insufficient response to non-corticosteroid treatments, although the company reported that in the published literature, patients who are insufficiently responsive to non-corticosteroid treatment are defined as having < 5 letters gain at 6 months post-treatment. The ERG's clinical experts agreed this is a reasonable definition and the ERG notes that the definition of insufficient response used in the UK RWE audit was ≤5 letter gain. However, the ERG notes that patients recruited to the MEAD trials were not required to meet any specific criteria of insufficient response to prior therapies. The inclusion criteria of the MEAD trials only required patients to have had previous medical or laser photocoagulation therapy, or to have refused, or in the opinion of the investigator be unable to benefit from laser photocoagulation therapy. The ERG is concerned that the total proportion of patients in the MEAD trials with prior anti-VEGF therapy (approximately [redacted]%) is [redacted] (ERG's clinical experts estimate 20 to 40%).

The ERG's clinical experts also reported that the prior use of laser in the MEAD trials (approximately [redacted]%) was [redacted] in current UK clinical practice for both centre involving DMO, which was the population in the MEAD trials, and the whole phakic DMO population. Additionally, the population of the MEAD trials comprised of [redacted]

[redacted] compared to the UK RWE audit and the ERG's clinical experts also agreed that the MEAD trials represented [redacted] compared to expected UK clinical practice.

In summary, the ERG is concerned that the data from the MEAD trials does not reflect patients with an insufficient response [redacted] and that the MEAD trials population has [redacted] than expected in UK clinical practice. The ERG is also unsure whether a difference in clinical efficacy would be seen in the unsuitable for non-corticosteroid therapy population compared to the insufficient response to non-corticosteroid population.

2.3.2 Intervention

Dexamethasone 700 µg (DEX700) intravitreal implant in applicator (Ozurdex®) is an injectable intravitreal implant that can be used to treat DMO and improve visual acuity. The company reports that DEX700 delivers high concentrations of dexamethasone during the initial 2 months post-implant, and levels decline over the following 4 months.[9] The recommended treatment regimen is therefore one DEX700 implant at approximately 6-month intervals for patients who experience a response to treatment that is subsequently followed by a decrease in visual acuity or increase in macular oedema and, in the treating clinician's opinion, may benefit from retreatment.

The ERG notes that DEX700 has European marketing authorisations that include 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.[10] Table 3 in the CS provides a summary of the key features of DEX700.

2.3.3 Comparators

The ERG sought clarification from the company for their decision to only include watch and wait as a comparator for patients who are unsuitable for non-corticosteroids and not also as a treatment option for patients with an insufficient response to non-corticosteroids. The company response included an argument that this was accepted in TA613,[5] and detailed that due to a lack of alternative treatments, phakic DMO patients who have an insufficient response to non-corticosteroids will continue to receive anti-VEGF/laser therapy to try to achieve a response and/or maintain the retinal architecture.[6, 11, 12] The company acknowledged that there is likely to be a small proportion (~5%) of complete non-responders who may discontinue anti-VEGF treatment, but these patients will be monitored and could receive further treatment if they deteriorate. The ERG notes that the

EURETINA guidelines for ranibizumab state that: "*If no more functional or anatomical benefit occurs, the treatment must be stopped, and extended monitoring intervals can be evaluated for each patient individually*".[13] The ERG therefore considers watch and wait to be a possible comparator for the patients with insufficient response to non-corticosteroids but acknowledges it is likely to be a small population.

The ERG does not consider the sham arm of the MEAD trials can be assumed to overestimate the efficacy of continued anti-VEGF use in patients deemed to be insufficiently responsive to anti-VEGF treatment as there are marked differences in the patient population in the MEAD trials compared to patients in UK clinical practice. Additionally, the ERG does not consider the ITC of the sham arm from the MEAD trials with continued anti-VEGF use in the UK RWE audit to be appropriate to draw conclusions regarding any differences in efficacy due to high levels of uncertainty in the results of the analyses. During clarification the ERG requested the company use the phakic cohort from the French RWD for DEX700 and the suboptimal responder cohort from the UK RWE to inform continued anti-VEGF treatment to conduct an adjusted indirect comparison that would help address the uncertainties with the MEAD trials. However, the company replied that they do not have access to the necessary data from the RWE studies to conduct these analyses.

Finally, as discussed in Section 2.2.1, the ERG's clinical experts agree with the company that use of laser in DMO has reduced and is likely to be lower than the 28% suggested in TA613.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trial (RCT) data and real world evidence (RWE) for phakic diabetic macular oedema (DMO) patients who are unsuitable for or insufficiently responsive to non-corticosteroid treatment. The Evidence Review Group (ERG) notes that the electronic database searches were conducted on 12 January 2021 with update searches undertaken on 24 September 2021.

A total of 44 studies (extracted from 94 publications) were included in the company's SLR, and evaluated either the use of DEX700 or a comparator of relevance (or both). The 44 included studies comprised of seven RCTs (the MEAD trials were counted as one RCT), two comparative non-RCTs, four single-arm non-RCTs and 31 RWE studies (CS appendices, Table 5). In addition, the ERG notes that the company included data from three further studies in the clinical effectiveness results section of the company submission (CS). These three studies comprised a collaborative study by AbbVie and PI to explore outcomes of DEX700 in treatment-naïve and/or previously treated DMO patients with phakic and pseudophakic eyes using existing databases to provide data (French real-world data [RWD]), a UK RWE audit of UK clinical practice that was conducted to [redacted] and a retrospective analysis of publicly available data from the Protocol T study[14, 15] to compare outcomes with anti-VEGF treatment in phakic versus pseudophakic eyes.

Of the 31 RWE studies identified by the SLR, 21 RWE studies provided data for DEX700. However, the company also identified and included a further 22 RWE studies for DEX700 that they deemed to be relevant to the decision problem, although they reported that they did not meet the restrictive inclusion criteria of the SLR. The ERG is unclear as to exactly how these additional 22 studies were identified as it is only reported that they were "known to AbbVie". Table 6 in the CS presents a list of all 43 published RWE studies identified for inclusion from either the SLR or directly by AbbVie.

The final list of studies used in the CS are detailed in Table 10. The ERG notes that some of the 44 studies identified from the SLR are not used in the CS and reasons for their exclusion from the indirect comparison are summarised in Table 6 of the CS appendices. The company considered the MEAD-010 and MEAD-011 RCTs to be the most robust data sources providing evidence for the use of DEX700 in phakic DMO patients who are unsuitable for or insufficiently responsive to non-

corticosteroid and has presented data from subgroup analyses and RWE studies to provide supportive evidence. Based on the advice of clinical experts, the ERG considers the company's choice of studies to be reasonable, with the exception of Protocol T which is reported to provide supportive clinical evidence.

Protocol T was a USA multicentre RCT conducted by the Diabetic Retinopathy Clinical Research (DRCR) Retina Network to compare the efficacy and safety of anti-VEGFs (aflibercept, bevacizumab and ranibizumab) in the treatment of visually impaired patients with centre-involved DMO. The company conducted a retrospective analysis using the publicly available 2-year data from the Protocol T study to assess whether outcomes in patients who were insufficiently responsive after 12 weeks of treatment were consistent between phakic and pseudophakic eyes, and robust to alternative definitions of insufficient response.[16] The company's analysis pooled data from the 3 anti-VEGF treatments and assessed BCVA change from baseline and 10-letter BCVA improvement at weeks 52 and 104. The company reported that there was a higher frequency of anti-VEGF injections compared with what has been observed in UK clinical practice, and they did not consider PROTOCOL T to be directly comparable to UK practice. The ERG does not consider the efficacy of anti-VEGFs in phakic compared to pseudophakic patients to be of relevance and given the availability of UK RWE on anti-VEGFs the ERG does not discuss the Protocol T study or its results further.

Table 10: Summary of evidence used in the CS (Reproduced from CS, Table 4)

Study name	Primary clinical evidence	Supportive clinical evidence	Economic model base case
DEX700			
MEAD-010/MEAD-011	✓	×	✓
MEAD-010/MEAD-011 subgroup analyses	×	✓	×
DEX700 published RWE studies	×	✓	×
French RWD	×	✓	×
Comparator treatments			
UK RWE audit	✓	×	✓
Protocol T	×	✓	×

Key: DEX700, dexamethasone 700 µg; RWD, real-world data; RWE, real-world evidence.

Notes: A full list of published RWE studies is provided in the company submission Section B.2.2.1.1 (Table 6). Of note, the efficacy for the comparator is based on the sham data presented in MEAD. Efficacy data from the UK RWE audit has been used to inform treatment costs and scenario analysis only.

An overview of the methods used by the company for the SLR, together with the evidence review group's (ERG) critique of the appropriateness of these methods, is presented in Table 11. In summary, the ERG considers the methods applied by the company to be robust and likely to have identified all clinical evidence of relevance to the decision problem although the ERG is unclear how the Protocol T study was identified.

Table 11. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data sources	Appendix D, section D1.1.	**The ERG considers the sources and dates searched to be appropriate.** Databases searched: MEDLINE, Embase, MEDLINE In-Process and the Cochrane Library (CENTRAL and CDSR). Additional sources: Checking reference lists of identified systematic reviews and meta-analyses, and hand-searching of conference proceedings (published in 2019 to 2021). Latest search update: 24 September 2021.
Search strategies	Appendix D, section D1.1	**The ERG is satisfied that searches have identified all evidence relevant to the decision problem.** Search strategies for the literature review combined comprehensive terms for the population, interventions and study designs, using free-text and medical subject headings.
Inclusion criteria	Appendix D, section D1.2	**The ERG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** Inclusion criteria were in line with the NICE final scope. Full reference details are available in the CS Appendix for included studies, and a supplementary file with studies excluded at full-text appraisal was also supplied.
Screening and data extraction	Appendix D, section D.1.2 and D.1.3	**The ERG considers the methods for screening and data extraction to be robust.** Two reviewers independently screened titles and abstracts, and subsequently studies selected for full text appraisal, against predefined criteria, with a third reviewer consulted when consensus could not be reached. Results of the literature screening processes were summarised in a PRISMA diagram. Data extraction was carried out by one reviewer, with a second researcher independently quality checking the extracted data.
Tool for quality assessment of included study or studies	B.2.5 & Appendix D, section D.4.	**The ERG agrees with the company's choice of quality assessment tool for assessing the pooled MEAD RCTs.** The company used the standard NICE checklist for the quality assessment of the MEAD trials. No quality assessments were provided for the non-RCT studies.

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; CDSR, Cochrane Database of Systematic Reviews; CS, company submission; ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

In subsequent sections, the ERG focuses on aspects of study design, conduct and external validity of the MEAD trials, the DEX700 RWE studies, the French RWD and the UK RWE audit.

3.2.1 MEAD-010 and MEAD-011

MEAD-010 and MEAD-011 were both 3-year, Phase III, multicentre 3-armed RCTs designed to assess the safety and efficacy of DEX700, DEX350 (i.e. dexamethasone 350 µg intravitreal implant in applicator) and sham (needleless applicator) in patients with DMO.[17] The ERG notes that the trial design, endpoints and patient eligibility criteria were consistent between the two trials. For this appraisal, only the DEX700 and sham arms from the phakic subgroups of the trials are of relevance and the data from MEAD-010 and MEAD-011 have been pooled with all analyses of the pooled data referred to as the MEAD trials.

The randomised intervention was given at Day 0 and assessment for re-treatment occurred every 3 months from Month 6 onwards with a maximum of six re-treatments allowed. The ERG notes that final treatment was initially allowed in Month 33 but after a study protocol amendment in May 2010, patients who had not yet completed the study and who met retreatment eligibility criteria could be retreated at Month 36 and received final study follow-up at an additional study visit at Month 39. However, the company reported that over 50% of patients had completed or discontinued the study before the protocol amendment (number for phakic subgroup not reported).[17] Full details of the MEAD trials interventions and timings are provided in the CS Figure 5.

The ERG's assessment of the design, conduct and internal validity of the MEAD trials is summarised in Table 12. The ERG broadly agrees with the company's assessment of the MEAD trials as generally being at low risk of bias for analysis of the primary outcome, based on the full trial population, although the ERG considers it important to highlight that results from the phakic subgroup are used in the economic model and this comprises a *post hoc* non-randomised subgroup that was not statistically powered to detect differences in efficacy for any of the outcomes. Additionally, the ERG notes that there was [redacted] proportion in the sham arm compared to the DEX700 arm.

The company has used the last observation carried forward (LOCF) approach to account for missing observations in the primary analysis of change in visual acuity outcomes over time in the MEAD trials. The company reports that there is, "*high risk of informative censoring as participants are lost to follow-up due to reasons related to the study*". The ERG notes that the primary reasons for missing data are due to patients discontinuing the study treatment (due to a lack or loss of efficacy or adverse events) or due to censoring of patients receiving of rescue therapy.

During clarification the ERG requested the company conduct analyses using the multiple imputation approach to inform the missing data but the company argued this approach was not appropriate and did not provide the requested analyses. The company's argument included concerns that the multiple imputation approach would likely overestimate the longer-term outcomes of the missing patients because it would be based on the remaining observed patients who were likely to be experiencing better vision-related outcomes to those who were censored or discontinued due to lack (or loss) of efficacy. The company were therefore concerned that multiple imputation analysis would bias in favour of the sham arm as there is a greater proportion of sham patients with missing data due to receipt of rescue therapy or lack (or loss) of efficacy.

The ERG acknowledges that the discontinuation rate in the MEAD trials was [redacted] in the sham arm of the phakic subgroup [redacted] compared with the DEX700 arm [redacted]. However, the ERG is concerned that patients in the DEX700 arm will potentially have a higher BCVA at the point of discontinuation compared with the sham arm, and this benefit will be retained in the LOCF analyses. Additionally, the ERG considers it possible that vision in DEX700 patients could deteriorate more after treatment discontinuation relative to any worsening of vision in sham patients after they have discontinued.

The ERG notes that the natural history of DMO suggests that vision deteriorates over time and therefore the LOCF approach may be optimistic for both the DEX700 and sham arms as vision in patients with missing data cannot worsen.[18] The ERG is, therefore, concerned that results for both the sham and DEX700 arms are likely to be biased and considers it difficult to predict the likely direction of the resulting bias for the comparison of DEX700 versus sham from using a LOCF approach to account for missing data.

The company also argued that the multiple imputation approach wasn't appropriate because data in the MEAD trials were not missing at random. However, the ERG considers the LOCF approach also requires data to be missing at random and considers all of the analyses using the LOCF approach are of questionable veracity.[18, 19]

Table 12. ERG's summary of the design and conduct of the MEAD trials

Aspect of trial design or conduct	Section of CS providing details on trial characteristic	Summary of MEAD trials
Trial conduct		
Randomisation	B.2.5 and Boyer *et al*. 2014[17]	**Appropriate** Randomised design with parallel assignment of participants in 1:1:1 ratio to DEX700, DEX350 or sham. The ERG notes that randomisation was not stratified by phakic/pseudophakic status at baseline.
Concealment of treatment allocation	B.2.5 and Boyer *et al*. 2014[17]	**Appropriate** Each site used an interactive voice-response or web-response system to assign randomisation numbers to patients. Treatment assignment was based on enrolment order and a computer-generated randomisation scheme provided by the sponsor.
Eligibility criteria	B.2.2.1 and B.2.3.1	**Appropriate** Patients aged > 18 years diagnosed with Type 1 or 2 diabetes mellitus who had fovea-involved macular oedema associated with diabetic retinopathy and had been previously treated with medical or laser therapy. Treatment-naïve patients who had refused laser treatment or who, in the opinion of the investigator, would not benefit from laser treatment were also enrolled. Additionally, only patients with a phakic lens at baseline were included in the phakic subgroup analyses. The MEAD trials inclusion and exclusion criteria are summarised in the CS Table 7.
Baseline characteristics	B.2.3.1.1	The ERG considers the baseline characteristics to be reasonably well balanced between the DEX700 and sham arms of the phakic subgroup of the MEAD trials although the ERG notes that there is a [redacted] in the DEX700 arm ([redacted]%) compared with the sham arm ([redacted]%). Full baseline characteristics from the MEAD trials available in Appendix 9.1.
Masking appropriate	B.2.5 and Boyer *et al*. 2014[17]	The patients, the study personnel who collected efficacy data, and the follow-up investigator who performed safety evaluations at other study visits, were all masked to the treatment assignment. However, the treating investigator who administered the study treatment was not masked and the ERG notes that the nature of the sham intervention prohibited masking.
No difference between groups in treatments	B.2.3.1	No evidence to suggest a difference between groups in treatments given for DMO additional to the allocated intervention.

given, other than intervention versus control		Escape therapy for macular oedema in the study eye including intravitreal steroids other than the study medication, periocular steroids, laser or surgical treatments for macular oedema, anti-VEGF therapy, systemic anti-VEGF therapy, and other pharmacologic therapy for macular oedema was not permitted during the study. However, therapy considered necessary for the patient's welfare could be given at the discretion of the investigator for other conditions such as the treatment of elevated IOP, proliferative diabetic retinopathy and cataracts. Cataract surgery was required to take place within 3 months of the last retreatment where possible and not within 30 days prior to a retreatment visit.
Dropouts (high dropout and any unexpected imbalance between groups)	Company response to CQ A1 and A13	The proportion of patients who discontinued study treatment was [redacted] the sham arm of the phakic subgroup [redacted] compared with the DEX700 arm [redacted]. Discontinuation due to lack (or loss) of efficacy occurred in [redacted]% of phakic DEX700 patients and [redacted]% of phakic sham patients whereas discontinuation due to AE or other non-efficacy related reasons was [redacted] ([redacted]% with DEX700 versus [redacted]% with sham). The ERG notes that [redacted]% of DEX700 patients and [redacted]% of sham patients were censored due to the receipt of rescue therapy.
Outcomes assessed	B.2.3.1	All clinically relevant outcomes appear to have been reported in publications for the full ITT population, although the ERG notes that only data from the phakic subgroup are discussed in the CS and used in the economic model. The ERG considers the company's reporting of outcomes to address the NICE decision problem to be appropriate. The primary outcome in the MEAD trials was mean BCVA average change from baseline[a] with BCVA measured using the ETDRS method. Average change in the study eye was measured using the AUC approach. Results for this outcome and other outcomes of relevance to the NICE final scope for the phakic subgroup are discussed in Section 3.3.1.
ITT analysis carried out	B.2.4 and company response to CQ A12	The modified ITT (mITT) population forms the basis for analyses of efficacy of the phakic subgroup. The mITT population of the pooled MEAD trial is defined as all DMO patients enrolled into the study who had attended at least 1 follow-up visit. The phakic-only mITT population consists of [redacted] phakic DMO patients, [redacted] in the DEX700 arm, and [redacted] into the sham arm. The ITT population comprised of an additional [redacted] patients who did not attend at least 1 follow-up visit and [redacted]
Subgroup analyses	B.2.7 and company response to CQ A8 to A10	The phakic subgroup from the MEAD trials comprised a *post hoc* analysis and additional subgroup analyses on the phakic population were reported in the CS to explore the impact of prior treatments for DMO and various outcomes relating to cataracts. These subgroup analyses and their results discussed in detail in Section 3.4. In addition, in response to clarification questions, the company provided further post-hoc exploratory subgroup analyses to explore outcomes by baseline CRT ≥ 400µm, and baseline CRT < 400µm. These are also discussed in Section 3.4
Statistical analysis plan		
Sample size and power	B.2.4	The sample size for the ITT population of the MEAD trials was based on the assumption of a four-letter mean difference (delta) in the change in average BCVA from baseline during the study for DEX700 over sham. The planned

		sample size was 170 patients per arm (510 patients total) for each of the MEAD trials and this meant each study would have a power of 86% (two-sided alpha of 0.05). The phakic subgroup of the MEAD trials comprised a retrospective *post hoc* analysis and therefore was not powered to detect a statistically significant difference between treatment groups (DEX700 and sham).
Analysis sets	B.2.4 and company response to CQ A11	The primary analysis included all randomised eyes and followed the ITT principle with missing values imputed by last observation carried forward except for AUC analysis that was conducted using observed data. The ERG notes that the efficacy results presented in the CS relate to the mITT population of the phakic subgroup (all DMO patients enrolled into the study who had attended at least 1 follow-up visit).

Abbreviations: CS, company submission; ERG, evidence review group; DMO, diabetic macular oedema; IOP, intra-ocular pressure; ITT, intention to treat; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; AUC, area under curve; NICE, National Institute for Health and Care Excellence,

Notes: [a], the primary outcome measure of clinical efficacy for Europe was mean change in average BCVA from baseline. 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. This amendment was in line with changes in regulatory precedent and standard of care for DMO in the period over which the MEAD trials were conducted.

3.2.1.1 External validity of the MEAD trials

Firstly, the ERG notes that when the MEAD trials were designed, anti-VEGFs were not widely used by patients enrolling into the study and therefore the proportion of phakic patients who have received prior anti-VEGF treatment in the DEX700 group [redacted] is [redacted] in current UK clinical practice. The generalisability of the results of the MEAD trials to the insufficiently responsive to non-corticosteroid population of interest is therefore questionable and the ERG is unable to predict which direction any potential bias may lie.

The ERG also notes that [redacted] of phakic DMO patients had pre-existing cataracts at baseline in the DEX700 arm of the MEAD trials, which ERG's clinical experts reported is [redacted] compared with UK clinical practice, although it is not clear what proportion of the cataracts in the MEAD trials were deemed to be clinically significant. The proportion of patients with lens opacity at baseline was confirmed in [redacted] of patients, and considered questionable in a further [redacted] of phakic DMO patients in the DEX700 arm of the MEAD trials. The ERG also notes that [redacted]% of phakic patients in the DEX700 arm of the MEAD trials had a baseline BCVA of <50 ETDRS letters and the ERG's experts reported that [redacted] would be expected in UK clinical practice.

The ERG notes that the company considers the baseline characteristics in the MEAD trials to be poorer than those observed in clinical practice and that the outcomes of the MEAD trials can be classified as being conservative. However, while the ERG does consider that the MEAD trials

comprise patients with a [redacted], the ERG does not consider it possible to predict the direction of any potential resulting bias related to baseline differences in the MEAD trials compared with UK clinical practice.

3.2.2 DEX700 real-world evidence studies

As discussed in Section 3.1, 43 RWE studies for DEX700 were included by the company. The ERG notes that one of the RWE studies comprised a review of studies evaluating the efficacy of anti-VEGF and dexamethasone (DEX) implants for DMO but there was no detail in the publication on the proportion of patients who were phakic.[7] The ERG also notes that a further two RWE studies[20, 21] comprised additional analyses from the MEAD trials. One of the additional MEAD publications was evaluating the occurrence, management, and clinical significance of increases in intraocular pressure (IOP) in the MEAD trials and other was a subgroup analysis of previously treated DMO patients.

The company has used the 43 RWE studies of DEX700 to provide supportive data for the safety and efficacy of DEX700 in the CS but the data from these studies are not used in the economic model. The ERG notes that the company uses data from the DEX700 RWE studies to provide information on the following:

- Outcomes in patients with phakic versus pseudophakic DMO (seven studies);
- Switching from anti-VEGFs to DEX700 (21 studies);
- Visual outcomes in treatment naïve patients with DMO (seven studies);
- Timing of DEX700 injections in relation to cataract surgery (four studies).

The ERG does not consider the comparison of DEX700 in phakic versus pseudophakic DMO patients to be of relevance as the NICE final scope specifies the population for this technology appraisal to be phakic patients, and the company has data for the phakic population from the MEAD trials. The ERG also notes that a large proportion of the remaining RWE studies included mixed pseudophakic and phakic populations and not all studies reported outcomes separately for the phakic subgroup. The results reported in the CS for the RWE studies are presented as a narrative synthesis and the ERG is concerned that some of the results are lacking in detail making interpretation challenging. Due to the large volume of RWE studies it was deemed not to be feasible for the ERG to review them all. Additionally, given that only the MEAD trials and French RWD are used to inform the estimates of DEX700 in the economic model, the ERG does not discuss the results of the 43 additional DEX700

RWE studies. However, the company's review of the RWE studies is available in the CS Section B.2.3 and the CS appendix M.1.

3.2.3 French RWD

The French real-world data (RWD) comprised of retrospective analysis of data from five French databases and was designed to explore outcomes following treatment with DEX700 in phakic eyes of treatment-naïve or previously treated DMO patients.[22] The French RWD also included a comparison of outcomes in phakic versus pseudophakic eyes which the ERG does not discuss. The ERG notes that the data from the phakic subgroup are used in a scenario analysis in the economic model and thus the ERG critiques these data.

In total, [redacted] eyes of [redacted] DMO patients were included in the French RWD study, of which [redacted] eyes were phakic at baseline. In the phakic subgroup, the mean age at baseline was [redacted] (standard deviation [SD] [redacted]) which is [redacted] compared to in the DEX700 arm of the MEAD trials ([redacted] years [SD [redacted]]) and to the ERG's clinical experts' expectations for the age of the expected UK phakic DMO population. However, the ERG notes that there is a [redacted] in the French RWD compared with in the MEAD trials ([redacted]% compared with [redacted]%, respectively). The ERG also notes from its clinical experts that the majority of phakic DMO patients in England who are likely to be treated with DEX700 would be expected to have received prior therapy (and be deemed to be insufficiently responsive to non-corticosteroid therapy) and therefore the ERG is [redacted] for this characteristic.

The mean baseline visual acuity (VA) for the phakic population was [redacted] ETDRS letters (SD [redacted]) but baseline VA for the MEAD trials was reported as proportion of patients with BCVA <50 so the ERG is unsure how the studies compare for this characteristic. Further baseline demographics for the French RWD are available in the CS Appendix M.2.1.

3.2.4 UK RWE audit

The UK RWE audit was a retrospective, cohort study that used data from two UK ophthalmology centre databases between 2015 and March 2020.[23] The company reported that the primary objectives of the UK RWE audit were to identify the proportion of phakic DMO patients who were insufficient responders to initial anti-VEGF injections evaluated at month 3 and month 6, and to provide long-term data on visual acuity and anatomical outcomes for these patients.

No significant difference was observed between the proportion of suboptimal and optimal responders at 3 and 6 months, although the company reported that the later time-point resulted in a larger sample size and so they presented results in the CS based on suboptimal responders at 6 months (the 3 month results were provided in the CS. Appendix M.3.2). The ERG's clinical experts reported that a 6-month cut-off for assessment of response to anti-VEGFs is reasonable and therefore the ERG also focuses on the population and results based on the 6-month definition of suboptimal response in the UK RWE audit.

The UK RWE audit included [redacted] phakic eyes from [redacted] patients who had received anti-VEGF treatment for DMO and [redacted] phakic eyes from [redacted] patients were deemed to be suboptimal responders to anti-VEGFs at 6 months. The ERG considers that the baseline characteristics reported for the UK RWE audit are limited as they relate to the baseline at time of first treatment with anti-VEGFs and data on prior laser therapy [redacted] of eyes.

The mean age for first anti-VEGF (first eye) for phakic patients deemed suboptimal responders at month 6 in the UK RWE audit was [redacted] years (SD [redacted]) which is [redacted] the mean age of patients included in the sham arm of the MEAD trials ([redacted] years [SD [redacted]]). The ERG notes that the suboptimal responders in the UK RWE audit had a [redacted] mean BRVA at baseline compared with the optimal responders, with [redacted] of eyes in the suboptimal responder group having a mean baseline BRVA of >70 letters compared with [redacted]% of eyes in the optimal responder cohort. Similar to the French RWD, the ERG is unable to directly compare the baseline VA in the UK RWE with the MEAD trials baseline due to differences in baseline measurements but the ERG notes that the inclusion criteria in the MEAD trials required patients to have a baseline BCVA score between 34 letters and 68 letters in the study eye measured by the ETDRS method. The ERG also notes that [redacted] of the suboptimal responders in the UK RWE audit had evidence of pre-existing cataract at baseline which is [redacted] the proportion of patients with pre-existing cataract in the sham arm of the MEAD trials ([redacted]%).

3.3 Clinical effectiveness results

3.3.1 MEAD trials

The company reported that similar to the pseudophakic DMO population appraised in TA349,[2] they consider the results from the MEAD trials for the phakic population would not differ between DMO patients who are insufficiently responding to prior treatment, and those who are unsuitable for treatment with non-corticosteroid treatment. The company also provided the results from

exploratory subgroup analyses of phakic patients in the MEAD trials to compare pre-treated and treatment naïve patients to help validate this assumption (Section 3.4.2).

Additionally, the company reported that they consider the results of sham in the MEAD trials to be an overestimate of watch and wait in the phakic population because of the exclusion of patients who required rescue therapy. The ERG notes that this is also consistent with TA349, but that for the insufficiently responsive to prior treatment population in this appraisal the key comparator is continued anti-VEGF treatment rather than watch and wait. The ERG is therefore unsure what direction any potential bias from the sham arm in the MEAD trials may be in relation to the anticipated clinical effectiveness of continued anti-VEGF treatment in insufficient responders.

3.3.1.1 Best corrected visual acuity

There was [redacted] in the mean change in average BCVA (area under the curve [AUC] approach) measured from baseline to 39 months with DEX700 compared with sham in the phakic mITT population of the MEAD trials ([redacted] versus [redacted] ETDRS letters, respectively; [redacted]).[24] The ERG notes that there is a [redacted] in the mean change in BCVA from baseline with DEX700 compared to sham between months [redacted] (

Figure 2). The company reported that their expert panel considered this [redacted]. Beyond month [redacted] the BCVA [redacted] with DEX700 compared to with sham, which the company reported coincided with the timing of cataract extraction surgery in the DEX700 patients. The ERG notes that various *post-hoc* exploratory analyses were conducted by the company to investigate the impact of early versus late cataract extraction, lens opacity, and cataract surgery on a patient's BCVA (Section 3.4).

Figure 2. Change in BCVA (ETDRS letters) from baseline in phakic study eyes in the phakic population of the MEAD trials (LOCF analysis) (Reproduced from CS, Figure 6)

Key: BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward.

Source: AbbVie, 2021 (MEAD post-hoc analyses – Figures).[25]

The ERG notes that the results for ≥ 10 letter improvement in BCVA from baseline for the phakic mITT population from the MEAD trials were used in the economic model and that the results showed [redacted] months, [redacted] patients treated with DEX700 achieved a BCVA [redacted] of ≥ 10 letters from baseline compared with those receiving sham ([redacted];

Table 13).[24] Additionally, the ERG notes that [redacted] from baseline to 39 months was used [redacted] difference between DEX700 and sham ([redacted] versus [redacted]; [redacted]; Figure 3).[24]

For the outcome of ≥ 10 letter worsening in BCVA from baseline in the phakic mITT subgroup of the MEAD trials, the ERG notes that [redacted]

Table 13).

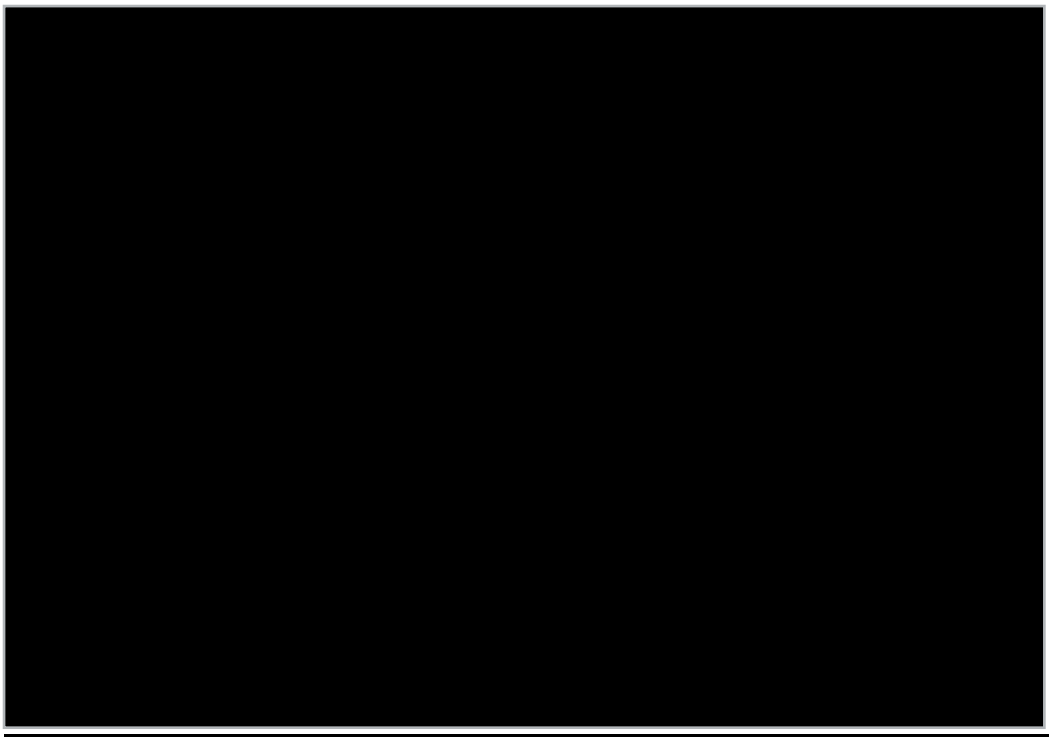
Table 13. Results for ≥ 10 letter improvement/worsening in BCVA from baseline for the phakic mITT population from the MEAD trials (LOCF analysis; Reproduced from company response to CQs, Table 7)

CQ A13		DEX700 (n=[redacted])	Sham (n=[redacted])	p-value	Difference, %	95% CI
a)	**≥ 10 letter improvement in BCVA from baseline, n (%)**					
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 391	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b)	**≥ 10 letter worsening in BCVA from baseline, n (%)**					
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BCVA, best-corrected visual acuity; CI, confidence interval; LOCF, last-observation carried forward; mITT, modified intention-to-treat.

Source: MEAD (2022)[26]

Figure 3. Proportion of patients with BCVA improvement of ≥ 15 letters from baseline in the phakic mITT population of the MEAD trials (Reproduced from CS, Figure 7)

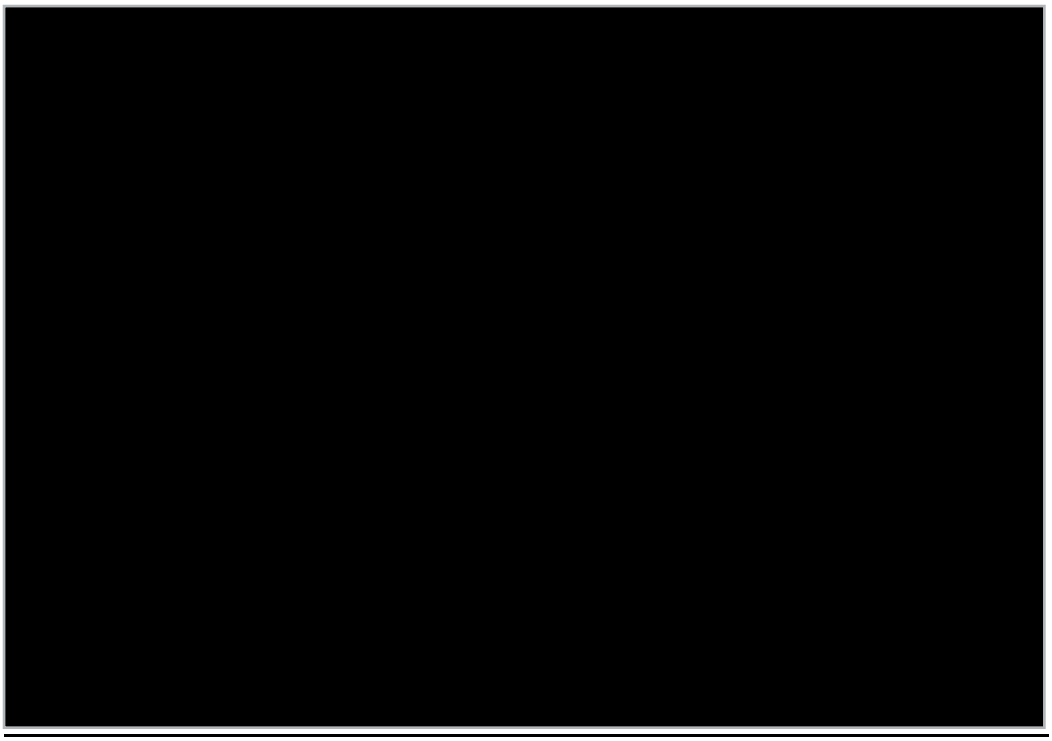


Key: BCVA, best-corrected visual acuity.
Source: AbbVie, 2021 (MEAD post-hoc analyses – Figures).[25]

3.3.1.2 Central retinal thickness

DEX700 [redacted] in study eye central retinal thickness (CRT) from baseline to 39 months for the phakic mITT population compared with sham (Figure 4). Additionally, the ERG notes that the mean [redacted] in CRT from baseline to month 39 with DEX700 compared with sham [redacted] versus [redacted]; [redacted]).[24]

Figure 4. Change in CRT from baseline in phakic study eyes from the MEAD trials mITT population (LOCF analysis; reproduced from CS, Figure 8)



Key: CRT, central retinal thickness; LOCF, last observation carried forward.
Source: AbbVie, 2021 (MEAD post-hoc analyses – Figures).[25]

3.3.1.3 Patient reported outcomes

Patient-reported outcomes in the *post hoc* phakic subgroup analysis of the MEAD trials were assessed using the National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25). The VFQ-25 consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item.[27] The ERG notes that VFQ-25 data were missing for some patients (%) in the phakic mITT population of the MEAD trials and missing data were not imputed in the analyses of average change in VFQ-25 scores from baseline to 39 months reported in Table 10 of the CS.

The results of the analyses for average change in VFQ-25 score from baseline to 39 months demonstrated for the overall composite VFQ-25 score, general vision, near vision, difficulty with distance vision and mental health symptoms due to vision domains (

Table 14).

Table 14. Average change in VFQ-25 scores from baseline to 39 months for phakic mITT population of the MEAD trials (Reproduced from CS, Table 10)

VFQ-25 parameter	DEX700 (n = [redacted])	Sham (n = [redacted])	p-value
Mean (SD) Overall Composite Score	[redacted]	[redacted]	[redacted]
Mean (SD) General Vision[a]	[redacted]	[redacted]	[redacted]
Mean (SD) Difficulty with Near Vision	[redacted]	[redacted]	[redacted]
Mean (SD) Difficulty with Distance Vision	[redacted]	[redacted]	[redacted]
Mean (SD) Mental Health Symptoms due to Vision	[redacted]	[redacted]	[redacted]

Key: SD, standard deviation; VFQ-25, Visual Functioning Questionnaire-25.

Notes: [a] The analysis included [redacted] patients in the DEX700 arm and [redacted] patients in the sham arm.

Source: AbbVie, 2021 (MEAD post-hoc analyses – Tables).[24]

3.3.2 *French RWD*

Phakic patients in the French RWD study received a mean of [redacted] (SD [redacted]) DEX700 injections and [redacted]% of phakic eyes also received focal laser during the follow-up, which the ERG notes was not allowed in the MEAD trials.

The French RWD [redacted] from baseline for mean change in BCVA at month 2 (mean improvement in BCVA of [redacted] letters; [redacted]), month 6 ([redacted] letters; [redacted]), month 12 ([redacted] letters; [redacted]), and month 36 ([redacted] letters; [redacted]) with DEX700 in the phakic subgroup of the French RWD. The ERG also notes that the mean change in BCVA from baseline to month 10 with DEX700 in the French RWD ([redacted] letters) was [redacted] compared to the change seen at 6 months ([redacted] letters) and 12 months ([redacted] letters), and the ERG is unsure of the rationale for this apparent [redacted] in efficacy.

The ERG considers that the improvement in visual acuity in the French RWD is generally [redacted] seen in the MEAD trials and also [redacted]. [redacted] The ERG is concerned that [redacted]

The ERG notes that data on the mean number of monitoring visits, the mean time to retreatment, reasons for discontinuation of DEX700 injections, and anatomical efficacy are presented in the CS Appendix M.2.2.

3.3.3 *UK RWE audit*

The UK RWE audit comprised [redacted] eligible phakic eyes from [redacted] patients that had received treatment for DMO with anti-VEGFs.[23] As discussed in Section 3.2.4, the ERG focuses its critique on the results from the UK RWE audit patients deemed suboptimal responders at 6-months. At [redacted] months, [redacted]% of eyes (n = [redacted]) in the UK RWE were deemed to have had a suboptimal response to treatment, defined as ≤ 5 letter gain at 6 months, and this increased to [redacted]% of eyes if suboptimal response is defined as ≤ 5 letter gain at 6 months or < 20% reduction in central subfield thickness. However, the ERG also notes that data were missing for [redacted]% of eyes at 6 months and it is unclear whether patients with missing data would differ from those with complete data.

The data available for BRVA in the UK RWE audit was originally reported in LogMAR and then converted to ETDRS letters. However, the company reported that because [redacted]% of the LogMAR results were only reported to one decimal place rather than two, some eyes were required to reach a 10 letter improvement (i.e. 2 lines) to make a > 5 letter gain, and therefore the proportion of patients classified as suboptimal responders may be overestimated. [redacted] the ERG also notes that the suboptimal group had a [redacted] and were [redacted] than those in the optimal group, which could also be related to the [redacted] resulting in [redacted] scope for improvement in the suboptimal group.

The mean change BRVA in the suboptimal group of the UK RWE audit is presented in Figure 5 and the ERG considers it important to highlight that in the analyses of the UK RWE audit data discussed in this section, the 6-month timepoint is when the patients are deemed to be suboptimal responders. The ERG thus considers that the 6-month timepoint should be assumed to be timepoint 0 in any comparisons, where the UK RWE audit data are used to reflect continued anti-VEGF treatment in patients deemed to be insufficient responders. The ERG considers that from 6 months to 48 months, the suboptimal responders from the UK RWE audit [redacted] letters (Figure 5).

Figure 5. Mean BRVA over time for the suboptimal group [redacted]

Abbreviations: BRVA, best recorded visual acuity

If 6-months is assumed to be the baseline in the UK RWE audit and 0-months the baseline in the MEAD trials, then the ERG considers the results from the UK RWE audit for change from baseline in mean BRVA (Figure 5) [redacted] (

Figure 2). However, the ERG notes that the MEAD trials report BCVA, whereas the UK RWE audit reports BRVA. In their response to clarification, the company reported that BCVA could result in a higher score than BRVA, but both use the same letter scales and so when considering improvements or worsening in vision as measured by gains or losses of letters, the two measures can be considered comparable.

The ERG notes that Figure 22 in the CS presents a naïve comparison of the mean BCVA change from baseline over time in the MEAD sham arm with UK RWE but as discussed above, the ERG is concerned that the baseline for the UK RWE audit is the start of anti-VEGF treatment and thus does not reflect the insufficiently responsive to non-corticosteroid treatment population that the company is modelling. The ERG does not consider a naïve comparison of the results from the UK RWE with the RCT data from the MEAD trials to be appropriate for numerous reasons, including concerns around the methodological robustness, especially given the difference in study designs and the differences in baseline characteristics between the studies. The ERG notes that some patients in the UK RWE audit had received prior laser therapy [redacted] compared to in the MEAD trials, and based on the advice of clinical experts, the ERG considers [redacted]

As discussed above, the ERG considers the 6-month timepoint from the UK RWE suboptimal responder cohort should be used to inform the baseline assessments for insufficient responders to anti-VEGFs (non-corticosteroids) rather than the 0-month timepoint from the UK RWE audit. The ERG, therefore, does not agree with the company's argument that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF (if sham is used as a proxy for continued anti-VEGF) and therefore likely results in a conservative estimate of the relative treatment effect. The ERG instead considers the MEAD sham arm is potentially a reasonable proxy for continued anti-VEGF use and that it is not possible to predict the likely direction of any potential bias in the comparison of DEX700 versus sham.

The ERG also considers it important to highlight that it is unclear what the mean baseline visual acuity in the sham arm of the MEAD trials was, but for the [redacted] who were included in the indirect treatment comparison reported in Section 3.6.3.1, the mean BCVA was [redacted] (SD [redacted]). The ERG notes the baseline BCVA in the sham arm of the MEAD trials appears to be [redacted] than the baseline BRVA in the UK RWE audit which was approximately [redacted] letters at baseline and [redacted] letters at month 6. The ERG is unsure what impact this potential discrepancy may have on the results of any comparison of DEX700 from the MEAD trials versus continued anti-VEGF treatment from the UK RWE audit.

3.4 Subgroup analyses

3.4.1 Cataract-related outcomes

The company reported that an advisory board conducted in 2021[6] suggested that the management of phakic DMO patients in the MEAD trials was not fully aligned with how patients would be expected to be managed in UK clinical practice in relation to cataract surgery timing and DEX700 treatment administration. In particular, the company reported that cataract surgery is performed earlier in UK clinical practice than was observed in the MEAD trials and DEX700 would be expected to be administered before or during cataract surgery to minimise inflammation and DMO progression post-cataract surgery, but this did not occur during the MEAD trials. The company, therefore, presented some exploratory *post-hoc* sub-analyses of the phakic-only population (mITT) from MEAD to investigate these potential limitations of the MEAD trials, although the results are not used in the economic model. The ERG notes that [redacted] patients in the DEX700 arm of the MEAD trials underwent cataract surgery compared to [redacted] patients in the sham arm.

3.4.1.1 Timing of cataract surgery

With regards the timing of cataract surgery, the company presented a *post hoc* subgroup analysis for mean BCVA change from baseline for patients who underwent cataract surgery less than 6 months, between 6 and 12 months, and over 12 months from cataract development. The ERG's clinical experts reported that not all cataracts are deemed clinically significant or severe enough to require immediate surgery after cataract diagnosis. Additionally, the ERG is concerned that the subgroup analyses presented by the company include patients with cataract at baseline and thus the analyses may be confounded by vision improvement in patients who would naturally have received an improvement in BCVA with cataract surgery in the absence of DEX700 treatment. The ERG thus does not consider the results of this subgroup analysis suitable for drawing conclusions.

3.4.1.2 Timing of DEX700 injection in relation to cataract surgery

The mean time between the last DEX700 injection and cataract surgery was [redacted] months in the phakic mITT population. The company reported that, "*phakic DMO patients without DEX700 in their last visit prior to cataract surgery had a greater BCVA loss prior to surgery, and therefore have more room to improve their BCVA following DEX700 injection*". The ERG notes that this is reflected in the subgroup results as patients who received DEX700 at their last visit before cataract surgery

experienced better outcomes than patients who did not receive DEX700 at the last visit prior to surgery.

3.4.1.3 Impact of cataract surgery

Subgroup analysis demonstrated that patients who underwent cataract surgery during the MEAD trials experienced [redacted] (CS, Figure 16). This is therefore likely to be due to the improvement in vision following cataract surgery for those [redacted]% of patients who underwent surgery during the study. Additionally, as over [redacted]% of patients had cataract at baseline, [redacted]. The ERG also notes that it is not reported in the CS how many patients develop cataract and do not receive surgery or what their visual outcomes are.

3.4.2 Impact of prior treatment

DEX700 appears to have [redacted] outcomes in previously treated and treatment- naïve phakic patients in the MEAD trials (Figure 6). The ERG notes that the company reported, "*to ensure as large a sample size as possible, we chose to have the full mITT population of phakic DMO patients in MEAD represent the population of phakic DMO patients who are either insufficiently responsive to prior non-corticosteroid therapy or are unsuitable for non-corticosteroid therapy (and therefore are treatment-naïve)*". However, as discussed in Section 3.2.1.1, [redacted] in the MEAD trials [redacted] and so the prior treatment subgroup [redacted] the UK population of insufficiently responsive to prior non-corticosteroid therapy.

Figure 6. Impact of prior treatment on BCVA (Reproduced from CS, Figure 17)

[redacted]

Key: BCVA, best-corrected visual acuity; DEX700, Dexamethasone 700 µg intravitreal implant.
Source: AbbVie, 2021 (MEAD post-hoc exploratory analyses).

3.4.3 *Baseline CRT ≥ 400µm; and baseline CRT < 400µm*

NICE technology appraisals TA274[28] and TA346[29] recommend the anti-VEGF treatments ranibizumab and aflibercept, as treatment options for visual impairment caused by DMO if the eye has a CRT of 400 micrometres or more at the start of treatment. The ERG, therefore, requested baseline data and results for the phakic subgroups from the MEAD trials with CRT ≥ 400 µm and CRT < 400 µm to explore if baseline CRT impacted on efficacy outcomes with DEX700. However, the ERG notes there are no restrictions based on CRT baseline for DEX700 in its UK marketing authorisation or the TA349 NICE guidance for DEX700 use in pseudophakic patients.

The baseline characteristics are for the CRT ≥ 400 µm and CRT < 400 µm phakic populations in the MEAD trials are [redacted]. The CRT ≥ 400 µm subgroup was [redacted] at baseline compared with the CRT < 400 µm subgroup (Company response to CQs, Table 3). The results for ≥ 10 letter improvement in BCVA from baseline, ≥ 10 letter worsening in BCVA from baseline and mean change in BCVA from baseline are presented in Table 15. The ERG considers given the differences in baseline characteristics and small patients numbers in terms of events, it is not possible to draw any conclusions from these results.

Table 15. Subgroup results from the pooled MEAD trial for the phakic-only mITT population patients with a baseline CRT ≥ 400 µm and <400 µm (LOCF analysis; Adapted from Company response to CQ's, Tables 3 and 4)

CQ A9 and A10	Outcome	≥ 400 µm		< 400 µm	
		DEX700 (n=[redacted])	Sham (n=[redacted])	DEX700 (n=[redacted])	Sham (n=[redacted])
a)	**≥ 10 letter improvement in BCVA from baseline, n (%)**				
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]	[redacted]	[redacted]
b)	**≥ 10 letter worsening in BCVA from baseline, n (%)**				
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]

	Month 36	[redacted]	[redacted]	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]	[redacted]	[redacted]
c)	**Mean change in BCVA from baseline**				
	Month 3	[redacted]	[redacted]	[redacted]	[redacted]
	Month 6	[redacted]	[redacted]	[redacted]	[redacted]
	Month 9	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]
	Month 15	[redacted]	[redacted]	[redacted]	[redacted]
	Month 18	[redacted]	[redacted]	[redacted]	[redacted]
	Month 21	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]
	Month 27	[redacted]	[redacted]	[redacted]	[redacted]
	Month 30	[redacted]	[redacted]	[redacted]	[redacted]
	Month 33	[redacted]	[redacted]	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]	[redacted]	[redacted]
	Month 39	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; BCVA, best-corrected visual acuity; CRT, central retinal thickness; IOP, intraocular pressure; LOCF, last observation carried forward; mITT, modified intention-to-treat.

Notes: [a] Percentages were calculated based on the number of patients remaining in the study at each visit as a denominator; [b] Percentages were calculated based on the number of patients with unilateral DMO at baseline as a denominator.

Source: MEAD (2022).[26]

3.5 Adverse events

3.5.1.1 Safety data from the MEAD trials

Safety data are reported for the duration of patient participation within the MEAD trials. Mean (SD) exposure across the trials was [redacted] treatment injections per patient in the DEX700 group and [redacted] treatment injections per patient in the sham group.

In the MEAD trials, [redacted] of patients in the DEX700 arm experienced adverse events (AEs) compared with patients in the sham arm (Table 16). Notably [redacted] of the participants in the DEX700 group experienced an ocular AE, compared to [redacted] in the sham group. The company note that this [redacted] rate of AEs in the DEX700 group was expected. Serious adverse events (SAEs) [redacted] in the DEX700 group ([redacted]) than in the sham group ([redacted]). [redacted].

Table 16. Summary of AEs observed in phakic DMO patients during the MEAD trials (Reproduced from CS, Table 14).

Event Type	DEX700 (n=[redacted])		Sham (n=[redacted])	
	All AEs, n (%)	Serious AEs, n (%)	All AEs, n (%)	Serious AEs, n (%)
All events	[redacted]	[redacted]	[redacted]	[redacted]
Ocular	[redacted]	[redacted]	[redacted]	[redacted]
Study eye	[redacted]	[redacted]	[redacted]	[redacted]
Non-study eye	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
Ocular	[redacted]	[redacted]	[redacted]	[redacted]
Study eye	[redacted]	[redacted]	[redacted]	[redacted]
Applicator/Insertion	[redacted]	[redacted]	[redacted]	[redacted]
DEX PS DDS	[redacted]	[redacted]	[redacted]	[redacted]
Non-study eye	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; DEX700, Dexamethasone 700 µg intravitreal implant; DEX PS DDS, Dexamethasone Posterior Segment Drug Delivery System.

In the DEX700 treatment arm, the most common treatment-related ocular AEs were [redacted] (Table 17). In the sham treatment arm, the most common treatment-related ocular AEs were [redacted].The ERG notes that the incidence of treatment-related cataracts was [redacted] in the DEX700 treatment arm ([redacted]%) compared with in the sham arm ([redacted]%). Discontinuation due to any treatment-related adverse event (TRAE) in the phakic subgroup of the MEAD trials was [redacted] ([redacted] in the DEX700 arm; [redacted]% in the sham arm).

Table 17. Treatment-related ocular AEs occurring in ≥ 2% of phakic DMO patients (Reproduced from CS, Table 15).

Adverse event	DEX700 (n=[redacted])	Sham (n=[redacted])
N, (%)		
Total events	[redacted]	[redacted]
Cataract	[redacted]	[redacted]
Cataract cortical	[redacted]	[redacted]
Cataract nuclear	[redacted]	[redacted]
Cataract subcapsular	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]

Conjunctival hyperaemia	[redacted]	[redacted]
Conjunctival oedema	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]
Lenticular opacities	[redacted]	[redacted]
Ocular hypertension	[redacted]	[redacted]
Vitreous floaters	[redacted]	[redacted]
Vitreous haemorrhage	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]

Abbreviations: AEs, adverse events; DEX700, Dexamethasone 700 µg intravitreal implant; DMO, diabetic macular oedema.

3.5.1.2 Safety data from the French RWD

The frequency of cataract surgery and occurrence of raised IOP were reported within the French RWD study. Cataract surgery was performed in [redacted]% (n = [redacted]) of phakic eyes and [redacted] patients had cataract surgery after their first DEX700 injection ([redacted]%). A further [redacted]% had cataract surgery after their second DEX700 dose, [redacted]% after the third and [redacted]% after the fourth.

Raised IOP (an increase of ≥ 10 mmHg from baseline IOP) occurred [redacted] frequently than cataracts in the French RWD, occurring in [redacted]% ([redacted]) of phakic eyes.

3.5.1.3 Safety data from the UK RWE audit

The safety data from the UK RWE audit relates to the full population and thus includes both the suboptimal responders and optimal responders. The UK RWE audit reported that recording of post-operative AEs may not be as accurate as recording of peri-operative AEs and the ERG considers limited data on AEs to be reported in the reference provided by the company for the UK RWE audit.

A total of [redacted] perioperative AEs were recorded from the [redacted] anti-VEGF injections administered to patients in the UK RWE audit, and the rate of perioperative AEs was [redacted] per 1,000 injections. The perioperative AEs included IOP spike ([redacted]), pain ([redacted]) and other – not specified ([redacted]). The most common post-operative AE was [redacted]) with [redacted] reports in [redacted] eyes and a rate of [redacted] per 1,000 injections. The AE incidence rates from the MEAD trials are not reported in a format that is directly comparable with the AE data reported from the UK RWE but the ERG notes that raised IOP was considered to be a treatment-related AE in [redacted]% of patients treated with DEX700 in the MEAD trials.

Cataract was recorded at baseline in [redacted]% ([redacted] eyes) in the UK RWE audit and the ERG notes that the proportion with baseline cataract in the suboptimal responder cohort ([redacted]%) was [redacted]

[redacted]. The presence of cataract [redacted]% of eyes at 48 months for the full cohort from the UK RWE audit. The ERG notes that at the last recorded visual acuity, [redacted]% ([redacted] eyes) from the overall cohort had undergone cataract surgery and the [redacted]).

3.6 Critique of the indirect comparison and/or multiple treatment comparison

3.6.1 Data sources and outcomes for the analysis

The company reported that they consider the most robust data sources to provide evidence for the use of DEX700 in phakic DMO patients who are unsuitable for or insufficiently responsive to non-corticosteroid therapies are the MEAD-010 and MEAD-011 RCTs of DEX700 versus sham. However, the company also acknowledged that there was an absence of head-to-head data in phakic DMO patients who are unsuitable for or are insufficiently responsive to non-corticosteroid treatment for DEX700 versus the comparators of interest for this technology appraisal. Additionally, the company reported a paucity of data suitable for use in ITCs to address the decision problem appropriately but has conducted ITCs to explore:

1) how the efficacy of DEX700 investigated in the MEAD trials compares with continued anti-VEGF treatment in the real-world (UK RWE audit);
2) how the efficacy of sham investigated in the MEAD trials compares with continued anti-VEGF treatment in the real-world (UK RWE audit); and
3) how the efficacy of DEX700 investigated in the phakic subgroup of the MEAD trials compares with DEX700 in the real-world data from Pareja-Ríos *et al.* 2018.

The ERG notes that the company used its SLR and the UK RWE audit to source studies for use in ITCs and that the company's reasons for inclusion/exclusion of studies can be found in the CS, Appendix D.

Outcomes considered in the ITCs were:

- Mean BCVA change from baseline to Year 1, Year 2 and Year 3;
- ≥ 10 letter BCVA improvement from baseline to Year 1, Year 2 and Year 3;
- ≥ 10 letter BCVA worsening from baseline to Year 1, Year 2 and Year 3;
- ≥ 15 letter BCVA improvement from baseline to Year 1, Year 2 and Year 3; and
- ≥ 15 letter BCVA worsening from baseline to Year 1, Year 2 and Year 3.

The ERG notes that mean BCVA was the primary endpoint in the MEAD trials and the 10 or 15 letter BCVA improvement or worsening endpoints were investigated by the company for potential use in the economic model. The UK RWE audit reported data for all of the outcomes but only mean change from baseline to Year 1 was available from Pareja-Ríos *et al.* 2018.[8]

3.6.2 Statistical methods

Pareja-Ríos *et al.* 2018[8] and the UK RWE audit[23] are non-comparative real-world retrospective studies, and so the company performed an unanchored matching-adjusted indirect comparison (MAIC) and an unanchored simulated treatment comparison (STC) to enable a comparison between each study and the MEAD RCTs. The ERG notes that both methods can be used to adjust for between-study differences in baseline patient characteristics (considered to be treatment effect modifiers or prognostic factors) in the absence of randomisation and are detailed in NICE DSU TSD 18.[30]

3.6.2.1 *Prognostic factors and treatment effect modifiers*

The company identified potential prognostic factors and treatment effect modifiers to use for population adjustment in the ITCs through published literature and clinician advice. The resulting characteristics deemed to be potential prognostic factors or treatment effect modifiers by the company were as follows:

- Percentage of patients with pre-existing cataracts at baseline;
- Timing of cataract surgery;
- Baseline BCVA;
- Prior anti-VEGF treatments; and
- Duration of oedema before treatment.

However, the ERG notes that data were not available from the comparator studies for all of the baseline characteristics identified as potential prognostic factors and treatment effect modifiers and so the results of the ITCs are likely to be unreliable and the direction of any potential bias is unknown.

3.6.3 Results

3.6.3.1 DEX700 and sham investigated in MEAD compared with suboptimal anti-VEGF treatment in the real-world (UK RWE audit)

Patient-level data for the [redacted] patients in the DEX700 arm and [redacted] patients in the sham arm of the MEAD trials with a phakic lens and who had received prior treatment were compared with the UK RWE audit summary data for the [redacted] phakic eyes who received anti-VEGF therapy (ranibizumab or aflibercept) and were classified as insufficient responders (≤5 letter gain after 6 months of treatment). Outcome data were available from the UK RWE audit for [redacted] eyes at Year 1, [redacted] eyes at Year 2 and [redacted] eyes at Year 3. Available patient characteristics were reasonably similar across the three UK RWE audit populations, with the exception of the [redacted], which was [redacted]% for the Year 1 population, [redacted]% in the Year 2 population and [redacted]% in the Year 3 population.

The ERG notes that patients in the UK RWE audit had a [redacted] mean BCVA at baseline (mean baseline BCVA was [redacted], [redacted]and [redacted] in the three different UK RWE audit populations) compared with patients in the MEAD trials ([redacted] and [redacted]in the DEX700 and sham arms of the MEAD trials, respectively). The company reported that adjusting for the difference in mean BCVA at baseline introduced high levels of uncertainty into both comparisons. The ERG notes that after all adjustments, the resulting effective sample sizes (ESSs) ranged from 1 to 2.1 across the analyses performed comparing DEX700 with suboptimal anti-VEGF, and they ranged from 3.2 to 6 across the analyses performed comparing sham with suboptimal anti-VEGF. The company reported that they also attempted to match only on mean baseline BCVA and the ESS still remained small (< 15). Further details on the baseline characteristics and matching variables included in the ITCs can be found in the CS, Appendix D.2.

The company reported that, "Across most endpoints compared, conflicting results between MAICs and STCs suggest these analyses are too uncertain to make any conclusions from" and so the company provided the results in CS, Appendix D.2 for information but does not discuss them in the CS. The ERG agrees with the company that the results are extremely unreliable due to the small ESSs and also advises against using the ITC results to draw conclusions. Additionally, the ERG notes that the ITCs comprise a comparison of RWE with RCT evidence and is concerned about the bias introduced from mixing studies with different methodologies.

3.6.3.2 *DEX700 investigated in MEAD compared with DEX700 in the real-world (Pareja-Ríos et al. 2018)*

Pareja-Ríos *et al.* 2018 was a retrospective study of 30 phakic eyes treated with DEX700 in a single-centre in Tenerife, Spain, for whom laser or anti-VEGF therapy had not shown to improve retinal thickness or visual acuity after 3 months of treatment. The ERG notes that the mean baseline BCVA was [redacted] in Pareja-Ríos *et al.* 2018 (42.4 letters) compared with in the DEX700 arm of the MEAD trials ([redacted]). The company reported that after adjusting for the difference in mean BCVA between the studies, the resulting ESS was extremely small in the MAIC analyses (ESS = 5.1 when matching for only mean BCVA and variance and ESS = 4.9 when matching for mean BCVA plus additional characteristics). The ERG is therefore concerned that the results from the ITCs are unreliable due to the small ESS.

Additionally, the ERG is concerned that the Pareja-Ríos *et al.* 2018 RWE comprises an extremely small population (30 phakic eyes) with [redacted] than the MEAD trials at baseline compared to that expected in UK patients, and that it is based in Spain where treatment for DMO may differ to the UK treatment pathway. The ERG is therefore concerned that the Pareja-Ríos *et al.* 2018 RWE is not generalisable to the UK population and so the ERG considers that ITCs matching the MEAD trials to Pareja-Ríos *et al.* 2018 are of limited relevance to the decision problem for this technology appraisal.

Nevertheless, the ERG notes that after matching, mean BCVA change from baseline (CFB) to Year 1 with DEX700 in the MEAD trials [redacted] in all analyses (adjusted mean CFB [redacted]), and [redacted] the mean CFB (4.8) reported in Pareja-Ríos *et al.* 2018 (CS, Table 12). However, the ERG considers caution should be exercised in drawing any conclusions based on the results of these ITCs.

3.7 Conclusions of the clinical effectiveness section

For this part review of TA349, a *post-hoc* pooled analysis of the phakic-only modified ITT (mITT) populations of the MEAD trials was the primary evidence source used to inform the efficacy of DEX700 in the company's base case in their economic model. The ERG considers the company's SLR to be of reasonable quality and likely to have retrieved all studies relevant to DEX700 and agrees with the company that the phakic subgroup of the MEAD trials are the most appropriate source of data on DEX700 to address the decision problem. However, the ERG notes that the phakic data are

from a *post-hoc* subgroup analysis that was not statistically powered to detect differences in efficacy for any of the outcomes.

The ERG notes that the sham arm in the MEAD trials comprises no treatment and patients requiring rescue therapy in any treatment arm were required to discontinue from the studies. Additionally, there is [redacted] for the DEX700 and sham arms of the MEAD trials ([redacted] respectively) and the company has used a LOCF approach to account for missing data. The ERG notes that the natural history of DMO suggests that vision deteriorates over time and therefore the LOCF approach may be optimistic for both the DEX700 and sham arms as vision in patients with missing data cannot worsen. The ERG is, therefore, concerned that results for both the sham and DEX700 arms are likely to be biased and considers it difficult to predict the likely direction of the resulting bias for the comparison of DEX700 versus sham from using a LOCF approach to account for missing data.

The ERG considers the [redacted] in the MEAD trials do not reflect current UK clinical practice, in particular clinical experts considered there to be [redacted] use in the MEAD trials and [redacted]. Additionally, the population of the MEAD trials comprised of a [redacted] compared to the UK RWE audit and what the ERG's clinical experts reported would be expected in UK clinical practice. The ERG is therefore concerned that the DEX700 data from the MEAD trials does not reflect patients with an insufficient response to [redacted] and that the population has [redacted] than expected in UK clinical practice.

The company conducted an ITC to compare DEX700 in the MEAD trials with DEX700 in the real-world. However, the ERG considers this ITC to be of little relevance to the decision problem given that [redacted] that in the MEAD trials, [redacted] than expected in UK clinical practice. Additionally, the resulting effective sample size for the ITC after matching was extremely low and thus the results are subject to high levels of uncertainty.

The population specified in the decision problem is, "*phakic DMO patients who are insufficiently responsive to or unsuitable for the non-corticosteroid treatment*" and the ERG considers that the population of insufficient responders to non-corticosteroid treatments has different comparators to the population unsuitable for treatment with non-corticosteroids. The ERG notes that the

populations are not considered separately in the model and cost-effectiveness of DEX700 versus watch and wait is not reported in the CS.

The ERG does not consider clinical evidence for the efficacy of laser alone compared with DEX700 has been provided in the CS. The ERG also notes that the company does not include bevacizumab in the economic model and that the anti-VEGFs, ranibizumab and aflibercept, are [redacted] in the economic model. However, the ERG considers this to be reasonable based on its clinical experts' advice.

Data from a UK RWE audit investigating suboptimal anti-VEGF treatment is used to provide supportive evidence for the insufficiently responsive to non-corticosteroid population but the ERG is concerned that these data are non-comparative and unsuitable for use in an ITC with evidence from the MEAD trials due to baseline differences between the studies resulting in low ESSs in MAICs. Additionally, the ERG is unsure what impact the potential bias from the differences between the MEAD trials and the UK RWE audit may have on the results of any comparison of DEX700 from the MEAD trials versus continued anti-VEGF treatment from the UK RWE audit.

Results from the MEAD trials demonstrated [redacted] in the mean change in average BCVA (area under the curve [AUC] approach) measured from baseline to 39 months with DEX700 compared with sham in the phakic mITT population ([redacted]versus [redacted] ETDRS letters, respectively; [redacted]).[24] [redacted] months, [redacted]patients treated with DEX700 achieved a BCVA [redacted] of ≥ 10 letters from baseline compared with those receiving sham ([redacted];

Table 13).[24] Additionally, for the outcome of ≥ 10 letter worsening in BCVA from baseline in the phakic mITT subgroup of the MEAD trials, the ERG notes that [redacted] (

Table 13).

DEX700 [redacted] in study eye central retinal thickness (CRT) from baseline to 39 months for the phakic mITT population of the MEAD trials compared with sham (Figure 4).

The company presented data from a French RWE study to support the efficacy data for DEX700 in the MEAD trials and the ERG considers that the improvement in visual acuity in the French RWD is generally [redacted] seen in the MEAD trials. However, the ERG is concerned

that [redacted]

In summary, the ERG is concerned that there is a lack of comparative data for DEX700 versus aflibercept and ranibizumab in the phakic population that is unresponsive to non-corticosteroid therapy, and that the results from the MEAD trials are not generalisable to UK clinical practice.

4 Cost effectiveness

The company's deterministic base case results are given in Table 18 using list prices. It is shown that dexamethasone 700 µg (DEX700) dominates treatment with anti–vascular endothelial growth factors (anti-VEGFs), as DEX700 is associated with lower costs and higher quality-adjusted life years (QALYs) compared with anti-VEGFs.

Table 18. Company's deterministic base case results (adapted from Table 54 of the CS)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NMB (£30,000/ QALY WTP threshold)
Anti-VEGFs	£38,695	7.4815	-	-	-	-
DEX700	£31,728	7.5853	-£6,968	0.1038	Dominant	£10,080

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; CS, company submission; DEX700, dexamethasone 700 µg; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

There are a number of parameters and assumptions that have been varied by the company and the Evidence Review Group (ERG) in scenario analysis; in most of these scenarios, DEX700 continues to dominate treatment with anti-VEGFs. To show which direction the scenario analysis is impacting the cost-effectiveness results in, the incremental (inc.) net monetary benefit (NMB) at a willingness-to-pay (WTP) threshold of £30,000 per QALY is reported. The inc. NMB measures the difference in NMB between the intervention and comparator; a positive inc. NMB indicates that the intervention is cost-effective while a negative inc. NMB indicates that the comparator is cost-effective, at the given WTP threshold.

4.1 ERG comment on the company's review of cost effectiveness evidence

The company performed three systematic literature reviews (SLRs) to identify published studies that could inform the cost-effectiveness evaluation of DEX700 for adult patients with phakic diabetic macular oedema (DMO) who are insufficiently responsive to or unsuitable for non-corticosteroid therapy.

The first search (cost-effectiveness SLR) attempted to identify full economic evaluations for treating refractory DMO patients whose disease is insufficiently responsive to or unsuitable for, non-steroidal therapies. The second search (HRQoL SLR) sought to identify studies reporting utility data in the same population as the first search, as well as disutilities associated with treatments and treatment-related adverse events (AEs). The third search (cost and resource use SLR) identified studies and prior economic evaluations which reported resource use data, cost of management of treatment-

related AEs, and direct and indirect costs including cost of blindness, health state costs, societal costs, cost of carer and productivity losses, etc., also in the same population as the previous searches.

Database searches were run on 18 January 2021 and were updated on 24 September 2021. The cost-effectiveness SLR and cost and resource use SLR were restricted to the studies published after 2010, while the HRQoL review was not restricted. Only English-language publications were included during secondary or full-text screening.

A summary of the ERG's assessment of the company's economic SLRs is presented in Table 19. The ERG's key concern is that the company did not provide search terms for each electronic database search or the number of hits from each search term and database. As such, the ERG was unable to validate the company's searches and appraisal of identified abstracts.

Table 19. Systematic literature review summary

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search Strategy	Appendix G	Appendix G	Appendix G	Appropriate sources were searched. Databases included: MEDLINE, Embase®, MEDLINE® In-Process, CRD HTAD & NHS EED, and EconLit®. Grey literature searches included: AAO, ARVO, EVER, COPHy, EURETINA, and ISPOR conference proceedings from 2018-202. NICE, SMC and EUnetHTA websites were also searched. However, no search terms or number of hits per term or per source were provided.
Inclusion/ exclusion criteria	Table 31 in Appendix G	Table 31 in Appendix G	Table 31 in Appendix G	Studies considering patients with refractory DMO that are insufficiently responsive or are unsuitable for non-steroidal therapies were included. No exclusions were made based on interventions or comparators, which the ERG considers to be inclusive. The 2010 date restriction is also considered to be appropriate as publications before this would likely reflect outdated practice; in the UK anti-VEGFs were first approved for use in DMO in 2013. It was noted that several studies were excluded from each search as they assessed pseudophakic patients. No further detail was provided about these exclusions; however, the ERG considers it would've been appropriate to include these

				studies as all patients with phakic lenses are at risk of cataract and publications with pseudophakic patients may help to inform the long-term modelling assumptions.
Screening	Appendix G	Appendix H	Appendix I	Appropriate, PRISMA flow diagram provided.
Data extraction	Tables 32 and 33 in Appendix G	Table 35 in Appendix H	Table 36 in Appendix I	Appropriate.
Quality assessment of included studies	Appendix G	Appendix H	Appendix I	Appropriate, Philips *et al.* 2004[31] and Papaioannou *et al.* 2013[32] checklists completed by the company.

Abbreviations: CS, company submission; ERG, evidence review group; HRQoL, health related quality of life; NHS, national health service; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium; CRD HTAD & NHS EED, Centre for Reviews and Dissemination Health Technology Assessment Database & National Health Service Economic Evaluation Database; AAO, American Academy of Ophthalmology; ARVO, The Association for Vision and Ophthalmology; EVER, The European Association for Vision and Eye Research; COPHy, Controversies in Ophthalmology; EURETINA, The European Society of Retina Specialists; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; DMO, diabetic macular oedema; VEGF, vascular endothelial growth factor.

The economic SLR included three publications; NICE TA613,[5] Pochopien *et al.* 2019,[33] and Beiderbeck *et al.* 2017.[34] All three presented UK cost-effectiveness analyses utilising Markov cost-utility models. However, none of these publications addressed the decision problem considered by this appraisal. As such, the company adapted the economic model from a previous NICE appraisal of DEX700 in DMO (TA349[2]). This model had a similar Markov state transition structure to that used in TA613 (which assessed the cost-effectiveness of fluocinolone acetonide in a similar but narrower population of patients with phakic eyes), although six BCVA health states were adopted rather than the eight used in TA613 and Pochopien *et al.* 2019.[33]

NICE TA613 and Pochopien *et al.* 2019[33] were also included in the HRQoL SLR. TA613 reported health state utility values (HSUVs) for the eight BCVA health states modelled in the best-seeing eye (BSE) and worst-seeing eye (WSE) using the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) during the FAME study.[35] These estimates were mapped to the EQ-5D using a published mapping algorithm (Rentz *et al.* 2014[36]). The company also extracted HSUVs from TA613 based on a time trade-off approach (Haig *et al*. 2014[37]). AE-related utility decrements used in the model for TA613 were sourced from TA346[29] (which assessed aflibercept for treating DMO) which, in turn, utilised a range of literature sources. Pochopien *et al*. 2019[33] reported the overall baseline utility of phakic and pseudophakic patients but no details were given on the elicitation or valuation method used to obtain them. The BCVA health state utility values in Pochopien *et al.* 2019 were based on Czoski-Murray *et al.* 2009.[38]

Three publications were included in the cost and resource use SLR; NICE TA613, Pochopien *et al.* 2019,[33] and Raman *et al.* 2018.[39] Of these, the company deemed TA613 to be most relevant and utilised cost and resource use assumptions from TA613 to help inform the model, supplemented by data sourced from the company's clinical experts, the Monthly Index of Medical Specialities (MIMS), the drugs and pharmaceutical electronic marketing tool (eMIT),[40] NHS Reference Costs 2019-2020,[41] and the previous DEX700 appraisal (TA349[2]). The ERG agreed that TA613 was the most relevant source for cost and resource use assumptions as much of the assumptions used in Pochopien *et al.* 2019[33] and Raman *et al*. 2018[39] were sourced from earlier NICE technology appraisals.

The ERG considers the company's review of the cost-effectiveness, HRQoL, cost and resource use evidence to be generally reasonable, though specific issues pertaining to their application in the model are discussed in the following sections.

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

4.2.1 NICE reference case checklist

Table 20 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 20. NICE reference case checklist

Element of HTA	Reference case	ERG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company undertook a cost-utility analysis to compare DEX700 to a composite comparator consisting of anti-VEGF treatments (aflibercept and ranibizumab). Although the ERG agrees with the market shares included in the composite comparator, the ERG presents results comparing DEX700 to the composite comparator, and ranibizumab and aflibercept separately as decision making comparing DEX700 to ranibizumab will be more sensitive to alternative modelling assumptions than in the company base case. For completeness, the ERG will also

		present fully incremental results using its preferred assumptions.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company used a lifetime time horizon (40 years). The ERG considers the company's long-term modelling assumptions to be too simplistic to accurately capture the costs and consequences over a lifetime time horizon. Shorter time horizons (10 and 15 years) have also been adopted in other DMO appraisals.[2, 42,28]
Synthesis of evidence on health effects	Based on systematic review	A systematic review was carried out and the company explored ITCs including the data from the MEAD trials, the UK RWE audit[23] and Pareja-Ríos *et al.* 2018[8]. The results from the ITCs were not utilised in the economic analysis due to their limitations, which the ERG agree with. In consequence, data from the company's RCT (MEAD) was implemented in the base case analysis.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects were expressed in QALYs. The EQ-5D does not appear to be appropriate for this population as it is relatively insensitive to changes in vision.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	HRQoL data was obtained from Czoski-Murray *et al*. 2009[38] who reported TTO utility values for members of the general population wearing lenses to simulate visual impairment.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes. Czoski-Murray *et al*. 2009 included 108 members of the general UK population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; CS, company submission; ERG, evidence review group; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; HRQOL, health-related quality of life; HTA, health technology appraisal; ITC, indirect treatment comparison; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year; RCT, randomised controlled trial; TTO, time trade-off; UK, United Kingdom.

4.2.2 Population

The NICE final scope[43] for this STA defines the population as phakic DMO patients who are insufficiently responsive to or unsuitable for non-corticosteroid treatment. However, the economic analysis only considers phakic DMO patients who are insufficiently responsive to non-corticosteroid treatment. According to the company, the appropriate comparator in this subpopulation differs to the appropriate comparator in the full population (see Section 4.2.3.2).

The economic analysis utilises data from a modified intention-to-treat (mITT) population, which only includes patients who had at least one follow-up visit. Additionally, the phakic-only mITT population of the pooled MEAD trials (MEAD-010 and MEAD-011) is used to represent the relevant subpopulation of patients insufficiently responsive to non-corticosteroid treatment. The company noted that this is consistent with the approach adopted in TA349,[2] where the full pseudophakic mITT population of the pooled MEAD trials was used to represent both patients who were insufficiently responsive or unsuitable for non-corticosteroid treatment.

The baseline characteristics of the modelled population are based on data obtained from the population of the pooled DEX700 arms of phakic patients in the MEAD trials. The following baseline characteristics are included in the model:

- The average age and gender of patients (to calculate age-and sex-related risk of mortality) (Table 21);
- The proportions of patients who have unilateral DMO in the BSE or the WSE, or bilateral DMO at baseline (Table 21); and,
- The baseline distribution of vision across the BCVA states in the BSE and WSE (Table 22).

Table 21. Baseline characteristics included in the model

Characteristic	Value
Mean age, years	[redacted]
Proportion male	[redacted]
Proportion female	[redacted]
Proportion phakic	[redacted]
Proportion treated bilaterally	[redacted]
Proportion treated unilaterally	[redacted]
Proportion of unilateral patients treated in their BSE	[redacted]
Proportion of unilateral patients treated in their WSE	[redacted]

Abbreviations: BSE, best-seeing eye; WSE, worst-seeing eye.

Table 22. Baseline distribution of vision across visual acuity states applied in the base case analysis (adapted from Table 22 in the CS and Table 33 of the company's clarification responses)

DMO status	Eye	Data used	Health State 1 (≤ 35 ETDRS letters)	Health State 2 (36-45 ETDRS letters)	Health State 3 (46-55 ETDRS letters)	Health State 4 (56-65 ETDRS letters)	Health State 5 (66-75 ETDRS letters)	Health State 6 (≥ 76 ETDRS letters)
Unilateral DMO in the BSE	BSE (treated)	Study eyes that were BSE; DEX700 arm (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE (untreated)	Non-study eyes that were WSE; DEX700 arm (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE (treated)	Study eyes that were WSE; DEX700 arm (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE (untreated)	Non-study eyes that were BSE; DEX700 arm (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE (treated)	Study eyes that were BSE; DEX700 arm (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE (treated)	Study eyes that were WSE; DEX700 arm (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSE, best-seeing eye; CS, company submission; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; WSE, worst-seeing eye.

Throughout the CS, the company argues that MEAD may under-estimate the efficacy of DEX700 in phakic patients that can be achieved in clinical practice, and may over-estimate the efficacy of the sham arm. Therefore, additional supplementary RWE was gathered and presented to provide supportive evidence for the population of interest and to provide data that give a better representation of the efficacy of existing therapies in UK clinical practice. This evidence is outlined and critiqued in Section 4.2.6.

4.2.2.1 ERG critique

The ERG's clinical experts were concerned that the participants in the MEAD trials are not representative of patients with DMO who are considered unsuitable for or non-responsive to non-corticosteroids, and most of them might, in fact, be eligible to be treated with an anti-VEGF, as the large majority had received no previous treatment with an anti-VEGF ([redacted] in the pooled DEX700 arm). Furthermore, clinical experts to the ERG expressed concerns that patients who are insufficiently responsive to anti-VEGF treatment may be less likely to respond to corticosteroid treatment than treatment-naïve patients (or those who have only ever received treatment with laser photocoagulation in the past). This means that consideration of the full phakic population of the pooled MEAD trials as a proxy for patients with DMO who are insufficiently responsive to non-corticosteroid therapy may overestimate the treatment effect in favour of DEX700 and subsequently the cost-effectiveness of DEX700.

Additionally, the population of the MEAD trials comprised of a [redacted] proportion of patients with [redacted] compared to the UK RWE audit and the ERG's clinical experts also agreed that the MEAD trials represented [redacted] compared to expected UK clinical practice. The ERG is unsure whether this would impact the cost-effectiveness results. On the one hand, patients may have a larger scope to improve from treatment. However, as it may affect both treatments equally it could lead to incremental results that are consistent with the base case.

In the absence of more appropriate data, the ERG accepts the company's approach to use full phakic population of the pooled MEAD trials as a proxy for patients who are insufficiently responsive to non-corticosteroid therapy. Even so, it is an important limitation of the economic analysis and should be considered in Committee decision making.

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

In terms of the modelled baseline characteristics, the ERG is unclear why the baseline distribution of vision was taken selectively from the DEX700 arm of the pooled MEAD trials, and not from the pooled population of both DEX700 and sham treatment arms of the pooled MEAD trials. In response to the ERG's clarification question the company explained that, "*The same distribution is applied to all treatments, therefore we assume that the dexamethasone patients are representative of a general phakic DMO population*". The company subsequently presented data on the proportions of patients within the cohort who have unilateral DMO in the BSE or the WSE, or bilateral DMO at baseline, by treatment arm in the pooled MEAD trials (see Table 31 in the company's clarification response) and the baseline distribution of vision for the sham arm and pooled DEX700 and sham arms (see Tables 34 to 36 in the company's clarification response). These data, as stated by the company and agreed by the ERG, demonstrate that there is little difference between the proportions observed in each of the DEX700, sham and pooled populations and therefore the choice to use the DEX700 data is unlikely to have affected the results of the economic analysis.

The ERG was also concerned that the baseline distribution of BSE and WSE in bilateral DMO was taken from respective DMO eyes in unilateral DMO and not from data on the subgroup of patients with bilateral DMO. The company stated in their clarification response that, "*The use of study eyes to represent all treated eyes and non-study eyes to represent all non-treated eyes was selected to maximise the sample size for each of the treated and untreated BSE and WSE. To further cut the data by whether a patient is unilateral or bilateral would lead to reduced sample sizes for each relevant category of patients, for whom we then want to estimate the distribution of vision across the 6 vision-related health states. As the submitted data are aligned with the data accepted as appropriate in TA349, we believe that it is appropriate to retain this approach in order to maximise the available sample size*.". The company then stated that they were unable to provide this data within the time constraints of the clarification response. Given that the model is sensitive to the proportion of patients treated bilaterally and the proportion of bilateral BSEs starting in health state 2 (see Section 5.1.3), the ERG submitted another request for these data. The company subsequently provided the data for the DEX700 and sham arms, and for the pooled DEX700 and sham arms (see Tables 38 to 41 of the company's amended clarification response) and included a model with the functionality to run data from the DEX700 arm (Table 23). Running these data in the model reduced the inc. NMB from

£10,080 to £7,396 which shows that the company's current assumption of using study eyes to represent all treated eyes and non-study eyes to represent all non-treated eyes introduces bias in favour of DEX700.

The ERG considers that as bilateral treatment would follow unilateral treatment for many patients (only a minority would be expected to start treatment in both eyes simultaneously), and it follows that the DMO health state for the initial unilaterally affected eye would have degraded in the time before the second eye becomes affects and bilateral treatment is initiated. Thus, the baseline distribution of vision is expected to differ by whether a patient has unilateral or bilateral DMO because one of the bilaterally treated eyes would be affected for longer and deteriorated further in that time. However, it is also possible that patients who develop DMO in their second eye are diagnosed and receive treatment sooner than patients with unilateral DMO as they are already being monitored in their first eye. With this in mind, the ERG compared the mean baseline BCVA resulting from the two analyses (Table 24). The ERG's expectations were not entirely confirmed as the WSE in a bilateral patient had a similar BCVA in both analyses and the BSE in a bilateral patient demonstrated better vision in the scenario (informed by the BSE of bilateral patients) than in the base case (informed by all study eyes that were the BSE; i.e., unilateral and bilateral patients). As such, the ERG agrees with the company that cutting the data by whether a patient is unilateral or bilateral leads to smaller sample sizes and a misalignment with the previous DEX700 appraisal and therefore considers these data appropriate for scenario analysis only.

The ERG also considers it important to highlight that the baseline distribution of vision across visual acuity states become relatively more important when constant vision is assumed for either treatment as this will dictate the HSUVs that are applied throughout the treatment period.

Table 23. Baseline distribution of vision across visual acuity states; phakic only DEX700 patients (adapted from Tables 38 and 39 of the company's clarification responses)

DMO status	Eye	Data used	Health State 1 (≤ 35 ETDRS letters)	Health State 2 (36-45 ETDRS letters)	Health State 3 (46-55 ETDRS letters)	Health State 4 (56-65 ETDRS letters)	Health State 5 (66-75 ETDRS letters)	Health State 6 (≥ 76 ETDRS letters)
Unilateral DMO in the BSE	BSE (treated)	Study eyes that were BSE; unilateral patients at baseline (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE (untreated)	Non-study eyes that were WSE; unilateral patients at baseline (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE (treated)	Study eyes that were WSE; unilateral patients at baseline (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BSE (untreated)	Non-study eyes that were BSE; unilateral patients at baseline (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE (treated)	Study or non-study eyes that were BSE; bilateral patients at baseline (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WSE (treated)	Study or non-study eyes that were WSE; bilateral patients at baseline (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSE, best-seeing eye; CS, company submission; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; WSE, worst-seeing eye.

Table 24. Mean BCVA resulting from the baseline distribution of vision across visual acuity states (base case vs scenario)

DMO status	Eye	Mean BCVA: scenario according to whether a patient is unilateral or bilateral	Mean BCVA: base case	Difference (base case – scenario)
Unilateral DMO in the BSE	BSE (treated)	[redacted]	[redacted]	[redacted]
	WSE (untreated)	[redacted]	[redacted]	[redacted]
Unilateral DMO in the WSE	WSE (treated)	[redacted]	[redacted]	[redacted]
	BSE (untreated)	[redacted]	[redacted]	[redacted]
Bilateral DMO	BSE (treated)	[redacted]	[redacted]	[redacted]
	WSE (treated)	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA, best-corrected visual acuity; BSE, best-seeing eye; CSR, Clinical Study Report; DMO, diabetic macular oedema; WSE, worst-seeing eye.

Note: Mean BCVA in each health state calculated as per the company (MEAD study phakic DEX700 patients: CSR, Table 01.1.2-1.1 - Table 01.1.2-1.4)

4.2.3 Interventions and comparators

4.2.3.1 Intervention

The NICE final scope[43] for this STA describes the intervention as dexamethasone intravitreal implant. For the economic analysis, the 700 µg formulation of dexamethasone (DEX700 pro re nata [PRN]) is the intervention of interest and is implemented in the model as per its marketing authorisation, with a minimum between-injection interval of approximately 6 months. This dosing regimen is in line with that used in the DEX700 arms in the MEAD trials (MEAD-010 and MEAD-011). As such, DEX700 has been considered in the company's economic analysis, based on dosing and efficacy observed from the phakic DMO patients in the DEX700 arms of the pooled MEAD trials.

The economic analysis also assumes a maximum duration of treatment of 5 years (for the intervention and comparator). Given that MEAD provides 3 years of data, assumptions are required to model Years 4 and 5 where patients are still expected to receive treatment based on feedback from the company's UK clinicians; these assumptions are described and critiqued throughout this report.

It is also important to add that the MEAD trials were 3-armed randomised controlled trials (RCTs), with one of the treatment arms being a lower dose of dexamethasone than that licensed for use in the UK (dexamethasone 350µg). The ERG thus does not consider data from this trial arm of relevance to this review and does not consider it further.

Consistent with the model from TA349[2] and based on clinician feedback, patients within the cohort who are affected bilaterally from baseline are assumed to receive the same treatment (intervention or comparator treatment) at the same frequency and achieve the same level of efficacy in both eyes. In addition, upon fellow eye involvement (FEI), the same treatment as received in the first eye would be given for a period of up to 5 years starting from this point (see Section 4.2.9).

Table 25 presents the average number of injections administered per model cycle, based on the DEX700 dosing schedule and the proportion of patients receiving treatment from the last observation to the current observation in MEAD. Given the follow-up time of 3 years in MEAD, the average number of injections in Years 1 to 3 are taken from MEAD, whereas the average in Years 4 and 5 were elicited from two practicing UK clinicians. The impact the number of DEX700 injections has on treatment costs is provided in detail in Section 4.2.14.1.

Table 25. Average number of DEX700 injections received by phakic DMO patients in the pooled MEAD trials (adapted from Table 9 of the CS and Table 58 of Appendix Q)

Model cycle	Month	Dosing schedule*	Proportion receiving treatment	Average number of treatments	Year	Average number of treatments per year
0	0	1	[redacted]	[redacted]	1	[redacted]
1	3	0	[redacted]	[redacted]		
2	6	1	[redacted]	[redacted]		
3	9	1	[redacted]	[redacted]		
4	12	1	[redacted]	[redacted]	2	[redacted]
5	15	1	[redacted]	[redacted]		
6	18	1	[redacted]	[redacted]		
7	21	1	[redacted]	[redacted]		
8	24	1	[redacted]	[redacted]	3	[redacted]
9	27	1	[redacted]	[redacted]		
10	30	1	[redacted]	[redacted]		
11	33	1	[redacted]	[redacted]		
12	36	1	[redacted]	[redacted]	4	1.000
13	39	1	[redacted]	[redacted]		
14	42	1	[redacted]	[redacted]		
15	45	1	[redacted]	[redacted]		
16	48	1	[redacted]	[redacted]	5	1.000
17	51	1	[redacted]	[redacted]		
18	54	1	[redacted]	[redacted]		
19	57	1	[redacted]	[redacted]		

Abbreviations: CS, company submission; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema
*The dosing schedule is the maximum number of treatments which would be given in each month, for those patients who remain on treatment.

4.2.3.2 Comparators

The following comparators are specified in the NICE final scope[43] for this STA:

- Laser photocoagulation alone;
- Watch-and-wait (for people who are unsuitable for treatment with both anti-VEGFs and laser photocoagulation);
- Aflibercept (only if the eye has a central retinal thickness [CRT] of 400 micrometres or more), alone or in combination with laser photocoagulation;
- Ranibizumab (only if the eye has a CRT of 400 micrometres or more), alone or in combination with laser photocoagulation; and,
- Bevacizumab (does not currently have a marketing authorisation in the UK for this indication), alone or in combination with laser photocoagulation.

As noted in Section 4.2.2, the economic analysis only considers a subpopulation of the full population in the NICE final scope (phakic DMO patients who are insufficiently responsive to the non-corticosteroid treatment). The company now understands that the appropriate comparator in this subpopulation is continued use of anti-VEGFs or (the rapidly declining use of) laser photocoagulation (as per TA613[5]), rather than watch and wait (as per TA349[2]). However, watch and wait would be the appropriate comparator for DMO patients with phakic eyes who are unsuitable for non-corticosteroid therapy. The company's clinical experts also confirmed anti-VEGFs are the only relevant comparator in the insufficiently responsive population.

For the base case, the company compared DEX700 to a composite comparator based on the proportion of patients receiving ranibizumab 0.5 mg ([redacted]) and aflibercept 2 mg ([redacted]) treatment in the UK RWE audit.[23] The average number of injections administered per model cycle was also taken from the UK RWE audit, which provided 42 months of data from the point at which the level of clinical response is defined (Table 26). Given the absence of data beyond 42 months, a simplifying assumption was made where the average number of injections from Year 3 remained constant until the end of Year 5. This assumption was based on feedback from two UK clinicians that although there may be some reduction in the average number of injections over time, a simplifying assumption that the average number of injections from the last 12 months remained constant until

60 months was reasonable. The impact the number of anti-VEGF injections has on treatment costs is provided in detail in Section 4.2.14.1.

Table 26. Average number of anti-VEGF injections received by phakic DMO patients in the UK RWE audit (adapted from Table 39 of the CS and Table 59 of Appendix Q)

Model cycle	Month	Dosing schedule*	Proportion receiving treatment	Average number of treatments†	Year	Average number of treatments per year
0	0	1.264	[redacted]	[redacted]	1	[redacted]
1	3	1.264	[redacted]	[redacted]		
2	6	0.980	[redacted]	[redacted]		
3	9	0.980	[redacted]	[redacted]		
4	12	0.980	[redacted]	[redacted]	2	[redacted]
5	15	0.980	[redacted]	[redacted]		
6	18	0.921	[redacted]	[redacted]		
7	21	0.921	[redacted]	[redacted]		
8	24	0.921	[redacted]	[redacted]	3	[redacted]
9	27	0.921	[redacted]	[redacted]		
10	30	1.034	[redacted]	[redacted]		
11	33	1.034	[redacted]	[redacted]		
12	36	1.034	[redacted]	[redacted]	4	[redacted]
13	39	1.034	[redacted]	[redacted]		
14	42	1.034	[redacted]	[redacted]		
15	45	1.034	[redacted]	[redacted]		
16	48	1.034	[redacted]	[redacted]	5	[redacted]
17	51	1.034	[redacted]	[redacted]		
18	54	1.034	[redacted]	[redacted]		
19	57	1.034	[redacted]	[redacted]		

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; CS, company submission; DMO, diabetic macular oedema; RWE, real world evidence; UK, United Kingdom

*The dosing schedule is the maximum number of treatments which would be given in each month, for those patients who remain on treatment.

†weighted by the proportion receiving ranibizumab and aflibercept ([redacted] and [redacted], respectively)

The company provided scenarios considering different proportions of ranibizumab and aflibercept, and including laser photocoagulation and bevacizumab (Table 27). As shown in Section 5.1.2, these scenarios had a relatively large impact on the company's results. Nevertheless, the ICER remained dominant in each scenario.

The company explained that laser photocoagulation was excluded from the base case due to clinical expert feedback and the Kodjikian *et al.* 2018[7] study (a SLR of observational studies concerning the

pharmacological management of DMO) who both concluded that laser photocoagulation is rarely used since anti-VEGFs have become available. The company also noted that laser photocoagulation is only recommended in patients with non-centre involved DMO (around 20% of the total DMO population). Bevacizumab was also omitted from the base case as it does not have a marketing authorisation in the UK for this indication whereas ranibizumab and aflibercept do. The company also noted that the SmPC for bevacizumab states it is not formulated for intravitreal use.[4]

Table 27. Composite comparator composition (adapted from Table 20 of the CS)

Comparator composition source	Ranibizumab	Bevacizumab	Aflibercept	Laser
Base case				
UK RWE audit (overall)	[redacted]	0.0%	[redacted]	0.0%
Scenario analyses				
UK RWE audit (latest 2 years)	[redacted]	0.0%	[redacted]	0.0%
UK RWE audit (overall) - including 5% laser	[redacted]	0.0%	[redacted]	5.0%
UK RWE audit (overall) - including 10% laser	[redacted]	0.0%	[redacted]	10.0%
NICE TA613 (excluding laser)	87.5%	12.5%	0.0%	0.0%

Abbreviations: CS, company submission; NICE, National Institute for Health and Care Excellence; RWE, real world evidence; TA, technology appraisal; UK, United Kingdom.

A composite comparator was accepted by the Committee for TA613.[5] However, this included anti-VEGF and laser therapies (28% laser, 63% ranibizumab and 9% bevacizumab), based on the proportion of patients using each treatment in the ICE-UK study.[44] The ICE-UK study informing TA613 did not capture any aflibercept use and the company suspected this was because it did not include data after 2018, which was when UK clinicians began to increase their use of aflibercept.

4.2.3.2.1 ERG critique

Clinical experts advising the ERG agreed with the company that bevacizumab is an irrelevant comparator as they would choose a licensed anti-VEGF like ranibizumab or aflibercept over bevacizumab. This is also supported by the UK RWE which observed a low usage of bevacizumab in phakic DMO patients ([redacted]).

The ERG's clinical experts also agreed that aflibercept is the most used anti-VEGF in clinical practice today and that the number of centres switching from ranibizumab to aflibercept appears to be increasing. When asked why, they revealed that publications have suggested greater improvements in vision (albeit not statistically significant improvement) using aflibercept compared to ranibizumab (e.g., the 2015 publication of the Protocol T study[45]).

The ERG's clinical experts also affirmed that the use of laser is rapidly declining. However, one noted that many experienced medical retina consultants still use laser in clinical practice (e.g., to target persistently leaky microaneurysms that might be driving the insufficient response to anti-VEGF treatment) and that some younger patients prefer the idea of laser photocoagulation to that of injections. They also expected laser photocoagulation to be used 10 to 15% of patients with predominantly non-centre involving DMO. Given that patients eligible for DEX700 had a mean age of [redacted] years in the MEAD trials and DEX700 is not limited to patients with non-centre involving DMO (CS, Figure 2), the ERG agrees with the omission of laser photocoagulation as a comparator. The ERG is also satisfied that laser is more likely to be used in combination with anti-VEGFs on an ad-hoc basis (reflected by the use of "rescue" laser therapy in clinical trials) rather than as a true combination therapy regimen.

On the one hand, the ERG agrees with the market shares included in the composite outcome ([redacted] ranibizumab and [redacted] aflibercept) and agrees that those receiving ranibizumab will not be a distinct clinical group from those receiving aflibercept. However, given that their treatment acquisitions costs vary, the ERG requested the company to provide results where DEX700 is compared to aflibercept and ranibizumab separately. During the clarification stage, the company provided these results (where only costs are changed) but stated these treatments are of the same class so there is no reason to suggest there would be differences in efficacy, and that this is supported by clinicians consulted for this appraisal and the findings in the 2017 publication of the Protocol T study.[46] When DEX700 was compared to aflibercept and ranibizumab separately, DEX700 remained dominant; the less expensive comparator (ranibizumab) reduced the inc. NMB from £10,080 to £6,291 and the more expensive comparator (aflibercept) increased the inc. NMB from £10,080 to £12,307. Given the magnitude of the change in the inc. NMB when the comparator is switched to ranibizumab, assessing ranibizumab as an individual comparator could be important for decision making when a number of modelling assumptions are changed. Thus, to minimise the decision risk for Committee, the ERG will present its preferred base for the composite comparator, and ranibizumab and aflibercept separately.

The ERG also sought clinical expert opinion on the role of watch and wait for DMO patients with phakic eyes after an insufficient response to previous non-corticosteroid therapy. The ERG's experts reported that watch and wait would be a relevant comparator for a small proportion (approximately 5%) of the patients who have no response to non-corticosteroid treatment. One expert also highlighted that [redacted] of patients in MEAD had a CRT <400 micrometres at baseline and that these

patients would not be eligible for anti-VEGF treatment. The NICE final scope also refers to CRT thresholds when listing ranibizumab and aflibercept as relevant comparators. Following this, the ERG presented an alternative number of comparisons to the company at the clarification stage, these are summarised in Table 28.

Table 28. Comparators according to CRT and response

Insufficient response group	CRT	Comparison
Partial response to non-corticosteroid treatment	=>400 micrometres	DEX700 vs ranibizumab
		DEX700 vs aflibercept
	<400 micrometres	DEX700 vs watch and wait
No response to non-corticosteroid treatment	=>400 or <400 micrometres	DEX700 vs watch and wait

Abbreviations: CRT, central retinal thickness; DEX700, dexamethasone 700 µg.

Subsequent to the feedback from the ERG, the company consulted additional clinicians on the types of insufficient responders and the use of CRT thresholds. These experts revealed that, "*Only a countable few patients will be disregarded as complete non-responders in whom even the retinal prevention is unlikely to be achieved*" and "*a fall in CRT levels below 400 micrometres would not in isolation be considered a reason to discontinue treatment*". In consequence, the company did not believe the group with no response to non-corticosteroid treatment was sufficiently large enough to justify the inclusion of watch and wait as an additional comparator, and that CRT thresholds should only be considered when starting anti-VEGF treatment.

During the clarification stage, the company also provided results for the phakic subgroups from the MEAD trials with CRT ≥ 400 µm and CRT < 400 µm to explore if baseline CRT impacted on visual outcomes with DEX700. However, the ERG considers given the differences in baseline characteristics and small patients numbers in terms of events, it is not possible to prove that there is a difference in visual outcomes based on CRT. As such, splitting the comparator and visual outcomes according to CRT may lead to unreliable estimates of cost-effectiveness.

Overall, the ERG considers the company's justifications to be generally reasonable and accepts the company's composite comparator of anti-VEGF treatments (outcome ([redacted] ranibizumab and [redacted] aflibercept) for the insufficiently responsive population. For completeness, results comparing DEX700 to ranibizumab and aflibercept separately will be presented using the ERG's preferred assumptions.

4.2.4 Modelling approach and model structure

The modelling approach and model structure for this appraisal is consistent with that used in the previous appraisal (TA349[2]), which was reviewed and updated by the ERG. The modelling assumptions also align with the Committee's stated preferred assumptions in TA349.

As per TA349, the Markov model consists of six visual acuity health states of 10-letter increments each, except the two extreme states (the mildest and the most severe). The definition of each health state is shown in Table 29.

Table 29. Visual acuity health state definitions (reproduced from Table 17 of the CS)

	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 6 m/20 ft	≤ 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
Notes	Legal blindness if BSE	-	-	-	20/40 in BSE is the legal threshold for driving	-

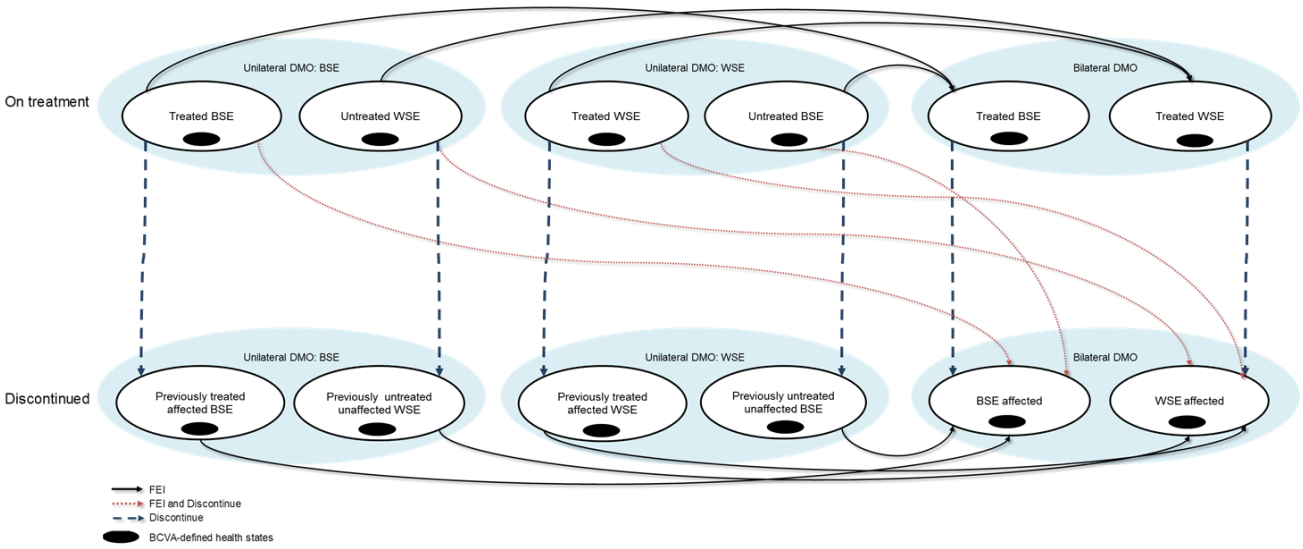
Abbreviations: BSE, best-seeing eye; CS, company submission; ETDRS, Early Treatment Diabetic Retinopathy Study.

Both eyes may transition between the six health states because BCVA changes in both eyes are modelled independently. Treatment may be modelled in both eyes (bilateral DMO) or in either the best-seeing eye (BSE) or worst-seeing eye (WSE) (unilateral DMO). Patients within the cohort who are affected unilaterally at baseline may develop DMO in their second eye, termed FEI and move to bilateral treatment. FEI might occur only at the end of Year 1 or Year 2 (see Section 4.2.9).

The BSE and WSE of each patient are defined at baseline and fixed throughout the time horizon. The distribution of vision at baseline for a BSE or WSE with DMO was taken from the study eye data for phakic patients from the DEX700 arm in the pooled MEAD trials (see Section 4.2.2).

Figure 7 shows all possible movements for all patients within the cohort.

Figure 7. Model structure (reproduced from Figure 21 of the CS)



Key: BCVA, best-corrected visual acuity; BSE, best-seeing eye; CS, company submission; DMO, diabetic macular oedema; FEI, fellow eye involvement; WSE, worst-seeing eye.

In each 3-month cycle an eye may move up (improved vision) or down (worsened vision), allowing patients to move between visual acuity health state, with no restrictions on the health state they can transition to in each model cycle in the model base case.

The MEAD 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 (see Section 4.2.6.1).

Treatment for DMO influences the probability of transitioning between the BCVA states. Eyes that are affected with DMO are assumed to receive treatment for up to 5 years and are assigned the efficacy associated with treatment for as long as they remain on treatment. During the 5-year treatment period, patients are at risk of discontinuation from treatment, either due to AEs and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment (see Section 4.2.7). Following discontinuation, it is assumed that patients receive no further treatment and 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 (see Section 4.2.8).

Eyes without DMO are assumed to retain constant vision and all patients are at risk of death throughout the model time horizon (see Section 4.2.12).

A half-cycle correction was also applied in the model as events may occur at any point during the cycle, not necessarily at the start or end of each cycle.

4.2.4.1 ERG critique

One key difference between the population modelled in TA349[2] and the population modelled in this appraisal relates to the proportion of patients with phakic eyes that enter the model. This appraisal only considers patients with phakic eyes at baseline; thus, all patients are at risk of cataracts. TA613 considered fluocinolone acetonide intravitreal implant in a similar but narrower population of patients with phakic eyes.[5] The state transition model presented in TA613 considered movements between BCVA states and divided patients according to lens status: phakic without cataract, phakic with cataract, undergoing cataract surgery or pseudophakic.

During the clarification stage the company provided several arguments why they saw no need to adapt the model from TA349 to include health states for patients undergoing cataract surgery or according to lens status. These included maintaining a consistent approach with TA349, including a broader population than TA613 and being able to incorporate data from the RWE studies. The ERG considers the company's key argument to relate to the modelling of patient-level data; "*Although cataract surgery is not explicitly captured within a distinct health state, the costs associated with cataract surgery, and the impact cataract surgery has on visual acuity outcomes are captured within the transition probabilities that are estimated from the MEAD data and applied in the model. Similarly, given visual acuity outcomes of patients following cataract surgery are captured in MEAD, the outcomes for patients who have a cataract extraction and subsequently become pseudophakic are also implicitly captured in the model*." Based on this, the ERG agrees with the company that adding additional distinct health states for cataract surgery and lens status would introduce additional complexity to an already complex model, and that this additional granularity is likely to have a minimal impact on the results of the economic analysis.

The ERG also notes that the model for TA613 considered two additional health states (8 health states in total) as the mildest and most severe health states included 10-letters. However, the ERG does not expect this additional granularity to have a meaningful impact on the results either as it affects the most effective and least effective treatments equally.

Finally, as per the ERG for TA349, the ERG believes that to assume that the distributions of vision in BSE and WSE are independent reduces the face validity of the model, as it does not restrict the

possibility that the WSE can over time become the BSE. This approach may have also introduced bias in the estimation of QALYs, as the baseline distribution of eyes and the 'fixing' of BSE and WSE throughout the model are central assumptions affecting estimation of QALYs. The ERG is unable to resolve this issue in the model and is unable to comment further on the likely impact of using correlated distributions of vision for the BSE and WSE.

4.2.5 Perspective, time horizon and discounting

The economic analysis is conducted from the perspective of the UK NHS and Personal Social Services in England, and discounting is applied at an annual rate of 3.5% for both costs and QALYs, as per the NICE reference case.[47]

A lifetime time horizon (40 years) was applied by the company to be consistent with the lifetime time horizons adopted in two previous NICE appraisals in DMO: TA613[5] (30 years) and TA346[29] (35 years). Based on a 40-year time horizon and a starting age of [redacted] years, patients would be [redacted] years old at the end of the time horizon. The company also presented results of scenario analyses in which the time horizon was set to 15 years and 30 years to determine the impact of varying the time horizon on the results.

4.2.5.1 ERG critique

The time horizon of the model (40 years) is notably longer than the time horizons accepted in TA613[5] (30 years), TA349[2] (15 years), TA271/301[42] (15 years) and TA237/274[28] (15 years in the original submission and 10 years in the revised submission).

On the one hand, the ERG agrees with the company that a 40-year time horizon is long enough to represent a lifetime time horizon. In the model, [redacted] and [redacted] of patients in the DEX700 arm had died after [redacted] and [redacted], respectively. On the other hand, the ERG considers the time horizon to be too long to capture the key costs and consequences of DEX700 and all comparator treatments.

As noted in Section 4.2.8 and illustrated in Figure 8 and

Figure 9 below, DEX700 maintains a benefit in visual acuity above anti-VEGFs beyond the 5-year treatment period and throughout the remaining time horizon, although the absolute treatment effect does decline over time. This is because no treatment waning assumptions are included in the model. The ERG's clinical experts fed back that they would expect visual acuity across all treatments to converge during the off-treatment period, but were unable to suggest how long this might take. The clinical experts also noted that when a patient becomes pseudophakic more treatment options become available to them. For these reasons, the company's long term modelling assumptions may be too simplistic to accurately capture all relevant downstream benefits and costs following discontinuation from treatment.

Figure 8. Mean BCVA in treated eye(s) over the modelled time horizon (produced by the ERG using the economic model)

Key: anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; BSE, best-seeing eye; CS, company submission; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ERG, evidence review group; WSE, worst-seeing eye.

Figure 9. Average BCVA letters change from baseline (in treated eye(s)) over the modelled time

horizon (produced by the ERG using the economic model)

Key: anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; BSE, best-seeing eye; CS, company submission; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ERG, evidence review group; WSE, worst-seeing eye.

The ERG for TA613 and Committee for TA274 also noted concerns relating to the persisting treatment benefits in visual acuity during the off-treatment period, and both reduced the model time horizon to address this uncertainty. The ERG for TA613 provided scenarios which reduced the 30-year time horizon to 18 years (to approximate treatment waning effects) then 6 years (to reflect

the maximum assumed duration of treatment) while the company for TA274 reduced the time horizon in their resubmission from 15 years to 10 years.

As shown in the company's scenario analysis (see Section 5.1.2), reducing the time horizon from 40 years to 30 years then 15 years favours the comparator (inc. NMB reduced from £10,080 to £10,074 then £9,294, respectively). Nevertheless, the ICER remains dominant. The ERG considers it reasonable to go one step further and explore time horizons of 5 years and 10 years. The company's clinical experts noted that 5 years was sufficiently long enough to capture key differences in treatment costs and 10 years is consistent with the approach adopted by the company in TA274 to reduce the uncertainty about the projected effects of treatment. The results of ERG scenario analysis can be found in Section 6.3. A 10-year time horizon is also implemented in the ERG preferred base case (see Section 6.4).

4.2.6 Treatment effectiveness

The following sections describe the efficacy data from the phakic-only mITT population of the pooled MEAD trials (Section 4.2.6.1) the company's justification for using the sham arm of MEAD as a proxy for continued anti-VEGF treatment (Section 4.2.6.2) and the scenarios using RWE which are intended to provide supportive evidence to validate the clinical data presented in the base case (Section 4.2.6.3).

4.2.6.1 Efficacy data from the phakic-only mITT population of the pooled MEAD trials

In the base case analysis, changes in BCVA resulting from DEX700 and anti-VEGF treatment during the 5-year treatment period are modelled using 3-monthly transition probabilities, derived from the DEX700 arm and the sham arm of the pooled MEAD trials, respectively. These are patient-level transition probability matrices.

To ensure that all small and large, improvements or worsening of vision observed in MEAD are captured in the model, there are no restrictions on the number of visual acuity health states an eye can transition to in each model cycle. An example of how transition probabilities were derived is presented using data from baseline to month 3 for the all-phakic DMO patient population in Table 30 and Table 31.

Table 30 shows that of the [redacted] patients whose study eye was in health state 3 at baseline, the number of patients whose study eye moved from health state 3 to health state 4 from baseline to

month 3 was [redacted]. Therefore, the probability of moving from health state 3 to health state 4 from baseline to month 3 in Table 31 is calculated as [redacted]. The numbers included in this example are bold in Table 30 and Table 31.

Additionally, each row of the transition probability matrix in Table 31 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.

The full set of transition probabilities from the DEX700 and sham arms of the pooled MEAD trials (12 matrices for each treatment) is provided in Appendix N of the CS. In probabilistic sensitivity analysis (PSA), these transition probability matrices are varied using the Dirichlet probability distribution.

Table 30. Patient-level study eye movements between visual acuity states: baseline to Month 3 for DEX700 patients; all phakic DMO patients (adapted from Table 50 of Appendix N)

		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]						
	Health State 2	[redacted]						
	Health State 3	[redacted]						
	Health State 4	[redacted]						
	Health State 5	[redacted]						
	Health State 6	[redacted]						

Table 31. Transition probability matrix: baseline to Month 3 for DEX700 patients; all phakic DMO patients (adapted from Table 51 of Appendix N)

		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]						
	Health State 2	[redacted]						

	Health State 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Health State 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Given the change in visual acuity was not reported for all patients in each cycle of the MEAD trials, the company used the last observation carried forward (LOCF) approach to account for the potential unobserved movements between states that were not observed. This approach used the total number of patients on each trial arm fixed as the denominator in each cycle, and therefore assumed that patients with a missing observation did not move to a different health state in that cycle.

Given the follow-up time of 3 years in MEAD, the 3-monthly transition probabilities in Years 1 to 3 are taken from MEAD, whereas the 3-monthly transition probabilities in Years 4 and 5 are assumed to equal the last transition probability matrix estimated from MEAD (using data from Months 33 to 36). This approach is adopted as the last transition matrix provides the most relevant data available from MEAD as it allows for any recovery in BCVA following the development and extraction of cataracts in a significant proportion of patients to be captured.

During the clarification stage the company explained that transition probability matrices from months 36-39 are not used in the model, as these are dependent on whether patients received a re-treatment at month 36 and event numbers in this cycle were particularly small ([redacted] patients observed in the DEX700 and sham arms, respectively). The protocol amendment which allowed an additional treatment at month 36 is discussed further in Section 3.2.1.

After the 5-year treatment period, vision declines at a rate that represents the natural history of vision in an eye with DMO (see Section 4.2.8).

4.2.6.1.1 ERG critique

The ERG considers that the company is reusing the MEAD trials as per TA349 and that no new evidence has been implemented in the base case. This is because the MEAD sham arm is being used as a proxy for continued anti-VEGF treatment and, therefore, the only real changes are a different comparator (which is more expensive) and a longer treatment period (which is accruing additional benefits and cost savings for DEX700).

The ERG also has concerns relating to the appropriateness of using a LOCF approach to handle missing data in the MEAD trials and the appropriateness of using the last transition probability matrix to estimate effectiveness in Years 4 and 5.

LOCF

The ERG considers all analyses using the LOCF approach to be of questionable veracity (Lachin 2016[19]) and would only consider this simplistic approach to have some credibility when patients have stable disease prior to discontinuing. This is unlikely to be the case in the MEAD trials. As noted in Section 3.2.1, a total of [redacted] patients in the DEX700 arm and [redacted] patients in the sham arm discontinued from the MEAD trials due to a lack or loss of efficacy or AEs or due to censoring because of receiving of rescue therapy. These high discontinuation rates could potentially confound the results using a LOCF approach and it is unlikely that the results presented would reflect the total population had discontinuations not occurred or patients been followed up post-discontinuation.

During clarification the ERG requested the company conduct analyses using the multiple imputation approach to inform the missing data, but the company argued this approach was not appropriate as the data is not missing at random, which invalidates the multiple imputation approach. However, the ERG also considers this finding to invalidate the LOCF approach as this approach also requires data to be completely missing at random.[18]

Based on the natural history of vision in eyes with DMO, patients have a higher probability of worsening vision than improving vision, and therefore, their condition is expected to deteriorate over time. As such, the LOCF approach may provide overly optimistic estimates for patients with missing data as they are retaining their benefit and cannot worsen.[18]

On the one hand, the discontinuation rate is [redacted] in the sham arm compared with the DEX700 arm of the MEAD trials, which may bias the analysis in favour of the sham arm. On the other hand, this is less of an issue for the sham arm if anti-VEGFs are assumed to only maintain vision. Additionally, due to the additional benefits in vision received from DEX700 treatment, DEX700-treated patient will have a higher BCVA retained in the analysis compared to sham patients; i.e. while there may be [redacted] withdrawals with DEX700, their vision could deteriorate more once they've withdrawn.

Overall, the ERG is unable to resolve this issue in the model and is concerned that results for both the sham and DEX700 arms are likely to be biased.

Assumptions used to model years 4 and 5

The 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. The ERG and its clinical expert consider that in the absence of any evidence to substantiate improvements in DEX700-treated patients in Years 4 and 5, assuming vision is maintained is more appropriate, if, conservative.

Following a clarification request, the company provided a scenario assuming a net-zero impact on vision for DEX700 in Years 4 and 5. The company also assumed that a net-zero impact on vision would be best represented using a 3-month probability of gaining or losing at least 10 letters of BCVA (that is, moving up or down one health state) of 3.5% as it is unlikely that vision would remain constant for each individual patient over time. The company choose 3.5% as this is consistent with the probability of gaining at least 10 letters from the natural history study data from Mitchell *et al.* 2012[48] (see Section 4.2.8). Under this scenario, DEX700 continued to dominate anti-VEGFs and the inc. NMB reduced from £10,080 to £7,280.

However, the ERG is concerned that the company is adding a layer of unnecessary uncertainty to this scenario by assuming a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.5% rather than 0%. To explore the impact of this additional assumption, the ERG explored a scenario where the probability of gaining or losing at least 10 letters of BCVA was set to 0%. The results of ERG scenario analysis can be found in Section 6.3.

4.2.6.2 Efficacy data for continued anti-VEGF treatment

There is limited evidence that directly compares the DEX700 with anti-VEGF treatments in the group of patients who are insufficiently responsive to anti-VEGF treatment. In addition, there is limited relevant RCT evidence on the use of anti-VEGF or laser in insufficient responders. As a result, the company used the sham arm of the MEAD trials as a proxy for continued anti-VEGF use. While the sham arm is not considered a perfect proxy for continued anti-VEGF use, the company it applied in the base case because the availability of patient-level data allows for a full set of transition probabilities to be estimated for this treatment arm, and there are significant imbalances between the data for DEX700 from MEAD and the available anti-VEGF study data.

The company also noted that this approach is consistent with TA613, in which the Committee considered it appropriate, in the absence of suitable alternative evidence, to assume that the relative efficacy of fluocinolone acetonide vs sham in FAME was a reasonable proxy for the relative efficacy of fluocinolone acetonide vs continued use of anti-VEGF or laser.[5, 35] The company acknowledged that there are key differences between the sham arms in MEAD and FAME, as patients in FAME could receive rescue therapy if they were unresponsive to therapy and remain in the trial, whereas in MEAD any patient who received rescue therapy was excluded from the trial.

However, a naïve comparison of the mean BCVA change from baseline over time in the MEAD sham arm with UK RWE shows that using the MEAD sham arm as a proxy for continued anti-VEGF use likely overestimates the efficacy of this treatment arm and therefore likely results in a conservative estimate of the relative treatment effect (Figure 10).[23] The company therefore concluded that use of the MEAD sham arm is reasonable as any bias in using these data is likely to favour the comparator rather than DEX700.

Figure 10. Comparison of BCVA change from baseline in MEAD sham arm (phakic) vs FAME sham arm (phakic) vs UK RWE for continued anti-VEGF use (phakic and insufficiently responsive) (reproduced from Figure 22 of the CS)

Key: anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; CS, company submission; RWE, real world evidence; UK, United Kingdom.

4.2.6.2.1 ERG critique

Firstly, the ERG does not consider the comparisons made within Figure 10 to justify the use of the MEAD sham arm to be meaningful. This is because MEAD and FAME are RCTs and it is widely accepted that this type of study design evaluates treatments under ideal conditions and among highly selective participants, whereas observational studies like the UK RWE audit have examined effects in a "real world" settings with a broader range of conditions and patients. Thus, the ERG would expect patients in sham arm of MEAD or FAME to achieve better changes in BCVA than the UK RWE audit. The ERG also suspects that the FAME and MEAD curves crossed between months 14 and 17 as rescue therapies were allowed in FAME but not in MEAD.

Secondly, the 6-month timepoint is when the patients are deemed to be suboptimal responders in the UK RWE audit. As shown in Figure 10, the suboptimal responders from the UK RWE audit [redacted] between months 6 and 39. Moreover, if 6-months is assumed to be the baseline in the UK RWE audit and 0-months the baseline in the MEAD trials, then the ERG considers the BCVA change from baseline for the UK RWE audit to be largely consistent with the change from baseline for the sham arm of the MEAD trials. However, the ERG also considers it important to highlight that a >5 letter change in BCVA would generally be deemed clinically significant, and therefore, [redacted].

Thirdly, in the CS, the company provided a scenario where anti-VEGF treatment has zero net impact on vision. As shown in Section 5.1.2, this scenario favoured anti-VEGF treatment which suggests the sham arm of MEAD is not actually leading to an overall net gain in BCVA in the model (inc. QALYs reduced from 0.104 to 0.033 and inc. NMB reduced from £10,080 to £8,076). Like the point made in Section 4.2.6.1.1, the ERG is concerned that the company is adding a layer of unnecessary uncertainty to this scenario by assuming a 3-month probability of gaining or losing at least 10 letters of BCVA (that is, moving up or down one health state) of 3.5% rather than 0%. Upon inspection of the model the ERG also found that the company used a restricted set of transition probabilities to inform DEX700 in this scenario, i.e. patients can only move up or down one health state in each model cycle. To explore the impact of these additional assumptions, the ERG explored a scenario where the probability of gaining or losing at least 10 letters of BCVA was set to 0% and there are no restrictions on the number of health states DEX700-treated patients can transition to in each model cycle. The results of ERG scenario analysis can be found in Section 6.3.

The ERG also considers it important to make a comparison between the findings from this scenario and those reported in TA613. The company for TA613, for the base case analysis, assumed constant vision in the usual care (anti-VEGF) arm for the duration of treatment (6 years). No probabilities of improving or worsening vision were reported for constant vision, which suggests the company applied probabilities of zero. The first scenario considered by the company for TA613 (and preferred by Committee) included using the sham arm of FAME to represent the efficacy of usual care in the study eye (the efficacy in the fellow eye was a combination of the efficacy in the sham arm and the efficacy from RISE and RIDE). Nevertheless, unlike the base case analysis, patients under this scenario showed some treatment effect in the usual care arm (total QALYs increased from 8.244 to 8.470). These results are opposite to the ones provided by the company for this appraisal, which is cause for concern (Table 32).

As an aside, the ERG does not consider the efficacy in the fellow eye to differ from the first eye as both clinical feedback and clinical data included in TA349 indicate that a symmetrical response would be seen with any treatment for DMO. [2, 49] Large structural changes would also be needed to incorporate additional transition probability matrices for the fellow eye. In addition, the ERG for TA613 considered an odds ratio of 1.00 for the anti-VEGF treatment effect relative to sham (laser) in the fellow eye (likely due to a lack of data than a formal demonstration of the two being clinically equivalent).

Table 32. Total QALYs associated with the anti-VEGF arm in TA613 analyses

Source	Total QALYs in the anti-VEGF arm resulting from different efficacy assumptions		
	Constant vision	Sham arm	Difference (sham arm – constant vision)
TA613 committee papers (Table B3. 42. and Table B3. 43.)	8.244	8.470	+0.226
CS	7.553	7.482	-0.071

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; CS, company submission; QALY, quality-adjusted life year; TA, technology appraisal.

Finally, it appears that the clinicians on the company's advisory board considered it unreasonable to use the MEAD sham arm as a proxy for continued anti-VEGF use. A relevant extract from this advisory board is provided in Figure 11.[6]

Figure 11. Advisory Board notes on the use of the sham arm in MEAD as a proxy for continued anti-VEGF use

For these reasons, the ERG's preferred approach is to assume that anti-VEGF treatment maintains vision (that is, a 0% probability of improving or worsening) as it is transparent in terms of the likely biases that exist in the comparison. However, as noted in Figure 11, this could be viewed as conservative estimate of anti-VEGF efficacy as, "[redacted]".

4.2.6.3 RWE as an alternative source to MEAD

The company explained that the UK RWE provides the strongest evidence available for the efficacy of anti-VEGFs in those that are insufficiently responsive to treatment, but these data have not been formally included in the base-case analysis due to the challenges of matching patient and study

characteristics between MEAD and the UK RWE, and because the study does not provide the data required to model the full set of transition probabilities.

The company also explained that some of the characteristics of the phakic patients from MEAD and the treatment practices observed in the trial do not align with what is expected in current UK clinical practice. This may underestimate the true efficacy of DEX700. Although the French RWE provides efficacy data for DEX700 in phakic DMO patients it cannot formally be included in the base-case analysis because the study does not provide the data required to model the full set of transition probabilities.

However, both sources reported the proportion of patients who experience a 10-letter improvement or worsening from baseline to Month 12, 24 or 36. The company utilised these data and provided six scenario analyses, three where the efficacy in the anti-VEGF treatment arm is based on UK RWE data and three where the efficacy in the DEX700 arm is based on French RWE data. The UK RWE data and French RWE data were not combined in any scenarios in the CS.

The three scenarios associated with each study relate to the probability of experiencing a 10-letter improvement or worsening in vision at three different timepoints: baseline to month 12, baseline to month 24 and baseline to month 36. As shown in Table 33, these data were recalculated into 3-month probabilities and applied throughout the treatment period.

Given that the scenarios utilised data on the proportion of patients who experience 10 letter improvement or worsening from baseline patients can only move up or down one health state at each time point. To ensure a consistent approach was taken to estimate transition probabilities in each treatment arm, the company also applied a restricted set of MEAD transition probabilities when modelling DEX700 (and the UK RWE data for anti-VEGFs) or anti-VEGFs (and the French RWE for DEX700).

As shown in Section 5.1.2, these scenarios favour DEX700 and increase the inc. NMB from £10,080 to a maximum of £25,825.

Table 33. >=10-letter improvement/worsening in RWE (adapted from Tables 26 and 27 of the CS)

	Proportion of patients			3-month probability		
	Scenario 1: Baseline to Month 12	Scenario 2: Baseline to Month 24	Scenario 3: Baseline to Month 36	Scenario 1: Baseline to Month 12	Scenario 2: Baseline to Month 24	Scenario 3: Baseline to Month 36
UK RWE on anti-VEGFs*						
>=10-letter improving	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=10-letter worsening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
French RWE on DEX700						
>=10-letter improving	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=10-letter worsening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: anit-VEGF, anti–vascular endothelial growth factor; CS, company submission; DEX700, dexamethasone 700 µg; RWE, real world evidence; UK, United Kingdom.

*Includes suboptimal responders only

4.2.6.3.1 ERG critique

As mentioned earlier, the 6-month timepoint is when the patients are deemed to be suboptimal responders in the UK RWE audit. However, the scenarios provided by the company models the probability of experiencing a 10-letter improvement or worsening in vision from baseline (Month 0) to Month 12, 24 or 36 as these were the only timepoints available to the company. The ERG considers that the 6-month timepoint should be the assumed baseline in any comparisons, where the UK RWE audit data are used to reflect continued anti-VEGF treatment in patients deemed to be insufficient responders.

Furthermore, the ERG considers it inappropriate to make any reliable comparisons using naïve comparisons of RCT evidence and observational evidence and therefore does not consider the scenarios provided by the company in the CS be reliable. During the clarification stage the company provided a naïve comparison using observational evidence to inform the intervention and comparator (UK RWE for DEX700 and French RWE for anti-VEGF treatment). As per the CS, the company provided three separate scenarios according to the timepoint of the assessment and the results were as follows:

- baseline to 12 months probabilities: DEX700 dominates anti-VEGFs, inc. NMB £32,898;
- baseline to 24 months probabilities: DEX700 dominates anti-VEGFs, inc. NMB £24,103;
- baseline to 36 months probabilities: DEX700 dominates anti-VEGFs, inc. NMB £25,019.

The ERG considers using the same study design for both treatments to be one small step closer to a robust analysis. However, given the high levels of heterogeneity between these studies and that no adjustments for treatment effect modifiers or prognostic factors have been undertaken, these analyses should not be used for decision making. If patient-level data became available from one of these RWE studies, the ERG would urge the company to utilise it as per the methods in NICE TSD 18.[50]

During the clarification stage the company was asked to clarify if the proportion of patients experiencing improvement or worsening in vision between the three timepoints (from 12 to 24 months and from 24 to 36 months) could be estimated so that different 3-monthly transition probabilities can be applied in Years 1, 2 and 3. The company agreed that this would be their preferred approach but explained that this data was only available for the UK RWE audit. The company subsequently provided these data (see Table 11 of the company's clarification responses) and reported a inc. NMB of £16,706 when utilising it in the model. However, given that this scenario is still comparing RCT data with observational data and using a month-0 baseline for the UK RWE data, the results cannot be considered valid.

Overall, the ERG does not consider the current analysis of the data within the RWE studies to provide reliable supportive evidence to validate the clinical data presented in the base case.

4.2.7 Discontinuation

The model assumes a maximum duration of treatment of 5 years across all treatments. This assumption was based on feedback provided by UK clinical experts which noted that 5 years was sufficiently long enough to capture key differences in treatment costs. The clinicians noted that although there will be a proportion who remain on treatment beyond 5 years, this group will be likely be small across for both those receiving DEX700 or anti-VEGFs. This is supported by data from MEAD trials and the French RWE audit,[22] which demonstrate that a proportion of patients were still receiving DEX700 at the end of the 3-year follow-up period. This assumption is also supported for anti-VEGFs by the UK RWE audit[23] and other published studies such as the RESTORE trial[51], which demonstrate that a sizeable proportion of patients were still receiving frequent anti-VEGFs after 3 to 4 years.

At any time during the 5-year treatment period in the model, DEX700 treated patients can discontinue treatment (and move to no treatment) either due to lack (or loss) of efficacy of

treatment or due to AEs and other non-efficacy related reasons. The company stated that these two reasons were modelled as independent in accordance with the way the data were reported and to allow disaggregation of outcomes attributable to each reason. However, visual acuity outcomes were not affected by the reason for discontinuation; visual acuity following discontinuation was assumed to follow the natural history of vision in eyes with DMO (see Section 4.2.8).

The proportion of patients who discontinued from DEX700 treatment due to either reason was taken from the full phakic population of the pooled MEAD trials, these data were collected every 3 months. Beyond the trial duration (beyond Month 39) the discontinuation rates were extrapolated using the average rate over the trial duration, applied in line with the relevant trial cycle length. The discontinuation rates applied in the model are given in Table 34.

Table 34. DEX700 discontinuation rates applied in the model

Assessment	Discontinuation due to AEs and other reasons			Discontinuation due to inefficacy		
	N	n	Mean	N	n	Mean
Month 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 51	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 57	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AEs, adverse events; DEX700, dexamethasone 700 µg; N, number on treatment; n, number who discontinue

The proportion of patients who remained on DEX700 treatment during the 5-year treatment period in the model are illustrated in Figure 12. These proportions were calculated using the discontinuation rates in Table 34 and including adjustments for mortality.

Figure 12. Proportion of patients remaining on DEX700 treatment during the 5-year treatment

period (produced by the ERG using the economic model)

Key: anti- DEX700, dexamethasone 700 µg; ERG, evidence review group.

For anti-VEGF treated patients, the company assumed, in line with TA613,[5] that patients do not discontinue treatment during the anti-VEGF treatment period because it represents the last therapeutic option for these patients. However, like DEX700, a decrease in the frequency of injections is considered over time (see Table 26 in Section 4.2.3.2).

The ERG considers it important to highlight that DEX700 and anti-VEGFs do not have treatment regimens where retreatment is defined at regular intervals, it is the need for retreatment that is assessed at regular intervals. As such, the proportion of patients receiving DEX700 in a given model

cycle (see Table 25 in Section 4.2.3.1) is not necessarily reflective of the proportion on continued treatment (Figure 12).

4.2.7.1 ERG critique

The ERG believes that patients with deteriorating vision are more likely to discontinue treatment. As the model does not account for any association between worsening of vision and treatment discontinuation it reduces the face validity of the model. On the one hand, this may introduce bias in favour of DEX700 (overall, the more effective treatment) as patients on anti-VEGF treatment could be incurring treatment costs for longer than they otherwise would. On the other hand, this may be less of an issue for anti-VEGFs, if patients stay on treatment because it is their last therapeutic option or because treatment is being used to maintain their retinal architecture. However, a larger proportion of DEX700-treated patients than anti-VEGF-treated patients reside in health state 1 which suggests deteriorating vision is an issue for DEX700 ([redacted], respectively). Overall, the ERG is unable to resolve this issue in the model and considers it to affect both treatments.

The ERG also verified the company's discontinuation assumptions with its clinical experts. They had concerns assuming patients would not discontinue anti-VEGF treatment during the treatment period, assuming patients would receive no treatment following discontinuation of DEX700 and assuming anti-VEGF and DEX700 treatment is given for up to 5 years. Each of these issues is described in turn below.

Anti-VEGF discontinuation

Clinical experts advised the ERG that all patients would discontinue anti-VEGF treatment if their vision worsened, and some patients would discontinue anti-VEGF treatment if they experienced an AE; this would depend on how well the AE could be managed alongside anti-VEGF treatment.

The ERG is aware that patients could not discontinue treatment during the anti-VEGF treatment period (a 6-year treatment period) in TA613[5] and that the experts advising Committee said they might be continued if they do not work well. However, the ERG and its clinical experts consider there to be a key difference between not working well and not working at all; anti-VEGFs may not work well in an insufficient responder, and they may not work at all if that insufficient responder experienced a lack (or loss) in efficacy.

In the CS, the company provided a scenario where it is assumed that those eyes included in UK RWE[23] that did not receive any treatment within a certain time period discontinued treatment. As shown in Section 5.1.2, this scenario favoured DEX700, but it had no meaningful impact on the results (inc. NMB increased from £10,080 to £10,472). However, the company highlighted concerns with this scenario as it is unclear if patients that did not receive anti-VEGF treatment within a certain time period permanently discontinued or received an injection at a much later time. It is unclear what time period was considered by the company.

Given these limitations and the way discontinuations are partly captured in the way the number of anti-VEGF injections has been calculated the ERG is satisfied with the company's base case assumption. Nevertheless, the ERG would ask the company to provide further details on the time period used in this scenario and test the impact of alterative time points on the results.

DEX700 discontinuation

Clinical experts advising the ERG said that DEX700-treated patients would be offered treatment with an anti-VEGF if they discontinued DEX700 due to an AE or due to lack (or loss) of efficacy. This would include re-treatment with an anti-VEGF if they previously demonstrated an insufficient response to anti-VEGFs. Given the clear direction from the ERG's clinical experts that patients would receive anti-VEGF treatment following DEX700, the company was asked to provide two exploratory scenarios to show how non-responders and partial responders to subsequent anti-VEGF treatment could impact the results of the economic analysis:

1. Assume patients receive anti-VEGF treatment for 1 year and vision follows the natural history of vision in eyes with DMO during and after this 1-year period; and,
2. Assume anti-VEGF treatment is given for 5 years and vision is maintained during this 5-year period, followed by the natural history of vision in eyes with DMO.

During the clarification stage the company presented results of the first scenario analysis. The company implemented this scenario by applying a one-off cost (£3,539) to patients who discontinue DEX700 due to an AE or other non-efficacy related reason or due to lack (or loss) of efficacy of treatment. This one-off cost consisted of drug acquisition and drug administration costs based on the ranibizumab and aflibercept market shares and number of injections in year 1 as observed UK RWE (as per company base case). For simplicity, AE costs and monitoring costs were not included, and as the model already assumes that vision follows the DMO natural history for patients who have

discontinued treatment no changes were made to efficacy. Following this, DEX700 remained dominant and the inc. NMB reduced from £10,080 to £8,373. The company response also included additional clinical expert feedback that, "*very few patients will receive anti-VEGF treatment upon discontinuing DEX700 and that these patients will only receive anti-VEGF treatment for a short period of time because this treatment is unlikely to be effective in this population*". This differs to feedback received from the ERG's clinical experts that most patients will receive anti-VEGF treatment upon discontinuing DEX700. Nevertheless, there appears to be some agreement between the experts that anti-VEGF treatment is likely to be given for a short period of time and likely to be ineffective in this population.

The second scenario analysis was not undertaken by the company. Clinicians advising the company considered the 5-year subsequent treatment duration to be long as it is unlikely to be effective in this population. In addition, the company considered it to be unfeasible within the current model structure to assume that vision is maintained for 5 years upon treatment discontinuation followed by DMO natural history without making significant structural changes to the model.

Given the clear direction from the ERG's clinical experts that patients would receive anti-VEGF treatment following DEX700 the ERG includes the first scenario in its preferred base case.

Treatment duration

On the one hand, the ERG considers that the 5-year stopping rule should be removed from the economic analysis. The ERG's clinical experts agreed that they would not take a patient off DEX700 or anti-VEGF treatment if they were still deriving a benefit after 5 years; no formal stopping rules are included in the SmPCs[10, 52, 53] for these treatments; and, around [redacted] of patients of patients were still on DEX700 treatment at the end of the 5-year treatment period in the model (see Figure 12).

On the other hand, the ERG's clinical experts agreed that the proportion of patients on-treatment at 5 years was expected to be small; the frequency of DEX700 injections decreases over time which means around [redacted] of patients on treatment in Years 4 and 5 received an injection in the 3-monthly cycles (see Table 25); and, a 3-year treatment duration was accepted in TA349[2] as there were no sufficient data to allow accurate prediction of the treatment effects beyond this period.

To align with TA349 and reduce the number of assumptions required to model Years 4 and 5, the company was asked to provide a scenario using a 3-year treatment duration for all treatments. The

company provided the requested scenario and found that DEX700 continued to dominate anti-VEGF, albeit the inc. NMB reduced substantially from £10,080 to £2,957. In their response the company also included additional clinical expert feedback that, "*the duration of treatment, and the number of injections patients receive, is largely driven by the level of treatment response that is achieved. Patients who experience a strong level of response to treatment in most cases only require a small number of injections over a short duration of time, but those with a sub-optimal response are often treated more intensively in an attempt to improve the level of response to treatment, and to prevent the decline in visual acuity*".

Overall, the ERG is satisfied that a treatment duration of 5 years is appropriate as additional assumptions and uncertainty would be needed to model longer durations while expert opinion to the company and ERG agree that shorter durations would underestimate the costs and consequences of treatment. The treatment effectiveness assumptions used to model Years 4 and 5 are outlined and critiqued in Section 4.2.6.

4.2.8 Natural history of vision in patients with DMO

After the 5-year treatment period or because of discontinuation within the 5-year treatment period, it is assumed that patients receive no further treatment. As a result, the vision in their DMO-affected eye(s) transitions through the BCVA states at a rate consistent with the natural history of vision in patients with DMO. As per TA349, these data were taken from Mitchell *et al*. 2012.[48] This study used data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) adjusted to account for the improvement in DMO management since WESDR was undertaken and calculated a 3-month probability of gaining or losing at least 10 letters of BCVA (moving up or down one health state) of 3.5% and 4.5%, respectively. This extrapolates the same improving and worsening of BCVA in both treatment arms. In consequence, DEX700 maintains a benefit in visual acuity above anti-VEGFs for the remaining 35 years of the model time horizon, at no additional cost (see Section 4.2.5.1).

The company also explored a scenario in which the natural history of vision was as per TA613:[5] a 3-month probability of gaining or losing at least 10 letters of BCVA of 0% and 3.5%, respectively. The ERG notes that this appears to be taken from the ranibizumab appraisal (TA274[28]). As shown in Section 5.1.2, this scenario favoured the comparator. Nevertheless, the ICER remained dominant (inc. NMB reduced from £10,080 to £8,725).

4.2.8.1 ERG critique

The ERG sought clinical expert opinion on the natural history of vision in patients with DMO. They expressed concerns that the same probability of improving or worsening vision was applied irrespective of where a patient's vision starts at. Additionally, the 3-month probability of gaining at least 10 letters of BCVA of 3.5% was considered too high. Given that WESDR was based on a population of patients with diabetic retinopathy who may not have had DMO, this could represent a less severe set of patients than the population for this appraisal. Furthermore, when the ERG's clinical experts were asked if the natural history from Mitchel *et al*. 2012 or TA613 was most reflective of their patients in clinical practice, their expectations would align more closely with TA613.

The ERG also considers it important to note that although the rate of decline in BCVA was adjusted to account for the improvement in DMO management since WESDR[54, 55] was undertaken, the publications[56-59] used for these adjustments are relatively old (1998 to 2004).

For these reasons, the natural history estimates accepted in TA613 are applied in the ERG's preferred base case.

4.2.9 Fellow eye involvement (FEI)

Patients who are affected unilaterally at baseline may develop DMO in their second eye, termed Fellow eye involvement (FEI), and move to bilateral treatment. As noted in Section 4.2.2, [redacted] and [redacted] of patients in the cohort are treated unilaterally and bilaterally, upon model entry, respectively.

Consistent with the model from TA349, and based on clinician feedback, it is assumed that patients are only at risk of FEI by the end of Year 1 or Year 2. The company also added that this simplifying assumption is needed given the memory-less property of the model and the additional complexity that is needed to capture potential FEI at future time points. The company also claimed that this assumption was validated against the MEAD clinical data, in which the majority of incidences of FEI occurred during Years 1 and 2.

The proportion of fellow eyes that develop DMO in each year was estimated using data from the full mITT population of the pooled MEAD trials, which indicated that approximately [redacted] of DEX700 patients developed FEI over the 3-year trial duration. This was converted into an annual probability

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:

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

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

The company also provided a scenario using the phakic mITT population of the pooled MEAD trials, which indicated that approximately [redacted] of DEX700 patients developed FEI over the 3-year trial duration. Using the same methods above, this was converted into an instantaneous rate of [redacted] and annual probability of [redacted]. As shown in Section 5.1.2, this scenario had a negligible impact on the results (inc. NMB reduced from £10,080 to £10,074).

Upon development of DMO in the fellow eye, the same treatment as received in the first eye was assumed to be given for a period of up to 5 years starting from this point. Treatment in the fellow eye was assumed to be initiated at the end of the year in which the eye developed DMO. For example, if a patient within the cohort was affected unilaterally at baseline in their BSE, and their WSE developed DMO during Year 1, it was assumed that the BSE would receive treatment during Years 1-5 and the WSE would receive treatment during Years 2-6, provided that the patient did not discontinue from treatment. The newly affected eye was assumed to receive treatment at the rate expected in Year 1, and to receive the efficacy of treatment associated with Year 1.

In the case of bilateral DMO at baseline or FEI, the model assumed that the patient, rather than each eye, was at risk of discontinuation. Since the initially affected eye will be associated with a different risk of discontinuation to the newly affected eye, the patient risk of discontinuation was calculated using the formula for the probability of either eye discontinuing, assuming that the probabilities are independent:

$$P(AUB) = P(A) + P(B) – (P(A) \times P(B))$$

4.2.9.1 ERG critique

The ERG is satisfied that there is very little difference between the proportion of fellow eyes that develop DMO in each of the populations (full population vs phakic population). The ERG also considers modelling FEI in Years 1 and 2 to be a reasonable simplification and in line with evidence from the UK RWE[23] which found that the mean time to second eye treatment is [redacted] ([redacted]

[redacted] when you include those where the second eye is treated at baseline). However, the ERG is concerned that there are differences between the treatment arms.

During the clarification stage the ERG asked the company to clarify why the modelled baseline distribution of vision were taken selectively from the DEX700 arm of the pooled MEAD trials, and not from the pooled population of both DEX700 and sham treatment arms of the pooled MEAD trials. In their response, the company provided FEI data for the sham arm and pooled DEX700 and sham arms separately (Table 35) and additional results utilising the pooled data (Table 36).

As shown in Table 35, the proportion of patients who develop FEI is [redacted] for DEX700 than sham which suggests the proportion may not be independent of treatment received in the first eye, as per the company's base case assumption. Following this, the ERG sought clinical expert advice on this finding. The ERG's clinical experts stated that DEX700 or anti-VEGF treatment could potentially help to stabilise the fellow eye and reduce the likelihood of FEI due to a small amount of systemic absorption of the drug that is injected into the eye, but that there is no prospective data on this. Thus, the finding that [redacted].

Overall, the ERG accepts the company assumption that the risk of FEI is equal for DEX700 and anti-VEGFS and agrees that the use the DEX700 data instead of pooled data does not have a meaningful impact on the results of the economic analysis.

Table 35. FEI by treatment arm (adapted from Table 31 of the company's clarification response)

Parameter	DEX700	Sham	Pooled DEX700 and sham
Proportion of patients who develop FEI (full mITT population of MEAD)	[redacted]	[redacted]	[redacted]
Proportion of patients who develop FEI (phakic only mITT population)	[redacted]	[redacted]	[redacted]

Abbreviations: DEX700, dexamethasone 700 µg; FEI, fellow eye involvement; mITT, modified intention-to-treat.

Table 36. Results using alternative FEI probabilities (adapted from Table 32 of the company's clarification response)

Input source	Annual probability	Inc. NMB
Full mITT; DEX700 arm ([redacted]): Base case (as per TA349)	[redacted]	£10,080
Full mITT; pooled DEX700 and sham arms ([redacted])	[redacted]	£10,087
Phakic mITT; DEX700 arm ([redacted])	[redacted]	£10,074

Phakic mITT; pooled DEX700 and sham arms ([redacted])	[redacted]	£10,082

Abbreviations: DEX700, dexamethasone 700 µg; FEI, fellow eye involvement; mITT, modified intention-to-treat; NMB, net monetary benefit.

4.2.10 Cataracts

All patients in the cohort entered the model with phakic eyes; each year, this number was reduced by the proportion of patients who had developed cataract within the previous year. The company acknowledged that, "*phakic eyes are at high risk of cataract progression after multiple DEX700 injections*" and therefore treatment specific cataract extraction rates were applied in the model.

For DEX700, the cataract extraction rates are based on the pooled DEX700 arms of phakic patients in the MEAD trials with those who had a cataract operation in the previous year subtracted.

For anti-VEGFs, the cataract extraction rates are based on the UK RWE audit.[23] This study provides data on the number of eyes having cataract extraction in five time periods: 3 to 6 months, 6 to 12 months, 12 to 24 months, 24 to 36 months and 36 to 48 months. However, only data from month 12 onwards was utilised in the model as this provides the first full year of data following an assessment of insufficient response.

For eyes receiving no treatment (including eyes without DMO), the cataract extraction rate is assumed equal to the diabetes mellitus (DM) population's risk of cataracts. As per TA349[2], this was taken from the Blue Mountain Eye Study,[60] which demonstrated a cumulative incidence of cataract extraction in a DM population of 20.9% over 10 years. Assuming that the risk is constant over time and using the exponential cumulative distribution function, this gives an annual probability of 2.32%:

Instantaneous rate $r = - [\ln (1-P)]/t = - [\ln (1- 0.209)]/10 = 0.0234$

Annual probability $p = 1 – \exp (-r \times t) = 1 – \exp (-0.0234 \times 1) = 0.0232$

The annual cataract extraction probabilities applied in the model are summarised in Table 37. The proportion of patients with phakic eyes over the duration of the model time horizon are illustrated in Figure 13.

Table 37. Annual cataract extraction probabilities for phakic eyes

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6 +
DEX700	Annual probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.32%

	Source	Pooled DEX700 arms of phakic patients in MEAD ([redacted])	Pooled DEX700 arms of phakic patients in MEAD ([redacted])	Pooled DEX700 arms of phakic patients in MEAD ([redacted])	Assumed to equal Year 3	Assumed to equal Year 3	Blue Mountain Eye Study
Anti-VEGFs	Annual probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.32%
	Source	Figure 50 in the UK RWE audit, Months 12 to 24	Figure 50 in the UK RWE audit, Months 24 to 36	Figure 50 in the UK RWE audit, Months 36 to 48	Assumed to equal Year 3	Assumed to equal Year 3	Blue Mountain Eye Study

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; DEX700, dexamethasone 700 µg; RWE, real world evidence; UK, United Kingdom.

Figure 13. Proportion of patients with phakic eyes in the model (produced by the ERG using the economic model)

Key: anti-VEGF, anti–vascular endothelial growth factor; DEX700, dexamethasone 700 µg; ERG, evidence review group.

The company considered the UK RWE audit[23] to underestimate cataracts extractions rates. This is because the rates observed in the RISE and RIDE trials[61] on ranibizumab in DMO were higher than the UK RWE (42% over 2 years vs [redacted]) and clinical experts advised the company that all patients with DMO with a phakic lens will eventually develop a cataract and therefore there is no reason for the cataract rates to differ between treatments in the long-term, but differences may be observed with regards to the timing of cataract development instead. To address this uncertainty, the

company explored a scenario where DEX700 cataract extraction rates were applied to anti-VEGFs. As shown in Section 5.1.2, this scenario favoured DEX700 (inc. NMB increased from £10,080 to £10,502).

Consistent with TA349, the model includes the cost of surgery for the proportion of phakic DMO patients experiencing cataracts requiring extraction (see Section 4.2.14.4), and the model structure does not include health states according to lens status (see Section 4.2.4).

4.2.10.1 ERG critique

The ERG has several issues with how the company estimated and implemented the proportion of patients having cataract surgery in the model. These issues include using different sources to inform the probability in patients on and off anti-VEGF treatment and the appropriateness of the source used to inform the probability in patients receiving no treatment.

Firstly, in TA613,[5] the probabilities of developing cataract and having cataract surgery were derived from the FAME trial.[35] It was assumed that patients treated with usual care (anti-VEGFs) had the same probability of developing cataract and having cataract surgery as patients in the sham arm in FAME, thus assuming no impact of anti-VEGFs on cataract. The ERG's clinical experts also agreed that anti-VEGFs do not accelerate the formation of cataract whereas steroids such as DEX700 are known to accelerate the formation of cataract and cause it.

For these reasons, the ERG is unclear why the company applied different cataract extraction rates to patients on and off anti-VEGF treatment. During the clarification stage, the company was asked to provide a clinical rationale for this. In their response, the company explained that both clinical feedback and clinical data indicate the potential for anti-VEGFs to increase the risk of cataract development relative to those who are not receiving any treatment. The company reiterated that the risk of cataracts for ranibizumab could be as high as 42% after only 2 years when looking at all types of cataracts reported in the RISE and RIDE trials.[61] The company also explained that given the age of the Blue Mountain Eye Study,[60] no patients will have received treatment with anti-VEGFs which limits its potential to represent an appropriate proxy for cataract extraction rates on the anti-VEGF arm.

In consequence, the ERG reviewed the cataract outcomes reported in the RISE and RIDE trials to determine if similar results were seen in the ranibizumab arms and sham arm. Using Table 11 in the online supplement, the ERG found no data to suggest patients on anti-VEGF treatment should have a

higher probability of developing cataract and having cataract surgery as patients on no treatment (Table 38).[62]

Table 38. Number of patients enrolled in RISE and RIDE with cataract event

Preferred term	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
RISE	N=123	N=125	N=124
Cataract	18 (14.6%)	21 (16.8%)	15 (11.9%)
Cataract cortical	13 (10.6%)	9 (7.2%)	10 (7.9%)
Cataract subcapsular	7 (5.7%)	10 (8.0%)	10 (7.9%)
Cataract nuclear	8 (6.5%)	4 (3.2%)	5 (4.0%)
Cataract operation	0	1 (0.8%)	0
RIDE	N=127	N=125	N=124
Cataract	30 (23.6%)	25 (20.0%)	29 (23.4%)
Cataract cortical	7 (5.5%)	7 (5.6%)	7 (5.6%)
Cataract subcapsular	6 (4.7%)	6 (4.8%)	5 (4.0%)
Cataract nuclear	5 (3.9%)	5 (4.0%)	6 (4.8%)
Cataract operation	0	1 (0.8%)	1 (0.8%)
TOTAL	**94/250 (37.6%)**	**89/250 (35.6%)**	**88/248 (35.5%)**

Furthermore, in the company's clarification response, clinical experts revealed to the company that, "*the Blue Mountain study is not an appropriate proxy for the cataract extraction rate in UK clinical practice. This is because the Blue Mountain study, which is not a UK-based study, considers a broader and less clinically severe population compared to the UK RWE. Further, the data were published in 2008 and assessed patients from as early as 1997. Therefore, this study does not capture the evolution in clinical practice over time including advanced patient management. UK clinical experts have highlighted that they are now far more proactive in extracting cataracts as soon as they develop than they were historically*". The ERG therefore suspects the proportion of patients needing cataract surgery in the model has been underestimated by utilising data from the Blue Mountain Eye Study for patients on no treatment.

For these reasons, the ERG concludes that patients treated with anti-VEGFs should have the same probability of developing cataract and having cataract surgery as patients on no treatment, and that the UK RWE audit[23] is a superior source to the Blue Mountain Eye Study as the UK RWE audit provides current data for cataract extraction rates in the relevant population of interest.

The ERG also considers the sham arm of MEAD to be another relevant source as this would be in line the approach accepted in TA613 (which utilised the sham arm of FAME), and reduce the differences

in the severity of the cataracts and the timing of cataract surgery that could be behind the differing results of the UK RWE audit and MEAD.

During the clarification stage, the company provided a scenario where patients treated with anti-VEGF treatment and no treatment (including those who discontinue DEX700) had the same probability of having cataract surgery, using the results from the UK RWE audit. Given that the ERG considers the 0-to-12-month data from the UK RWE audit to be relevant as the incidence of cataract surgery should not depend on response status, the company was asked to include 0-to-48-month data in this scenario.

The company found that [redacted] had cataract surgery between Month 0 and 48 in the UK RWE audit. Assuming that the risk is constant over time using the exponential cumulative distribution function the annual risk is [redacted]. The company also used the same method (for consistency) to adjust the cataract extraction rate for DEX700 from MEAD to be a constant risk over time and calculated an annual risk of [redacted]. Nevertheless, applying these data in the model had a minimal impact on the results (inc. NMB reduced from £10,080 to £9,822). However, the ERG is unclear how the company estimated that [redacted] of patients had cataract surgery in the UK RWE audit as Figures 49 and 50 suggest this is closer to [redacted] using an exponential cumulative distribution ([redacted] were also used to represent the rates in Years 1, 2 and 3 in the company's base case analysis). For completeness the ERG ran a scenario using this estimate. The results of ERG scenario analysis can be found in Section 6.3.

The company also provided cataract extraction rates from the sham arm of MEAD in their clarification response (Table 39). The ERG has used these data to provide a scenario where patients treated with anti-VEGF treatment and no treatment (including those who discontinue DEX700) had the same probability of having cataract surgery, using the results from the sham arm of MEAD. The results of ERG scenario analysis can be found in Section 6.3. The ERG also applies these estimates in its preferred base case.

Table 39. Cataract surgery rates obtained from the pooled MEAD trials

	DEX700	Sham

Year 1	[redacted]	[redacted]
Year 2	[redacted]	[redacted]
Year 3	[redacted]	[redacted]
Annual risk assuming an exponential CDF	[redacted]	[redacted]

Abbreviations: CDF, cumulative distribution function; DEX700, dexamethasone 700 µg.
*Used in place of the Blue Mountain Eye Study (2.39%) in the ERG's scenario

Finally, the ERG also had concerns that cataract extractions were not modelled according to a patient's visual acuity, as per TA613. In response to a clarification question the company explained that the adopted modelling approach was consistent with that accepted for TA349 and that the inclusion of additional health states to explicitly capture the link between cataract extractions and visual acuity would add additional model complexity without significant benefit as visual acuity outcomes of patients in the MEAD trial who underwent cataract surgery were implicitly captured within the transition probabilities applied in the model. The ERG note that this is a limitation of the company's model structure, but one which is not expected to have a large impact on the results.

4.2.11 Other adverse events

The company modelled five AEs that may require medical or surgical intervention; cataracts (discussed separately in Section 4.2.10), raised intraocular pressure (IOP), retinal detachment, endophthalmitis and vitreous haemorrhage. These were consistent with the AEs considered in TA349,[2] although TA613[5] also considered glaucoma and complications of cataract surgery (endophthalmitis and retinal detachment). The proportion of eyes which experience each AE during each year of the 5-year treatment period are provided in Table 40. For the DEX700 arm, AE occurrence data was sourced from the pooled phakic population of the MEAD trials while AE data for anti-VEGFs were taken primarily from TA613 (using AE data from the RISE and RIDE trials for ranibizumab in DMO[63]).

As the TA613 ERG report provided AE estimates for Years 1 to 3, with Years 1 and 2 combined, the company estimated the AE probability in Years 1 and 2 separately assuming a constant risk over time. As AE data were not available for the full 5-year expected duration of DEX700 or anti-VEGF treatment, the company applied a LOCF type approach to the MEAD data. Thus, the estimates in Years 4 and 5 were assumed equal to Year 3. As previously mentioned in Section 4.2.10, cataract extraction rates from anti-VEGFs were estimated from the company's UK RWE audit, though could not be used for other AE due to poor reporting.

Table 40. Proportion of patients experiencing each AE, by year, according to treatment arm

AE	DEX700				Anti-VEGF			
	Year 1	Year 2	Year 3-5*	Source	Year 1	Year 2	Year 3-5*	Source
Cataract extraction	[redacted]	[redacted]	[redacted]	Pooled DEX700 phakic population of the MEAD trials	[redacted]	[redacted]	[redacted]	UK RWE audit[23]
Raised IOP (≥30 mmHg)	[redacted]	[redacted]	[redacted]		8.57%	8.57%	7.90%	RISE and RIDE trial data provided in the TA613 ERG report[5, 63†]
Retinal detachment	[redacted]	[redacted]	[redacted]		0.20%	0.20%	0.20%	
Endophthalmitis	[redacted]	[redacted]	[redacted]		0.40%	0.40%	0.40%	
Vitreous haemorrhage	[redacted]	[redacted]	[redacted]		0.40%	0.40%	0.40%	

Note: All DEX700 AE data was sourced from the MEAD safety population of phakic patients (MEAD study CSRs).

*Constant AE rates applied in years 3, 4 & 5.

†Years 1 & 2 calculated assuming constant risk with exponential CDF

Abbreviations: AE, adverse event; anti-VEGF, anti-vascular endothelial growth factor; DEX700, dexamethasone 700 µg; ERG, evidence review group; IOP, intraocular pressure; mmHg, millimetres of mercury; RWE, real world evidence; TA, technology appraisal; UK, United Kingdom.

4.2.11.1 ERG critique

The ERG notes that AEs of treatment, including cataract formation and glaucoma, were included in the NICE final scope[43] for this STA. Unlike in TA613, the company did not model glaucoma. However, the ERG does not consider this to be a major concern given the [redacted] and the low incidence modelled by TA613 for anti-VEGFs (around 1.4% per year[63]). The ERG also notes that the company modelled raised IOP and glaucoma can be characterised by raised IOP.

Additionally, the ERG's clinical experts agreed with the company that it is appropriate to use the ranibizumab AE estimates for aflibercept as there are no signals to think AEs differ between ranibizumab and aflibercept.[64]

However, clinical experts also advised the ERG that raised IOP is a known complication of intravitreal steroid use, which questions the face validity of the company's raised IOP rates. Firstly, the raised IOP rate is [redacted]. Secondly, there is a [redacted].

The ERG's clinical experts noted that some of these differences may be explained by a larger proportion of patients undergoing cataract extraction in the DEX700 arm compared to the anti-VEGF arm, which can help to reduce IOP, or that more patients in the DEX700 arm are being treated for

their raised IOP. However, this does not explain the very high raised IOP rates associated with anti-VEGF treatment. The clinical experts subsequently stated that they would assume the RISE and RIDE results are based on a lower mmHg than MEAD (≥30 mmHg). In consequence, the ERG sought the mmHg measure applied in the RISE and RIDE trials which were used to inform the rates in TA613. Unfortunately, the ERG was unable to identify this, which means the raised IOP results in RISE and RIDE may not be comparable with MEAD. To explore the impact of this uncertainty the ERG ran a scenario using the raised IOP rates from the sham arm of MEAD to inform the rates associated with anti-VEGF treatment (Table 41). This scenario ensures that the same mmHg measure is applied to both treatment arms and satisfies clinical expert opinion to the ERG that DEX700 should have a higher incidence of raised IOP than anti-VEGF treatment. The results of the ERG scenario analysis can be found in Section 6.3.

Table 41. Incidence of raised IOP ≥30mmHg in the sham arm of MEAD

Year 1	Year 2	Years 3-5
[redacted]	[redacted]	[redacted]

Abbreviations: IOP, intraocular pressure; mmHg, millimetres of mercury.

Aside from issues pertaining to cataract extraction (discussed in Section 4.2.10) and raised IOP, the ERG considers the company's estimation of AE rates for the DEX700 and anti-VEGF arms reasonable. Issues pertaining to the cost and QoL impact each AE has in the model are discussed in Sections 4.2.13.1 and 4.2.14.4, respectively.

4.2.12 Mortality

As per TA349, 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 population with DM) and assuming that mortality occurs equally across all BCVA states in the base case.

All-cause mortality was taken from 2020 life tables for England.[65] These rates were adjusted for age and the proportion of patients who are male and female over time. The hazard ratio (HR) for the additional mortality due to DM relative to the general population was 1.93 (Mulnier *et al.* 2006[66]) and the HR for the additional mortality due to DMO relative to the DM population without DMO was 1.27 (Hirai *et al.* 2008[67]). These two HR were multiplied together to give a HR for the additional mortality relative to DM and DMO of 2.45. The company acknowledged that there may be some

double counting in the application of these two HRs as the HR derived for the additional mortality due to DM may include some patients with DMO.

The company also considered a scenario which considered additional mortality for patients whose BSE fell into BCVA state 1 (severe vision loss considered clinical blindness, BCVA ≤ 35 letters), as there is evidence of increased mortality in blind patients (Christ *et al.* 2008[68]). This did not form part of the base case as the company expected the HR for DMO to include some patients who are clinically blind. The company then decided not to present the results of this scenario as the impact was expected to be minimal. For completeness, the ERG ran the scenario outlined by the company (and included in TA349) and found that applying a mortality multiplier of 1.54 to patients whose BSE fell into BCVA state 1 favoured the comparator. Nevertheless, the ICER remained dominant (inc. NMB reduced from £10,080 to £9,821).

The company did, however, present the results of scenarios which explored the HRs used in TA613. These included a HR of 1.95 (Preis *et al*. 2009[69]) for the additional mortality due to DM and a HR of 1.23 (Christ *et al.* 2008[68]) for the additional mortality due to DMO. As shown in Section 6.3, these scenarios had a negligible impact on the results (inc. NMB amended from £10,080 to £10,064 and £10,130, respectively).

4.2.12.1 ERG critique

The ERG notes that the company's scenario using the HRs accepted in TA613[5] for the additional mortality due to DMO (a HR of 1.23 from Christ *et al.* 2008) does not fully align with the methods in TA613. In TA613, the additional mortality due to DMO was only applied to the health states associated with BCVA ≤ 35 letters, not all health states.

Furthermore, the ERG considers the approach in TA613 to address the double-counting concerns expressed by the company (as DMO related mortalities are limited to blind patients), and represent the evidence of increased mortality in blind patients. However, to inform the increased mortality in blind patients (BCVA ≤ 35 letters), the ERG considers the multiplier associated with "severe visual impairment" (1.54) to be of more relevance than the multiplier associated with "some visual impairment" (1.23). The ERG has taken these steps in the ERG preferred base case (see Section 6.4).

4.2.13 Health-related quality of life

In each model cycle, the QALYs accrued by the patient cohort are dependent on the utility attributable to each model health state based on the distribution of the patient cohort's eyes across the modelled health states in a given cycle. Utility decrements due to AEs or ageing were not included in the base case but were explored as scenario analyses. The details of each are given below.

The ERG noted some inconsistencies between the utility approach adopted in the company's base case model and the explanation provided in Section B.3.4.5 and Appendix P of the CS. Foremost, the company have provided, in Table 55 of the CS appendices, utility values purported to have been used for an individual's WSE. These are not, in fact, used in the company's base case. BSE and WSE utility contributions (which sum to an individual's whole utility) are defined based on bilateral HSUVs derived from the Czoski-Murray *et al.* 2009[38] study.

Secondly, the purported BSE and WSE utilities in Table 35 of CS, are not in fact health state utilities, rather they are double the contributions of an individual's BSE and WSE to their overall utility. Doubling the utility contributions is an adjustment made in the model which cancels an implicit modelling assumption that distribution of eyes across all possible model health states (including death) sums to one (the patient cohort has one eye on average). This distinction in interpretation is important, as the BSE and WSE values in Table 35 of the CS lack face validity when they are viewed as discrete utility values. For these reasons, the ERG has provided an alternative and simplified explanation which describes the implicit mechanism by which utilities are incorporated into the model, ignoring modelling assumptions and corrections which counteract one another.

Czoski-Murray *et al.* 2009[38] reported TTO utility values for members of the general population wearing lenses to simulate bilateral visual impairment resulting from age-related macular degeneration. A regression analysis of the TTO results was performed which estimates a relationship between these directly estimated utilities and bilateral visual acuity, as measured on the VA logMAR scale. The company used these results to estimate the utility values for 8 health state divisions on the EDTRS score continuum. Table 42 provides the estimated utility values for 8 ETDRS health states and demonstrates how the two highest and two lowest estimates were collapsed to align with the 6 modelled ETDRS health states.

As BSE and WSE are modelled individually, the company has assumed that the utility contribution of the WSE was 30% of that attributable to the BSE. This was implemented by multiplying the bilateral health state utility values by the factors 3/13 and 10/13, giving the utility contributions for a WSE or a BSE in each ETDRS health state, respectively. These contribution estimates are in line with the approach accepted by the NICE Committee for TA349.[43]

Table 42. Breakdown of utility contributions made by BSE and WSE, to an individual's overall utility, in the company's base case

ETDRS Health State	Company estimates derived from Czoski-Murray[38] TTO study	Modelled Health states	Bilateral utility values applied for a given ETDRS health state	BSE utility contribution (10/13† of bilateral utility)	WSE utility contribution (3/13† of bilateral utility)
86-100	0.850	6	0.804*	0.618	0.186
76-85	0.758				
66-75	0.685	5	0.685	0.527	0.158
56-65	0.611	4	0.611	0.470	0.141
46-55	0.537	3	0.537	0.413	0.124
36-45	0.464	2	0.464	0.357	0.107
26-35	0.390	1	0.372*	0.286	0.086
0-25	0.353				

Abbreviations: BSE, best-seeing eye; ETDRS, Early Treatment Diabetic Retinopathy Study; TTO, time-trade off; WSE, worst-seeing eye.

*Simple average of utility estimates for 86-100 and 76-85 used for health state 6 and average 26-35 and 0-25 utility estimates used for health state 1.

†BSE and WSE contribute 10/13 and 3/13 of an individual's utility, respectively.

Note: the model allows for a BSE and WSE to occupy different health states, in these instances BSE and WSE for the respective health states are summed to give an individual's total utility.

The model did not require an individual's BSE and WSE to occupy the same ETDRS health state, rather combinations of BSE and WSE health states were permitted provided the WSE was in an equal or worse state than the BSE. The utility contributions from each eye sum to a patient's overall utility. Table 43 provides the effective utility values applied to patients with each permitted BSE/WSE combination. Note that these are not explicitly modelled (as eyes are independently modelled), rather they are deduced based on the company's modelling assumptions.

Table 43. Effective utility values applied to BSE and WSE health state combinations permitted in model (calculated by the ERG based on utility contributions assigned to the BSE and WSE in company base case)

Utility		BSE health state					
		6	5	4	3	2	1
WSE health state	6	0.804					
	5	0.776	0.685				
	4	0.759	0.668	0.611			
	3	0.742	0.651	0.594	0.537		
	2	0.725	0.634	0.577	0.520	0.464	
	1	0.704	0.613	0.556	0.499	0.443	0.372

Abbreviations: BSE, best-seeing eye; WSE, worst-seeing eye.

The company has also provided scenario analyses where utility estimates, for overall utility for a BSE with a given ETDRS health state, were sourced from Brown 1999[70] and Brown *et al.* 2000.[71] In these scenarios, utility values for a given WSE (irrespective of what ETDRS state the BSE has) were estimated assuming worsening in ETDRS score in the WSE reduced a patient's overall quality of life by 30% of what the utility reduction caused by an equivalent reduction of BSE ETDRS score. Further details of these scenarios are provided in Appendix P of the CS. The company has also provided, either as part of the original submission or in response to clarification questions, scenario analyses assessing the impact of AE related disutilities and age-adjusted utilities. Details of these scenario analyses are provided in the ERG critique below.

4.2.13.1 ERG critique

The company has aligned the approach to derive utilities within this submission with the approach preferred by Committee for the previous NICE appraisal of DEX700 in DMO (TA349[2]) and appraisal of aflibercept in DMO (TA346[29]); using utility values derived from Czoski-Murray *et al.* 2009.[38] Even though Czoski-Murray *et al.* 2009 was the preferred source at the time of TA346 and TA349, the elicitation method used in this study to derive utilities is not in line with the NICE reference case[47] as Czoski-Murray *et al.* 2009 directly elicited utilities in a sample of the general public rather than from a DMO patient population. The Committee for TA613[5] preferred the use of pooled QoL data directly elicited from DMO patients during the FAME studies,[35] using the NEI-VFQ-25 and mapped to EQ-5D using an algorithm published by Rentz *et al.* 2014.[36] To explore the uncertainty associated with the company's chosen utility values, the ERG requested a scenario analysis where the utility values accepted in TA613 were applied. However, the company did not provide this scenario stating that major simplifying assumptions would be needed to incorporate the utility values. The ERG accepts the company's rationale and concludes this to be a relatively minor area of uncertainty in the economic analysis.

As was the case in TA349,[2] the ERG is unclear how the relationship between VA logMAR and TTO utilities (reported by Czoski-Murray *et al.* 2009[38]) was used to estimate the ETDRS utilities applied in the company's base case. An attempt by the ERG to replicate the conversion from VA logMAR to ETDRS yielded HSUVs which deviated slightly from the company's estimates. Table 44 compares the utility values estimated from Czoski-Murray *et al.* 2009 by the company for each ETDRS division with estimates the ERG derived from the same publication. Given that the estimates were largely similar and the source of the discrepancy was not determinable, the ERG did not alter the utility values used in the ERG preferred case, but has provided a scenario analysis applying ERG estimates. The results of ERG scenario analysis can be found in Section 6.3.

Table 44. Comparison of company and ERG estimates of utility by ETDRS division, derived from Czoski-Murray *et al*. 2009[38]

ETDRS division	Company estimates from Czoski-Murray	ERG estimates from Czoski-Murray
86-100	0.850	0.850
76-85	0.758	0.760
66-75	0.685	0.688
56-65	0.611	0.616
46-55	0.537	0.544
36-45	0.464	0.473
26-35	0.390	0.401
0-25	0.353	0.272

Abbreviations: ERG, Evidence Review Group; ETDRS, Early Treatment Diabetic Retinopathy Study

As per TA349, the company did not include utility decrements due to AEs in the base case. However, this was identified as a weakness of TA349, and utility decrements due to AEs were included in the economic analysis for TA613. As such, the company was asked to provide a scenario analysis including the AE related disutility and duration estimates accepted in TA613 during the clarification stage. The company provided this scenario including one-off QALY decrements based on the proportion of patients who experience an AE over the 5 years of DEX700 or anti-VEGF treatment, multiplied by the TA613 disutilities for 3 months (consistent with the assumptions adopted in TA613). Table 45 provides the unit disutilities associated with each AE and the proportion of patients experiencing each AE over the 5-year treatment period. When these estimates were applied in the mode, the impact on the results was minimal (inc. NMB reduced from £10,080 to £10,050).

The company noted that the once-off utility decrements applied in this scenario (-0.0018 and -0.0008 for the DEX700 and anti-VEGF arms, respectively) likely overestimate the true decrement as

discounting and mortality have not been accounted for. The ERG notes that these overestimates are small as over the 5-year treatment period, where AE disutility's are applicable, only [redacted]% and [redacted]% of the patient population are predicted to die in the DEX700 and anti-VEGF or laser arms, respectively. The impact of benefit discounting is also limited over this 5-year treatment period. Due to observed differences in AE frequency, cataract surgery in particular, the ERG has implemented this scenario (using its preferred AE rates) as part of the ERG preferred case.

Table 45. Breakdown of AE disutilities applied in a company scenario analysis and the ERG's preferred case

AE	Disutility	Proportion of patients experiencing AE over 5-year treatment period*	
		DEX700†	Anti-VEGF‡
Raised IOP	0	[redacted]	40.9%
Retinal detachment	-0.13	[redacted]	1.0%
Endophthalmitis	0	[redacted]	2.0%
Vitreous haemorrhage	-0.02	[redacted]	2.0%
Cataract surgery	-0.034	[redacted]	47.0%

Abbreviations: AE, adverse event; anti-VEGF, anti-vascular endothelial growth factor; DEX700, dexamethasone 700 µg; ERG, evidence review group; IOP, intraocular pressure; LOCF, last observation carried forward.

Note: In line with TA613, AEs are assumed to last for 3 months.

* LOCF used to estimate AE occurrence where observed data falls short of 5-year treatment period.

† AE and cataract surgery rates obtained from the DEX700 arm of MEAD

‡ cataract surgery rates were obtained from the company's UK RWE audit, while other AE rates were based on anti-VEGF AE data from the RISE and RIDE trials[61, 63] and sourced from TA613.[5]

Finally, in the CS, the company explored a scenario analysis including the impact of age-adjusted utilities by applying the methods described in Sullivan *et al.* 2011.[72] The ERG considers the age-adjustment described by Ara *et al*. 2010[73] to be more robust and more frequently used in NICE appraisals. Following a clarification request, the company provided a scenario analysis utilising the adjustment described by Ara *et al*. 2010 during the clarification stage. Nevertheless, the impact on the results was found to be minimal (inc. NMB reduced from £10,080 to £9,916). As the ERG have elected to reduce the time horizon to 10 years for the ERG preferred case (see Section 4.2.5.1), the application of age-related utility adjustments was deemed to be of limited impact and not applied by the ERG.

4.2.14 Resource use and costs

The costs included in the economic model consist of drug acquisition costs, administration costs, disease management costs, costs for managing AEs and healthcare costs associated with severe

vision loss. The details of each are given in the following subsections. Unit costs used in the model were inflated to 2020 prices using the NHS Cost Inflation Index reported by the Personal Social Services Research Unit (PSSRU).[74]

4.2.14.1 Drug acquisition costs

Dexamethasone 700 µg pro re nata (DEX700 PRN)

DEX700 is given as an intravitreal implant. The list price per 0.7mg intravitreal implant is £870.00 and the company sourced this from the Monthly Index of Medical Specialities (MIMS).[7] The ERG also notes that a price of £870.00 is reported for the same formulation in the British National Formulary (BNF).[75] No patient access scheme (PAS) is in place for DEX700.

The cost of one 0.7mg intravitreal implant is applied per round of unilateral treatment, while two 0.7mg intravitreal implants are costed per round of bilateral treatment. The dosing schedule of the MEAD clinical trials specified that patients could be retreated from 6 months post-randomisation and would be assessed for retreatment every 3 months thereafter. The modelled dosing regimen reflects this schedule with the proportion of patients receiving DEX700 retreatment between each 3-month assessment timepoint in the MEAD clinical trials (pooled data of the phakic-only mITT population) used to calculate the average number of injections administered per 3-month model cycle (derivations summarised in Table 25 and provided in detail in Table 58 of the CS appendices).

Given that the MEAD clinical trials provided data for only 3 years of follow up, the company used clinical expert estimates for the average number of injections received by patients in Years 4 and 5 of treatment. Based on input from the company's clinical expert, it was assumed that treatment (DEX700, anti-VEGF or laser) would not continue past 5 years.

Anti-VEGF and laser

In the company base case the composite comparator includes only the anti-VEGF treatments; ranibizumab and aflibercept. Bevacizumab and laser treatment are included within the composite comparator in scenario analyses. Table 46 provides the list price for each treatment considered by the composite comparator. Ranibizumab and aflibercept are subject to PAS discounts and results including these discounts can be found in the confidential appendix.

Table 46. Unit acquisition costs of anti-VEGF and laser treatments (list prices) (adapted from Table 37 of the CS)

Treatment	Unit	List price	Reference
Ranibizumab	0.5 mg prefilled syringe	£551.00	MIMS 2021[76]
Aflibercept	2 mg prefilled syringe	£816.00	MIMS 2021[77]
Bevacizumab	1.25 mg prefilled syringe	£50.00	NICE DSU report - Poku *et al.* 2012[78]
Laser	-	£0.00	Zero acquisition costs assumed - cost of procedure included in administration costs

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; CS, company submission; DSU, Decision Support Unit; MIMS, Monthly Index of Medical Specialities; NICE, National Institute for Health and Care Excellence.

As per the DEX700 arm, the cost of one anti-VEGF injection is applied per round of unilateral treatment, while two injections are costed per round of bilateral treatment. The company conducted a UK RWE audit[23] to estimate the average number of injections received by anti-VEGF patients over time (by treatment received) and the proportion of patients receiving an anti-VEGF treatment at each timepoint. These estimates were used to approximate a dosing schedule for anti-VEGF treatment.

The company considered that UK RWE audit to be the most relevant data source available to estimate long-term treatment costs for continued anti-VEGF use given its UK-based phakic DMO patient population who are insufficient responders to anti-VEGF treatment. The UK RWE audit collected data on the average number of injections administered in five time periods: 3-6 months, 6-12 months, 12-24 months, 24-36 months, and 36-48 months. As insufficient response was determined at 6 months, RWE data from 6-12 months informed months 0-6 in the model, RWE data from 12-24 months informed months 6-18 in the model, and so on - in the manner described by Table 38 of the CS.

As only 48 months of RWE data was available, the 36–48-month data was used to inform months 30-60 in the model assuming a constant number of injections for the remainder of the treatment period. The company noted that although this assumption may overestimate the average number of anti-VEGF injections received towards the end of the modelled 5-year treatment period the assumption was considered reasonable as the company's clinical experts suggested that a small proportion of patients would likely continue anti-VEGF treatment beyond 5 years. The company also noted that the estimates for the average number of injections from the RWE audit were lower than those observed in the RESTORE study.[51,55]

A weighted average of the number of injections for each anti-VEGF or laser treatment was calculated based on market share estimates. In the base case the company applied estimates based on the

proportion of patients receiving ranibizumab [redacted] and aflibercept [redacted] treatment in the UK RWE audit (bevacizumab and laser were excluded).

Table 47 below provides a summary of the annual number of treatments modelled for both the DEX700 and anti-VEGF arms of the model. As mentioned above, the model uses more granular 3-monthly data (the breakdown of which is summarised in Table 25 and Table 26 and provided in detail in Tables 58 and 59 of the CS appendices) from which these annual estimates are derived.

Table 47. Average number of treatments per year; DEX700 vs anti-VEGF or laser (adapted from Tables 36 and 39 of the CS)

Treatment arm	Average number of treatments per year					Reference
	Year 1	Year 2	Year 3	Year 4	Year 5	
DEX700	[redacted]	[redacted]	[redacted]	1.00*	1.00*	Pooled MEAD trials (phakic-only mITT population)
Anti-VEGF (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK RWE audit[23]
Anti-VEGF (scenario)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	RESTORE study[51, 79]

* Informed by the company's clinical experts

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; CS, company submission; DEX700, dexamethasone 700 µg; mITT, modified intention-to-treat; RWE, real world evidence; UK, United Kingdom.

In the company's base case, no subsequent treatment costs were applied to either treatment arm.

Time on treatment

As described above, neither DEX700 nor anti-VEGFs have a predefined treatment regimen where retreatment is defined at regular intervals, rather the need for retreatment is assessed at regular intervals. As such the proportion of patients receiving a DEX700 intravitreal implant, an anti-VEGF injection or laser treatment in a given model cycle is not necessarily reflective of the proportion on continued treatment. Treatment discontinuation is modelled independently of the average number of treatments received by patients on treatment.

As described in Section 4.2.7, patients are at risk of discontinuation for two explicit and independent reasons; due to lack (or loss) of efficacy of treatment or due to AEs and other non-efficacy related reasons. In the DEX700 arm, the proportion of patients who discontinue in each cycle due to either reason is informed by the pooled data from the MEAD trials. Beyond the duration of the MEAD trials, discontinuation rates were extrapolated using the average rate over the trial duration. In the

anti-VEGF arm, the company assumed that patients do not discontinue during the 5-year treatment period as anti-VEGF treatment represents the last therapeutic option for the patient population.

4.2.14.2 Administration costs

Administrations costs for DEX700 and anti-VEGF or laser therapies were based on two activity cost codes from NHS Reference Costs 2019-2020[10] for day case (BZ87A) or outpatient (BZ87A) minor vitreous retinal procedures. A weighted average administration cost is applied based on the proportion of patients who receive inpatient or outpatient procedures.

For patients who receive bilateral treatment an additional multiplier, the expected number of visits needed to treat both eyes, is applied to account for the additional administration costs associated with those patients needing two visits. In the base case the company assumed, based on clinical opinion and in line with TA349, that all patients are treated in an outpatient setting, with 75%, 50% and 0% of bilateral DMO patients requiring separate appointments for each eye treated with DEX700, anti-VEGF, and laser treatments, respectively.

Table 48 below presents the breakdown of administration costs applied in the company's base case analysis. These costs were applied in each model cycle for the average number of unilateral and bilateral treatments received in that cycle.

Table 48. Administration costs breakdown (adapted from Tables 40 and 41 of the CS)

Treatment setting	Unit cost	Proportion outpatient procedures	Treatment	Average number of appointments for bilateral treatment	Administration cost per	
					Unilateral treatment	Bilateral treatment
Outpatient	£129.61	100%	DEX700	1.75	£129.61	£226.82
			Anti-VEGF	1.5	£129.61	£194.42
			Laser	1	£129.61	£129.61
Day case	£668.31	0%*	-	-	-	-

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; CS, company submission; DEX700, dexamethasone 700 µg.
* In the base case 100% of treatments are assumed to occur in an outpatient setting, however scenario analyses assess the impact of a proportion of inpatient treatments.

4.2.14.3 Disease management costs

Disease management costs were applied in the model independent of health state occupancy and based on the estimated healthcare resource use for patients receiving no treatment, DEX700, anti-VEGF or laser therapy. Unit healthcare resource costs were applied equally to each treatment arm

but frequency estimates for each resource used were treatment specific. The unit healthcare resource costs considered in the model are provided in Table 49.

Table 49. Unit costs of healthcare resources (adapted from Table 48 of the CS)

Resource	Unit cost	Source
Routine monitoring visit	£101.95	NHS Reference Costs 2019-20 - WF01A code 130 Ophthalmology; consultant led non-admitted, face to face attendance, follow-up
OCT	£52.47	NHS Reference Costs 2019-20 - weighted average of RD40Z and RD41Z, diagnostic imaging - direct access: ultrasound scan less than 20 minutes
Fluorescein angiography	£129.61	NHS Reference Costs 2019-20 - Outpatient procedure - service code 130 Ophthalmology - BZ87A - Minor vitreous retinal procedures
IOP check	£101.95	NHS Reference Costs 2019-20 - WF01A code 130 Ophthalmology; consultant led non-admitted, face to face attendance, follow-up

Abbreviations: CS, company submission; IOP, Intraocular pressure; NHS, National Health Service; OCT, optical coherence tomography.

Company estimates for the frequency of each medical resource used, by treatment received, are provided in Tables 49 to 52 of the CS. The estimates for no treatment, DEX700, laser and anti-VEGF therapies were sourced from TA271,[42] TA349,[2] TA613,[5] and the UK RWE audit,[23] respectively.

The RWE data from months 12-24, 24-36, 36-48 post treatment initiation were used to estimate the number of monitoring visits in Years 1, 2 and 3, respectively. The one-year offset was due to the unavailability of data from the first three months of Year 1.

The monitoring frequency of resource use in Years 4 and 5 were assumed equal to that applied in Year 3. For all treatments IOP checks were assumed to be included in routine monitoring visit costs in line with the ERG-preferred assumption in TA349 and TA613. An additional cost of an optical coherence tomography test (OCT) was applied for each routine monitoring visit and a single fluorescein angiography test was assumed in Year 1 but not in subsequent years. The per-cycle disease management costs applied in the model, by treatment and year of treatment are provided in Table 50 below.

Table 50. Medical resource costs applied in the model

Treatment	Total medical resource use cost per patient				
	Year 1	Year 2	Year 3	Year 4	Year 5
No treatment (watch and wait)	£747.29	£747.29	£747.29	£747.29	£747.29
DEX700	£622.59	£393.84	£413.82	£463.26	£463.26
Anti-VEGF	£747.29	£586.79	£525.03	£525.03	£525.03
Laser	£531.10	£401.49	£401.49	£401.49	£401.49

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; DEX700, dexamethasone 700 µg.

The company noted that the number of routine monitoring visits recorded in the UK RWE was lower than that applied in TA613 and provided a scenario analysis to assess the impact of the TA613 assumptions. Another scenario was provided which explored no difference in the number of routine monitoring visits between patients treated with DEX700 and anti-VEGF treatment, assuming 4 visits each year. The results of these scenario analyses are provided in Section 5.1.2.

4.2.14.4 Adverse event (AE) costs

The AE management costs applied in the model are summarised in Table 51. The cost components associated with each AE are given in full in Table 43 to 47 of the CS. Unit costs were derived from the NHS Reference Costs 2019-2020[41] with supplemental costs for medications used to treat raised IOP sourced from the drugs and pharmaceutical electronic marketing tool (eMIT).[40]

As discussed in Section 4.2.11, AE occurrence data from the pooled MEAD clinical trials was used for the DEX700 arm, while data reported in TA613 was primarily used to inform the anti-VEGF arm, with the company's UK RWE audit used to estimate cataract extraction rates for patients receiving anti-VEGFs.

Table 51. Costs to manage AEs

Resource	Unit cost	Source
Cataract extraction	£966.72	NHS reference costs 2019-2020 – BZ34C – Phacoemulsification cataract extraction and lens implant, with CC score 0-1 (day case).
Pharmaceutical intervention for raised IOP	£679.36	eMIT, weighted average cost assuming mean duration of treatment of 1096 days and that raised IOP medication comprises 70% generic prostaglandins, 10% generic beta-blockers, and 20% equal used of CA inhibitors, brimonidine and combination treatments (consistent with the ERG's preferred assumptions in TA349). Full cost breakdown provided in Table 43 of the CS. In addition, six extra IOP visits were added to patients with DMO who were treated for raised IOP, consistent with the preferred ERG assumption in TA349. The cost of each additional IOP check was in line with that provided in Table 49.
Surgical intervention for raised IOP (trabeculectomy)	£1,239.70	NHS reference costs 2019-2020 - BZ94B/BZ93B – Intermediate/Major Glaucoma or Iris Procedures, with CC Score 0-1 (day case). Assuming 50% of procedures were intermediate and 50% were major. In addition, six extra IOP visits were added to patients with DMO who were treated for raised IOP, consistent with the preferred ERG assumption in TA349. The cost of each additional IOP check was in line with that provided in Table 49.
Retinal detachment	£781.54	Assuming 80% of procedures for the attachment of retina were intermediate vitreous day case procedures and 20% were major (consistent with the ERG's preferred assumptions in TA349).

		NHS reference costs 2019-2020 BZ86B was used for intermediate procedure costs, while BZ84B was used for major procedure costs. The non-elective long and short stay costs associated with each code were weighted based on the patient numbers for each activity cost.
Vitreous biopsy for endophthalmitis	£925.26	NHS reference costs 2019-2020 BZ87A – Minor Vitreous Retinal Procedure, 19 years and over. The elective inpatient and non-elective short stay costs were weighted based on the patient numbers for each activity cost.
Vitrectomy for vitreous haemorrhage	£483.22	NHS reference costs 2019-2020 BZ86B – Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1. The non-elective long and short stay costs associated with each code were weighted based on the patient numbers for each activity cost.

Abbreviations: AE, adverse event; CA carbonic anhydrase; CC, complications and comorbidities; CS, company submission; eMIT, electronic market information tool; IOP, intraocular pressure; NHS, National Health Service.

AE management costs were applied in each model cycle and are dependent on whether a patient is on or off treatment. Patients who are on treatment are at risk of treatment-related AEs (including cataract extraction), while patients who discontinue treatment during the treatment period or discontinue treatment because of the 5-year stopping rule are only at risk of cataract extraction. As discussed in Section 4.2.10, the model includes a background risk of cataract extraction (2.32% per year) for an untreated phakic DMO patient population and this is applied to all patients beyond the 5-year treatment period. Table 52 summarises the annual AE management costs applied in the company base case for each treatment arm, for patients on- and off-treatment. Where patients receive bilateral treatment, a weighted average of the resource use associated with the year of treatment each eye is receiving is applied.

Table 52 Adverse event costs (undiscounted) applied in company base case

Treatment		Year 1	Year 2	Year 3	Year 4	Year 5	Years 6 to 40 (off-treatment)*
DEX700	On-treatment	£241.61	£375.41	£166.74	£166.74	£166.74	£4.92 to £2.21
	Off-treatment	£22.43	£19.77	£12.33	£9.07	£6.68	£4.92 to £2.21
Anti-VEGF or laser	On-treatment	£166.12	£167.59	£178.79	£178.79	£178.79	£11.78 to £5.30
	Off-treatment	£22.43	£20.36	£18.27	£15.78	£13.64	£11.78 to £5.30

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; DEX700, dexamethasone 700 µg.
*Annual cost slowly decreases from year 6 to 40 (remainder of the time horizon)
Note: the model utilises a 3-month cycle length, as such these costs are divided by 4 before application at the per-cycle level.

4.2.14.5 Severe vision loss costs

Patients for whom both eyes have entered health state one of the model (BCVA score ≤ 35 letters) are classified as having severe vision loss and have additional costs associated with community care, residential care, hip replacement, depression, blind registration, low-vision aids and rehabilitation.

These can be direct costs or indirect costs, and one-off costs or annual costs. The company noted that inclusion of these costs is consistent with TA349 and TA613. Unit costs were sourced from NHS Reference Costs 2019-2020,[41] Curtis 2014,[80] Curtis 2020,[74] and Colquitt *et al.* 2008,[81] while estimates for the proportion of severe vision loss patients requiring each resource were taken from Colquitt *et al*. 2008[81] and Meads and Hyde.[82] The estimates from these sources are given in Table 53 below.

In the company's base case analysis, an annual cost of £13,297 was applied to all patients for whom both eyes are in health state one. An additional one-off cost of £235 was also applied to all patients with severe vision loss to cover the indirect cost associated with hip replacement. In line with TA349, direct one-off costs (amounting to £251 per patient) incurred when patients first become blind (blind registration, low vision aids, low vision rehabilitation) were excluded from the company base case, however the company has provided a scenario analysis assessing their impact on the results. The ERG also notes that these one-off costs were not considered in TA613.

Table 53. Severe vision loss costs

Resource	Unit cost	% severe vision loss patients requiring service	Source
Direct one-off costs*			
Blind registration	£154.06	95%	Colquitt *et al.* 2008;[81] 2008 costs inflated based on the NHS Cost Inflation Index – PSSRU.[74]
Low vision aids	£200.95	33%	
Low vision rehabilitation	£346.97	11%	
Direct ongoing costs			
Community care	£12,617.35	6%	Curtis 2014;[80] annual cost calculated based on weekly cost of community care package for the elderly (excluding accommodation costs). 2014 costs inflated based the NHS Cost Inflation Index – PSSRU.[74]
Residential care	£38,531.27	30%	Curtis 2020;[74] annual cost calculated based on private sector residential weekly cost and local authority residential care cost, assuming 95% of residential care provision is private sector based.
Indirect costs			
Hip replacement (one-off)	£4,700.12	5%	Colquitt *et al.* 2008;[81] 2008 costs inflated based using the NHS Cost Inflation Index – PSSRU.[74]
Depression (annual)	£2,513.92	39%	NHS Reference Costs 2019-2020 – HT14C – intermediate hip procedures for trauma, with CC Score 0-1 (non-elective short, long stay, elective inpatient and day case activity costs weighted by occurrence).

Abbreviations: CC, complications and comorbidities; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

*In line with TA349, one-off costs incurred when a patient first becomes blind (blind registration, low-vision aids, and low vision rehabilitation) are excluded from the base case but are explored as a scenario analysis.

4.2.14.6 ERG critique

As noted in Section 4.2.3.2.1, the ERG considers the market shares included in the composite comparator to be reasonable. The ERG's key concerns relate to the number of DEX700 and anti-VEGF injections and the assumptions associated with severe vision loss costs. Each of these is described below along with other noteworthy points of consideration. Concerns regarding the company's approach to modelling treatment discontinuation are given in Section 4.2.7.1.

Number of DEX700 injections

The ERG notes that due to the 3 years follow up period of the MEAD trials, the company's estimation of DEX700 administration costs for Years 4 and 5 of treatment was reliant on the company's clinical expert's estimation of the average number of intravitreal implants patients would receive in the two remaining years of treatment. These estimates suggested reduced treatment (1 implant per year) in Years 4 and 5. The ERG's clinical experts instead considered that the average number of intravitreal implants observed in Year 3 ([redacted] implants per year) would be maintained for Years 4 and 5 for those patients remaining on treatment. This is also consistent with company's assumption that the average number of anti-VEGF injections from Year 3 remained constant until the end of Year 5 (see Section 4.2.3.2). Following a clarification request the company provided a scenario where the average number of DEX700 injections from Year 3 remained constant until the end of Year 5 and found that the inc. NMB reduced from £10,080 to £9,565. The ERG suspects the impact of this scenario is limited given the [redacted] proportion of patients receiving treatment in Years 4 and 5 (around [redacted] in Table 25).

Number of anti-VEGF injections

The ERG's clinical experts also considered that estimates for the average annual number of anti-VEGF injections derived from the UK RWE audit[23] were particularly low in Year 1 and more likely to lie between the UK RWE and RESTORE study[51, 79] estimates. One clinician estimated that a patient

who is considered insufficiently responsive to non-corticosteroid treatment at 6 months post-treatment could receive 5 injections in their first year of continued anti-VEGF treatment and that the UK RWE estimates would be appropriate thereafter. Thus, the company's base case approach may be viewed as conservative. As shown in the company's scenario analysis (Section 5.1.2), using data from the RESTORE study had a large impact in favour of DEX700 (inc. NMB increased from £10,080 to £14,929).

Severe vision loss costs

The company's methodology for estimating the residential care costs associated with severe vision loss largely followed the methods used in TA613.[5] However, the ERG for TA613 implemented an adjustment for the proportion of residential care recipients who self-fund. This was based on the Competition and Marketing Authority (CMA) 2017 analysis of care home provision which noted that 41% of residents in care homes self-fund.[83] For completeness the ERG explored an equivalent scenario where residential care costs are zero for 41% of patients requiring this service.

Given that the ongoing annual severe vision loss cost is reduced in this scenario (from £13,297 to £8,558), the ERG would expect it to favour the least effective treatment (anti-VEGFs) as a higher proportion of these patients would experience worsening vision and transition to health state 1 (BCVA score ≤ 35 letters). In the model this is not observed as the inc. cost increases (from -£6,968 to -£7,449) and inc. NMB increases (from £10,080 to £10,561), thus favouring the most effective treatment (DEX700). As a result, the ERG sought how many patients were entering health state 1 in the model. As shown in Table 54 a larger proportion of DEX700-treated patients than anti-VEGF-treated patients reside in health state 1 (1.57 vs 1.47 life years, respectively).

The ERG notes that there is a [redacted] in the mean change in BCVA from baseline with DEX700 compared to sham between months [redacted] in the MEAD trials (see Figure 6 of the CS and

Figure 2 in Section 3.3.1.1). The company reported that their expert panel considered this [redacted]. This may explain why a notable proportion of DEX700-treated patients entered health state 1 during this period in the model. This finding also suggests that cataract is a larger issue for DEX700 that initially anticipated.

The ERG suspects the company is aware of this phenomenon in the model as severe vision loss costs were excluded by the company in a scenario provided to the ERG at the clarification stage. This related to a scenario assuming no movement up or down health states within the anti-VEGF arm. The company argued that as DEX700-treated patients can transition between any of the health states, some patients will move into the worst health state and incur the costs associated with severe vision loss. However, if patients receiving anti-VEGF treatment do not transition between any of the health states, no patients can move into the worst health state and incur these costs. Therefore, to remove the bias against DEX700, the company provided a scenario which excluded severe vision loss costs. The ERG acknowledges the company's rationale but considers the company's modifications to the scenario to inherently limit the findings from assuming there are no movements up or down health states within the anti-VEGF arm. This scenario has no relation to the changes in BCVA resulting from DEX700, and because of the company's modifications, it is impossible to directly compare the scenario results with the base case results.

Overall, the ERG considers the model results regarding the number of DEX700-treated patients residing in health state 1 to a major concern as one of the key benefits of DEX700 should be improvements in BCVA.

Table 54. Consequences of severe vision loss in the model

Treatment	LYs				SVL costs (discounted)			
	Uni. affected BSE	Uni. affected WSE	Bil. affected	Total	Uni. affected BSE	Uni. affected WSE	Bil. affected	Total
Base case								
Anti-VEGFs	0.19	0.00	1.28	1.47	£1,665	NA	£11,161	£12,826
DEX700	0.19	0.00	1.38	1.57	£1,752	NA	£12,430	£14,182
Scenario where 41% who receive residential care self-fund								
Anti-VEGFs	0.19	0.00	1.28	1.47	£1,074	NA	£7,201	£8,275

DEX700	0.19	0.00	1.38	1.57	£1,130	NA	£8,019	£9,150

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; Bil., bilaterally; BSE, best-seeing eye; DEX700, dexamethasone 700 µg; LYs, life years; SVL, severe vision loss; Uni., unilaterally; WSE, worst-seeing eye.

Resource use assumptions

The ERG's clinical experts disagreed with some of the company's resource use assumptions. Namely that fluorescein angiography was rarely used in clinical practice (once every 5 years for patients on and off treatment) and that most bilateral patients receiving anti-VEGF treatment would have both eyes treated on the same day to reduce the number of appointments (a single appointment on 75% of occasions / 1.25 appointments rather than on 50% of occasions / 1.5 appointments). During the clarification stage, the company provided additional scenarios to address these concerns. Nevertheless, the impact of these alternative assumptions was found to be minimal. The ERG's clinical experts also acknowledged that clinical practice is variable and therefore no changes to these resource use assumptions have been made to the ERG's preferred base case.

Finally, the company made a 1-year offset to the disease management costs associated with anti-VEGFs as data were unavailable for the first three months of Year 1. The ERG is surprised the company did not mention the 6-month assessment point (when patients are deemed to be suboptimal responders) as a reason for the 1-year offset. Nevertheless, the ERG is concerned that nine months of data (or six months if we assume resource use depends on response status) has been disregarded and would like to see how these data compare to the 12–24-month data (assuming a multiplier of 1.33 or 1.5 can be applied to 9- or 6-month data to estimate 12-month data). However, given that anti-VEGF disease management costs appear to reduce over time the company's approach is unlikely to favour DEX700.

5 Cost effectiveness results

5.1.1 Company's cost effectiveness results

The results included in this section are based on list prices. Results including comparator patient access scheme (PAS) discounts can be found in the confidential appendix. As noted in Section 4.2.14.1, no PAS is in place for dexamethasone 700 µg (DEX700).

5.1.1.1 Deterministic results

The company's deterministic base case results are given in Table 55. It is shown that DEX700 dominates treatment with anti-vascular endothelial growth factors (anti-VEGFs), as DEX700 is associated with lower costs and higher quality-adjusted life years (QALYs) compared with anti-VEGFs. During the clarification stage, the company also provided results comparing DEX700 to each anti-VEGF separately, these results are given in Table 56.

Table 55. Company's deterministic base case results (adapted from Table 54 of the CS)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NMB (£30,000/ QALY WTP threshold)
Anti-VEGFs	£38,695	7.4815	-	-	-	-
DEX700	£31,728	7.5853	-£6,968	0.1038	Dominant	£10,080

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; CS, company submission; DEX700, dexamethasone 700 µg; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 56. Company's deterministic base case results considering ranibizumab and aflibercept as separate comparators (adapted from Tables 8 and 9 of the company's clarification response)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NMB (£30,000/ QALY WTP threshold)
DEX700 vs ranibizumab						
Ranibizumab	£34,906	7.4815	-	-	-	-
DEX700	£31,728	7.5853	-£3,179	0.1038	Dominant	£6,291
DEX700 vs aflibercept						
Aflibercept	£40,922	7.4815	-	-	-	-
DEX700	£31,728	7.5853	-£9,194	0.1038	Dominant	£12,307

Abbreviations: DEX700, dexamethasone 700 µg; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

5.1.1.2 Probabilistic results

The company performed a probabilistic sensitivity analysis (PSA), where all inputs were varied simultaneously over 1,000 iterations based on their distributional information (see Appendix S of the company submission [CS]). Generally, costs were varied using a gamma distribution, probabilities using a beta-distribution and continuous variables using a normal distribution. Transition probability matrices were also varied in PSA using the Dirichlet probability distribution.

The company's mean probabilistic results are reported in Table 57 and these are consistent with the company's deterministic results. The company also provided a cost-effectiveness plane (

Figure 14) which shows that most iterations lie in the south-east quadrant (DEX700 is less costly and more effective than anti-VEGFs). The company also noted in the CS that there is a 100% probability that DEX700 is the most cost-effective option at willingness-to-pay (WTP) thresholds between £0 and £100,000 per QALY.

When the ERG ran the company's PSA, the ERG could produce similar results to the company. The ERG also considers the distributions assigned to each parameter reasonable. However, upon inspection of the model the ERG found that +/-10% of the mean value was assumed for the standard error (SE) when measures of uncertainty were not reported. A variation of 10% can be considered low. Typically, a SE of 20% is used when measures of uncertainty are unavailable. This may explain the relatively narrow eclipse of iterations in

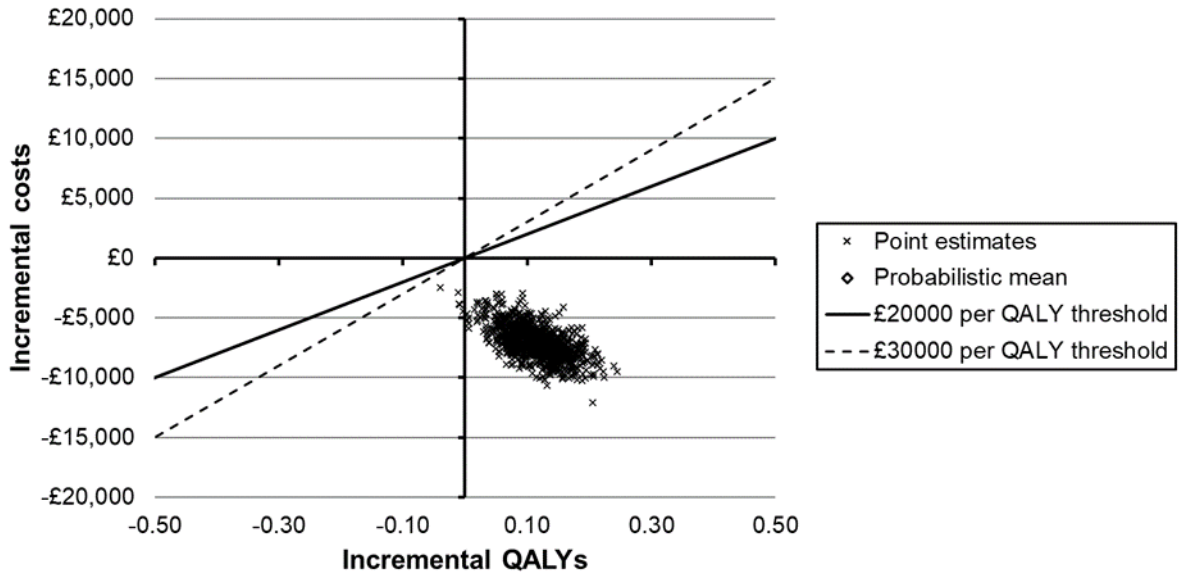
Figure 14.

Table 57. Company's probabilistic results (adapted from Table 55 of the CS)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NMB (£30,000/ QALY WTP threshold)
Anti-VEGFs	£39,457	7.4029	-	-	-	-
DEX700	£32,446	7.5157	-£7,011	0.1128	Dominant	£10,396

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; CS, company submission; DEX700, dexamethasone 700 µg; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Figure 14. Cost-effectiveness plane (reproduced from Figure 23 of the CS)



Key: CS, company submission; QALYs, quality-adjusted life years.

5.1.2 Company's scenario analysis

The company varied a number of assumptions and sources in scenario analysis. The results of these scenarios are outlined in Table 58, with the results demonstrating that DEX700 remains dominant across all scenarios tested.

Excluding scenarios on efficacy, the scenario with the most significant change in the results is the use of the anti-VEGF costing assumptions applied in TA613[5] rather than the application of data from the UK Real World Evidence (RWE) study[23] (inc. NMB reduced from £10,080 to £4,170). The company presented this scenario to have consistency with the approach adopted in TA613, but the UK RWE audit data is used in the base case analysis as it is considered a superior source of evidence. As stated by the company and agreed by the ERG, the ICE-UK data[44] applied in TA613 is associated with limitations including a short follow-up period (1 year) and outdated practice (no use of aflibercept).

A scenario which had a meaningful impact in favour of DEX700 included using data from the RESTORE study to estimate the number of anti-VEGF injections per model cycle (inc. NMB increased from £10,080 to £14,929).[51, 79] The values from this study indicate that the base case analysis may underestimate the true cost of anti-VEGFs in UK clinical practice. As noted in Section 4.2.14.6, the ERG's clinical experts also considered estimates from the UK RWE audit to be low in the first year and more likely to lie in between the RESTORE study and the UK RWE audit. Thus, the company's base case approach may be viewed as conservative.

As for the alternative sources of efficacy data to inform the transition probabilities, all (except the scenario which assumed a net-zero change in vision over time for the anti-VEGFs) increased the relative benefit of DEX700 vs anti-VEGFs, which improved the cost-effectiveness of DEX700. However, as explained in Section 4.2.6.3.1, the ERG does not consider comparisons of the MEAD trials and RWE studies to be reliable as they include different study designs. Moreover, the company's advisory board agreed that pseudophakic patients in MEAD performed better than the overall intention-to-treat (ITT) population in the MEAD trials, which suggests using the MEAD pseudophakic population to inform the transition probabilities in the phakic population is overly optimistic.[6]

The company acknowledged that their scenario which assumes a net-zero change in vision over time for the anti-VEGF arm lacks face validity given patients in the sham arm in MEAD experienced an overall net gain in BCVA, and therefore assuming a net-zero gain should increase the incremental QALY gain. The company subsequently noted that this result is likely driven by the simple application of this scenario given it assumes a 3.5% improvement/worsening over time, and therefore it may not capture the full distribution of visual acuity outcomes expected to occur over time. However, as noted in Section 4.2.6.2.1, the ERG considers a 0% probability of improvement/worsening over time to be least biased.

Table 58. Scenario analyses results (adapted from Tables 56 and 57 of the CS)

Model assumption	Base case	Scenario	ICER (DEX700 vs anti-VEGFs)	Inc. NMB (WTP threshold £30,000/QALY)
Base case			Dominant	£10,080
Time horizon	40 years	15 years	Dominant	£9,294
		30 years	Dominant	£10,074
Baseline characteristics	[redacted] unilateral DMO in the BSE	100% unilateral DMO in the BSE	Dominant	£11,913
	[redacted] unilateral DMO in the WSE	100% unilateral DMO in the WSE	Dominant	£9,581
	[redacted] bilateral DMO	100% bilateral DMO	Dominant	£14,782
Comparator composition	UK RWE (overall) ([redacted] ranibizumab; [redacted] aflibercept)[23]	UK RWE (latest 2 years)	Dominant	£10,886
		UK RWE (overall) - including 5% laser	Dominant	£8,656
		UK RWE (overall) - including 10% laser	Dominant	£7,296

Model assumption	Base case	Scenario	ICER (DEX700 vs anti-VEGFs)	Inc. NMB (WTP threshold £30,000/QALY)
		NICE TA613 (excl. laser) (aligned with NICE TA613 anti-VEGF dosing)[5]	Dominant	**£4,170**
Dosing DEX700	MEAD	French RWE[22]	Dominant	£10,285
Dosing anti-VEGF	UK RWE[23]	The RESTORE study[51, 79]	Dominant	**£14,929**
Discontinuation anti-VEGF	Assume no discontinuation	Assume eyes included in UK RWE that did not receive any treatment within a certain time period have permanently discontinued treatment	Dominant	£10,472
Cataract extraction rate anti-VEGF	UK RWE[23]	Assume equal to DEX700	Dominant	£10,502
Mortality hazard ratio diabetes	Mulnier *et al.* 2006[66]	Preis *et al*. 2009[69]	Dominant	£10,064
Mortality hazard ratio DMO	Hirai *et al.* 2008[67]	Christ *et al.* 2008[68]	Dominant	£10,130
Fellow eye involvement	From MEAD ITT population	From MEAD phakic population	Dominant	£10,074
Routine monitoring visits	DEX700 as per ERG preferred assumptions in TA349;[2] Anti-VEGF from UK RWE	Anti-VEGF routine monitoring visits as per ERG preferred assumptions in TA613[5]	Dominant	£11,088
		Assume equal number of routine monitoring visits for DEX700 and anti-VEGF	Dominant	£9,674
OCT costs	Exclude OCT cost at each administration visits; Include OCT cost at each routine monitoring visit	Include OCT cost at each administration visit; Exclude OCT cost at each routine monitoring visit	Dominant	£10,253
Administration costs	All intravitreal injection procedures 100% outpatient	All intravitreal injection procedures 50% day case and 50% outpatient	Dominant	£12,541
Number of appointments for bilateral injection	DEX700: 1.75; anti-VEGF: 1.5	DEX700 and anti-VEGF: 1.1	Dominant	£10,389
		DEX700 and anti-VEGF: 1.9	Dominant	£9,944
Severe vision loss costs	Exclude one-off severe vision loss direct medical costs	Include one-off severe vision loss direct medical costs	Dominant	£10,080

Model assumption	Base case	Scenario	ICER (DEX700 vs anti-VEGFs)	Inc. NMB (WTP threshold £30,000/QALY)
Utilities	Czoski-Murray *et al*. 2009[38]	Brown 1999[70]	Dominant	£8,549
		Brown *et al*. 2000[71]	Dominant	£9,469
Efficacy scenario analyses				
Efficacy DEX700	MEAD DEX700 - phakic population	MEAD pseudophakic population	Dominant	£20,920
		French RWE (baseline to Month 12 probabilities recalculated into 3-month probabilities)[22]	Dominant	£24,988
		French RWE (baseline to Month 24 probabilities recalculated into 3-month probabilities)[22]	Dominant	£22,507
		French RWE (baseline to Month 36 probabilities recalculated into 3-month probabilities)[22]	Dominant	£25,825
Efficacy anti-VEGF	MEAD sham - phakic population	UK RWE (baseline to Month 12 probabilities recalculated into 3-month probabilities)[23]	Dominant	£19,417
		UK RWE (baseline to Month 24 probabilities recalculated into 3-month probabilities)[23]	Dominant	£12,393
		UK RWE (baseline to Month 36 probabilities recalculated into 3-month probabilities)[23]	Dominant	£10,071
		DMO natural history	Dominant	£12,258
		Net-zero impact on vision	Dominant	£8,076
		Net-zero impact on vision (excluding severe vision loss costs, provided at the clarification stage)	Dominant	£8,861
DMO natural history	DMO natural history from Mitchell *et al.* 2012 (3.5% improving/4.5% worsening per cycle)[48]	DMO natural history as per TA613 (0% improving/3.5% worsening per cycle)[5]	Dominant	£8,725

Abbreviations: anti-VEGF, anti-vascular endothelial growth factors; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; NICE, National Institute for Health and Care Excellence; NMB, net monetary benefit; OCT, optical coherence tomograph; QALY, quality-adjusted life year; RWE, real world evidence; TA, technology appraisal; UK, United Kingdom.

5.1.3 Company's one-way sensitivity analysis (OWSA)

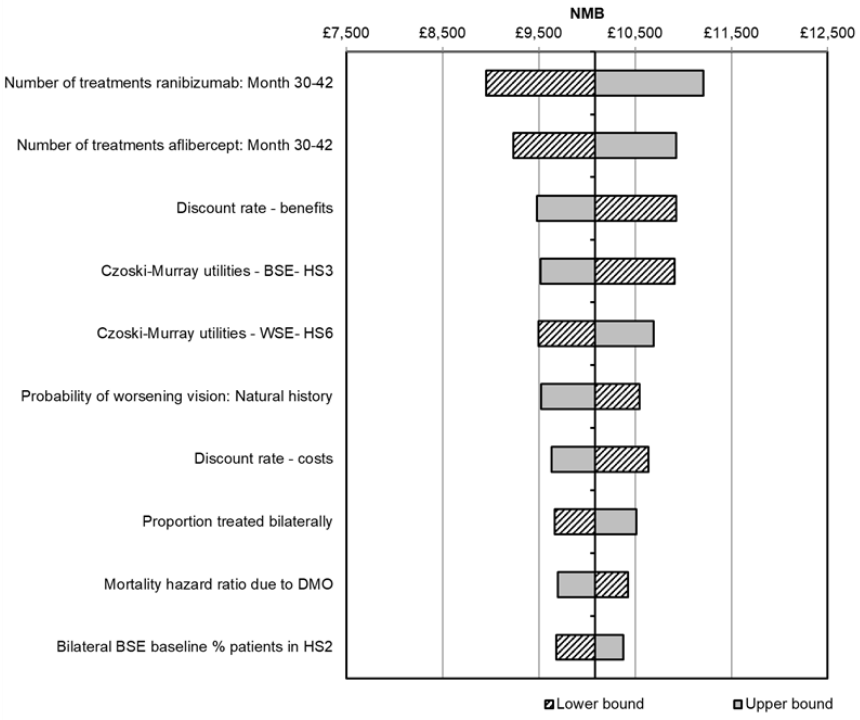
Appendix S of the CS reports the lower and upper bounds of parameters that were varied in the company's OWSA. The company noted in the CS that when confidence intervals were not reported, upper and lower bounds were calculated from the mean, SE and assumed distribution of each parameter.

As shown in Figure 15, the parameters with the greatest impact on the incremental cost-effectiveness ratio (ICER) are the average number of aflibercept and ranibizumab injections patients are assumed to receive in later timepoints. Nevertheless, DEX700 remains dominant even if the lower bound estimates are applied. The discount rate, natural history of vision (probability of losing at least 10 letters of BCVA) and some health state utility values (HSUVs) also had a noteworthy impact on the results.

Changes in BCVA resulting from DEX700 and anti-VEGF treatment (modelled using 3-monthly transition probabilities) were not varied in OWSA and the ERG considers this reasonable given the nature of patient-level transition probability matrices and the large number of matrices that would need to be varied. However, the ERG considers the last transition probability matrix (used to inform Years 4 and 5) to be a key efficacy outcome, thus it would've been helpful to vary this matrix in scenario analysis to assess what impact the long-term extrapolation has on the results. The ERG also notes that the company considered alternative efficacy estimates in scenario analysis (see Section 5.1.2).

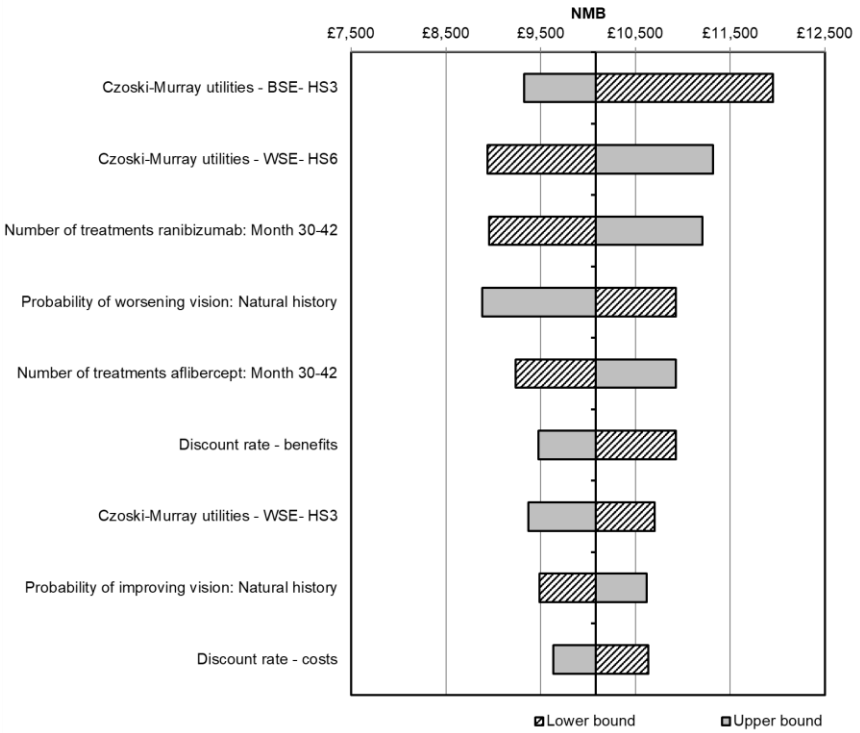
As noted in Section 0, +/-10% of the mean value was assumed for the SE when measures of uncertainty were not reported. A variation of 10% can be considered low. In consequence, the ERG ran the company's OWSA replacing the 10% variation associated with the natural history probabilities and HSUVs with 20%. As shown in Figure 16, the top 10 most influential parameters changed, but DEX700 remained dominant in each analysis.

Figure 15. Results of OWSA (reproduced from Figure 24 of the CS)



Key: BSE, best-seeing eye; CS, company submission; DMO, diabetic macular oedema; HS, health state; NMB, net monetary benefit; OWSA, one-way sensitivity analysis; WSE, worst-seeing eye.

Figure 16. Results of OWSA assuming 20% of the mean value for the SE for the natural history probabilities and HSUVs



Key: BSE, best-seeing eye; HS, health state; HSUVs, health state utility values; NMB, net monetary benefit; OWSA, one-way sensitivity analysis; SE, standard error; WSE, worst-seeing eye.

5.1.4 Model validation and face validity check

The company performed an initial validation step which involved a programmer (other than the one who built the model) reviewing all formulae and labelling in the model. Following this, extreme value analysis was conducted by inputting sensible upper and lower bounds into the model, one parameter at a time, and observing the corresponding changes in the results. An academic health economist also validated the model and critiqued the modelling strategy and methodology. The company also validated a number of the parameters and assumptions included in the model with UK clinical experts. First, an advisory board was conducted involving three UK-based clinical experts to validate key assumptions;[6] subsequently, interviews were conducted with two UK treating clinicians to validate parameters and assumptions applied in the model.[64]

The ERG has made no corrections to the company's model, which suggests the company's internal validity checks were sufficient. The ERG regards the discussions held at the advisory board meetings and interviews to be described in detail within the reference documents and does not consider the questions asked to be open ended or misleading. The ERG also notes that inputs of the economic model were compared against previous NICE TAs for the treatment of DMO to ensure consistency, and the company undertook a wide range of sensitivity analyses to test the robustness of the model results.

However, the ERG identified a few flaws in the model structure and assumptions, described in respective sections of this report, which may have introduced bias in the analysis. The following findings are of particular concern and question the external validity of the model:

- DEX700 maintains a benefit in visual acuity above anti-VEGFs beyond the 5-year treatment period and throughout the remaining time horizon (see Section 4.2.5.1);
- more DEX700-treated patients than anti-VEGF-treated patients reside in health state 1 (see Section 4.2.14.6); and,
- anti-VEGF-treated patients accrue more QALYs when they maintain constant vision compared to when they follow vision as per the sham arm of MEAD (see Section 4.2.6.2.1).

6 Additional economic analysis undertaken by the ERG

6.1 Model corrections

The Evidence Review Group (ERG) has made no corrections to the company's model.

6.2 Exploratory and sensitivity analyses undertaken by the ERG

The company provided a number of additional scenarios during the clarification stage. These included:

- Presenting pairwise comparisons for each anti-vascular endothelial growth factor (anti-VEGF) (see Section 4.2.3.2.1);
- Assuming dexamethasone 700 µg (DEX700) has a net-zero impact on vision in Years 4 and 5 (see Section 4.2.6.1.1);
- Alternative approaches to model RWE data (see Section 4.2.6.3.1);
    - Estimating different 3-monthly probabilities in Years 1, 2 and 3 from the UK Real Word Evidence (RWE) study[23] for anti-VEGFs,
    - Providing naïve comparisons using the French RWE audit[22] for DEX700 and the UK RWE audit[23] for anti-VEGFs.
- Alternative assumptions and sources to model adverse events (AEs) rates and cataract extraction rates (see Section 4.2.10.1 and 0);
    - Using the sham arm of MEAD to inform the AE rates associated with anti-VEGFs,
    - Assuming the cataract extraction rate is equal for patients on and off treatment (using the UK RWE audit[23] or Blue Mountain Eye Study[60]),
    - Including 0-to-12-month data from the UK RWE audit[23] to estimate cataract extraction rates.
- Alternative assumptions to model discontinuations (see Section 4.2.7.1);
    - Assuming a 3-year treatment duration,
    - Assuming patients who discontinue DEX700 receive anti-VEGFs as a subsequent treatment.
- Alternative assumptions to model utility decrements (see Section 4.2.13.1);
    - Including utility decrements due to AEs,
    - Using an alternative source to inform age-related utility decrements (Ara and Brazier 2010).[73]

- Alternative assumptions to model costs and health care resource use (see Section 4.2.14.6);
    - Using the average number of DEX700 injections in Year 3 to inform Years 4 and 5,
    - Assuming 1.25 appointments for anti-VEGF bilateral injections,
    - Costing intraocular pressure (IOP) checks and removing fluorescein angiograms.

The ERG would like to expand on the company's scenarios which used alternative assumptions and sources to model cataract extraction rates (see Section 4.2.10.1). This includes assuming patients treated with anti-VEGF treatment and no treatment (including those who discontinue DEX700) have the same probability of having cataract surgery using the results from the sham arm of MEAD (rather than the UK RWE audit[23] or Blue Mountain Eye Study[60]) and using the ERG's estimate of cataract extraction rates from the UK RWE audit (assuming [redacted] undergo surgery in Months 0 to 48 rather than [redacted]).

The ERG also questions why a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.5% is applied to the company's scenarios which assume a zero-net impact on vision and why the company applied restricted transition probabilities to DEX700 when a zero-net impact was applied to anti-VEGFs (see Sections 4.2.6.1.1 and 4.2.6.2.1). A 3-monthly probability of 0% would be more transparent and restricted transition probabilities have been heavily criticised in TA349.

Other key scenarios the ERG explored include reducing the time horizon (see Section 4.2.5.1), using mortality assumptions which are closer aligned to the methods and sources accepted in TA613 (see Section 4.2.12.1), assuming some residential care is self-funded (see Section 4.2.14.6), using an alternative set of utility values based on a different conversion of VA logMAR to ETDRS letters (see Section 4.2.13.1) and using the sham arm of MEAD to inform the raised IOP rates associated with anti-VEGF treatment (Section 4.2.11.1).

6.3 ERG scenario analysis

Results of the ERG's scenario analyses are provided in Table 59.

The scenario with the most significant change in the results is the scenario which assumes a net-zero change in vision over time for the anti-VEGF arm, using a probability of gaining or losing at least 10 letters of BCVA of 0% and using unrestricted DEX700 transitions (inc. NMB reduced from £10,080 to £615).

Scenarios that also have a meaningful impact on the results include reducing the time horizon and assuming DEX700 has a zero-net impact vision on vision in years 4 and 5, with a probability of gaining or losing at least 10 letters of BCVA of 0%.

The ERG also considers it important to highlight that the scenario which reduces severe vision loss costs (41% of residential care is self-funded) favours DEX700. This finding could be considered contradictory to the view that DEX700 leads to greater improvements in BCVA than anti-VEGFs (see Section 4.2.14.6).

Finally, the ERG notes that in some analyses, Scenarios 1 to 5 in particular (shorter time horizons and alternative changes in BCVA resulting from DEX700 and anti-VEGF treatment), incremental quality-adjusted life years (QALYs) are relatively small resulting in extremely sensitive incremental cost-effectiveness ratios (ICERs).

Table 59. Results of the ERG's scenario analyses

	Results per patient	Intervention	Comparator	Incremental value
0	Company base case			
	Total costs	£31,728	£38,695	-£6,968
	QALYs	7.585	7.482	0.104
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£10,080
1	5-year time horizon			
	Total costs	£14,998	£22,040	£7,042
	QALYs	2.802	2.783	0.018
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£7,595
2	10-year time horizon			
	Total costs	£21,451	£28,059	-£6,609
	QALYs	4.861	4.799	0.062
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£8,466
3	DEX700 has a net-zero impact on vision in years 4 and 5, with a probability of gaining or losing at least 10 letters of BCVA of 0%			
	Total costs	£32,121	£38,695	-£6,575
	QALYs	7.508	7.482	0.027
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£7,383

4	Anti-VEGFs have a net-zero impact on vision in years 1 to 5, with a probability of gaining or losing at least 10 letters of BCVA of 0% (restricted DEX700 transitions)			
	Total costs	£27,756	£31,805	-£4,049
	QALYs	7.585	7.567	0.018
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£4,592
5	Anti-VEGFs have a net-zero impact on vision in years 1 to 5, with a probability of gaining or losing at least 10 letters of BCVA of 0% (unrestricted DEX700 transitions)			
	Total costs	£31,728	£31,805	-£77
	QALYs	7.585	7.567	0.018
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£615
6	Cataract extraction rates for patients on and off anti-VEGF treatment based on the UK RWE audit and assuming [redacted] undergo surgery in months 0 to 48[23]			
	Total costs	£31,999	£39,170	-£7,171
	QALYs	7.585	7.482	0.104
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£10,284
7	Cataract extraction rates for patients on and off anti-VEGF treatment based on the sham arm of MEAD			
	Total costs	£31,733	£38,265	-£6,532
	QALYs	7.585	7.482	0.104
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£9,644
8	Mortality as per TA613: a HR of 1.95 the additional mortality due to DM and a HR of 1.54 for the additional mortality due to blindness[5, 68, 69]			
	Total costs	£32,168	£39,230	-£7,063
	QALYs	8.032	7.927	0.105
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£10,209
9	Alternative utility conversion from VA logMAR (Czoski-Murray *et al.* 2009[38]) to ETDRS			
	Total costs	£31,728	£38,695	-£6,968
	QALYs	7.589	7.491	0.098
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£9,911
10	Severe vision loss costs adjusted such that residential care costs are zero for 41% of patients requiring this service[83]			
	Total costs	£26,696	£34,144	-£7,449
	QALYs	7.585	7.482	0.104
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£10,561

11	Raised IOP rates from the sham arm of MEAD assumed for anti-VEGF treatment			
	Total costs	£31,728	£38,238	-£6,510
	QALYs	7.585	7.482	0.104
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£9,623

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; DEX700, dexamethasone 700 µg; DM, diabetes mellitus; ERG, evidence review group; ETDRS, Early Treatment Diabetic Retinopathy Study; HR, hazard ratio; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure; NMB, net monetary benefit; QALY, quality adjusted life year; RWE, real world evidence; TA, technology appraisal.

6.4 ERG preferred assumptions

As shown in Section 4.2.3.2.1, amending the composite comparator ([redacted] ranibizumab and [redacted] aflibercept) to a 100% ranibizumab comparator has no impact on decision making in the company base case as DEX700 remains dominant. However, given the magnitude of the change in the inc. NMB (£10,080 vs £6,291 for the composite comparator vs ranibizumab, respectively) assessing ranibizumab as an individual comparator could be important for decision making when a number of modelling assumptions are changed. Additionally, clinical experts to the ERG have suggested that the use of aflibercept estimated based on the latest 2 years of the UK RWE audit ([redacted]) is not unreasonable as the use of aflibercept appears to be increasing.[23] For these reasons, the ERG will present its preferred base case for the composite comparator, a 100% ranibizumab comparator and a 100% aflibercept comparator.

Results of the ERG's preferred assumptions are reported cumulatively in Table 60. Detailed deterministic and probabilistic results including all preferred assumptions are reported in Table 61, Table 62 and Table 63 for the composite comparator, ranibizumab and aflibercept, respectively. For completeness, full incremental results are reported in Table 64.

The ERG notes that utility decrements due to AEs could not be included in the probabilistic analysis due to time constraints. However, given that the one-off QALY decrement is relatively small the ERG still considers the probabilistic results to be meaningful. Moreover, there is no variation in the transition probability matrix when a zero-net impact on vision is assumed (that is, the probability of improving/worsening is always set to zero).

Following ERG amendments to the model, the deterministic and probabilistic ICERs switched from DEX700 dominating the composite comparator, and a 100% ranibizumab comparator, to DEX700 being dominated. For a 100% aflibercept comparator, the deterministic and probabilistic ICERs switched from DEX700 dominating aflibercept to a south-west quadrant ICER (DEX700 less costly and

less effective than aflibercept). These findings are very different from the company's base case analysis and indicate the considerable impact of the company's assumptions on the results of the economic analysis.

However, the ERG cautions the interpretation of the cost-effectiveness results presented in the ERG report as they are based on list prices. The cost-effectiveness results presented in the confidential appendix to the ERG report, which includes the patient access scheme (PAS) discounts for comparator treatments (DEX700 does not have a PAS discount), are more relevant for decision-making. The ERG also considers it important to note that incremental QALYs are relatively small when a number of the ERG's preferred assumptions are applied, which results in extremely sensitive ICERs.

Table 60. ERG's preferred model assumptions (cumulative deterministic results, DEX700 vs comparator)

Preferred assumption	Section in ERG report	Inc. cost	Inc. QALY	Cumulative ICER (£/QALY)	Inc. NMB (£30,000/QALY)
Composite comparator					
Company base case	5.1.1.1	-£6,968	0.104	DEX700 dominant	£10,080
10-year time horizon	4.2.5.1	-£6,609	0.062	DEX700 dominant	£8,466
Average number of DEX700 injections from Year 3 remained constant until the end of Year 5 (as per company's assumption for anti-VEGFs)	4.2.14.6	-£6,093	0.062	DEX700 dominant	£7,950
Patients who continue DEX700 receive anti-VEGF treatment for 1 year[§] and vision follows the natural history of vision in eyes with DMO during and after this 1-year period (as per clinical expert opinion*)	4.2.7.1	-£4,385	0.062	DEX700 dominant	£6,242
Cataract extraction rates for patients on and off anti-VEGF treatment based on the sham arm of MEAD (as per TA613 using the sham arm of FAME[5, 35])	4.2.10.1	-£3,885	0.062	DEX700 dominant	£5,742
Mortality as per TA613: a HR of 1.95 the additional mortality due to DM and a HR of 1.54[†] for the additional mortality due to blindness[5, 68, 69]	4.2.12.1	-£3,916	0.060	DEX700 dominant	£5,709
Utility decrements due to AEs included as per TA613[5]	4.2.13.1	-£3,916	0.058	DEX700 dominant	£5,670
Natural history of vision in eyes with DMO as per TA613: a 3-month probability of gaining or losing at least 10 letters of BCVA of 0% and 3.5%, respectively.	4.2.8.1	-£3,463	0.038	DEX700 dominant	£4,616
DEX700 has a net-zero impact on vision in Years 4 and 5, with a probability of gaining or losing at least 10 letters of BCVA of 0%	4.2.6.1.1	-£3,573	-0.007	£481,583 (SW quadrant[‡])	£3,351
Anti-VEGFs have a net-zero impact on vision in Years 1 to 5, with a probability of gaining or losing at least 10 letters of BCVA of 0% (unrestricted DEX700 transitions)	4.2.6.2.1	£1,713	-0.063	DEX700 dominated	-£3,597

Ranibizumab comparator					
Base case using 100% ranibizumab use	4.2.3.2.1	-£3,179	0.104	DEX700 dominant	£6,291
All preferred assumptions	-	£5,530	-0.063	DEX700 dominated	-£7,415
Aflibercept comparator					
Base case using 100% aflibercept use	4.2.3.2.1	-£9,194	0.104	DEX700 dominant	£12,307
All preferred assumptions	-	-£530	-0.063	£8,436 (SW quadrant‡)	-£1,355

Abbreviations: AE, adverse event; anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; DEX700, dexamethasone 700 µg; DM, diabetes mellitus; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality adjusted life year; SW, south-west; TA, technology appraisal.

*most patients will receive anti-VEGF re-treatment for a short period of time and it is unlikely to be effective

†the ERG considers the multiplier associated with "severe visual impairment" (1.54) to be of more relevance than the multiplier applied in TA613 associated with "some visual impairment" (1.23) for patients whose BSE falls into BCVA state 1

‡DEX700 less costly and less effective than the comparator

§One-off cost of £3,539 based on the ranibizumab and aflibercept market shares and number of injections in year 1 as observed UK RWE (as per company scenario)

Table 61. ERG's base case results vs composite comparator

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NMB (£30,000/ QALY WTP threshold)
Deterministic						
Anti-VEGFs	£23,028	4.904	-	-	-	-
DEX700	£24,741	4.841	£1,713	-0.063	Dominated	-£3,597
Probabilistic (1,000 iterations)						
Anti-VEGFs	£23,653	4.8920				-
DEX700	£24,598	4.8235	£945	-0.069	Dominated	-£3,001*

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; DEX700, dexamethasone 700 µg; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

*DEX700 has a 7% chance of being the most cost-effective option at a WTP threshold of £30,000/QALY

Table 62. ERG's base case results vs ranibizumab

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NMB (£30,000/ QALY WTP threshold)
Deterministic						
Ranibizumab	£19,211	4.904	-	-	-	-
DEX700	£24,741	4.841	£5,530	-0.063	Dominated	-£7,415
Probabilistic (1,000 iterations)						
Ranibizumab	£19,864	4.895	-	-	-	-
DEX700	£24,702	4.825	£4,839	-0.069	Dominated	-£6,223*

Abbreviations: DEX700, dexamethasone 700 µg; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

*DEX700 has a 1% chance of being the most cost-effective option at a WTP threshold of £30,000/QALY

Table 63. ERG's base case results vs aflibercept

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NMB (£30,000/ QALY WTP threshold)
Deterministic						
Aflibercept	£25,271	4.904	-	-	-	-
DEX700	£24,74	4.841	-£530	-0.063	£8,436*	-£1,355
Probabilistic (1,000 iterations)						
Aflibercept	£25,869	4.888	-	-	-	-
DEX700	£24,601	4.818	-£1,268	-0.070	£18,177*	-£825†

Abbreviations: DEX700, dexamethasone 700 µg; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

*South-west quadrant ICER (DEX700 less costly and less effective than aflibercept)

†DEX700 has a 34% chance of being the most cost-effective option at a WTP threshold of £30,000/QALY

Table 64. ERG's fully incremental base case results

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Ranibizumab	£19,211	4.904	-	-	-
Aflibercept	£25,271	4.904	£6,060	0.000	Aflibercept dominated by ranibizumab
DEX700	£24,741*	4.841	£5,530	-0.063	DEX700 dominated by ranibizumab

Abbreviations: DEX700, dexamethasone 700 µg; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; WTP, willingness-to-pay

*Subsequent treatment one-off cost of £3,539 based on the ranibizumab and aflibercept market shares and number of injections in year 1 as observed UK RWE.

6.5 Conclusions of the cost effectiveness sections

The company submitted an economic analysis comparing DEX700 to a composite comparator consisting of anti-VEGF treatments (aflibercept [redacted] and ranibizumab [redacted]), in phakic diabetic macular oedema (DMO) patients who are considered insufficiently responsive to non-corticosteroid treatment. The company considered watch and wait to only be a comparator in patients who are considered unsuitable for non-corticosteroid treatment and choose not to provide an economic analysis for this comparison in the CS as it had already been considered in the previous DEX700 appraisal (TA349).[2]

Although the ERG considers the treatments and market shares included in the composite comparator to be reasonable, the ERG also considers it worthwhile to assess them separately as the incremental cost between DEX700 and the comparator reduces substantially when ranibizumab is assessed as a separate comparator, which could be important for decision making. Moreover, clinical experts to the ERG have suggested that the use of aflibercept appears to be increasing.

Having a robust analysis of clinical effectiveness is fundamental to having reliable estimates of cost-effectiveness for this appraisal. As mentioned throughout this report, the study population in the MEAD trials was not directly relevant to the subpopulation considered in the economic analysis. Efficacy data on DEX700 for phakic DMO patients who are considered insufficiently responsive to non-corticosteroid therapy were taken from the whole phakic population in the MEAD trials. However, participants in the MEAD trials were not representative of the subpopulation examined in the economic analysis. For example, less than [redacted] had previously received anti-VEGF treatment, and a patient who has not previously responded to anti-VEGF treatment, may be overall treatment-resistant and less likely to respond to other treatments as well; this means that consideration of the

whole phakic MEAD population as a proxy for patients with DMO who are insufficiently responsive to non-corticosteroid therapy has likely overestimated the treatment effect in favour of DEX700.

The ERG is also concerned that the company has used a last observation carried forward (LOCF) approach to account for missing data on changes in BCVA from MEAD. The ERG notes that the natural history of DMO suggests that vision deteriorates over time and therefore the LOCF approach may be optimistic for both the DEX700 and sham arms as vision in patients with missing data cannot worsen. The ERG is, therefore, concerned that results for both the sham and DEX700 arms are likely to be biased and considers it difficult to predict the likely direction of the resulting bias for the comparison of DEX700 vs sham from using a LOCF approach to account for missing data.

The ERG is satisfied that the modelling approach and model structure chosen by the company follows the precedent set in TA349 and therefore promotes consistent decision making.[2] However, unlike TA349, the time horizon is set to lifetime (vs 15 years in TA349), the model assumes a maximum duration of treatment of 5 years across all treatments (vs 3 years in TA349) and all patients enter the model with phakic eyes (vs including pseudophakic TA349). A key concern with the economic analysis relates to the time horizon, which is lifetime (40 years). The ERG considers the company's long-term modelling assumptions to be too simplistic to accurately capture the costs and consequences over a lifetime time horizon. This is because more treatment options may become available to patients when they become pseudophakic. In addition, no treatment waning assumptions have been modelled, which means DEX700 maintains a benefit in visual acuity above anti-VEGFs beyond the 5-year treatment period and throughout the remaining time horizon. Shorter time horizons (10 and 15 years) have also been adopted in other DMO appraisals in order to reduce the uncertainty about the projected effects of treatment. As shown in the exploratory analysis conducted by the company and ERG, reducing the time horizon favours anti-VEGF treatment.

Another key concern with the economic analysis, is with the company's assumption that the sham arm of the MEAD trials likely overestimates the efficacy (changes in BCVA) of continued anti-VEGF use (sham is used as a proxy for continued anti-VEGF use). The ERG agrees this approach is consistent with TA613, in which the Committee considered it appropriate, in the absence of data, to assume that the relative efficacy of fluocinolone acetonide vs sham in FAME was a reasonable proxy for the relative efficacy of fluocinolone acetonide vs continued use of anti-VEGF or laser.[5, 35] However, in the CS, the company provided a scenario where anti-VEGF treatment has zero net impact on vision. This scenario favoured anti-VEGF treatment which is counterintuitive to the

company's argument that the sham arm of MEAD results in a conservative estimate of the relative treatment effect.

Moreover, the company made additional assumptions in their scenario which assumed a zero net impact on vision. These include a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.5% and using a restricted set of transition probabilities to inform DEX700, i.e. patients can only move up or down one health state in each model cycle. A 3-monthly probability of 0% would be more transparent and restricted transition probabilities have been heavily criticised in TA349.[2] What's more, the ERG found that removing these additional assumptions had a larger impact in favour of the anti-VEGF treatment, albeit the ICER remained dominant.

Given the large assumptions needed to model continued anti-VEGF treatment, the ERG considers that Committee may want to account for this uncertainty by using the lower threshold for cost-effectiveness (that is, an ICER below £20,000 per QALY gained). The ERG would also urge the company to explain how utilising the sham arm of MEAD in the model does not lead to an overall net gain in BCVA.

An additional and related area of concern is related to the assumed changes in BCVA resulting from DEX700 treatment in Years 4 and 5, in the absence of long-term data. Given the follow-up time of 3 years in MEAD, the 3-monthly transition probabilities in Years 1 to 3 were taken from MEAD, whereas the 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. The ERG and its clinical experts consider that in the absence of any evidence to substantiate improvements in vision in Years 4 and 5, assuming vision is maintained is more appropriate, if, conservative. To align with TA349 and reduce the number of assumptions required to model Years 4 and 5, the company provided a scenario using a 3-year treatment duration for all treatments. Reducing the treatment duration to 3 years had a larger impact in favour of the comparator, albeit the ICER remained dominant. Thus, additional clinical expert input would be helpful to verify the company's assumptions that 5 years is sufficiently long enough to capture key differences in treatment costs and that the last transition matrix provides the most relevant data available from MEAD as it allows for any recovery in BCVA following the development and extraction of cataracts in a significant proportion of patients to be captured.

After the 5-year treatment period, or as a result of discontinuation within the 5-year treatment period, patients are assumed to receive no further treatment. However, clinical experts advising the

ERG revealed that DEX700-treated patients would be offered re-treatment with an anti-VEGF if they discontinued DEX700 due to an AE or due to lack (or loss) of efficacy. It was also noted that subsequent anti-VEGF treatment would be given for a relatively short period of time, and it would be unlikely to be effective. Even so, excluding subsequent treatment costs introduces bias in favour of DEX700 as there are no subsequent treatments available for the comparator. The ERG is unaware of any evidence that could inform the efficacy of subsequent treatment in patients who have received prior DEX700 to resolve the uncertainty surrounding subsequent treatment. Therefore, additional clinical expert input would be helpful to determine if the simplistic scenario provided by the company at the clarification stage (one-off cost to represent 1 year of subsequent treatment with anti-VEGFs) resolves this uncertainty.

The ERG's clinical experts also disagreed with the company's base case assumption that patients cannot discontinue anti-VEGF treatment during the treatment period. However, given that this is in line with the assumption accepted in TA613,[5] and partly captured in the way the number of anti-VEGF injections has been calculated (frequency of injections decreases over time), the ERG is satisfied with the company's base case assumption.

After the 5-year treatment period or as a result of discontinuation within the 5-year treatment period, patients are also assumed to follow the natural history of vision in patients with DMO. As per TA349, these data were taken from Mitchell *et al.* 2012 who estimated a 3-month probability of gaining or losing at least 10 letters of BCVA (moving up or down one health state) of 3.5% and 4.5%, respectively.[48] However the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) data used to inform these estimates in Mitchell *et al.* 2012 were based on a population of patients with diabetic retinopathy who may not have had DMO, which means WESDR could represent a less severe set of patients than the population for this appraisal. What's more, the data may reflect outdated practice as it was analysed and adjusted between 1998 and 2004. The ERG's clinical experts also considered the 3-month probability of gaining at least 10 letters of BCVA of 3.5% to be too high and considered the probabilities employed and accepted in TA613 to be closer to their expectations (a 3-month probability of gaining or losing at least 10 letters of BCVA of 0% and 3.5%, respectively).[5] In the CS, the company provided a scenario using the natural history employed in TA613 and found this to favour anti-VEGF treatment, albeit the ICER remained dominant.

Health-related quality of life (HRQoL) in the model was based on utility values obtained from Czoski-Murray *et al*. 2009,[38] which is consistent with TA349.[2] However, the ERG considers the elicitation

and valuation methods used in Czoski-Murray *et al.* 2009 to differ substantially from those recommended in the NICE guide to the methods of technology appraisal.[47] Moreover, TA613 employed HRQoL data directly elicited from DMO patients during the FAME studies, using the NEI-VFQ-25, which was mapped to the EQ-5D.[5, 35, 36] However, major assumptions would be needed to incorporate these utility values in this model as they represent the utility of the overall patient (given different possible combinations of BCVA scores in the BSE and WSE) and not utility estimates by eye. In consequence, the ERG is satisfied with the company's base case assumption and does not consider the complexity of this scenario to be justified given the precedent set in TA349. The ERG does however consider the omission of disutilities due to AEs to be a resolvable issue. This was identified as a weakness of TA349, and utility decrements due to AEs were included in the economic analysis for TA613.

As for the estimation of unit costs and resource use, the ERG considers the company's methods to be generally reasonable. However, when the ERG sought how severe vision loss costs impacted the results of the economic analysis the ERG found that a larger proportion of DEX700-treated patients than anti-VEGF-treated patients resided in health state 1 ([redacted] life years, respectively). In the MEAD trials, there was a [redacted] in the mean change in BCVA from baseline with DEX700 compared to sham between months [redacted], and the company reported that their expert panel considered this [redacted]. In consequence, cataract and severe vision loss could be larger issues for DEX700 that initially anticipated.

Finally, cataract and raised IOP are known complications of DEX700 use and the ERG has several issues with the sources used to inform the rates of these complications in anti-VEGF-treated patients. This is because the rates used by the company suggest these complications are also big issues for anti-VEGF treatment. As a result, the ERG considered it more reasonable to use the rates from the sham arm of MEAD to inform anti-VEGFs. However, utilising these data in the model had a minimal impact on the results.

Following ERG amendments to the model, the deterministic and probabilistic ICERs switched from DEX700 dominating the composite comparator, and a 100% ranibizumab comparator, to DEX700 being dominated. For a 100% aflibercept comparator, the deterministic and probabilistic ICERs switched from DEX700 dominating aflibercept to a south-west quadrant ICER (DEX700 less costly and less effective than aflibercept). These findings are very different from the company's base case

analysis and indicate the considerable impact of the company's assumptions on the results of the economic analysis.

However, the ERG cautions the interpretation of the cost-effectiveness results presented in the ERG report as they are based on list prices. The cost-effectiveness results presented in the confidential appendix to the ERG report, which includes the PAS discounts for comparator treatments (DEX700 does not have a PAS discount), are more relevant for decision-making. The ERG also considers it important to note that incremental QALYs are relatively small when a number of the ERG's preferred assumptions are applied, which results in extremely sensitive ICERs.

Overall, the ERG considers that the company is reusing the MEAD trials as per TA349 and that no new evidence has been implemented in the base case. This is because the MEAD sham arm is being used as a proxy for continued anti-VEGF treatment and, therefore, the only real changes are a different comparator (which is more expensive) and a longer treatment period and time horizon (which is accruing additional benefits and cost savings for DEX700).

7 End of Life

The company has not made a case for the committee to consider DEX700 as an end of life treatment and the Evidence Review Group (ERG) agrees with this assessment.

8 References

1. American Society of Aerospace Medicine Specialists. Clinical Practice Guideline for Cataracts. Available from: http://www.asams.org/guidelines/Completed/NEW%20Cataract.htm. Date accessed: Jun 2021.
2. National institute for Health and Care Excellence (NICE). Dexamethasone intravitreal implant for treating diabetic macular oedema: Technology appraisal [TA349], 2015. Available from: https://www.nice.org.uk/guidance/ta349. Date accessed: Feb 2022.
3. The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines, 2012. Available from: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-301-FINAL-DR-GUIDELINES-DEC-2012-updated-July-2013.pdf. Date accessed: Mar 2022.
4. Amoaku WM, Ghanchi F, Bailey C, Banerjee S, Banerjee S, Downey L, et al. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. *Eye (Lond)* 2020; **34**: 1-51.
5. National Institute for Health and Care Excellence (NICE). Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy: Technology appraisal [TA613], 2019. Available from: https://www.nice.org.uk/guidance/ta613. Date accessed: Feb 2022.
6. AbbVie. Virtual Advisory Board for Ozurdex® in Phakic Patients with Diabetic Macular Oedema – Report. 2021.
7. Kodjikian L, Bellocq D, Mathis T. Pharmacological Management of Diabetic Macular Edema in Real-Life Observational Studies. *BioMed Research International* 2018; **2018**: 8289253.
8. Pareja-Ríos A, Ruiz-de la Fuente-Rodríguez P, Bonaque-González S, López-Gálvez M, Lozano-López V, Romero-Aroca P. Intravitreal dexamethasone implants for diabetic macular edema. *International journal of ophthalmology* 2018; **11**: 77-82.
9. Dutra Medeiros M, Alkabes M, Nucci P. Effectiveness of the Dexamethasone Intravitreal Implant for Treatment of Patients with Diabetic Macular Oedema. *Eur Endocrinol* 2014; **10**: 111-6.
10. European Medicines Agency. Dexamethasone intravitreal implant 700 micrograms (Ozurdex®), 2015. Available from: https://www.ema.europa.eu/en/documents/product-information/ozurdex-epar-product-information_en.pdf. Date accessed: June 2021.
11. Shah SU, Maturi RK. Therapeutic Options in Refractory Diabetic Macular Oedema. *Drugs* 2017; **77**: 481-92.
12. AbbVie. Allergan Ozurdex HTA Digital Advisory Board Interim Report. 2022.
13. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica Journal international d'ophtalmologie International journal of ophthalmology Zeitschrift fur Augenheilkunde* 2017; **237**: 185-222.
14. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology* 2016; **123**: 1351-9.
15. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *N Engl J Med* 2015; **372**: 1193-203.
16. Bressler NM, Beaulieu WT, Maguire MG, Glassman AR, Blinder KJ, Bressler SB, et al. Early Response to Anti-Vascular Endothelial Growth Factor and Two-Year Outcomes Among Eyes With Diabetic Macular Edema in Protocol T. *Am J Ophthalmol* 2018; **195**: 93-100.
17. Boyer DS, Yoon YH, Belfort R, Jr., Bandello F, Maturi RK, Augustin AJ, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology* 2014; **121**: 1904-14.

18. Committee for Medicinal Products for Human Use (CHMP). GUIDELINE ON MISSING DATA IN CONFIRMATORY CLINICAL TRIALS, 2009. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-missing-data-confirmatory-clinical-trials_en.pdf. Date accessed: Feb 2022.
19. Lachin JM. Fallacies of last observation carried forward analyses. *Clin Trials* 2016; **13**: 161-8.
20. Augustin AJ, Kuppermann BD, Lanzetta P, Loewenstein A, Li X-Y, Cui H, et al. Dexamethasone intravitreal implant in previously treated patients with diabetic macular edema: subgroup analysis of the MEAD study. *BMC Ophthalmology* 2015; **15**: 150.
21. Maturi RK, Pollack A, Uy HS, Varano M, Gomes AM, Li XY, et al. Intraocular Pressure in Patients with Diabetic Macular Edema Treated with Dexamethasone Intravitreal Implant in the 3-year MEAD study. *Retina (Philadelphia, Pa)* 2016; **36**: 1143-52.
22. AbbVie. French RWD. Real World Study in Diabetic Macular Oedema Treated with Dexamethasone Implant: phakic vs pseudophakic (Data on file). 2021.
23. AbbVie. Long-term Follow Up of anti-VEGF use in Phakic Patients with Diabetic Macular Oedema: Real World Outcomes (Data on file). 2021.
24. AbbVie. MEAD Post-hoc analysis: Tables for Phakic Input. 2021.
25. AbbVie. MEAD Post-hoc Analysis: Figures for Phakic Inputs. 2021.
26. AbbVie. MEAD ERG Questions Analyses. 2022.
27. The National Eye Institute. 25-Item Visual Function Questionnaire (VFQ-25), 2000. Available from: https://www.nei.nih.gov/sites/default/files/2019-06/manual_cm2000.pdf. Date accessed: Mar 2022.
28. National Institue for Health and Care Excellence (NICE). Ranibizumab for treating diabetic macular oedema: Technology appraisal [TA274], 2013. Available from: https://www.nice.org.uk/guidance/ta274. Date accessed: Feb 2022.
29. National Institute for Health and Care Excellence (NICE). Aflibercept for treating diabetic macular oedema: Technology appraisal [TA346], 2015. Available from: https://www.nice.org.uk/guidance/ta346. Date accessed: Feb 2022.
30. National Institute for Health and Care Excellence. NICE DSU Technical support document 18: Methods for Population-adjusted Indirect Comparisons in Submissions to NICE. 2016.
31. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004; **8**.
32. Papaioannou D, Brazier J, Paisley S. Systematic Searching and Selection of Health State Utility Values from the Literature. *Value in Health* 2013; **16**: 686-95.
33. Pochopien M, Beiderbeck A, McEwan P, Zur R, Toumi M, Aballéa S. Cost-effectiveness of fluocinolone acetonide implant (ILUVIEN®) in UK patients with chronic diabetic macular oedema considered insufficiently responsive to available therapies. *BMC Health Serv Res* 2019; **19**: 22.
34. A. Beiderbeck SA, M. Pochopien, K. Maman, R. M. Zur, M. Toumi. Cost-effectiveness of a 0.2 MG/day fluocinolone acetonide (FAC) implant in the treatment chronic diabetic macular oedema (DMO) in the UK. *Value Health* 2017; **20**: 804.
35. Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology* 2012; **119**: 2125-32.
36. Rentz AM, Kowalski JW, Walt JG, Hays RD, Brazier JE, Yu R, et al. Development of a preference-based index from the National Eye Institute Visual Function Questionnaire-25. *JAMA Ophthalmol* 2014; **132**: 310-8.
37. Haig J, Regnier SA, Malcom W, Xue W. Cost-Effectiveness of Ranibizumab Verse Aflibercept in Treatment of Treatment of Visual Impairment Due to Diabetic Macular Oedema (Dmo). *Value Health* 2014; **17**: A609.

38. Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. *Value Health* 2009; **12**: 793-9.
39. Raman V. A cost analysis comparing continued 3-year aflibercept monotherapy versus a switch from aflibercept to the fluocinolone acetonide intravitreal implant in phakic patients with chronic diabetic macular edema. *Expert Review of Ophthalmology* 2018; **13**: 299-307.
40. Government UK. Drugs and pharmaceutical electronic market information tool (eMIT). 2021. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Date accessed: 1 July 2021.
41. NHS Improvement. NHS Reference Costs 2019/20, 2020. Available from: https://improvement.nhs.uk/resources/national-cost-collection/. Date accessed: June 2021.
42. National Institute for Health and Care Excellence (NICE). Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy: Technology appraisal [TA301], 2013. Available from: https://www.nice.org.uk/guidance/ta301. Date accessed: Feb 2022.
43. National Institue for Health and Care Excellence (NICE). Final scope for the appraisal of dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens (part review of TA349), 2021. Available from: https://www.nice.org.uk/guidance/gid-ta10889/documents/final-scope. Date accessed: Feb 2022.
44. Holden SE, Currie CJ, Owens DR. Evaluation of the clinical effectiveness in routine practice of fluocinolone acetonide 190 microg intravitreal implant in people with diabetic macular edema. *Curr Med Res Opin* 2017; **33**: 5-17.
45. The Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *N Engl J Med* 2017; **372**: 1193-203.
46. Cai S, Bressler NM. Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: recent clinically relevant findings from DRCR.net Protocol T. *Curr Opin Ophthalmol* 2017; **28**: 636-43.
47. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013 - Process and methods [PMG9], 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Date accessed: Feb 2022.
48. Mitchell P, Annemans L, Gallagher M, Hasan R, Thomas S, Gairy K, et al. Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial. *Br J Ophthalmol* 2012; **96**: 688-93.
49. Guillard M, Dupas B, El Sanharawi M, Erginay A, Tadayoni R, Massin P. Symmetry in early response to intravitreal ranibizumab in bilateral diabetic macular oedema. *Acta Ophthalmol* 2016; **94**: e356-60.
50. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE., 2016. Available from: https://nicedsu.sites.sheffield.ac.uk/tsds/population-adjusted-indirect-comparisons-maic-and-stc. Date accessed: Feb 2022.
51. Schmidt-Erfurth U, Lang GE, Holz FG, Schlingemann RO, Lanzetta P, Massin P, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology* 2014; **121**: 1045-53.
52. electronic medicines compendium (emc). SmPC: Eylea 40mg/ml solution for injection in a vial. Available from: https://www.medicines.org.uk/emc/product/2879/smpc#gref. Date accessed: Feb 2022.
53. electronic medicines compendium (emc). SmPC: Lucentis 10 mg/ml solution for injection. Available from: https://www.medicines.org.uk/emc/product/307/smpc#gref. Date accessed: Feb 2022.

54. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Archives of ophthalmology (Chicago, Ill : 1960)* 1984; **102**: 520-6.
55. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Archives of ophthalmology (Chicago, Ill : 1960)* 1984; **102**: 527-32.
56. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). *Diabetologia* 2004; **47**: 1747-59.
57. Diabetes Control and Complications Trial Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 2000: 342-81e9.
58. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; **321**: 405-12.
59. Group UPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998: 352:837e53.
60. Tan JS, Wang JJ, Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. *Ophthalmic Epidemiol* 2008; **15**: 317-27.
61. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012; **119**: 789-801.
62. Ranibizumab for Diabetic Macular Edema: Supplementary data, 2012. Available from: https://www.aaojournal.org/cms/10.1016/j.ophtha.2011.12.039/attachment/6c597fc0-94ea-42fe-837e-294f7883f5cd/mmc1.pdf. Date accessed: Feb 2022.
63. Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two Phase III Trials: RISE and RIDE. *Ophthalmology* 2013; **120**: 2013-22.
64. AbbVie. Clinical Interview: Model Assumptions and Inputs (Data on file). 2021.
65. Office for National Statistics (ONS). National life tables, UK: 2017 to 2019, 2020. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Date accessed: Feb 2022.
66. Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA. Mortality in people with type 2 diabetes in the UK. *Diabetic medicine : a journal of the British Diabetic Association* 2006; **23**: 516-21.
67. Hirai FE, Knudtson MD, Klein BE, Klein R. Clinically Significant Macular Edema and Survival in Type 1 and Type 2 Diabetes. *Am J Ophthalmol* 2008; **145**: 700-6.
68. Christ SL, Lee DJ, Lam BL, Zheng DD, Arheart KL. Assessment of the effect of visual impairment on mortality through multiple health pathways: structural equation modeling. *Invest Ophthalmol Vis Sci* 2008; **49**: 3318-23.
69. Preis SR, Hwang SJ, Coady S, Pencina MJ, D'Agostino RB, Sr., Savage PJ, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation* 2009; **119**: 1728-35.
70. Brown GC. Vision and quality-of-life. *Transactions of the American Ophthalmological Society* 1999; **97**: 473-511.
71. Brown GC, Sharma S, Brown MM, Kistler J. Utility Values and Age-related Macular Degeneration. *Archives of Ophthalmology* 2000; **118**: 47-51.

72. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D Scores for the United Kingdom. *Medical Decision Making* 2011; **31**: 800-4.
73. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010; **13**: 509-18.
74. Curtis L and Burns A. Unit Costs of Health and Social Care, 2020. Available from: https://kar.kent.ac.uk/84818/13/Unit_Costs_of_Health_and_Social_Care_2020%20%281%29.pdf. Date accessed: Feb 2022.
75. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press, 2022. Available from: http://www.medicinescomplete.com. Date accessed: Feb 2022.
76. MIMS UK. Ranibizumab NHS list price. 2021. Available from: https://www.mims.co.uk/drugs/eye/diagnostic-and-surgical/lucentis. Date accessed: 29 September 2021.
77. MIMS UK. Aflibercept NHS list price. 2021. Available from: https://www.mims.co.uk/drugs/eye/diagnostic-and-surgical/eylea. Date accessed: 29 September 2021.
78. Poku E, Rathbone J, Everson-Hock E, Messat M, Wong R, Pandor A, et al. Bevacizumab in eye conditions: Issues related to quality, use, efficacy and safety, 2012. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/Bevacizumab-report-NICE-published-version-11.04.13.pdf. Date accessed: Feb 2022.
79. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011; **118**: 615-25.
80. Curtis L. Unit costs of health and social care, 2014. Available from: https://www.pssru.ac.uk/pub/uc/uc2014/full-with-covers.pdf. Date accessed: Feb 2022.
81. Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2008; **12**: iii-iv, ix-201.
82. Meads C, Hyde C. What is the cost of blindness? *Br J Ophthalmol* 2003; **87**: 1201.
83. Competition and Markets Authority. Care homes market study: summary of final report. 2017. Available at: https://www.gov.uk/government/publications/care-homes-market-study-summary-offinal-report. Accessed: 25 Febrary 2022. . Date accessed.
84. AbbVie. MEAD Studies: Demographics and Baseline Characteristics of Phakic Patients. 2021.
85. AbbVie. MEAD Post-hoc Exploratory Analyses. 2021.

9 Appendices

9.1 Baseline characteristics

Table 65. Patient baseline demographics and disease characteristics of phakic DMO patients in the MEAD trials (pooled data) (Reproduced from CS, Table 8)

	DEX700 (n = [redacted])	Sham (n = [redacted])
Mean age, years (SD)	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Treated eye, n (%)		
Better seeing eye	[redacted]	[redacted]
Worse seeing eye	[redacted]	[redacted]
Bilateral DMO, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior laser, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior anti-VEGF, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
BCVA < 50 letters, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Treatment-naïve at baseline, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
DMO duration > 1.3 years[a], n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
DMO duration ≥ 3 years, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
CRT ≥ 400 microns, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Cataract, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Lens opacity, n (%)		

Questionable	[redacted]	[redacted]
Present	[redacted]	[redacted]
Absent	[redacted]	[redacted]

Key: CRT, central retinal thickness; DMO, diabetic macular oedema; SD, standard deviation; VEGF, vascular endothelial growth factor.

Notes: [a] A DMO duration of 1.3 years was based on the median of the intention-to-treat population of the MEAD clinical trials.

Source: AbbVie, 2021 (MEAD subgroup analysis – baseline characteristics).[84]; Exploratory analysis slide deck, version 2.2. [85]

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 25 March 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

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

Issue 1 Time horizon

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 1.3, Table 3, Page 19 *"Shorter time horizons (10 and 15 years) have also been adopted in other DMO appraisals."* Section 1.3, Table 3, Page 19 *"The company's clinical experts noted that 5 years was sufficiently long enough to capture key differences in treatment costs and 10 years is consistent with the approach adopted by the company for the ranibizumab appraisal (TA274) to reduce the uncertainty about the projected effects of treatment."* Section 4.2.1, Page 73 "*Shorter time horizons (10 and 15 years) have also been adopted in other DMO appraisals*" Section 4.2.5.1, Page 90 "*The time horizon of the model is notably longer than the time horizons accepted in TA613 (30 years), TA349 (15 years), TA271/301 (15 years) and TA237/274 (15 years in the original submission and 10 years in the revised submission).*"	The company request the ERG revise any statements made when referencing the time horizon adopted in previous appraisals to acknowledge that the assumption of a lifetime horizon is consistent with the approach that was accepted in multiple appraisals.	These excerpts from the ERG report lead the reader to assume that previous appraisals in ophthalmology have consistently adopted a base-case time horizon of 10-15 years. However, NICE TA613, TA346 and NG82, all adopted a lifetime horizon. Indeed, a lifetime horizon was accepted in the most recent appraisal in DMO which was the re-appraisal of Iluvien (NICE TA613). This appraisal considered a similar patient population to the one of interest for this appraisal and utilised primary trial evidence with three years of follow-up. Despite a shorter time horizon being adopted in the original appraisal (TA301) a lifetime horizon was accepted in TA613. In TA346 a lifetime horizon (35 years) was also used in the base case analysis despite utilizing data of a similar maturity to MEAD. The NG82 wet AMD guideline model also assumed a lifetime horizon	The text in Section 4.2.5 has been amended to state TA613 and TA346 adopted a lifetime horizon.

Section 4.2.5.1, Page 92 *"The company's clinical experts noted that 5 years was sufficiently long enough to capture key differences in treatment costs and 10 years is consistent with the approach adopted by the company in TA274 to reduce the uncertainty about the projected effects of treatment."* Section 6.5, Page *158* *"A key concern with the economic analysis relates to the time horizon, which is lifetime (40 years). The ERG considers the company's long-term modelling assumptions to be too simplistic to accurately capture the costs and consequences over a lifetime time horizon. This is because more treatment options may become available to patients when they become pseudophakic. In addition, no treatment waning assumptions have been modelled, which means DEX700 maintains a benefit in visual acuity above anti-VEGFs beyond the 5-year treatment period and throughout the remaining time horizon. Shorter time horizons (10 and 15 years) have also been adopted in other DMO appraisals in order to reduce the uncertainty about the projected effects of treatment. As shown in the*		based on 2 years of comparative efficacy data, which is shorter than the follow-up of MEAD.(1)	

exploratory analysis conducted by the company and ERG, reducing the time horizon favours anti-VEGF treatment."			

Issue 2 Anti-VEGF efficacy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 6.2, Page 149 *"The ERG also questions why a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.5% is applied to the company's scenarios which assume a zero-net impact on vision and why the company applied restricted transition probabilities to DEX700 when a zero-net impact was applied to anti-VEGFs (see Sections* ***Error! Reference source not found.*** *and* ***Error! Reference source not found.****). A 3-monthly probability of 0% would be more transparent and restricted transition probabilities have been heavily criticized in TA349"*	The following amendments are proposed: • Clearly state the justification provided in response to ERG clarification questions regarding why a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.5% is applied • Clearly state the justification provided in response to ERG clarification questions regarding why a restricted set of transition probabilities was applied for the DEX700 arm when net-zero changes in vision were assumed for the anti-VEGF arm • Remove statements that claim that the company add "unnecessary uncertainty" or	A very clear justification for the application of the net-zero anti-VEGF scenario analysis which assumed a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.5% was provided in response to ERG clarification question B5, but this rationale is not noted in the ERG report. The response states: *"The requested scenario that assumed no movement between health states requested by the ERG is associated with a bias against DEX700 related to severe vision loss costs. As DEX700 patients can transition between any of the health states, some patients will move into the worst health state and incur the costs associated with severe vision loss. However, if patients on the anti-*	This is not a factual inaccuracy and therefore no changes to the report are required. The justification for a 3-monthly probability of 3.5% has already been provided in Section 4.6.2.1.1, "The company choose 3.5% as this is consistent with the probability of gaining at least 10 letters from the natural history study data from Mitchell *et al.*" As for the restricted set of transition probabilities applied to the DEX700 arm, the ERG considers that the company is picking justifications from other scenarios where this

Section 6.5, Page 159 *"Moreover, the company made additional assumptions in their scenario which assumed a zero net impact on vision. These include a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.5% and using a restricted set of transition probabilities to inform DEX700, i.e. patients can only move up or down one health state in each model cycle. A 3-monthly probability of 0% would be more transparent and restricted transition probabilities have been heavily criticised in TA349. What's more, the ERG found that removing these additional assumptions had a larger impact in favour of the anti-VEGF treatment, albeit the ICER remained dominant."* Section 4.2.14.6, Page 137	"made additional assumptions" relative to the ERGs approach	*VEGF arm do not transition between any of the health states, no patients can move into the worst health state and incur these costs. In reality, even if BCVA is maintained on average over time, some anti-VEGF patients would fall into the most severe health states and others could move into the better health states at different timepoints. The scenario requested by the ERG does not take this into account and therefore biases against DEX700. To account for this, we have presented a scenario assuming no movement up or down health states within the anti-VEGF arm, but excluding severe vision loss costs in both treatment arms to avoid bias."* It was also clearly stated in response to clarification question B9 that a restricted set of transition probabilities from MEAD was used to model DEX700 in this scenario to ensure that each arm adopted a consistent approach to reduce the risk of bias.	assumption was explicitly made. For example, the company's response to clarification question B9 relates to a scenario using RWE data for one treatment and not a zero net impact on vision. Furthermore, the company's response to clarification question B5 has been discussed in Section 4.2.14.6.

"The ERG acknowledges the company's rationale but considers the company's modifications to the scenario to inherently limit the findings from assuming there are no movements up or down health states within the anti-VEGF arm. This scenario has no relation to the changes in BCVA resulting from DEX700, and because of the company's modifications, it is impossible to directly compare the scenario results with the base case results." Similar statements are made on pages 97 (Section 4.2.6) and 99 (Section 4.2.6.2.1)		The ERG also claim that *"the company is adding a layer of unnecessary uncertainty"* with the net-zero scenario and that *"the company made additional assumptions".* However, the ERG's approach also requires significant assumptions to be made, notably that all patients receiving anti-VEGFs will have no change in vision whatsoever, that there is no uncertainty associated with this assumption (as the estimate is not varied in sensitivity analysis) and that none will move to the most severe health state and therefore incur severe vision loss costs. The net-zero approach is more consistent with the observed data from the UK RWE study. Data presented in Table 11 of the response to ERG clarification question B9 shows that the 3-month probability of gaining at least 10 letters ranged between 1.5%-1.8% and the probability of losing at least 10 letters ranged between 3.2%-4.5%. Therefore, we do not believe it is fair to imply that we are making "additional"	

		assumptions and adding "unnecessary uncertainty" as it could be argued that the ERGs approach requires more significant assumptions to be made.	

Issue 3 Treatment effect of DEX700 in years 4 & 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.6.1.1, Page 96 "*The 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. The ERG and its clinical expert consider that in the absence of any evidence to substantiate improvements in DEX700-treated patients in Years 4 and 5, assuming vision is maintained is more appropriate, if, conservative"* Section 6.5, Page 159	Please consider amending to: Section 4.2.6.1.1, Page 96: *"The 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. Given the uncertainty, the ERG believe assuming vision is maintained is more appropriate."* Section 6.5, Page 159: *"An additional and related area of concern is related to the assumed changes in BCVA resulting from DEX700 treatment in Years 4 and 5, in the absence of long-term data. Given the follow-up time of 3 years in MEAD, the 3-monthly transition probabilities in Years 1 to 3 were taken*	The claim that *"in the absence of any evidence to substantiate improvements in DEX700-treated patients in Years 4"* fails to acknowledge the fact that the BCVA outcomes on the DEX700 arm of MEAD were improving prior to the end of the follow-up period and that exploratory sub-group analyses from MEAD that were presented in Section B.2.7 of the company submission consistently demonstrated that the decline in visual acuity was driven by the development of cataract and that outcomes continued to improve substantially following cataract	This is not a factual inaccuracy and therefore no changes to the report are required.

"*An additional and related area of concern is related to the assumed changes in BCVA resulting from DEX700 treatment in Years 4 and 5, in the absence of long-term data. Given the follow-up time of 3 years in MEAD, the 3-monthly transition probabilities in Years 1 to 3 were taken from MEAD, whereas the 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. The ERG and its clinical experts consider that in the absence of any evidence to substantiate improvements in vision in Years 4 and 5, assuming vision is maintained is more appropriate, if, conservative*"	*from MEAD, whereas the 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. The ERG and its clinical experts consider that assuming vision is maintained is more appropriate."*	surgery. It also fails to acknowledge data presented from RWE studies in section B.2.6.2 of the company submission that consistently showed that the effect of treatment was sustained in each of those studies, and that clinicians have stated that MEAD likely provides an underestimate of the true treatment effect as treatment practice has evolved from MEAD to limit the impact that cataracts have on long-term visual acuity. Therefore, although there is uncertainty, there is certainly evidence to at least support the assumption that outcomes could improve in years 4 and 5, and there is certainly no evidence to support the claim that *"assuming vision is maintained is more appropriate, if, conservative"* as there is no indication that visual acuity would remain unchanged or decline while receiving DEX700 in years 4 and 5.	

Issue 4 Interpretation of the advisory board report

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.6.2.1, Page 101 *"For these reasons, the ERG's preferred approach is to assume that anti-VEGF treatment maintains vision (that is, a 0% probability of improving or worsening) as it is transparent in terms of the likely biases that exist in the comparison. However, as noted in Figure 11, this could be viewed as conservative estimate of anti-VEGF efficacy as, "it does not make sense to add the anti-VEGF costs but assume no efficacy whatsoever*"." Section 5.1.4, Page 147: *"First, an advisory board was conducted involving six UK-based clinical experts to validate key assumptions"*	Please consider amending to: Section 4.2.6.2.1, Page 101: *"For these reasons, the ERG's preferred approach is to assume that anti-VEGF treatment maintains vision (that is, a 0% probability of improving or worsening) as it is transparent in terms of the likely biases that exist in the comparison."* Section 5.1.4, Page 147: *"First, an advisory board was conducted involving three UK-based clinical experts to validate key assumptions"*	There appears to have been some misunderstandings about the details of the advisory board that was conducted for this appraisal. Firstly, the advisory board was not attended by six UK clinicians, but was instead attended by three UK clinical experts, two Health Economists and an additional member who acted as the chair for the meeting. The advisory board also took place in March of 2021, which was prior to the availability of the UK and French RWE studies, and the exploratory sub-group analyses from MEAD which were presented in the submission. The quote pulled out in Figure 11 of the ERG report was made by a Health Economist, not a clinical expert, who was simply making the point that it would be challenging to assume that there are costs incurred on the comparator arm while assuming	The text on Page 147 of the ERG report was reproduced from Page 171 of the CS, "First, an advisory board was conducted involving six UK-based clinical experts to validate key assumptions". The ERG has amended the text on Page 147 as requested based on the assumption that the text in the CS is factually inaccurate.

		minimal efficacy gains and therefore it would be good to identify another data source that supports this claim rather than just relying on the sham arm from MEAD. During the advisory board, and in subsequent discussions, clinicians have made clear that patients in UK clinical practice who are insufficiently responsive to anti-VEGFs continue to receive treatment despite experience little improvements in visual acuity given the lack of available treatment options. Additionally, UK RWE has been made available which strongly supports this claim, demonstrating that patients receive a large number of anti-VEGF injections for many years with little benefit. Additionally, this assumption was accepted in TA613, but the expert was almost certainly not aware of this fact at the time of making this comment.	

Issue 5 Data used in the UK RWE efficacy scenarios

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.6.3.1, Page 103 **"***As mentioned earlier, the 6-month timepoint is when the patients are deemed to be suboptimal responders in the UK RWE audit. However, the scenarios provided by the company models the probability of experiencing a 10-letter improvement or worsening in vision from baseline (Month 0) to Month 12, 24 or 36. The ERG considers that the 6-month timepoint should be the assumed baseline in any comparisons, where the UK RWE audit data are used to reflect continued anti-VEGF treatment in patients deemed to be insufficient responders***"**	The company propose the statement is changed to: Section 4.2.6.3.1, Page 103: *"As mentioned earlier, the 6-month timepoint is when the patients are deemed to be suboptimal responders in the UK RWE audit. However, the scenarios provided by the company models the probability of experiencing a 10-letter improvement or worsening in vision from baseline (Month 0) to Month 12, 24 or 36 as these were the only timepoints available. A scenario using data from baseline (Month 0) to Month 12, Month 12 to Month 24 and Month 24 to Month 36 was provided in response to clarification questions. "*	As noted in response to ERG clarification question B9, the analysis was conducted using the data that was made available from the UK RWE study, which presented efficacy outcomes at baseline and months 12, 24 and 36. Therefore, although we agree that the six-month timepoint would be the ideal baseline timepoint, it was not possible to present this analysis. Additionally, the analyses that were requested in B9 relating to the UK RWE (where the proportion of patients with ≥ 10-letter improvement or worsening were requested from baseline to Month 12, Month 12 to Month 24 and Month 24 to Month 36) were all provided.	The ERG has amended the text to state which timepoints were available to the company. The scenario using baseline to Month 12, Month 12 to Month 24 and Month 24 to Month 36 data is already discussed in Section 4.2.6.3.1 and therefore no further amendments are needed on this issue.

Issue 6 Subsequent treatment following discontinuation of DEX700

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.7.1, Page 108 "*Given the clear direction from the ERG's clinical experts that patients would receive anti-VEGF treatment following DEX700 the ERG includes the first scenario in its preferred base case"*	Please consider also reflecting the views of the clinical experts that were consulted by the company who held contrary views so ensure a more complete set of views is presented throughout the document.	The ERG does not make reference to the response provided to ERG clarification question B18 which notes that: *"UK clinicians consulted subsequent to feedback from the ERG have indicated that very few patients will receive anti-VEGF treatment upon discontinuing DEX700 and that these patients will only receive anti-VEGF treatment for a short period of time because this treatment is unlikely to be effective in this population."* Simply referencing the views of the clinical experts consulted by the ERG is mis-leading. Summarising the views of all clinical experts consulted during this appraisal would aid decision making.	The text in Section 4.2.7.1 has been amended as requested.

Issue 7 Number of anti-VEGF injections in Years 4 and 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.3.2, P.82 *"The average number of injections administered per model cycle was also taken from the UK RWE audit (Table 26). Given the absence of data beyond Year 3, a simplifying assumption was made where the average number of injections from Year 3 remained constant until the end of Year 5."*	The company propose the statement is changed to: Section 4.2.3.2, P.82: *"The average number of injections administered per model cycle was also taken from the UK RWE audit (Table 26). The UK RWE provides 42 months of data from the point at which the level of clinical response is defined. Given the absence of data beyond 42 months, a simplifying assumption based on feedback by UK clinical experts was made that the average number of injections from the last 12 months with data remained constant until 60 months*	This assumption was supported by UK clinical experts which is not made clear in the ERGs statement.	The text in Section 4.2.3.2 has been amended as requested.

Issue 8 Severe vision loss costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.14.6, P.137 "*Therefore, to remove the bias against DEX700, the company provided a scenario which excluded severe vision loss costs. The ERG acknowledges*	We are unclear of the argumentation the ERG is putting forward in this paragraph and would request that this text be revised for clarity.	We find the ERG's argumentation in this paragraph confusing, in particular we are unclear how the final statement relates to the rest of the paragraph.	The ERG has amended the last paragraph to, "Overall, the ERG considers the model results regarding the number of DEX700-treated patients residing in health

the company's rationale but considers the company's modifications to the scenario to inherently limit the findings from assuming there are no movements up or down health states within the anti-VEGF arm. This scenario has no relation to the changes in BCVA resulting from DEX700, and because of the company's modifications, it is impossible to directly compare the scenario results with the base case results. *Overall, the ERG considers this finding to a major concern as one of the key benefits of DEX700 should be improvements in BCVA.* "		The ERG's statement does not acknowledge the bias against DEX700 associated with restricting movements in one arm (anti-VEGF, by assuming no change in vision is possible at all) but not the other (DEX, by using unrestricted transition probabilities).	state 1 to a major concern as one of the key benefits of DEX700 should be improvements in BCVA."

Issue 9 Interpretation of the UK RWE results

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.6.1, Page 99 "*However, the ERG also considers it important to highlight that a >5 letter change in BCVA would*	Please consider removing this statement.	The data from the UK RWE does show that across the full group of sub-optimal responders, the average change in visual in acuity at	This is not a factual inaccuracy and therefore no changes to the report are required.

generally be deemed clinically significant, and therefore, none of the observed changes in Figure 10 would be considered clinically meaningful."		each timepoint is relatively small. However, as Figure 10 only shows the average change, it does not capture the fact that some patients may experience a decline in BCVA that is >10 letters at certain timepoints (as evidenced by our response to clarification question B9). Therefore, it is mis-leading to imply that no patients would experience a change in BCVA that is >5 letters	

Issue 10 Treatment waning

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.5.1, Page 90/91 *"As noted in Section 4.2.8 and illustrated in Figure 8 and Figure 9 below, DEX700 maintains a benefit in visual acuity above anti-VEGFs beyond the 5-year treatment period and throughout the remaining time horizon. This is because no treatment waning assumptions are included in the model. The ERG's clinical experts fed back that they*	Please consider amending to: Section 4.2.5.1, Page 90/91: *"As noted in Section 4.2.8 and illustrated in Figure 8 and Figure 9 below, patients who receive DEX700 continue to maintain a level of benefit in visual acuity above those who initially received anti-VEGFs beyond the 5-year treatment period and throughout the remaining time horizon, although the absolute treatment effect does decline over time. The ERG's clinical experts fed back that they would expect visual acuity across all treatments to converge during*	The ERG indicate that there is no waning of the treatment effect reflected in the model. However, the figures that the ERG reference demonstrate that the absolute difference in outcomes between the treatment arms does in fact converge over time.	The ERG has updated the text in Section 4.2.5.1 as suggested by the company. The text in Section 4.2.8 has also been amended.

would expect visual acuity across all treatments to converge during the off-treatment period, but were unable to suggest how long this might take. The clinical experts also noted that when a patient becomes pseudophakic more treatment options become available to them. For these reasons, the company's long term modelling assumptions may be too simplistic to accurately capture all relevant downstream benefits and costs following discontinuation from treatment." Section 4.2.8, Page 110: *"This extrapolates the same improving and worsening of BCVA in both treatment arms. In consequence, it maintains the year 5 treatment gains in BCVA from DEX700 over anti-VEGFs for the remaining 35 years of the model time horizon, at no additional cost (see Section 4.2.5.1)."*	*the off-treatment period, but were unable to suggest how long this might take. The clinical experts also noted that when a patient becomes pseudophakic more treatment options become available to them. For these reasons, the company's long term modelling assumptions may be too simplistic to accurately capture all relevant downstream benefits and costs following discontinuation from treatment."* Section 4.2.8, Page 110: *"This extrapolates the same improving and worsening of BCVA in both treatment arms."*		

Issue 11 Comparison of MEAD and UK RWE

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.6.2.1, Page 98/99 *"Firstly, the ERG does not consider the comparisons made within Figure 10 to justify the use of the MEAD sham arm to be meaningful. This is because MEAD and FAME are RCTs and it is widely accepted that this type of study design evaluates treatments under ideal conditions and among highly selective participants, whereas observational studies like the UK RWE audit have examined effects in a "real world" settings with a broader range of conditions and patients. Thus, the ERG would expect patients in sham arm of MEAD or FAME to achieve better changes in BCVA than the UK RWE audit"*	Please consider removing this statement as it is mis-leading	We agree in principle that results from an RCT may be expected to be more favourable than results from RWE for the reasons explained by the ERG, if the treatments evaluated were comparable, however here the difference in BCVA is likely also to be explained by the different treatment regimens administered in each of the RCT (sham in MEAD) and the RWE (anti-VEGF in the UK RWE audit).	This is not a factual inaccuracy and therefore no changes to the report are required.

Issue 12 Anti-VEGF discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.7.1, Page 107 *"Clinical experts advised the ERG that all patients would discontinue anti-VEGF treatment if their vision worsened, and some patients would discontinue anti-VEGF treatment if they experienced an AE; this would depend on how well the AE could be managed alongside anti-VEGF treatment."*	Please consider also reflecting the views of the clinical experts that were consulted by the company who held contrary views so ensure a more complete set of views is presented throughout the document.	No reference is made to the clinical expert opinion that we received during the submission process that was provided in response to ERG clarification question B2 which states: *"Subsequent to the feedback from the ERG, the company has consulted additional clinicians who have indicated that in UK clinical practice almost all patients continue to receive anti-VEGF treatment.(2) Clinicians will treat to obtain treatment-related benefits with the aim of obtaining improvement in vision, and/or with the aim of maintaining the retinal architecture and preventing irreversible loss of photoreceptors due to prolonged oedema.(3) Only a countable few patients will be disregarded as complete non-responders in whom even the retinal prevention is unlikely to be achieved."*	This is not a factual inaccuracy and therefore no changes to the report are required.

		The ERG's statement is mis-leading as it does not reflect the full array of clinical opinion gathered for this appraisal.	

Issue 13 Cataracts

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.14.6, Page 107 *"The ERG notes that there is a [redacted] in the mean change in BCVA from baseline with DEX700 compared to sham between months [redacted] in the MEAD trials (see Figure 6 of the CS and* ***Error! Reference source not found.*** *in Section* ***Error! Reference source not found.****). The company reported that their expert panel considered this [redacted]. This may explain why a notable proportion of DEX700-treated patients*	Please consider removing the statement: *"This finding also suggests that cataract is a larger issue for DEX700 that initially anticipated."*	The ERG state "*This finding also suggests that cataract is a larger issue for DEX700 that initially anticipated."* However, the submission has been transparent that in MEAD the emergence of cataracts resulted in a decline in visual acuity outcomes, but also that published studies and clinical experts have consistently stated that this decline would not be expected to occur in UK clinical practice as cataracts would be removed earlier in current clinical practice than they were in the MEAD study. Therefore, this statement is mis-leading.	This is not a factual inaccuracy and therefore no changes to the report are required.

entered health state 1 during this period in the model. This finding also suggests that cataract is a larger issue for DEX700 that initially anticipated."			

Issue 14 Face validity of net-zero impact approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 5.1.2, Page 142 *"The company acknowledged that their scenario which assumes a net-zero change in vision over time for the anti-VEGF arm lacks face validity given patients in the sham arm in MEAD experienced an overall net gain in BCVA, and therefore assuming a net-zero gain should increase the incremental QALY gain."* Section 6.5, Page 158 *"However, in the CS, the company provided a scenario where anti-VEGF treatment has zero net impact on vision. This scenario favoured anti-VEGF*	Please consider removing these statements	These statements imply that the company's net-zero impact approach is biased because it gives counter-intuitive results. However, it neglects the fact that the ERG approach also gives counter-intuitive results as their 0% approach also worsens the incremental QALY	This is not a factual inaccuracy and therefore no changes to the report are required.

treatment which is counterintuitive to the company's argument that the sham arm of MEAD results in a conservative estimate of the relative treatment effect"			

Issue 15 Minor text amendments

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 1.3, Table 6, Page 21 "*During the clarification stage, the company provided a simplistic scenario which included a one-off cost to represent 1 year of subsequent treatment with anti-VEGFs. Including this cost in the model had a noteworthy impact on the results in favour of the comparator (inc. NMB reduced from £10,080 to £8,373).*"	Please remove the word "noteworthy"	The change in the inc. NMB is less than £2,000, therefore calling this change noteworthy is overstating the impact.	This is not a factual inaccuracy and therefore no changes to the report are required.
Section 4.1, Page 72 "*Of these, the company deemed TA613 to be most relevant and utilised cost and resource use assumptions from TA613 to help inform the model, supplemented by data sourced from the company's clinical experts, the British National Formulary (BNF), the Monthly Index of Medical Specialities (MIMS), the drugs and pharmaceutical electronic marketing tool (eMIT),*	Please change to: "*Of these, the company deemed TA613 to be most relevant and utilised cost and resource use assumptions from TA613 to help inform the model, supplemented by data sourced from the company's clinical experts, the Monthly Index of Medical Specialities (MIMS), the drugs and pharmaceutical electronic marketing tool (eMIT), NHS Reference*	The British National Formulary (BNF) is not used as a source for costs.	The ERG thanks the company for identifying the error. The ERG report has been amended.

NHS Reference Costs 2019-2020, and the previous DEX700 appraisal (TA349)".	*Costs 2019-2020, and the previous DEX700 appraisal (TA349)*".		
Section 4.2.2.1, Page 76 "*Furthermore, patients who are insufficiently responsive to anti-VEGF treatment may be less likely to respond to corticosteroid treatment than treatment-naïve patients (or those who have only ever received treatment with laser photocoagulation in the past).*"	We would request the ERG please make clear whether this statement was provided by clinical experts, or if it was not then remove as this is speculative.	This statement is not referenced to clinical opinion or another source, so we are unclear of the validity of this claim.	The text has been amended to state it was provided by the ERG's clinical experts.
Section 4.2.4.1, Pages 89/90 "*Finally, as per the ERG for TA349, the ERG believes that to assume that the distributions of vision in BSE and WSE are independent reduces the face validity of the model, as it does not restrict the possibility that the WSE enters the model with better vision than the BSE, and potentially throughout the duration of the model*."	Change to: "*Finally, as per the ERG for TA349, the ERG believes that to assume that the distributions of vision in BSE and WSE are independent reduces the face validity of the model, as it does not restrict the possibility that the WSE can over time become the better seeing eye.*"	The distribution of vision at baseline in WSE is by definition worse than the BSE.	The ERG thanks the company for identifying the error. The ERG report has been amended.
Section 4.2.6.3, Page 102 "*As shown in Section 5.1.2, these scenarios favour DEX700 and increase the inc. NMB from £10,080 to a maximum of £24,988*"	Change to: "*As shown in Section 5.1.2, these scenarios favour DEX700 and increase the inc. NMB from £10,080 to a maximum of £25,825*"	The French RWE (baseline to Month 36 probabilities recalculated into 3-month probabilities) scenario increases the inc. NMB to £25,825	The ERG thanks the company for identifying the error. The ERG report has

<table>
<tr><td></td><td></td><td></td><td>been amended.</td></tr>
<tr><td>Section 4.2.14.2, Page 130:

“In the base case the company assumed, based on clinical opinion and in line with TA349, that all patients are treated in an outpatient setting, with 75%, 50% and 100% of bilateral DMO patients requiring separate appointments for each eye treated with DEX700, anti-VEGF, and laser treatments, respectively.

Table 48 below presents the breakdown of administration costs applied in the company’s base case analysis. These costs were applied in each model cycle for the average number of unilateral (with or without FEI) and bilateral treatments received in that cycle.”</td><td>Change to:

“In the base case the company assumed, based on clinical opinion and in line with TA349, that all patients are treated in an outpatient setting, with 75%, 50% and 0% of bilateral DMO patients requiring separate appointments for each eye treated with DEX700, anti-VEGF, and laser treatments, respectively.

Table 48 below presents the breakdown of administration costs applied in the company’s base case analysis. These costs were applied in each model cycle for the average number of unilateral and bilateral treatments received in that cycle.”</td><td>Bilateral patients receiving laser treatment were assumed to require just one appointment.

Additionally, patients with fellow eye involvement were treated as bilateral patients in the model.</td><td>The ERG thanks the company for identifying the error. The ERG report has been amended.</td></tr>
<tr><td>Section 4.2.14.4, Table 51
<table><tr><td>Pharmaceutical intervention for raised IOP</td><td>£67.67</td><td>eMIT, weighted average cost assuming mean duration of treatment of 1096 days and that raised IOP medication comprises 70% generic prostaglandins, 10% generic beta-blockers, and 20% equal used of CA inhibitors,</td></tr></table></td><td>Change to:
<table><tr><td>Pharmaceutical intervention for raised IOP</td><td>£679.36</td><td>eMIT, weighted average cost assuming mean duration of treatment of 1096 days and that raised IOP medication comprises 70% generic prostaglandins, 10% generic beta-blockers, and 20% equal used of CA inhibitors,</td></tr></table></td><td>Six extra IOP visits were added to patients with DMO who were treated for raised IOP, consistent with the preferred ERG assumption in TA349. The unit costs of each IOP visit is assumed to be £101.95 (NHS reference costs 2019/20 - WF01A</td><td>The ERG thanks the company for identifying the error. The ERG report has been amended.</td></tr>
</table>

		brimonidine and combination treatments (consistent with the ERG's preferred assumptions in TA349). Full cost breakdown provided in Table 43 of the CS.			brimonidine and combination treatments (consistent with the ERG's preferred assumptions in TA349). Full cost breakdown provided in Table 43 of the CS.	code 130 Ophthalmology; consultant-led non-admitted, face-to-face attendance, follow-up).(4) As a result, total average costs for patients treated with medications for raised IOP are £679.36 and the total average costs for patients treated with surgery for raised IOP are £1,239.70.	
Surgical intervention for raised IOP (trabeculectomy)	£628.01	NHS reference costs 2019-2020 - BZ94B/BZ93B – Intermediate/Major Glaucoma or Iris Procedures, with CC Score 0-1 (day case). Assuming 50% of procedures were intermediate and 50% were major.			In addition, six extra IOP visits were added to patients with DMO who were treated for raised IOP, consistent with the preferred ERG assumption in TA349. The unit costs of each IOP visit is assumed to be £101.95 (NHS reference costs 2019/20 - WF01A code 130 Ophthalmology; consultant-led non-admitted, face-to-face attendance, follow-up).		
			Surgical intervention for	£1,239.70	NHS reference costs 2019-2020 - BZ94B/BZ93B –		

	raised IOP (trabeculectomy)		Intermediate/Major Glaucoma or Iris Procedures, with CC Score 0-1 (day case). Assuming 50% of procedures were intermediate and 50% were major. In addition, six extra IOP visits were added to patients with DMO who were treated for raised IOP, consistent with the preferred ERG assumption in TA349. The unit costs of each IOP visit is assumed to be £101.95 (NHS reference costs 2019/20 - WF01A code 130 Ophthalmology; consultant-led non-admitted, face-to-face attendance, follow-up).		
Section 4.2.14.3, Page 132 "*The one-year offset was due to the unavailability of data from the first three months of Year 1*"	Please consider removing these statements			It is mentioned in section B.3.5.4 from document B (page 156) that the UK RWE provides data	This is not a factual inaccuracy and therefore

Section 4.2.14.6, Page 138 "*Finally, the company made a 1-year offset to the disease management costs associated with anti-VEGFs as data were unavailable for the first three months of Year 1. The ERG is surprised the company did not mention the 6-month assessment point (when patients are deemed to be suboptimal responders) as a reason for the 1-year offset.*"		on the number of clinic visits in five time periods: 3–6 months, 6–12 months, 12–24 months, 24–36 months and 36–48 months. Data from months 12–24, 24–36 and 36–48 have been used in this scenario for Year 1, Year 2 and Year 3, respectively, given that the data from months 12–24 provide the first full year of data following an assessment of insufficient response. The corresponding number of routine monitoring visits for anti-VEGF in this scenario are 4.0, 3.8 and 3.4 in Year 1, Year 2 and Year 3, respectively. Data from Year 3 has been used for Year 4 and Year 5 as well.	no changes to the report are required.

Issue 16 Clarification of ERG comment on summary of decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Clarification of statement Section 2.3, Page 30 Table 9 of the ERG report states "*However, the ERG considers this ITC to be of little relevance to the decision problem given that* [redacted] Section 3.7, Page 67 The ERG report states "*However, the ERG considers this ITC to be of little relevance to the decision problem given that* [redacted] *that in the MEAD trials…*"	The company suggest the following changes. "*However, the ERG considers this ITC to be of little relevance to the decision problem given that* [redacted] The company suggest the following changes. The ERG report states "*However, the ERG considers this ITC to be of little relevance to the decision problem given that* [redacted] *that in the MEAD trials…*"	Clarification of statement to avoid misinterpretation.	The ERG has updated the text as suggested by the company.

Issue 17 Incorrect interpretation of UK RWE audit

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.3.3, Page 37 The ERG report states "*The ERG also notes that in the UK RWE audit[5] only [redacted]% of patients who were insufficient responders (≤ 5 letter gain at month 6) continued to receive anti-VEGFs.*"	The company suggest removing this statement from page 37.	The data from the UK RWE audit has been misinterpreted. The [redacted]% of eyes refers to the proportion of eyes that had a suboptimal response to treatment, rather than the proportion of insufficient responders that continued to receive treatment. As stated in document B (page 129), "*UK RWE provides data on the proportion of patients receiving anti-VEGF treatment over time. However, there is no clear data on whether the patients that did not receive anti-VEGF treatment within a certain time period in fact permanently discontinued anti-VEGF treatment, or whether these patients simply did not receive an injection within that period of time but may have received injections at later time periods."* Therefore, it is assumed that all of the [redacted]% of patients that were insufficiently responsive to anti-VEGF remained on	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.

		treatment, but received treatment at the frequency observed in the UK RWE audit, which accounts for periods in which some patients may not have received any treatment with anti-VEGF.	
Section 2.3.1, Page 35 The ERG report states "*The ERG's clinical experts agreed this is a reasonable definition and the ERG notes that the definition of insufficient response used in the UK RWE audit was ≤5 letter gain or <20% reduction in central subfield thickness.*"	The company suggest removing the latter half of the sentence. "*The ERG's clinical experts agreed this is a reasonable definition and the ERG notes that the definition of insufficient response used in the UK RWE audit was ≤5 letter gain.*"	The company suggests amendments to this statement to clarify that the UK RWE audit results presented in the company submission use the ≤5 letter gain criteria only, unless otherwise specified.	The ERG has updated the text as suggested by the company.
Section 3.1, Page 38 The ERG report states "*a UK RWE audit of UK clinical practice that was commissioned by AbbVie to* [redacted]	The company suggests the following amendment, "*a UK RWE audit of UK clinical practice that was conducted to* [redacted]	AbbVie did not commission this study. It was conducted in collaboration with University Hospital Southampton.	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.

Issue 18 Incorrect data points

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 3.2.1, Table 12, Page 44 The ERG report states "…*and [redacted]% of phakic sham patients…*".	This should state "…*and [redacted]% of phakic sham patients…*".	The value presented is incorrect.	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company. The ERG notes that [redacted]% is also reported in Table 1 of the company response to clarification questions.

Issue 19 Incorrect cross-referencing

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 3.2.1, Page 41 The ERG report states "*Full details of the MEAD trials interventions and timings are provided in the CS Figure 4*."	This should state "*Full details of the MEAD trials interventions and timings are provided in the CS Figure 5*."	The cross reference is incorrect	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.
Section 3.2.1, Table 12, Page 43 The ERG report states "*Full baseline characteristics from the MEAD trials available in Appendix 8.2*."	This should state "*Full baseline characteristics from the MEAD trials available in Appendix 9.1.*"	The cross reference is incorrect	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.

Issue 20 Incorrect references

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.3.2, Page 84 Incorrect reference to TA681	Amend in-text references to TA681 to TA613.	TA681 is referred to in the text incorrectly which is misleading to readers.	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.

Issue 21 Spelling/typos

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 2.2.1, Page 25 The ERG report states "*The ERG's clinical experts reported that there <u>are is</u> no specific NICE guideline covering all available treatments for diabetic retinopathy and DMO*"	Remove word "are" This should state "*The ERG's clinical experts reported that there <u>is</u> no specific NICE guideline covering all available treatments for diabetic retinopathy and DMO*"	Editorial amendment	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.
Section 2.2.1, Page 25 The ERG report states "*although there is guidance for individual pharmacological <u>therapy's</u> such as dexamethasone*"	Spelling error "therapies" This should state "*although there is guidance for individual pharmacological <u>therapies</u> such as dexamethasone*"	Editorial amendment	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.

Section 3.2.1, Page 42 The ERG report states "*Additionally, the ERG considers it possible that vison in DEX700 patients …*"	Spelling error "vision" This should state "*Additionally, the ERG considers it possible that vision in DEX700 patients …*"	Editorial amendment	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.
Section 3.2.4, Page 48 The ERG report states "*…and [redacted] phakic eyes from [redacted] eyes …*"	Typing error This should state "*…and [redacted] phakic eyes from [redacted] patients …*"	Editorial amendment	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.
Section 3.2.4, Page 48 The ERG report states "*Similar to for the French RWD…*"	Remove word "for" This should state "*Similar to the French RWD…*"	Editorial amendment	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.
Section 3.7, Page 67 The ERG report states "*the ERG considers that the population of insufficient responders to non-corticosteroid treatments has different comparators to the population of insufficient responders to non-corticosteroids*."	Typing error This should state "*the ERG considers that the population of insufficient responders to non-corticosteroid treatments has different comparators to the population unsuitable for treatment with non-corticosteroids*."	Editorial amendment	The ERG thanks the company for highlighting the factual error and has updated the text as suggested by the company.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG comment
Section 4.2.5, Page 90	Starting age is marked as AIC, time horizon is not marked and neither is the age at end of time horizon (meaning starting age can be calculated). Request that age at end of time horizon is also marked so this remains AIC until published, whilst enabling the time horizon to remain visible.	The time horizon of the model is 40 years, which was considered to cover a lifetime. Based on a starting age of [redacted] years, patients would be [redacted] years old at the end of the time horizon.	The ERG thanks the company for highlighting the incorrect marking and has updated the marking as suggested by the company.
Section 4.2.13.1, Table 45, Page 126-127	Proportion of patients experiencing AE over 5-year treatment duration in the DEX700 arm from MEAD should be marked AIC until published	DEX700† [redacted]	The ERG thanks the company for highlighting the incorrect marking and has updated the marking as suggested by the company.

References

1. Boyer DS, Yoon YH, Belfort R, Jr., Bandello F, Maturi RK, Augustin AJ, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014;121(10):1904-14.
2. AbbVie. Allergan Ozurdex HTA Digital Advisory Board Interim Report. 2022.
3. Shah SU, Maturi RK. Therapeutic Options in Refractory Diabetic Macular Oedema. Drugs. 2017;77(5):481-92.
4. National Health Service. 2019/20 National Cost Collection data 2021 [Available from: https://www.england.nhs.uk/national-cost-collection/.
5. AbbVie. Long-term Follow Up of anti-VEGF use in Phakic Patients with Diabetic Macular Oedema: Real World Outcomes (Data on file). 2021.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **11 May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AbbVie Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Uncertainty around the generalisability of the results from the MEAD trials	No	The ERG notes uncertainty around the generalisability of the results from the MEAD trials. Whilst the company acknowledge there are differences between MEAD and current UK clinical practice, we believe that it represents the most appropriate source of evidence and that the impact of the differences is not likely to favour the efficacy of DEX700. The outcomes presented in MEAD can therefore be considered a conservative estimate of the absolute and relative efficacy of DEX700 arm. The conservative nature of the MEAD trial results for DEX700 were accepted in the previous appraisal (TA349), in which MEAD was considered appropriate evidence to support decision-making.[1] Further, several RWE studies published since the last appraisal (TA349) have also demonstrated superior outcomes for DEX700 compared to MEAD.[1] The majority of the published RWE studies presented in the company submission and below assess the efficacy of DEX700 in a pooled phakic and pseudophakic population, however several RWE studies have reported no significant differences in efficacy between the phakic and pseudophakic population.[2-6] All efficacy data from pooled phakic and pseudophakic RWE studies can therefore be deemed relevant and representative of the expected outcomes in a phakic-only population. Further detailed comparisons of the two populations are provided in Document B and the corresponding appendices.

		In particular, the ERG notes uncertainty around the generalisability of the results from the MEAD trials, due to: • Differences in the baseline characteristics of the patient population in MEAD compared with current clinical practice, and • The large imbalance between discontinuations for the DEX700 and sham treatment arms in MEAD, and the approach used to account for this missing data We address these points in turn below. **<u>Differences in baseline characteristics between MEAD and current clinical practice</u>** Although the MEAD trials provide key evidence for the efficacy and safety of DEX700 in phakic DMO patients (N = [redacted], 39 month follow-up), the company acknowledge that several of the patient baseline characteristics of the MEAD phakic population were not fully aligned with current UK practice. However, in many cases these likely contributed to poorer outcomes for DEX700 than may be expected in clinical practice. These were: • Proportion of patients receiving prior anti-VEGF therapy in MEAD was low • Proportion with cataract at baseline in MEAD was higher than expected in clinical practice • Baseline BCVA in MEAD was lower than expected in clinical practice The company acknowledge there was a high proportion of phakic patients who received prior laser treatment ([redacted]%), and a low proportion of phakic patients who received prior anti-VEGF treatment ([redacted]%) at baseline in the MEAD trials compared to current UK clinical practice.[7] The MEAD trials were conducted over 10 years ago (i.e. February 2005 to June 2012). A higher proportion of trial patients were therefore relying on the limited number of treatments established in clinical practice at that time, such as laser, given that the anti-VEGF service was not established in the UK until around 2015.

		Several published RWE studies have demonstrated the efficacy of DEX700 in DMO patients who have been previously treated with anti-VEGFs, in which the mean change in BCVA from baseline was generally superior to that reported by patients enrolled in the MEAD trials ([redacted] letters in the DEX700 arm). This therefore suggests the MEAD trial outcomes are a conservative estimate of the efficacy of DEX700 in the population of interest. Of note, these studies reported on DMO patients with a similar baseline BCVA to patients enrolled in the MEAD trials. RWE examples include: • Chatziralli et al. 2017* assessed the visual outcomes of DEX700 in DMO patients (N = 54).[8] At the 12 month follow-up, the mean change in BCVA from baseline (52.0 letters) was +5.2 letters, and 53.7% of patients showed an improvement in BCVA • Busch et al. 2019* was conducted to assess efficacy of DEX700 in DMO patients who switched to DEX700 following 3 initial anti-VEGF injections (Month 0 - Month 3).[9] The mean change in BCVA was +7.8 letters between Month 3 and Month 12, and +8.9 letters between Month 3 and Month 24 • Demir et al. 2020^ reported efficacy outcomes for DMO patients (N = 68) switching from anti-VEGFs to DEX700 after 3 or 6 consecutive months.[10] The mean BCVA at 6, 9, and 12 months was statistically better than baseline in the early-switch group (p = 0.011, p = 0.03 and p = 0.005, respectively). There was no significant difference in mean BCVA from baseline at 3, 9 and 12 months Furthermore, UK clinicians have confirmed there are a subset of DMO patients who do not respond to treatment with anti-VEGF, but do respond to DEX700 injections.[11] As well as inhibiting the expression of VEGF, corticosteroids have been shown to be effective on multiple inflammatory mediators, including preventing the release of prostaglandins – some of which identified as mediators of macular oedema.[12] When questioned about the difference, if any, in the efficacy of DEX700 between treatment-naïve patients and patients previously treated with either laser or anti-VEGFs, UK clinicians confirmed that they would expect the outcomes of DEX700 to be comparable. Several published RWE studies reported non-significant differences between treatment-naïve and previously treated DMO patients:

		• Mathis et al. 2020 reported that eyes previously treated by anti-VEGF treatment (n = 122) showed significantly poorer BCVA at baseline than treatment-naïve eyes (n = 105, p = 0.30).[5] However, BCVA gains remained non-significantly different between the 2 groups at each time points • Rosenblatt et al. 2019 reported that the mean change in BCVA was slightly better in treatment-naive eyes compared with the previously treated patients (8.1 ± 12.5 ETDRS letters vs. 6.2 ± 10.4 ETDRS letters, respectively), yet this difference was not statistically significant.[13] • Malcles et al. 2016 presented a subgroup analyses for treatment-naïve (n = 34) and previously treated eyes (n = 94).[4] Compared with previously treated patients, treatment-naïve eyes seemed to have a greater improvement in BCVA (mean recovery 6.6 vs. 3.5 letters at Month 12 [P = 0.41], 6.8 vs. 4.5 letters at Month 24 [P = 0.68], and 18 vs. 7.8 letters at Month 36 [P = 0.40]), but these differences were not statistically significant To support these findings, a post-hoc exploratory analysis was conducted to investigate the impact of prior treatment on the visual outcomes of phakic DMO patients in MEAD. Overall, DEX700 appears to have similar outcomes in previously treated and treatment-naive patients (Document B, Figure 17). Furthermore, subgroup analyses of MEAD trials demonstrated that the proportion of previously treated patients experiencing ≥15 letter was similar to the overall MEAD study cohort.[14] Clinical opinion also indicated that duration of DMO, and non-response to prior treatment, are more likely to be treatment effect modifiers than the prior treatment itself.[11] The company also acknowledge a higher proportion of phakic patients in the DEX700 arm of the MEAD trial ([redacted]%) had cataracts at baseline compared to the UK RWE audit ([redacted]%).[7, 15] The visual acuity improvements in MEAD are limited by the presence of cataracts in phakic patients awaiting extraction, as described in document B. Patients who underwent cataract surgery during MEAD experienced [redacted] visual acuity between 18–30 months but had better outcomes by the end of the trial than those patients who did not receive surgery. This is likely due to the recovery of vision following the cataract surgery for those who underwent surgery during the study. Those who did not

		have cataract surgery during the study would have their visual outcomes impacted by the presence of cataract. Moreover, patients who have a shorter gap between cataract development and surgery do not experience as much of a decline in their BCVA from baseline.[16] The time between cataract progression and the cataract extraction is longer in the MEAD trials compared to what is now expected in current UK clinical practice.[17] An adjusted analysis of the phakic-only mITT patients of the MEAD trials was conducted to assess the subgroup of patients with a shorter time to cataract extraction. In patients who underwent cataract extraction within 6 months of cataract development, the mean change in BCVA was greater in the DEX700 arm compared to the sham arm at 39 months (+[redacted] letters versus +[redacted] letters, respectively; p = [redacted]). Therefore, if timing of cataract progression and treatment is more aligned with what is expected in clinical practice, outcomes for DEX700 can be expected to be improved compared with that observed in the MEAD mITT phakic-only population. Finally, the company acknowledges that the baseline BCVA in the DEX700 arm of MEAD is lower than that expected in UK clinical practice for phakic DMO patients, as demonstrated by the best-reported visual acuity (BRVA) in the UK RWE audit ([redacted] versus [redacted], respectively). Several published RWE studies report on the efficacy of DEX700 in patients with a similar baseline BCVA to MEAD (i.e. [redacted] letters in the DEX700 arm) and consistently show superior outcomes for DEX700 compared with MEAD, therefore suggesting MEAD presents a conservative estimate of the efficacy of DEX700: • Chatziralli et al. 2017* - as previously described • Demir et al. 2020^ - as previously described • Busch et al. 2019* conducted a trial to assess efficacy of DEX700 in DMO patients (N = 105) who switched to DEX700 following 3 initial anti-VEGF injections (Month 0 - Month 3).[9] From a baseline VA of LogMAR 0.57, the mean change in BCVA was +7.8 letters between Month 3 and Month 12, and +8.9 letters between Month 3 and Month 24

		• Malcles et al. 2017* conducted a trial to assess the efficacy of DEX700 in DMO patients (N = 89).[4] The mean change in BCVA from baseline (50.2 letters) was +3.6 letters at Month 2 (p = 0.005), +4.2 letters at Month 12 (p = 0.006), 5.3 at Month 24 (p = 0.007), and 9.5 letters at Month 36 (p = 0.023). The proportion of eyes achieving at least a 15-letter improvement from baseline was 25.4% at Month 36 • Mathis et al. 2020* assessed the efficacy of DEX700 in DMO patients (N = 152) over an extended 5-year follow-up.[5] The mean duration of follow-up was 20.1 months. The mean change in VA from baseline (51.4 letters) was +5.7 letters at Month 2 (p < 0.001), 3.2 letters at Month 12 (p < 0.001), 5.1 letters at Month 24 (p < 0.001), 6.8 letters at Month 36 (p < 0.001), 15.0 letters at Month 48 (p < 0.001), and 14.7 letters at Month 60 (p = 0.012). These functional results remain significant when considering only patients with more than 3 years of follow-up (n = 37) • Guigou et al. 2015* assessed the efficacy of DEX700 in DMO patients (N = 152) over a 6-month follow-up.[2] The mean BCVA increased from a baseline of 53.9 letters by + 5.3 letters at Month 1, reached a steady phase between Month 2 (+ 7.6 letters) and Month 4 (+ 8 letters), and then decreased again gradually until Month 6 (+ 6.2 letters; P < 0.001 at all time points) • Kaldirim et al. 2020* was conducted to assess the efficacy of DEX700 in DMO patients (N = 79) who had an inadequate response to prior therapy over a 6 month period.[3] In the phakic subgroup, mean BCVA improved from 0.58 logMAR at baseline to 0.29 at Month 1, 0.30 at Month 3, and 0.34 at Month 6. BCVA significantly improved in both the phakic and pseudophakic groups (p < 0.001) • Mello Filho et al. 2019* assessed the efficacy of DEX700 in DMO patients (N = 282).[6] The median BCVA was 50 letters at baseline and 70 letters after treatment (p < 0.001). A gain of ≥ 15 letters was registered for 59 (59.0%) of 100 phakic eyes with available data, 9 (45.0%) of 20 phakic eyes with cataract, and 86 (53.7%) of 160 pseudophakic eyes • Menezo et al. 2019* assessed the efficacy of DEX700 in treatment-naïve DMO patients (N = 50).[18] From a baseline of 52.4 letters, the mean change in BCVA improved significantly to 62.6 letters at Month 2, 61.2 letters at Month 4, 61.6 letters at Month 6, 60.6 at Month 12 (p = 0.0008)

		• Pinto et al. 2021* also assessed the efficacy of DEX700 in treatment-naïve DMO patients (N = 107).[19] From a baseline BCVA of 54 letters, the mean change in BCVA was + 7.3 letters at Month 2 (n = 97), + 4.9 letters at Month 8 (n = 59), + 4.7 letters at Month 12 (n = 48), and + 7.0 letters at Month 24 (n = 25) Furthermore, a published review of real-world observational studies was conducted to identify all articles investigating the efficacy of anti-VEGFs (ranibizumab, aflibercept and bevacizumab) and DEX700 in DMO patients between 2005 and 2016, each of which primarily reporting on the change in VA from baseline.[20] Subgroup analyses of DMO patients with the lowest baseline visual acuity (i.e. < 50 letters) demonstrated a notable difference in gain of visual acuity from baseline between the anti-VEGF studies (+4.3 letters) and the DEX700 studies (+10.5 letters), although the baseline visual acuity was relatively similar (anti-VEGFs, 42.4 letters; DEX700 39.4 letters). The greatest difference in mean change between DEX700 studies and anti-VEGF studies was however seen in the subgroup of patients with baseline visual acuity of > 60 letters, with a mean gain of 3.1 letters in the anti-VEGF studies, and 8.8 letters in the DEX700 studies, resulting in a mean final visual acuity of 65.3 letters and 68.4 letters, respectively. This therefore supports that, even if there is a possibility of a ceiling effect, the mean visual acuity gain seen following treatment with DEX700 is not only due to the lower mean baseline visual acuity, but also persists in a subgroup of patients with a higher baseline visual acuity. Therefore, as the baseline characteristics in the MEAD trials tend to be poorer than those observed in UK clinical practice, the MEAD trial can be considered to underestimate the efficacy of DEX700 in phakic patients and therefore provides a conservative estimate of the efficacy of DEX700 in the population of interest. In addition to this, the use of the MEAD sham arm as a proxy for continued anti-VEGF use also likely overestimates the efficacy of continued anti-VEGF use in patients deemed to be insufficiently responsive to anti-VEGF treatment versus observed RWE in the UK and therefore underestimates the expected relative difference between DEX700 and continued use of anti-VEGF therapy in insufficient responders.

Several sources of evidence were provided in Document B to demonstrate the poor efficacy of the continued use of anti-VEGFs in real-world practice. The UK RWE audit confirmed that patients who continued to receive anti-VEGF treatment failed to demonstrate a notable improvement in the patients' BCVA; of the [redacted] eyes ([redacted] patients) enrolled, [redacted]% of eyes were insufficiently responding to treatment at 6 months. When comparing to the sham arm of the phakic-only mITT MEAD population, the mean BCVA change from baseline was consistently higher than in insufficient responders in the UK RWE audit (Table 1). Furthermore, when comparing the MEAD sham arm to the UK RWE audit, the proportion of phakic DMO patients with an improvement of ≥ 15 letters was considerably higher at 12 months ([redacted]% versus [redacted]%, respectively) and 24 months ([redacted]% versus [redacted]%, respectively), whereas the proportion of patients with a ≥ 15 letter loss was similar also at 12 months ([redacted]% versus [redacted]%, respectively) and 24 months ([redacted]% versus [redacted]%, respectively). This therefore suggests that on average the sham arm performs better than continued use of anti-VEGF per the UK RWE audit. Please refer to the ERG clarification letter response (A14; Figure 1) for further details.

Table 1: Mean change in BCVA from baseline for the sham arm of MEAD (phakic-only mITT) versus UK RWE audit

Mean change in BCVA from baseline	MEAD Sham arm (n = [redacted]	UK RWE audit (n = [redacted]; insufficient responders)
Month 3	[redacted]	[redacted]
Month 6	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
Month 36	[redacted]	[redacted]

Key: BCVA, best-corrected visual acuity; ITT, intention-to-treat; mITT, modified intention-to-treat.
Source: MEAD (2022)[21]

		Formal indirect treatment comparisons were explored for MEAD compared to published RWE studies, the UK RWE audit and French RWD study, but results were ultimately shown to be inconclusive and unfeasible, mainly driven by differences in baseline BCVA across evidence sources and lack of available data on treatment effect modifiers and prognostic variables in the comparator evidence. The comparability of data sources for these analyses is also uncertain due to limitations with comparing RCT data to RWE. **Imbalance in discontinuation rates between the DEX700 and sham arms of MEAD** The company acknowledge that there is an imbalance in the proportion of patients discontinuing in the DEX700 and sham arms of the MEAD trial. In the phakic-only mITT population of MEAD, [redacted]% of patients in the sham arm were discontinued (primarily due to lack of efficacy or receipt of rescue therapy), compared to [redacted]% in the DEX700 arm (where the majority of discontinuations were due to adverse events).[22] The ERG notes that the natural history of DMO is to decline, and therefore assuming no change in BCVA for patients with missing data is optimistic. The ERG is therefore concerned that the LOCF approach biases both the sham and DEX700 arms and considers it difficult to predict the direction of the bias. Whilst we acknowledge the LOCF approach is limited, and may introduce bias, we note that LOCF was used to handle missing data in the primary analysis of the MEAD visual acuity outcomes. Therefore, all data that have been presented in the company submission and that have fed through into the cost-effectiveness model have consistently adopted this approach throughout this appraisal and throughout the previous appraisal TA349[1] (in which a similar level of missing data were also present and in which the MEAD analyses were deemed suitable to inform decision-making). A far larger number of sham patients went on to receive rescue therapy ([redacted]) or were discontinued due to lack (or loss) of efficacy ([redacted]), compared with DEX700 patients ([redacted]% and [redacted]% respectively). Rescue therapy is typically offered to patients who experience poor outcomes on their

		existing treatment regimen, and by definition patients who discontinued due to lack (or loss) of efficacy had lost more than 15 letters from baseline. Therefore, any approach for handling these missing data will be limited as the data are not missing at random; we can expect that the vision would decline further however the magnitude of this decline is unknown and cannot be modelled. Given the higher proportion of discontinuations for these reasons on the sham arm, any bias is likely to favour the sham arm, and therefore the relative difference between the DEX700 arm and the sham arm is under-estimated. Given that the sham arm is used as a conservative proxy for the efficacy of continued use of anti-VEGF, as outlined above the relative efficacy between DEX700 and anti-VEGF is therefore also under-estimated. *Please note that these published RWE studies assess efficacy of DEX700 patients in a pooled phakic and pseudophakic population. ^Please note that this published RWE study did not report the proportion of phakic versus pseudophakic DMO patients enrolled in the trial.
Time horizon considered for the economic analysis	No	The company base-case adopts a lifetime time horizon ([redacted] years based on a MEAD starting age of [redacted]), consistent with NICE TA613 and TA346. The NICE health technology evaluations manual states that the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.[23] A lifetime horizon is required to ensure all relevant downstream benefits and costs are captured following discontinuation from treatment. The ERG instead applies a 10-year time horizon in their revised base-case based on three core justifications. One justification is precedent from previous NICE appraisals in DMO, with the ERG citing the ranibizumab appraisal (TA274) which adopted a 10-year time horizon in the final base case. However, this 10-year time horizon represents the shortest time horizon that has been adopted across all of the previous appraisals. NICE TA613, TA346 and NG82, all adopted a lifetime horizon. Indeed, a lifetime horizon (30 years) was accepted in the most recent appraisal in DMO which was the re-appraisal of fluocinolone acetonide (NICE TA613). This appraisal considered a similar patient population to the one of interest for this appraisal and utilised primary trial evidence with three years of follow-up. Despite a shorter time horizon being adopted in the original appraisal (TA301) a lifetime

		horizon was accepted in TA613. In TA346 a lifetime horizon (35 years) was also used in the base case analysis despite utilizing data of a similar maturity to MEAD. The NG82 wet AMD guideline model also assumed a lifetime horizon based on 2 years of comparative efficacy data, which is shorter than the follow-up of MEAD. Therefore, the ERG adopts the shortest time horizon utilised in past appraisals which leads to overly pessimistic base case results. A second justification provided by the ERG for assuming a 10-year time horizon is the claim that there is an absence of data on treatment effect waning. However, in the company base-case analysis, no further treatment effect is assumed after the 5-year treatment duration, as the same natural history estimates for the proportion of patients whose vision improves and worsens at each time point are applied equally between the treatment arms. Therefore, it could be argued that treatment effect waning is applied from 5 years, as although the absolute change in BCVA outcomes does not become equalised at this point in time, the rates of improvement and worsening vision are set to be equal. Using survival modelling for an oncology NICE appraisal as a comparative example, this approach would be akin to setting the hazards for the survival curves to be equal between the treatment arms at cessation of treatment, which in this setting would be interpreted as an application of treatment effect waning. The final justification provided by the ERG for assuming a 10-year time horizon is that the ERG's clinical experts fed back that they would expect visual acuity across all treatments to converge over time during the off-treatment period. However, in the company's base-case analysis outcomes do converge over time. This is demonstrated by the figure that was presented by the ERG (ERG report, figure 8) which shows that although the mean change in BCVA is never equal between the treatment arms, the absolute difference between the treatment arms does decline over time. This is because as patients experience natural history transition probabilities, there is a higher probability of worsening vision than improving vision and so over time, patients will tend towards the worst vision-related health state. This occurs faster in the anti-VEGF arm due to the lower BCVA at the end of the treatment period, but eventually more and more patients in the DEX700 arm also reach this state. Therefore, the company's base-case approach is already consistent with the feedback from clinicians.

		Further feedback elicited from multiple UK clinical experts during technical engagement does align with the ERGs clinical expert's assertion that there would be some convergence over time, but the clinicians noted there was considerable uncertainty regarding the form this would take.[11] In a separate consultation with a UK clinician, the expert also highlighted that although there would likely be no ongoing treatment effect after discontinuation, there was no reason to expect the rate of improvement and worsening would be different between a patient who received DEX700 and a patient who received anti-VEGFs, from the point of discontinuation. We accept that there is uncertainty in the long-term visual acuity outcomes. However, we believe our approach of using data from MEAD, which is considered to underestimate the outcomes for DEX700 patients and to overestimate the outcomes for anti-VEGF patients, to model to the treatment period and then applying the same natural history data across the arms is already conservative and therefore helps to mitigate against the uncertainty. We consider the ERGs assumption to be extreme and therefore we do not believe this scenario represents the most appropriate base-case assumption that best captures long-term outcomes. The ERG's approach uses an extreme and arbitrary cut-off point in the time horizon, and is therefore considered to be a simplified assumption that is not clinically justified, is not consistent with recent precedent in DMO or other ophthalmology indications and results in outcomes that are extremely pessimistic.
Changes in BCVA resulting from DEX700 treatment in Years 4 and 5	No	The company base-case used data from MEAD to inform the transitions between health states for DEX700 over the assumed treatment duration of 5 years. As noted in the company submission and in response to key issue 1, the outcomes from MEAD are considered to represent an underestimate the efficacy of DEX700 and overestimate the efficacy of anti-VEGFs that would be observed in clinical practice, and therefore use of MEAD for the base-case analysis results in modelled outcomes for DEX700 which are considered to be conservative. The data from MEAD demonstrate that treatment with DEX700 resulted in significant improvements in visual acuity outcomes in the phakic population initially, but the development of cataract requiring

		extraction resulted in patients experiencing poorer outcomes, with visual acuity scores decreasing as the number of patients with cataracts increased. Clinical expert opinion has consistently stated that this significant decline in visual acuity due to cataract development does not occur in clinical practice as treatment practices have evolved since the MEAD study. Firstly, UK clinicians have stated that they will perform cataract surgery more proactively upon cataract development, which helps halt the decline in visual acuity over time. Secondly, patients are now treated with a DEX700 injection just prior to cataract surgery, which ensures the adequate control of postoperative inflammation and prevents deterioration of macular oedema. In the RELDEX trial for example, no visual impairment was experienced in the months after cataract surgery, with patients in this study treated with DEX700 one month prior to their cataract surgery.[4] Instead in this trial the BCVA showed a trend of continued improvement throughout the study duration. In contrast, in MEAD, the mean time between the last DEX700 injection and cataract surgery in the mITT population was [redacted] months, with exploratory analyses presented in the company submission (Figure 14, Document B) demonstrating that patients who received DEX700 at their last visit before cataract surgery experienced better outcomes than patients who did not receive DEX700 at the last visit prior to surgery. Therefore, the assumed changes in visual acuity outcomes over the treatment period in the company base-case analysis include a decline in outcomes that is not expected to occur in reality. In the absence of data in years 4 and 5 from MEAD, assumptions are required regarding how the trend in visual acuity will continue to change. The company base-case utilises the last set of observed transition probabilities from the trial for several reasons. Firstly, there is a clear and well-established upward trend in visual acuity outcomes from the end of MEAD, which is likely driven by two factors. The first is that by the end of year 3 [redacted] of patients are still receiving treatment with DEX700, and therefore, it is considered reasonable to assume that these patients are still benefiting from treatment. In addition, in response to key issue 3, we have updated the costing assumptions in our revised base-case to assume the number of DEX700 injections administered in year 3 of MEAD is applied in year 4 and 5, i.e., the patients will continue to receive the same number of injections in year 4 and 5 as in year 3. Increasing the number of injections patients are assumed to receive ([redacted] per year instead of

		1.0) aligns with the ERG's base-case and helps mitigate against uncertainty by more closely aligning treatment costs with the assumptions related to efficacy. The second factor causing an upward trend in visual acuity outcomes is the fact that the decline in visual acuity outcomes was driven by the development of cataract, and therefore the loss in vision is expected to be temporary, with improvements observed once the cataract is resolved through surgery. As presented in Figure 15 of Document B, [redacted] of DEX700 patients had developed cataract but had not had cataract surgery during the MEAD study duration and it could be expected that they would have receive their cataract extraction during Year 4 or Year 5 of treatment, had the study continued. Therefore, the model is not assuming a sizeable treatment effect from DEX700 in years 4 and 5 but is instead capturing the recovery in vision from the resolution of cataract, using the Month 33-Month 36 transition probability matrix to approximate this. By artificially capping the benefit at year 3, the ERG is preventing the benefit from the observed trend from being realised which is an extreme and pessimistic assumption, particularly when coupled with the evidence that the MEAD data provide a conservative estimate of the efficacy of DEX700. The recovery in vision attributed to the resolution of cataract is made clear in exploratory analyses that were conducted using data from MEAD. Figure 1 demonstrates that patients who underwent cataract surgery at earlier timepoints in the trial fully recovered the initial gains in visual acuity outcomes that they had initially made after receiving treatment with DEX700. It is noted in the ERG report that: *"The ERG and its clinical experts consider that in the absence of any evidence to substantiate improvements in vision in Years 4 and 5, assuming vision is maintained is more appropriate, if, conservative".* However, the exploratory analyses from MEAD highlight the potential for this upward trend in visual acuity outcomes observed towards the end of MEAD to continue as those who had their cataracts removed later would, with continued treatment, continue to recover their vision beyond the end of the study. There is also supportive data from the published literature that demonstrates that treatment with DEX700 results in a strong and continued treatment effect, with one study demonstrating a benefit up to five years.[4, 5]

		Figure 1: Change in mean BCVA from MEAD stratified by the timing of cataract surgery from the start of the trial  **Key:** BCVA, best corrected visual acuity. Source: AbbVie, 2022 (MEAD post-hoc exploratory analyses).[24] Additionally, the extrapolated mean change in BCVA in the company base-case analysis does not implicitly assume that patients fully recover the initial gains in visual acuity that were achieved prior to the development of cataract. As a figure that was presented by the ERG (ERG report, figure 8), demonstrates, the assumptions made in years 4 and 5 lead to visual acuity outcomes improving in those years, but by the end of year 5 the outcomes do not match or exceed the improvement in visual acuity that was observed in the first year in MEAD.

		The ERG's alternative base-case approach, which is to hold vision constant in years 4 and 5, is considered to lack clinical plausibility and face validity. Firstly, the ERG's base-case assumptions result in negative incremental QALYs, which means that anti-VEGFs are considered to provide more benefit to patients than DEX700 in a patient population who are insufficiently responsive to anti-VEGF treatment. We acknowledge that there is uncertainty regarding the magnitude of benefit that DEX700 could provide relative to anti-VEGFs in this patient group, but the assumption that DEX700 is less effective contradicts evidence from MEAD, the published literature (that consistently shows superior outcomes for DEX700 compared with MEAD) and clinical expert opinion. Secondly, even in the most extreme scenario where DEX700 yielded no additional benefit to patients in Year 4 and Year 5 for those still receiving treatment or those who have discontinued, we would still expect to observe some improvements in visual acuity solely from the resolution of cataracts post-surgery which is not captured in the ERG's base-case analysis. Thirdly, we do not believe it reasonable to resolve the uncertainty attributed to a lack of follow-up data that extends beyond year 3 by assuming no additional benefit after the trial period. This type of uncertainty is observed across all NICE appraisals in all disease areas and is remedied by trying to identify the most plausible extrapolation based on an assessment of the trend in the observed data, data from the published literature and clinical expectations, rather than artificially capping the treatment effect at the end of the trial duration. If we consider the case of an appraisal in oncology, it is highly unlikely to be considered clinically plausible that the hazard of disease progression or death would immediately change to one assuming no treatment effect at the end of the trial period, especially if the patients were assumed to continue to receive treatment. We believe it is clinically implausible to make a similar assumption here and this is supported by clinical expert opinion as described in the response to key issue 2. We believe the ERG's base-case analysis is a reasonable extreme scenario analysis to explore to show how the results are impacted when applying extreme pessimistic assumptions regarding the treatment effect, and therefore we presented this analysis in response to ERG clarification question B7. However, we do not believe this scenario represents the most plausible base-case extrapolation that best reflects the trends in the observed trial data, the data from the published literature and clinical expert opinion. We therefore retain our assumption that the last transition probability matrix

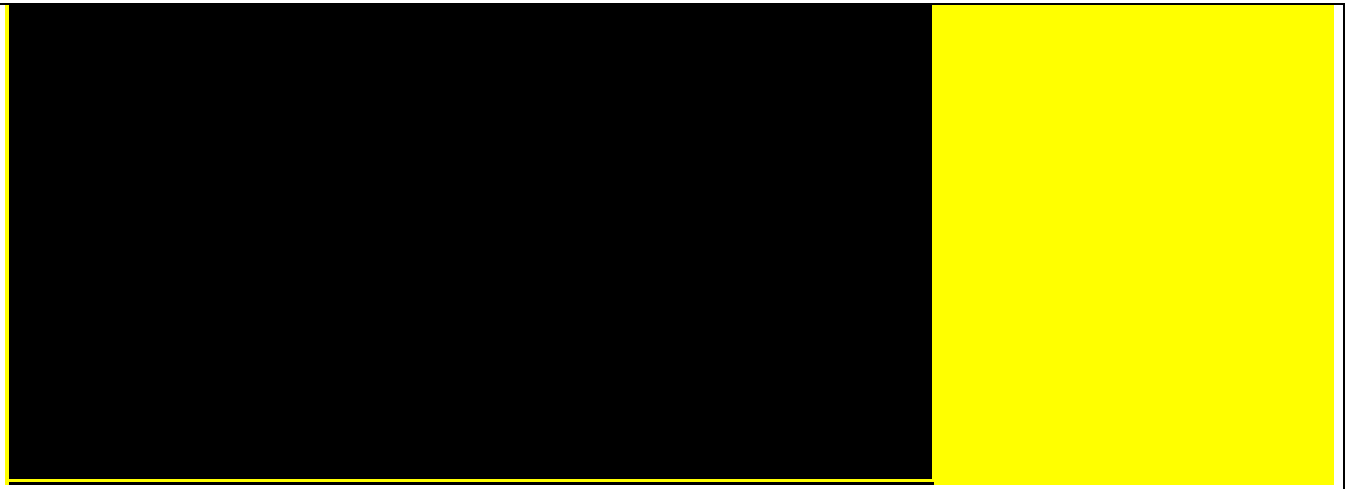
		from MEAD can be applied in each 3-month cycle during Years 4 and 5 for those who continue to receive DEX700.
Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5	No	The ERG makes the assumption in their revised base-case analysis that patients receiving anti-VEGFs experience no changes in vision (with certainty) for the 5 years for which they receive treatment, while for DEX700 they still utilise the full set of transition probabilities estimated from MEAD that allow unrestricted movement between health states over the same period of time. However, we believe these assumptions contradict both clinical expert opinion and the available data in this population, and therefore introduce significant bias into the analysis. Firstly, the assumption that patients receiving continued anti-VEGFs despite insufficient response would experience no changes in vision for the duration of treatment contradicts both UK clinical expert opinion and what is observed in the UK RWE data that has been collected. These data demonstrate that a proportion of patients will experience some improvement in visual acuity, while another proportion will experience some worsening of vision, but on an aggregate level there will be little difference in the overall mean change in BCVA. Therefore, the ERG's approach does not account for the fact that individual patients within the cohort in the UK RWE experienced gains and losses of letters. For example, in the response to ERG clarification question B9 we provided the data on the proportion of patients in the UK RWE who gained and lost at least 10 letters from baseline to month 12, month 12 to month 24 and month 24 to month 36 (presented in Table 2). These data demonstrated that a meaningful proportion of patients experienced changing vision throughout the study and that a higher proportion of patients lost at least 10 letters ([redacted]) than gained at least 10 letters ([redacted]) at each timepoint. At the same time Figure 2 demonstrates that on an aggregate level the overall mean change in BCVA is minimal. The ERG note that they are concerned that the baseline for the UK RWE study is the start of anti-VEGF treatment and thus does not reflect the insufficiently responsive to non-corticosteroid treatment population that the company is modelling. However, these data demonstrate that a greater proportion of patients experience worsening of their vision than improvement at every time point and therefore later years capture the changes in vision after patients were deemed insufficiently responsive to anti-VEGFs, and show the same trend as observed in Year 1. The ERG's base-case assumes that in the cohort of patients receiving anti-VEGF

therapies, no patient experiences a gain or loss of at least 10 letters, with no uncertainty, which is not clinically plausible based on the evidence from the UK RWE study. We therefore believe that our base case assumption which uses the sham arm of MEAD is a more appropriate yet conservative proxy for the efficacy of continued anti-VEGFs in insufficient responders as this allows us to model the individual variations in vision losses and gains, whilst on average resulting in a small gain in vision.

Table 2: >=10-letter improvement/worsening over time UK RWE [ERG clarification letter Figure 12]

Criteria	Proportion of patients			3-month probability		
	Baseline to Month 12	Month 12 to Month 24	Month 24 to Month 36	Baseline to Month 12	Month 12 to Month 24	Month 24 to Month 36
>=10-letter improving						
>=10-letter worsening						

Figure 2: Comparison of mean change from baseline BRVA over time from the UK RWE [Document B, Figure 10]

		 **Key**: BRVA, best recorded visual acuity Secondly, the ERG's approach results in significant bias related to the costs associated with severe vision loss. In the company base-case analysis, patients on both the DEX700 and anti-VEGF treatment arms could transition to the most severe vision related health state and incur costs associated with the management of severe vision loss. A slightly greater proportion of patients in the DEX700 arm transitioned into this health state relative to the sham arm in MEAD given the higher rate of cataract development, and although we do not expect to see as many patients transition to this health state in clinical practice as patients with cataract will undergo surgery more promptly than they did in MEAD, these additional costs were still added to the DEX700 arm to ensure the analysis is conservative. The ERG's approach assumes patients receiving anti-VEGF remain in their baseline health state for the duration of treatment (of note, very few patients were occupying the most severe health state based on the patients enrolled in the MEAD studies). By artificially stopping patients on the anti-VEGF arm from transitioning to the most severe health state, not only are the severe vision

		loss costs associated with DEX700 higher than would be expected in clinical practice, but the costs on the anti-VEGF arm are also now significantly lower. In light of these issues, we presented scenario analyses in the company submission and in response to ERG clarification questions. The first scenario was presented in the original company submission and assumed a net-zero impact on vision where it is assumed that, on average, patients in the anti-VEGF arm maintain constant vision. This scenario assumes 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%, consistent with the probability of gaining at least 10 letters from the natural history study data from Mitchell et al. (2012).[25] We believe that this scenario is more realistic than assuming no movement up or down health states, as it is unlikely that vision would remain constant for every individual patient over time. To complement this, we now provide an additional scenario analysis in the technical engagement response, which assumes a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.0%, which is consistent with the estimates applied in the NICE TA274 appraisal where they modelled a period of stable vision during the on-treatment period.[26] When exploring these scenarios, a restricted set of MEAD transition probabilities was applied to the DEX700 arm, whereby the transitions were restricted to a maximum of one health state improvement or worsening to ensure there was consistency in the approach between the two treatment arms. The ERG correctly noted that use of a restricted set of transition probabilities is associated with limitations, but for the purposes of this scenario analysis this is required to ensure a consistent approach between the arms to minimise the risk of bias. The ERG also raised concerns that this scenario did not result in an increase in the incremental QALY gains as would be expected given that sham patients from MEAD experienced a small overall improvement in mean BCVA. However, we believe that this is due to the exclusion of extreme changes in BCVA from the ERG analysis, that are allowed when modelling using the sham arm of MEAD. It is feasible that two populations with very different BCVA distribution could have the same resulting mean BCVA, but result in a different range of utility

		values, and therefore different QALY outcomes. The ERG's alternative approach also does not address this issue, and actually causes the incremental QALYs to go further in the direction we were not expecting a priori. In addition, another scenario was presented in response to ERG clarification question B5, assuming no movement up or down health states within the anti-VEGF arm but excluding severe vision loss costs in both treatment arms to reduce the risk of bias. Although neither of these scenarios are considered more appropriate than those made in the company's base-case, they are both considered to be associated with less bias than the ERG's base-case analysis, and in both analyses DEX700 remained dominant. We do not believe this scenario represents the most plausible base-case, and believe the assumptions made are extreme, overly simplified, and highly biased against DEX700, in addition to being clinically implausible.
Subsequent treatment following discontinuation of DEX700	No	The ERG has highlighted that the UK clinical feedback they have received indicated that patients who are insufficient responders to anti-VEGF and then receive treatment DEX700 would likely be offered re-treatment with an anti-VEGF in UK clinical practice for a short period of time, despite the fact the clinicians also highlighted this would likely ineffective. In response to ERG clarification B18, a scenario analysis was presented assuming that 100% of patients would receive subsequent anti-VEGF treatment for 1 year following cessation of treatment with DEX700, as the feedback indicated that any patient who would receive subsequent treatment would only receive this for a short period of time. This scenario has subsequently been adopted in the ERG's revised base-case analysis. It has been highlighted in the response to key issue 2 that the ERG's base-case assumptions result in negative incremental QALYs which lacks face validity, as this means that anti-VEGFs are considered to provide more benefit to patients than DEX700 in a patient population who are insufficiently responsive to anti-VEGF treatment when there is a large body of evidence in MEAD, RWE and clinical opinion that indicates DEX700 to be an effective treatment option. This issue of face validity is then further exacerbated if subsequent therapy costs are then added on to the DEX700 arm, as this

		would then mean that patients with access to treatment with DEX700, followed by subsequent treatment with anti-VEGFs would experience worse visual acuity outcomes than patients who only have access to anti-VEGFs alone. This further highlights the implausibility of the ERG's choice of base case assumptions. Based on the ERG's feedback, we further consulted with UK clinical experts who confirmed that some patients would likely receive anti-VEGF again following discontinuation from DEX700 in the absence of other options. We therefore accept that there could be a proportion of patients who would receive subsequent treatment with anti-VEGFs following DEX700. However, the feedback received also highlighted again that this treatment would be given for a short period of time and would likely be ineffective, consistent with the ERG's clinical expert opinion. The UK clinical experts we consulted also indicated that not all patients would receive treatment, estimating that approximately 80% of patients who discontinue DEX700 would likely receive subsequent treatment. Therefore, the company's base-case analysis has been updated to reflect this, assuming 80% of patients who discontinue treatment with DEX700 will receive subsequent anti-VEGFs for 1 year. A one-off cost has been estimated, assuming 5.0 injections would be administered, consistent with the number assumed to be administered in Year 1 for patients on the anti-VEGF arm in the company's revised base-case, giving an additional one-off cost of £4,009.85 for DEX700 patients. However, as is noted in the ERG report, there is no evidence that could inform the efficacy of subsequent treatment in patients who have received prior DEX700, and therefore although these costs have been included in the revised base-case, no changes have been made to the efficacy assumptions for the DEX700 arm, creating a mis-match between costs and efficacy that may bias against DEX700.
The natural history of vision in eyes with DMO	No	The transition probabilities representing natural history of vision in DMO that were applied in the company's original base-case analysis were sourced from Mitchell et al. 2012[25] consistent with the original DEX700 appraisal (TA349).[27] These transition probabilities were applied across both treatment arms following the initial five-year treatment period. The Mitchell et al. 2012[25] study used data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), adjusted to account for the improvement in diabetes mellitus 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%. The ERG has flagged several limitations with the WESDR data including that the estimates were based on a population with diabetic retinopathy that may not have had DMO (i.e., WESDR may be less severe) and that the ERG's clinical experts considered the 3-month probability of gaining 10 letters of 3.5% to be too high. The ERG has therefore adopted the scenario analysis that was presented in the company submission where the natural history estimates were instead aligned with the fluocinolone acetonide appraisal (TA613)[28], assuming a 3-month probability of gaining or losing at least 10 letters of BCVA of 0% or 3.5%, in their base-case analysis, however the ERG also notes that it is not fully clear where these estimates were derived from. We have therefore conducted a detailed review to try and fully understand the source of the natural history data used in TA613 in order to assess the quality and appropriateness of the study compared with Mitchell et al. 2012[25], and determine whether this provides a more relevant source of evidence. It appears that this data is taken from the ranibizumab appraisal (TA274)[26], however, after a review of this appraisal, no reference appears to be made to these estimates throughout the submission, and instead a 3-month probability of gaining or losing at least 10 letters of BCVA of 2.5% or 3.5% is referenced. Therefore, it is not clear what, if anything, the estimate of 0% improvement in TA613 is based on. The ERG has highlighted that one of issues with the probabilities from Mitchell et al. 2012[25] is that the 3.5% probability of improvement may be too high. However, similar to the argument presented in response to key issue 4, the assumption that no patient would experience any improvement in vision lacks clinical plausibility and is not consistent with what was observed in the WESDR study, what was accepted in TA274, and also data from the sham arm from MEAD and the UK RWE. Therefore, the assumption adopted in the ranibizumab appraisal may have greater clinical plausibility, while also addressing the concern raised by the ERG's clinical expert that the probability of 3.5% may be too high. Therefore, the company's revised base-case assumes a 3-month probability of gaining or losing at least 10 letters of BCVA of 2.5% or 3.5%.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Cataract rates for anti-VEGF patients	Section 4.2.10.1, pages 115-118	No	In the company submission, cataract extraction rates for patients receiving anti-VEGF were taken from the UK RWE audit[15], and cataract extraction rates for patients no longer receiving treatment (on either treatment arm) were taken from the Blue Mountain Eye Study.[29] The ERG has received clinical advice that indicates the rate of cataract extraction would not be expected to differ in patients receiving anti-VEGF treatment compared with patients receiving no treatment, and consider the UK RWE audit to be a superior source to the Blue Mountains Eye Study as the UK RWE audit provides more recent data in the population of interest. However, despite the UK RWE audit being considered a relevant source, the ERG prefers to use the sham arm of MEAD to represent the rate of cataract extraction for patients receiving anti-VEGF treatment, and for patients receiving no treatment (i.e., natural history), citing precedent from TA613 which used the sham arm of FAME to represent anti-VEGF cataract extraction rates. The ERG also prefers to use a single annual risk,

			assuming an exponential cumulative distribution function (CDF), in all years of the model, rather than modelling the data over each year of the study. We accept that there is limited evidence to indicate that the risk of cataract extraction would differ between patients receiving anti-VEGF treatment compared with patients receiving no treatment and therefore accept the ERG's assumption that the risk of cataract extraction for anti-VEGF would be equal to that of no treatment and we therefore adopt this approach within our revised base case. We believe, however, that the UK RWE audit is the most relevant source to estimate the risk of cataract extraction in the UK patients with DMO in phakic eyes, and we therefore use these data to model the risk of cataract extraction for anti-VEGF treatment, and for no treatment in our revised base case analysis. In our revised base-case, we still maintain the use of cataract extraction data split by year for patients on treatment (based on MEAD for DEX700 and based on UK RWE audit for anti-VEGF). This is because this approach allows for the evolution in cataract extraction rates over time observed in MEAD and the UK RWE to be captured. However we explore in scenario analysis the impact of assuming a constant risk over time, which has minimal impact on the results.
Additional issue 2: Mortality hazard ratios	Section 4.2.12, pages 121-122; Section 6.4, page 154.	No	In the company submission, all-cause mortality was adjusted for the additional mortality due to diabetes mellitus (DM) (relative to the general population) and due to DMO (relative to the population with DM) and assuming that mortality occurs equally across all BCVA states. The additional mortality hazard ratios (HRs) due to DM and due to DMO were 1.93[30] and 1.27[31], consistent with the base case assumptions from TA349. The ERG prefers to adopt the HR accepted in TA613 (1.95)[28] for the additional mortality due to DM, and a HR of 1.54[32] for the additional mortality due to blindness (applied only to patients in whom both eyes are in the worst health state), to avoid

			issues with double-counting when applying HRs for both DM and DMO to all patients. We accept that the ERG's preference to use the HR of 1.95 for DM based on the accepted HR in TA613, as this is taken from a more recent source, and we therefore adopt this value in our revised base case and do not apply an additional mortality HR due to DMO. We also accept that it may be appropriate to apply the HR due to blindness of 1.54 applied only when both eyes experience severe vision loss, however in exploring this further have identified a correction required in the economic model to this application, described below. When applying additional mortality due to blindness in the submitted model, this resulted in an error on the 'Markov Calc' sheet that had not been identified before as this setting was not used in the base case analysis. The error stems from the approach taken within the Markov structure to calculate the proportion of patients for whom both eyes (both BSE and WSE) are in health state 1 and for whom the additional mortality associated with blindness applies. Within the calculation, it was assumed that, for each type of patient, the proportion of WSE in health state 1 is always higher than the proportion of BSE in health state 1. This is however not the case as we cannot restrict that the WSE always has more patients in HS1 than the BSE by individual patient types. This is best explained if we look at an example patient cohort, for example the group of patients with unilateral DMO in the BSE: vision in the WSE (which does not have DMO) stays constant over time, therefore the proportion of patients with their WSE in health state 1 can only decline over time as patients die or experience FEI (and therefore move to a different cohort within the model calculations). The proportion of patients with their BSE (which is treated for DMO) in health state 1 may increase or decrease because eyes with DMO can move up or down health states. Once treatment ceases, natural history dictates that the probability of decline in vision is

			greater than the probability of improvement. At some point it can therefore be the case that we have more BSE than WSE in health state 1 for a specific cohort of patients, which we acknowledge is a limitation of our analysis, however when reviewing the proportion of BSE and WSE in health state 1 at the full population level, the proportion of WSE in health state 1 is always greater than the proportion of BSE in health state 1 as expected. That the proportion of WSE in health state 1 for a specific cohort of patients could be very small, or indeed smaller than the proportion of BSE in health state 1 led to mortality risks that were implausible when applying additional mortality due to blindness. This is not an issue when the mortality is assumed to be the same across all health states as it was in the company submitted base case. In the revised submitted model we have therefore corrected for this by assuming that all BSE only in health state 1 have the additional mortality due to blindness applied as a simplifying assumption to correct for this inconsistency. This aligns with the approach taken for the additional costs due to blindness. We have also provided an additional scenario, assuming that the additional mortality due to blindness is applied to all BSE and WSE in health state 1. This is likely to over-estimate the additional mortality due to blindness. We have included a switch in the model to allow the impact of these corrections to be explored and reviewed and further details of the changes made are described in the appendix.
Additional issue 3: Assumed number of injections for anti-VEGF may be conservative	Section 4.2.14.6, page 135-136	No	In the company submission, the number of anti-VEGF injections assumed in each year of treatment were taken from the UK RWE audit.[15] The ERG state in their report that their clinical experts considered the estimate for Year 1 from the UK RWE audit ([redacted] injections) to be “particularly low”, and that this would more likely lie between the UK RWE audit and the RESTORE study[15, 33], citing 5 injections in Year 1 to be a plausible alternative assumption. Despite acknowledging that the

			company base case is therefore conservative on this point, the ERG has not explored the impact of this in their revised base case or sensitivity analyses, despite acknowledging that this could have a large impact on the results following the scenario analysis provided in the company submission using data from the RESTORE study (5.5 injections).[33] We have therefore revised our base-case analysis to assume 5 injections of anti-VEGF in the first year and illustrate the impact of applying the original company base-case assumption in scenario analysis. Importantly, under all plausible Year 1 injection frequencies for anti-VEGF treatment, DEX700 remains a cheaper, and less burdensome treatment option.
Additional issue 4: Misleading statement regarding impact on costs of DEX700	Section 1.2, page 17	No	The ERG states in its report that: "*Overall, the technology [DEX700] is modelled to affect costs by:* • *Its higher unit price than anti-VEGF treatment* • *Increasing the number of cataract extractions compared to anti-VEGF treatment;* • *Lowering the number of medical resource use requirements (routine monitoring visits and optical coherence tomography tests) compared to anti-VEGF treatment*." We believe that the first bulled point in this statement is misleading. Whilst the unit price of DEX700 is indeed higher than that of anti-VEGF treatments, DEX700 has a lower annual cost compared with anti-VEGF due to the lower frequency of administration, even when conservative estimates of injection frequency are assumed for anti-VEGF treatment, based on the UK RWE audit.[15] In the company original base case in Year 1 DEX700 is assumed to require an average of [redacted] injections (acquisition cost £[redacted]), compared with [redacted] injections for anti-VEGF (weighted acquisition cost at list price £[redacted]). The ERG acknowledges that this is a conservative estimate for anti-VEGF, and that 5 injections (weighted acquisition cost at list price £3,606) could be a plausible assumption, and per their

			labels, the required injection frequency could be as high as 6 injections for aflibercept and 12 for ranibizumab. [34, 35] Therefore, it is important to note that under all plausible injection frequencies for anti-VEGF when anti-VEGF treatment is at list price, DEX700 is a cheaper and less burdensome treatment option that provides additional clinical benefit compared with continued use of anti-VEGF in phakic patients who are insufficiently responsive to anti-VEGF treatment.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER, inc. NMB at WTP £30,000/QALY)
Original company base-case	**Incremental QALYs: 0.1038**	**Incremental costs: -£6,968**	**ICER: Dominant** **Inc. NMB: £10,080**
N/A – correction to the model regarding treatment acquisition costs in fellow eyes	N/A	Upon development of DMO in the fellow eye, it is assumed that the fellow eye receives the same treatment as the first eye, for a	ICER: Dominant Inc. NMB: £10,421 (+£341)

		period of up to 5 years starting from this point. However, we have identified that the submitted model did not account for treatment acquisition costs in any eye beyond Year 5 (i.e., after the end of the initial treatment duration). Therefore, treatment acquisition costs in Year 6 and 7 for those eyes who developed DMO during Year 1 or Year 2 were neglected. This has been corrected in the revised model, and the corrections are described further in the appendix.	
N/A – correction to the model regarding proportion of treated eyes at risk of cataract surgery in Y4 and Y5	N/A	We have identified that in the submitted model, the proportion of patients that remained phakic in Year 3 was being used to calculate of the proportion of patients receiving cataract surgery in Year 4 and Year 5, instead of the proportion of patients that remained phakic in Year 4 and in Year 5, respectively. This has been corrected in the revised model and the corrections are described further in the appendix	ICER: Dominant Inc. NMB: £10,156 (+£76)

Key issue 5: Subsequent treatment following discontinuation of DEX700	No additional treatment assumed following discontinuation of DEX700	80% of patients who discontinue DEX700 during Years 1-5 receive 1 additional year of anti-VEGF treatment	ICER: Dominant Inc. NMB: £8,714 (-£1,366)
Key issue 6: The natural history of vision in eyes with DMO	Natural history based on Mitchell et al.: 3.5% probability of improvement and 4.5% probability of worsening per 3-month cycle	Natural history based on TA274: 2.5% probability of improvement and 3.5% probability of worsening per 3-month cycle	ICER: Dominant Inc. NMB: £10,224 (+£144)
Additional issue 1: Cataract rates for anti-VEGF patients	On treatment: UK RWE audit (Years 2-4 of the study used for Years 1-3 of the model) Off treatment: Blue Mountains Eye Study	On treatment: UK RWE audit (Years 2-4 of the study used for Years 1-3 of the model) Off treatment: UK RWE audit (Year 4 data applied each year)	ICER: Dominant Inc. NMB: £10,316 (+£236)
Additional issue 2: Mortality HRs due to DM and DMO	HR due to DM: 1.93	HR due to DM: 1.95	ICER: Dominant Inc. NMB: £10,064 (-£16)
Additional issue 2: Mortality HRs due to DM and DMO	HR due to DMO: 1.27 No additional mortality due to blindness	No HR due to DMO Additional mortality applied (HR = 1.54) applied to all BSE in health state 1 (consistent with ERG base case with corrections, see Table 3, additional issue 2, and appendix for further details).	ICER: Dominant Inc. NMB: £10,264 (+£184)

Additional issue 3: Assumed number of injections for anti-VEGF may be conservative	Anti-VEGF injections in Year 1 based on UK RWE audit ([redacted] injections)	Anti-VEGF injections in Year 1 based on ERG clinical opinion (5 injections)	ICER: Dominant Inc. NMB: £11,906 (+£1,826)
N/A – acceptance of ERG base case assumption: Number of DEX700 injections in Year 4 and Year 5	1 DEX700 injection assumed per year in Year 4 and in Year 5	Assume number of DEX700 injections in Year 4 and in Year 5 is equal to the number in Year 3 ([redacted] injections)	ICER: Dominant Inc. NMB: £9,565 (-£515)
N/A – acceptance of ERG base case assumption: Utility decrements due to adverse events	No utility decrement due to adverse events	Include utility decrement due to adverse events	ICER: Dominant Inc. NMB: £10,050 (-£30)
Revised base case (incorporating all of the above changes)	**Incremental QALYs: 0.1139**	**Incremental costs: -£6,969**	**ICER: Dominant** **Inc. NMB: £10,386**

Sensitivity analyses around revised base case

Scenario description	Revised base case assumption	Scenario assumption	ICER (DEX700 vs anti-VEGF)	Inc. NMB (WTP threshold £30,000/QALY)
Base case			**Dominant**	**£10,386**
Time horizon	[redacted] years	30 years	Dominant	£10,367
		15 years	Dominant	£9,336
		10 years	Dominant	£8,418
Dosing anti-VEGF	5 injections in Year 1, UK RWE thereafter	The RESTORE study	Dominant	£13,468
		[redacted] injections in Year 1, UK RWE thereafter (original company base-case	Dominant	£9,132
Mortality due to blindness	HR of 1.54 applied only to BSE in health state 1	HR of 1.54 applied to both BSE and WSE in health state 1	Dominant	£10,374
		No mortality due to blindness	Dominant	£10,179
Cataract extraction rate off-treatment	UK RWE (last observed year)	Blue Mountain study (original company base-case)	Dominant	£10,142
Off-treatment efficacy	Natural history based on NICE TA274 (2.5% improvement, 3.5% worsening)	Natural history based on Mitchell et al. (3.5% improvement, 4.5% worsening)	Dominant	£10,213

Scenario description	Revised base case assumption	Scenario assumption	ICER (DEX700 vs anti-VEGF)	Inc. NMB (WTP threshold £30,000/QALY)
Base case			**Dominant**	**£10,386**
Efficacy DEX700	MEAD DEX700 - phakic population	MEAD pseudophakic population	Dominant	£22,552
		French RWE (baseline to Month 12 probabilities recalculated into 3-month probabilities)	Dominant	£27,325
		French RWE (baseline to Month 24 probabilities recalculated into 3-month probabilities)	Dominant	£24,560
		French RWE (baseline to Month 36 probabilities recalculated into 3-month probabilities)	Dominant	£28,302
Efficacy anti-VEGF	MEAD sham - phakic population	UK RWE (baseline to Month 12 probabilities recalculated into 3-month probabilities)	Dominant	£21,105
		UK RWE (baseline to Month 24 probabilities recalculated into 3-month probabilities)	Dominant	£13,138
		UK RWE (baseline to Month 36 probabilities recalculated into 3-month probabilities)	Dominant	£10,509
		UK RWE TPs calculated per year	Dominant	£18,035
		DMO natural history (2.5% improve / 3.5% worsen)	Dominant	£12,067

Scenario description	Revised base case assumption	Scenario assumption	ICER (DEX700 vs anti-VEGF)	Inc. NMB (WTP threshold £30,000/QALY)
Base case			**Dominant**	**£10,386**
		Net-zero impact on vision (3.0% improve / 3.0% worsen)	Dominant	£7,768
		Net-zero impact on vision (3.5% improve / 3.5% worsen)	Dominant	£8,295
		No change in vision (excluding severe vision loss costs)	Dominant	£8,266

References

1. National Institute for Health and Care Excellence. Dexamethasone intravitreal implant for treating diabetic macular oedema (final appraisal determination). 2015. Available at: https://www.nice.org.uk/guidance/ta349/resources/macular-oedema-diabetic-dexamethasone-intravitreal-implant-final-appraisal-determination-document2. Accessed: 11 October.
2. Guigou S, Pommier S, Meyer F, et al. Efficacy and Safety of Intravitreal Dexamethasone Implant in Patients with Diabetic Macular Edema. *Ophthalmologica*. 2015; 233(3-4):169-75.
3. Kaldırım H, Savur F, Kırgız A and Atalay K. Comparison of Anatomical and Functional Outcomes of Intravitreal Dexamethasone Implant between Phakic and Pseudophakic Eyes with Diabetic Macular Edema. *Korean J Ophthalmol*. 2020; 34(5):383-91.
4. Malclès A, Dot C, Voirin N, et al. Real-life Study in Diabetic Macular Edema Treated with Dexamethasone Implant: The Reldex Study. *RETINA*. 2017; 37(4).
5. Mathis T, Lereuil T, Abukashabah A, et al. Long-term follow-up of diabetic macular edema treated with dexamethasone implant: a real-life study. *Acta Diabetol*. 2020; 57(12):1413-21.
6. Mello Filho P, Andrade G, Maia A, et al. Effectiveness and Safety of Intravitreal Dexamethasone Implant (Ozurdex) in Patients with Diabetic Macular Edema: A Real-World Experience. *Ophthalmologica*. 2019; 241(1):9-16.
7. AbbVie. MEAD Studies: Demographics and Baseline Characteristics of Phakic Patients. 19 May 2021.
8. Chatziralli I, Theodossiadis P, Parikakis E, et al. Dexamethasone Intravitreal Implant in Diabetic Macular Edema: Real-Life Data from a Prospective Study and Predictive Factors for Visual Outcome. *Diabetes Ther*. 2017; 8(6):1393-404.
9. Busch C, Fraser-Bell S, Iglicki M, et al. Real-world outcomes of non-responding diabetic macular edema treated with continued anti-VEGF therapy versus early switch to dexamethasone implant: 2-year results. *Acta Diabetol*. 2019; 56(12):1341-50.
10. Demir G, Ozkaya A, Yuksel E, et al. Early and Late Switch from Ranibizumab to an Intravitreal Dexamethasone Implant in Patients with Diabetic Macular Edema in the Event of a Poor Anatomical Response. *Clin Drug Investig*. 2020; 40(2):119-28.
11. AbbVie. Ozurdex HTA Digital Advisory Board Final Report (10 May 2022). 2022.
12. European Medicines Agency. Dexamethasone intravitreal implant 700 micrograms (Ozurdex®). *Summary of Product Characteristics*. 2015.
13. Rosenblatt A, Udaondo P, Cunha-Vaz J, et al. A Collaborative Retrospective Study on the Efficacy and Safety of Intravitreal Dexamethasone Implant (Ozurdex) in Patients with Diabetic Macular Edema: The European DME Registry Study. *Ophthalmology*. 2020; 127(3):377-93.
14. Augustin AJ, Kuppermann BD, Lanzetta P, et al. Dexamethasone intravitreal implant in previously treated patients with diabetic macular edema: subgroup analysis of the MEAD study. *BMC Ophthalmol*. 2015; 15:150.
15. AbbVie. Long-term Follow Up of anti-VEGF use in Phakic Patients with Diabetic Macular Oedema: Real World Outcomes (Data on file). 2021.
16. AbbVie. MEAD Post-hoc Exploratory Analyses. 14 July 2021.

17. AbbVie. Virtual Advisory Board for Ozurdex® in Phakic Patients with Diabetic Macular Oedema – Report. 1 March 2021.
18. Menezo M, Roca M, Menezo V and Pascual I. Intravitreal dexamethasone implant Ozurdex in the treatment of diabetic macular edema in patients not previously treated with any intravitreal drug: a prospective 12-month follow-up study. *Curr Med Res Opin*. 2019; 35(12):2111-6.
19. Pinto M, Mathis T, Massin P, et al. Visual Acuity Gain Profiles and Anatomical Prognosis Factors in Patients with Drug-Naive Diabetic Macular Edema Treated with Dexamethasone Implant: The NAVEDEX Study. *Pharmaceutics*. 2021; 13(2).
20. Kodjikian L, Bellocq D and Mathis T. Pharmacological Management of Diabetic Macular Edema in Real-Life Observational Studies. *BioMed Research International*. 2018; 2018:8289253.
21. AbbVie. MEAD ERG Questions Analyses. 16 February 2022.
22. AbbVie. MEAD Post-Hoc Analysis: Tables for Phakic Inputs (model) (Data on file). 24 May 2021.
23. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022. Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Accessed: 05/05/2022.
24. AbbVie. MEAD Post-Hoc Analysis: Additional tables (Data on file). 2022.
25. Mitchell P, Annemans L, Gallagher M, et al. Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial. *Br J Ophthalmol*. 2012; 96(5):688-93.
26. National Institute for Health and Care Excellence. Ranibizumab for treating diabetic macular oedema. 2013. (Updated: 27 February 2013) Available at: https://www.nice.org.uk/guidance/ta274/resources/ranibizumab-for-treating-diabetic-macular-oedema-pdf-82600612458181.
27. National Institute for Health and Care Excellence. Dexamethasone intravitreal implant for treating diabetic macular oedematreating diabetic macular oedema (final appraisal determination). 2015. Available at: https://www.nice.org.uk/guidance/ta349/resources/macular-oedema-diabetic-dexamethasone-intravitreal-implant-final-appraisal-determination-document2.
28. National Institute for Health and Care Excellence. Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy. 2019. (Updated: 20 November 2019) Available at: https://www.nice.org.uk/guidance/ta613/resources/fluocinolone-acetonide-intravitreal-implant-for-treating-chronic-diabetic-macular-oedema-in-phakic-eyes-after-an-inadequate-response-to-previous-therapy-pdf-82608955110853.
29. Tan JS, Wang JJ and Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. *Ophthalmic Epidemiol*. 2008; 15(5):317-27.
30. Mulnier HE, Seaman HE, Raleigh VS, et al. Mortality in people with type 2 diabetes in the UK. *Diabet Med*. 2006; 23(5):516-21.
31. Hirai FE, Knudtson MD, Klein BE and Klein R. Clinically Significant Macular Edema and Survival in Type 1 and Type 2 Diabetes. *Am J Ophthalmol*. 2008; 145(4):700-6.

32. Christ SL, Lee DJ, Lam BL, et al. Assessment of the effect of visual impairment on mortality through multiple health pathways: structural equation modeling. *Invest Ophthalmol Vis Sci*. 2008; 49(8):3318-23.
33. Schmidt-Erfurth U, Lang GE, Holz FG, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology*. 2014; 121(5):1045-53.
34. European Medicines Agency. Summary of Product Charactersitics. Ranibizumab 10 mg/ml solution for injection (Lucentis). 23 October 2020 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/lucentis-epar-product-information_en.pdf. Accessed: 29 September 2021.
35. European Medicines Agency. Summary of Product Characteristics. Aflibercept 40 mg/mL solution for injection in pre-filled syringe (Eylea). 3 August 2021 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/eylea-epar-product-information_en.pdf. Accessed: 29 September 2021.

Appendix: Model updates

Change	Model worksheet affected	Formula changes
Correction: Treatment acquisition costs in fellow eyes	Markov_Calc	**FROM** Cells AEN29 =IF($B29>p_Treatment_Duration-1,0,((SD29+SJ29+SP29+TH29+TN29+UF29)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_C0,$B29,0)+IF(AND($B29>3,$B29-3<p_Fellow_Eye_Tx_Duration*4),(((SV29+TB29)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B29-3,0)),0)+IF(AND($B29>7,$C29-7<p_Fellow_Eye_Tx_Duration*4),(((TT29+TZ29)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B29-7,0)),0)) Cells AEN30:AES397 =IF($F30="","",IF($B30>p_Treatment_Duration-1,0,((SD30+SJ30+SP30+TH30+TN30+UF30)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_C0,$B30,0)+IF(AND($B30>3,$B30-3<p_Fellow_Eye_Tx_Duration*4),(((SV30+TB30)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B30-3,0)),0)+IF(AND($B30>7,$B30-7<p_Fellow_Eye_Tx_Duration*4),(((TT30+TZ30)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B30-7,0)),0))) **TO** Cells AEN29 (Please note that AEO29:AES29 have been amended in the same way) =CHOOSE(**TE_change1.NR**, IF($B29>p_Treatment_Duration-1,0,((SD29+SJ29+SP29+TH29+TN29+UF29)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_C0,$B29,0))+IF(AND($B29>3,$B29-3<p_Fellow_Eye_Tx_Duration*4),(((SV29+TB29)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B29-3,0)),0)+IF(AND($B29>7,$C29-7<p_Fellow_Eye_Tx_Duration*4),(((TT29+TZ29)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B29-7,0)),0),

		IF($B29>p_Treatment_Duration-1,0,((SD29+SJ29+SP29+TH29+TN29+UF29)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_C0,$B29,0)+IF(AND($B29>3,$B29-3<p_Fellow_Eye_Tx_Duration*4),(((SV29+TB29)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B29-3,0)),0)+IF(AND($B29>7,$C29-7<p_Fellow_Eye_Tx_Duration*4),(((TT29+TZ29)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B29-7,0)),0)))
		
		Cells AEN30:AES397 (Please note that cells AEO30:AES397 have been amended in the same way)
		=IF($F30="","",CHOOSE(**TE_change1.NR**,
		IF($B30>p_Treatment_Duration-1,0,((SD30+SJ30+SP30+TH30+TN30+UF30)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_C0,$B30,0))+IF(AND($B30>3,$B30-3<p_Fellow_Eye_Tx_Duration*4),(((SV30+TB30)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B30-3,0)),0)+IF(AND($B30>7,$B30-7<p_Fellow_Eye_Tx_Duration*4),(((TT30+TZ30)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B30-7,0)),0),
		IF($B30>p_Treatment_Duration-1,0,((SD30+SJ30+SP30+TH30+TN30+UF30)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_C0,$B30,0)+IF(AND($B30>3,$B30-3<p_Fellow_Eye_Tx_Duration*4),(((SV30+TB30)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B30-3,0)),0)+IF(AND($B30>7,$B30-7<p_Fellow_Eye_Tx_Duration*4),(((TT30+TZ30)*2)*p_Cost_TxN*OFFSET(p_Doses_TxN_FEI_C0,$B30-7,0)),0)))

Additional functionality to explore % of patients receiving subsequent anti-VEGF treatment after DEX700 discontinuation	Nextline_Efficacy; Nextline_AE	Cell F20 amended: **FROM** =IF(ERG_Scenarios!D78=FALSE,IF(C20="No further treatment",0,VLOOKUP(C20,$B$157:$G$164,Duration_Nextline_Efficacy+1,FALSE)),3538.69) **TO** IF(ERG_Scenarios!D78=FALSE,IF(C20="No further treatment",0,VLOOKUP(C20,$B$157:$G$164,Duration_Nextline_Efficacy+1,FALSE)),3538.69*TE_change2)
Additional functionality to include alternative	Inp_Treatment	**FROM** Cell C64

number of anti-VEGF injections in Year 1		= p_Prop_Tx_Tx2_M0*p_Doses_Tx2_M0+p_Prop_Tx_Tx2_M1*p_Doses_Tx2_M1+p_Prop_Tx_Tx2_M2*p_Doses_Tx2_M2 Cell D64 = p_Prop_Tx_Tx2_M3*p_Doses_Tx2_M3+p_Prop_Tx_Tx2_M4*p_Doses_Tx2_M4+p_Prop_Tx_Tx2_M5*p_Doses_Tx2_M5 Cell E64 = p_Prop_Tx_Tx2_M6*p_Doses_Tx2_M6+p_Prop_Tx_Tx2_M7*p_Doses_Tx2_M7+p_Prop_Tx_Tx2_M8*p_Doses_Tx2_M8 Cell F64 =p_Prop_Tx_Tx2_M9*p_Doses_Tx2_M9+p_Prop_Tx_Tx2_M10*p_Doses_Tx2_M10+p_Prop_Tx_Tx2_M11*p_Doses_Tx2_M11 Cell G64 =p_Prop_Tx_Tx2_M0*p_Doses_Tx2_M0+p_Prop_Tx_Tx2_M1*p_Doses_Tx2_M1+p_Prop_Tx_Tx2_M2*p_Doses_Tx2_M2+p_Prop_Tx_Tx2_M3*p_Doses_Tx2_M3+p_Prop_Tx_Tx2_M4*p_Doses_Tx2_M4+p_Prop_Tx_Tx2_M5*p_Doses_Tx2_M5+p_Prop_Tx_Tx2_M6*p_Doses_Tx2_M6+p_Prop_Tx_Tx2_M7*p_Doses_Tx2_M7+p_Prop_Tx_Tx2_M8*p_Doses_Tx2_M8+p_Prop_Tx_Tx2_M9*p_Doses_Tx2_M9+p_Prop_Tx_Tx2_M10*p_Doses_Tx2_M10+p_Prop_Tx_Tx2_M11*p_Doses_Tx2_M11 Cell C65 =p_Prop_Tx_Tx2_FEI_M0*p_Doses_Tx2_FEI_M0+p_Prop_Tx_Tx2_FEI_M1*p_Doses_Tx2_FEI_M1+p_Prop_Tx_Tx2_FEI_M2*p_Doses_Tx2_FEI_M2 Cell D65 =p_Prop_Tx_Tx2_FEI_M3*p_Doses_Tx2_FEI_M3+p_Prop_Tx_Tx2_FEI_M4*p_Doses_Tx2_FEI_M4+p_Prop_Tx_Tx2_FEI_M5*p_Doses_Tx2_FEI_M5 Cell E65 =p_Prop_Tx_Tx2_FEI_M6*p_Doses_Tx2_FEI_M6+p_Prop_Tx_Tx2_FEI_M7*p_Doses_Tx2_FEI_M7+p_Prop_Tx_Tx2_FEI_M8*p_Doses_Tx2_FEI_M8

		Cell F65 =p_Prop_Tx_Tx2_FEI_M9*p_Doses_Tx2_FEI_M9+p_Prop_Tx_Tx2_FEI_M10*p_Doses_Tx2_FEI_M10+p_Prop_Tx_Tx2_FEI_M11*p_Doses_Tx2_FEI_M11 Cell G65 =p_Prop_Tx_Tx2_FEI_M0*p_Doses_Tx2_FEI_M0+p_Prop_Tx_Tx2_FEI_M1*p_Doses_Tx2_FEI_M1+p_Prop_Tx_Tx2_FEI_M2*p_Doses_Tx2_FEI_M2+p_Prop_Tx_Tx2_FEI_M3*p_Doses_Tx2_FEI_M3+p_Prop_Tx_Tx2_FEI_M4*p_Doses_Tx2_FEI_M4+p_Prop_Tx_Tx2_FEI_M5*p_Doses_Tx2_FEI_M5+p_Prop_Tx_Tx2_FEI_M6*p_Doses_Tx2_FEI_M6+p_Prop_Tx_Tx2_FEI_M7*p_Doses_Tx2_FEI_M7+p_Prop_Tx_Tx2_FEI_M8*p_Doses_Tx2_FEI_M8+p_Prop_Tx_Tx2_FEI_M9*p_Doses_Tx2_FEI_M9+p_Prop_Tx_Tx2_FEI_M10*p_Doses_Tx2_FEI_M10+p_Prop_Tx_Tx2_FEI_M11*p_Doses_Tx2_FEI_M11 **TO** Cell C64 =**CHOOSE(TE_change3.NR,1.25,**p_Prop_Tx_Tx2_M0*p_Doses_Tx2_M0+p_Prop_Tx_Tx2_M1*p_Doses_Tx2_M1+p_Prop_Tx_Tx2_M2*p_Doses_Tx2_M2**)** Cell D64 =**CHOOSE(TE_change3.NR,1.25,**p_Prop_Tx_Tx2_M3*p_Doses_Tx2_M3+p_Prop_Tx_Tx2_M4*p_Doses_Tx2_M4+p_Prop_Tx_Tx2_M5*p_Doses_Tx2_M5**)** Cell E64 =**CHOOSE(TE_change3.NR,1.25,**p_Prop_Tx_Tx2_M6*p_Doses_Tx2_M6+p_Prop_Tx_Tx2_M7*p_Doses_Tx2_M7+p_Prop_Tx_Tx2_M8*p_Doses_Tx2_M8) Cell F64 =**CHOOSE**(**TE_change3.NR,1.25,**p_Prop_Tx_Tx2_M9*p_Doses_Tx2_M9+p_Prop_Tx_Tx2_M10*p_Doses_Tx2_M10+p_Prop_Tx_Tx2_M11*p_Doses_Tx2_M11**)** Cell G64 =**CHOOSE(TE_change3.NR,5,**p_Prop_Tx_Tx2_M0*p_Doses_Tx2_M0+p_Prop_Tx_Tx2_M1*p_Doses_Tx2_M1+p_Prop_Tx_Tx2_M2*p_Doses_Tx2_M2+p_Prop_Tx_Tx2_M3*p_Doses_Tx2_M3+p_Prop_Tx_Tx2_M4*p_Doses_Tx2_M4+p_Prop_Tx_Tx2_M5*p_Doses_Tx2_M5+p_Prop_Tx_Tx2_M6*p_Doses_Tx2_M6+p_Prop_Tx_Tx2_M7*p_Doses_Tx2_M7+p_Prop_

		Tx_Tx2_M8*p_Doses_Tx2_M8+p_Prop_Tx_Tx2_M9*p_Doses_Tx2_M9+p_Prop_Tx_Tx2_M10*p_Doses_Tx2_M10+p_Prop_Tx_Tx2_M11*p_Doses_Tx2_M11) Cell C65 =CHOOSE(TE_change3.NR,1.25,p_Prop_Tx_Tx2_FEI_M0*p_Doses_Tx2_FEI_M0+p_Prop_Tx_Tx2_FEI_M1*p_Doses_Tx2_FEI_M1+p_Prop_Tx_Tx2_FEI_M2*p_Doses_Tx2_FEI_M2) Cell D65 =CHOOSE(TE_change3.NR,1.25,p_Prop_Tx_Tx2_FEI_M3*p_Doses_Tx2_FEI_M3+p_Prop_Tx_Tx2_FEI_M4*p_Doses_Tx2_FEI_M4+p_Prop_Tx_Tx2_FEI_M5*p_Doses_Tx2_FEI_M5) Cell E65 =CHOOSE(TE_change3.NR,1.25,p_Prop_Tx_Tx2_FEI_M6*p_Doses_Tx2_FEI_M6+p_Prop_Tx_Tx2_FEI_M7*p_Doses_Tx2_FEI_M7+p_Prop_Tx_Tx2_FEI_M8*p_Doses_Tx2_FEI_M8) Cell F65 =CHOOSE(TE_change3.NR,1.25,p_Prop_Tx_Tx2_FEI_M9*p_Doses_Tx2_FEI_M9+p_Prop_Tx_Tx2_FEI_M10*p_Doses_Tx2_FEI_M10+p_Prop_Tx_Tx2_FEI_M11*p_Doses_Tx2_FEI_M11) Cell G65 =CHOOSE(TE_change3.NR,5,p_Prop_Tx_Tx2_FEI_M0*p_Doses_Tx2_FEI_M0+p_Prop_Tx_Tx2_FEI_M1*p_Doses_Tx2_FEI_M1+p_Prop_Tx_Tx2_FEI_M2*p_Doses_Tx2_FEI_M2+p_Prop_Tx_Tx2_FEI_M3*p_Doses_Tx2_FEI_M3+p_Prop_Tx_Tx2_FEI_M4*p_Doses_Tx2_FEI_M4+p_Prop_Tx_Tx2_FEI_M5*p_Doses_Tx2_FEI_M5+p_Prop_Tx_Tx2_FEI_M6*p_Doses_Tx2_FEI_M6+p_Prop_Tx_Tx2_FEI_M7*p_Doses_Tx2_FEI_M7+p_Prop_Tx_Tx2_FEI_M8*p_Doses_Tx2_FEI_M8+p_Prop_Tx_Tx2_FEI_M9*p_Doses_Tx2_FEI_M9+p_Prop_Tx_Tx2_FEI_M10*p_Doses_Tx2_FEI_M10+p_Prop_Tx_Tx2_FEI_M11*p_Doses_Tx2_FEI_M11)
Correction regarding additional mortality due to blindness	Markov_Calc	**FROM** Cell R30:R397 =IF($F30="","", IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(RG29:RK29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*RF29-

		(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(RM29:RQ29))/RL29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)))) Cell X30:X397 =IF($F30="","", IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(RY29:SC29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*RX29- (VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(RS29:RW29))/RR29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)))) Cell AD30:AD397 =IF($F30="","", IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(SE29:SI29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*SD29- (VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(SK29:SO29))/SJ29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)))) Cell AJ30:AJ397 =IF($F30="","",IF(D30<1,0, IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(SQ29:SU29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*SP29- (VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(SW29:TA29))/SV29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))))) Cell AP30:AP397 =IF($F30="","",IF(D30<1,0, IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(TC29:TG29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*TB29- (VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(TI29:TM29))/TH29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))))) Cell AV30:AV397 =IF($F30="","",IF(D30<2,0, IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(TO29:TS29)+(VLOOKUP(ROUNDDOWN($F29,

		0),Mortality,11,FALSE))*TN29- (VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(TU29:TY29))/TT29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))))) Cell BB30:BB397 =IF($F30="","",IF(D30<2,0, IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(UA29:UE29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*TZ29- (VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(UG29:UK29))/UF29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))))) Cell BH30:BH397 =IF($F30="","",IF(UR29=0,(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE)), (VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(UM29:UQ29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*UL29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(US29:UW29))/UR29))) Cell BN30:BN397 =IF($F30="","",IF(UX29=0,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE), (VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(VE29:VI29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*VD29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(UY29:VC29))/UX29))) Cell BT30:BT397 =IF($F30="","",IF(VP29=0,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE), VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(VK29:VO29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*VJ29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(VQ29:VU29))/VP29))) Cell BZ30:BZ397 =IF($F30="","",IF(XX29=0,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE), VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(XS29:XW29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*XR29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(XY29:YC29))/XX29))) Cell CF30:CF397

		=IF($F30="","",IF(YD29=0,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE), VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(YK29:YO29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality ,11,FALSE))*YJ29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(YE29:YI29))/YD29))) Cell CL30:CL397 =IF($F30="","",IF(YV29=0,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE), (VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(YQ29:YU29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortalit y,11,FALSE))*YP29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(YW29:ZA29))/YV29))) Cell NJ37:NO397 =IF($F37="","",MMULT(NJ36:NO36* (1-$BT37:$BY37),IF($B37- 1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist)) + MMULT(LB36:LG36*(1-$BZ37:$CE37)*(1-Prop_EyeSwitch)*(IF($D37=2,p_Prop_FEI,0)),MMULT(IF($B37- 1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist),TPM_Bilateral)) + MMULT(LN36:LS36*(1-$L37:$Q37)*Prop_EyeSwitch*(IF($D37=2,p_Prop_FEI,0)),MMULT(IF($B37- 1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist),TPM_Bilateral))) Cell NV37:OA397 =IF($F37="","",MMULT(NV36:OA36*(1-$BT37:$BY37),IF($B37- 1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist)) + MMULT(LH36:LM36*(1-$CF37:$CK37)*(1-Prop_EyeSwitch)*(IF($D37=2,p_Prop_FEI,0)),IF($B37- 1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist)) + MMULT(KV36:LA36*(1-$L37:$Q37)*Prop_EyeSwitch*(IF($D37=2,p_Prop_FEI,0)),IF($B37- 1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist))) **TO** Cell R30:R397

		=IF($F30="","",**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(RG29:RK29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*RF29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(RM29:RQ29))/RL29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)))) Cell X30:X397 =IF($F30="","",**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(RY29:SC29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*RX29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(RS29:RW29))/RR29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)))) Cell AD30:AD397 =IF($F30="","",**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(SE29:SI29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*SD29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(SK29:SO29))/SJ29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)))) Cell AJ30:AJ397 =IF($F30="","",IF(D30<1,0,**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(SQ29:SU29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*SP29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(SW29:TA29))/SV29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))))) Cell AP30:AP397 =IF($F30="","",IF(D30<1,0,**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(TC29:TG29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*TB29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(TI29:TM29))/TH29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)))))

		Cell AV30:AV397 =IF($F30="","",IF(D30<2,0,**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(TO29:TS29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*TN29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(TU29:TY29))/TT29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))))) Cell BB30:BB397 =IF($F30="","",IF(D30<2,0,**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**IFERROR((VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(UA29:UE29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*TZ29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(UG29:UK29))/UF29,VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))))) Cell BH30:BH397 =IF($F30="","",IF(UR29=0,(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE)),**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(UM29:UQ29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*UL29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(US29:UW29))/UR29))) Cell BN30:BN397 =IF($F30="","",IF(UX29=0,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(VE29:VI29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*VD29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(UY29:VC29))/UX29))) Cell BT30:BT397 =IF($F30="","",IF(VP29=0,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(VK29:VO29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*VJ29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(VQ29:VU29))/VP29))) Cell BZ30:BZ397

		=IF($F30="","",IF(XX29=0,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(XS29:XW29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*XR29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(XY29:YC29))/XX29))) Cell CF30:CF397 =IF($F30="","",IF(YD29=0,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(YK29:YO29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*YJ29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(YE29:YI29))/YD29))) Cell CL30:CL397 =IF($F30="","",IF(YV29=0,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),**CHOOSE(TE_change4.NR,VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE),VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE),**(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE)*SUM(YQ29:YU29)+(VLOOKUP(ROUNDDOWN($F29,0),Mortality,11,FALSE))*YP29-(VLOOKUP(ROUNDDOWN($F29,0),Mortality,10,FALSE))*SUM(YW29:ZA29))/YV29))) Cell NJ37:NO397 =IF($F37="","",MMULT(NJ36:NO36***CHOOSE(TE_change4.NR,(1-$CL37:$CQ37),(1-$CL37:$CQ37),(1-$BT37:$BY37)),**IF($B37-1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist)) + MMULT(LB36:LG36*(1-$BZ37:$CE37)*(1-Prop_EyeSwitch)*(IF($D37=2,p_Prop_FEI,0)),MMULT(IF($B37-1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist),TPM_Bilateral)) + MMULT(LN36:LS36*(1-$L37:$Q37)*Prop_EyeSwitch*(IF($D37=2,p_Prop_FEI,0)),MMULT(IF($B37-1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist),TPM_Bilateral))) Cell NV37:OA397 =IF($F37="","",MMULT(NV36:OA36***CHOOSE(TE_change4.NR,(1-$CL37:$CQ37),(1-$CL37:$CQ37),(1-$BT37:$BY37)),**IF($B37-1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist)) + MMULT(LH36:LM36*(1-$CF37:$CK37)*(1-Prop_EyeSwitch)*(IF($D37=2,p_Prop_FEI,0)),IF($B37-1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist)) +

		MMULT(KV36:LA36*(1-$L37:$Q37)*Prop_EyeSwitch*(IF($D37=2,p_Prop_FEI,0)),IF($B37-1<p_Treatment_Duration,TPM_TxN_Nextline_Disc_AEs_Cont,TPM_DMO_Nat_Hist)))
Correction regarding proportion of treated eyes at risk of cataract surgery in Y4 and Y5	Data	**FROM** Cell O46 =(p_Cost_Cataract_Proc+p_Add_Appt_Cataract*p_Cost_Resource_1)*(p_Prop_Phakic_TxN_Y3*p_Prop_Cataract_TxN_Y3)+(p_Cost_IOP_Proc+p_Add_Appt_IOP_Surg*p_Cost_Resource_1)*p_Prop_IOP_Surg_TxN_Y3+(p_Cost_IOP_Med+p_Add_Appt_IOP*p_Cost_Resource_1)*p_Prop_IOP_Med_TxN_Y3+(p_Cost_Attach_Retina+p_Add_Appt_Ret*p_Cost_Resource_1)*p_Prop_Ret_Detach_TxN_Y3+(p_Cost_Endophthalmitis_Proc+p_Add_Appt_End_Surg*p_Cost_Resource_1)*p_Prop_Endoph_Surg_TxN_Y3+(p_Cost_Vitrectomy+p_Add_Appt_Vit*p_Cost_Resource_1)*p_Prop_Vit_Haem_TxN_Y3 Cell P46 =(p_Cost_Cataract_Proc+p_Add_Appt_Cataract*p_Cost_Resource_1)*(p_Prop_Phakic_TxN_Y3*p_Prop_Cataract_TxN_Y3)+(p_Cost_IOP_Proc+p_Add_Appt_IOP_Surg*p_Cost_Resource_1)*p_Prop_IOP_Surg_TxN_Y3+(p_Cost_IOP_Med+p_Add_Appt_IOP*p_Cost_Resource_1)*p_Prop_IOP_Med_TxN_Y3+(p_Cost_Attach_Retina+p_Add_Appt_Ret*p_Cost_Resource_1)*p_Prop_Ret_Detach_TxN_Y3+(p_Cost_Endophthalmitis_Proc+p_Add_Appt_End_Surg*p_Cost_Resource_1)*p_Prop_Endoph_Surg_TxN_Y3+(p_Cost_Vitrectomy+p_Add_Appt_Vit*p_Cost_Resource_1)*p_Prop_Vit_Haem_TxN_Y3 **TO** Cell O46 =(p_Cost_Cataract_Proc+p_Add_Appt_Cataract*p_Cost_Resource_1)***CHOOSE(TE_change5.NR,(p_Prop_Phakic_TxN_Y4*p_Prop_Cataract_TxN_Y4),(p_Prop_Phakic_TxN_Y3*p_Prop_Cataract_TxN_Y3))**+(p_Cost_IOP_Proc+p_Add_Appt_IOP_Surg*p_Cost_Resource_1)*p_Prop_IOP_Surg_TxN_Y3+(p_Cost_IOP_Med+p_Add_Appt_IOP*p_Cost_Resource_1)*p_Prop_IOP_Med_TxN_Y3+(p_Cost_Attach_Retina+p_Add_Appt_Ret*p_Cost_Resource_1)*p_Prop_Ret_Detach_TxN_Y3+(p_Cost_Endophthalmitis_Proc+p_Add_Appt_End_Surg*p_Cost_Resource_1)*p_Prop_Endoph_Surg_TxN_Y3+(p_Cost_Vitrectomy+p_Add_Appt_Vit*p_Cost_Resource_1)*p_Prop_Vit_Haem_TxN_Y3 Cell P46 =(p_Cost_Cataract_Proc+p_Add_Appt_Cataract*p_Cost_Resource_1)***CHOOSE(TE_change5.NR,(p_Prop_Phakic_TxN_Y5*p_Prop_Cataract_TxN_Y5),(p_Prop_Phakic_TxN_Y3*p_Prop_Cataract_TxN_Y3))**+(p_Cost_IOP_Proc+p_Add_Appt_IOP_Surg*p_Cost_Resource_1)*p_Prop_IOP_Surg_TxN_Y3+(p_Cost_IOP_Med+p_Add_Appt_IOP*p_Cost_Resource

		_1)*p_Prop_IOP_Med_TxN_Y3+(p_Cost_Attach_Retina+p_Add_Appt_Ret*p_Cost_Resource_1)*p_Prop_Ret_Detach_TxN_Y3+(p_Cost_Endophthalmitis_Proc+p_Add_Appt_End_Surg*p_Cost_Resource_1)*p_Prop_Endoph_Surg_TxN_Y3+(p_Cost_Vitrectomy+p_Add_Appt_Vit*p_Cost_Resource_1)*p_Prop_Vit_Haem_TxN_Y3

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **11 May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating Diabetic macular oedema (DMO) and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Winfried Amoaku
2. Name of organisation	The Royal College of Ophthalmologists
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with DMO? ☐ A specialist in the clinical evidence base for DMO or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links	None

to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for DMO? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of DMO treatment is to reduce macular oedema, and the associated progression of visual loss.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant treatment response in DMO is the maintenance of vision (visual acuity [VA] change +/- 5 letters and achieving resolution or reduction of macular oedema, as defined by Amoaku et al (2020). Full response will result in complete resolution of DMO and/or VA gain of >5 letters. Partial response is considered as (VA change of <5 letter gain and/or >20% reduction in central retina thickness). A poor or 'non-response' to treatment is defined as VA loss of 5 letters and/or <20% reduction in central retina thickness.
10. In your view, is there an unmet need for patients and healthcare professionals in DMO?	There is a significant unmet need in the treatment of DMO. Currently, patients will normally be started on ranibizumab or aflibercept. Approximately 25% these patients are poor responders (Protocol I, VIVID/VISTA 100 weeks). It is known that approximately 40% of eyes still have evident macular oedema at 12-24 months after commencing treatment, despite optimum treatment. If a poor response is demonstrated (<5 letter gain and/or <20% reduction in central retina thickness) then they will be switched to the other anti-VEGF, if deemed appropriate by the treating consultant ophthalmologist. If they continue to show a poor response to the second anti-VEGF then dexamethasone implant will be considered. However, the choice of dexamethasone implant is currently not available for eyes that are phakic. In the DRCR.net Protocol T, 29% of eyes treated with aflibercept, 59% of bevacizumab, 35% ranibizumab eyes had central foveal thickness of >250 microns at 24 months despite monthly treatment. Visual acuity (VA) improvement from baseline levels were found to be lower in eyes that had chronic persistent macular oedema compared to eyes without persistent oedema. Corticosteroids, including dexamethasone implant, target the non-VEGF pathway in DMO. As such it is effective in eyes with chronic DMO. This is further underscored by the fact that VA improvements in eyes with chronic persistent DMO is less with anti-VEGFs compared with those where DMO is not chronic.

	Real world data indicates that there is significant under-treatment of DMO with anti-VEGFs because of non-attendance or reduced treatment frequency (Weiss et al, 2018; Jansen et al, 2018). A recent systematic review reported a variable adherence to intravitreal injection schedules in DMO patients receiving anti-VEGF therapies. (Rose MA et al. Adherence of patients with DMO to intravitreal injections: A systematic review. Clin Exp Ophthalmol 2020;48(9):1286-1298. As such there is a significant need for treatments in phakic as well as pseudophakic eyes with DMO, especially when unresponsive to anti-VEGFs.
11. How is DMO currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Laser photocoagulation- laser is still recommended in eyes with non-centre involving leakage. However, where laser photocoagulation is considered detrimental or not beneficial (leakage too close to the fovea, centre involving, or too diffuse), alternative therapies are indicated. Ranibizumab as per NICE TA 274, and aflibercept (NICE TA 346), are recommended by NICE specifically to treating DMO but excludes eyes with foveal thickness <400 microns on OCT, whilst Fluocinolone implant (NICE TA 301) is recommended in eyes with DMO that are pseudophakic, and where ranibizumab or aflibercept are not indicated, or after other therapies have failed, or are not indicated. There is no reference to chronicity in this guidance. The treatment regimens for the anti-VEGF agents are: i) ranibizumab, 3 monthly initiating doses followed by a PRN/Treat & Extend regime; ii) aflibercept, 5 monthly initiating doses followed by 2 monthly treatments. In year 2 onwards this treatment interval can be extended. Ranibizumab and aflibercept are the only agents recommended for the treatment of phakic patients with centre-involving DMO. However, anti-VEGF drugs are not the best treatment option in some patients. These include pregnant women, recent cardiovascular events, or where patient does not like frequent injections, or cannot attend at monthly intervals (as required with anti-VEGF therapies) resulting in suboptimal treatment. Furthermore, it is known that some eyes with DMO do not respond completely to treatment with anti-VEGFs especially in cases of chronic DMO (Amoaku et al, 2015, 2020). The RCOphth DMO Guidelines (2012), available @ https://www.rcophth.ac.uk/resources-listing/diabetic-retinopathy-guidelines/) currency has been updated by the UK Consensus document. (Amoaku WM et al. Diabetic retinopathy and DMO pathways and management: UK Consensus Working Group. Eye 34, 1–51 (2020). https://doi.org/10.1038/s41433-020-0961-6* Eye (2020) 34:1–51 and Corrigendum https://doi.org/10.1038/s41433-020-1087-6. Other guidelines exist elsewhere, e.g. EURETINA: Schmidt-

	Erfurth U et al. Guidelines for the management of DME. Ophthalmologica 2017; 237:185–222. Figueira J et al. Guidelines for the management of center-involving DME. Clin Ophthalmol 2021;15:3221-3230. The **clinical pathway** is well defined. Only a modification of usage of the technology (already in use) is being evaluated in this TA. Some clinicians are, however, less willing to use intravitreal corticosteroid injections because of the perceived adverse event profile, especially as it is not currently recommended by NICE. Furthermore, local funding requests are considered cumbersome and/or over-burdening for some clinicians. **Impact.** The technology will allow the inclusion of dexamethasone implant as a treatment option in eyes insufficiently responsive to non-corticosteroid therapies in DMO. The recommended dose is 1 implant (700 µg) into the affected phakic eye with DMO who are unsuitable for non-corticosteroid therapy (i.e. 1st line, rarely), or who are considered insufficiently responsive to alternative non-corticosteroid therapy e.g. those who have failed to respond to laser photocoagulation and anti- VEGF treatments or do not meet the requirements for treatment with ranibizumab (NICE TA 274), or aflibercept (NICE TA 346) (2nd/3rd line, less rarely). The second eye may receive similar treatment if the first treated eye shows good response, and there are no safety concerns. Retreatment at 4-6 month intervals (see NICE TA 349). These patients will be reviewed at 2 monthly intervals.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Dexamethasone implant is already used in the treatment of DMO in pseudophakic eyes (and in other indications of retinal vein occlusion, and non-infectious intraocular inflammation, irrespective of lens status). The use in phakic eyes will be similar. The proposed use will include treatment of eyes that are phakic, but unresponsive, or unsuitable for other (non-corticosteroid) DMO treatments. Access to the technology in phakic DMO will provide physicians with an opportunity at an early stage to switch non/sub-optimal responding patients from anti-VEGF treatment to dexamethasone implant hence likely avoid any damage to the retina and improve patient outcomes: more cost-effective of the technology. Capacity sparing: Use of intravitreal dexamethasone implant results in a reduced burden of injections when compared to intravitreal anti-VEGF injections and, therefore, capacity sparing. It is expected that patients treated with the technology will attend fewer appointments due to longer injection intervals resulting in reduction in clinic visits. This is even more important during current COVID pandemic. Adoption of the expanded technology indication can further “free-up” clinic slots and staff resources which can potentially be made available for other conditions and services.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology should be used by retinal specialists with expertise in the treatment of patients with diabetic retinopathy, including DMO. This would normally occur in secondary care. No further investment is required in introducing the technology, as it is already used in other indications in the NHS. The injection room facilities, equipment, and expertise already exist, and are in use in the NHS.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. Phakic eyes that are insufficiently unresponsive to non-corticosteriod intravitreal therapies will benefit meaningfully from this technology. Non-response or very suboptimal response to anti-VEGF in DMO is well characterised (summarised in section 7). This often leads to frequent treatments with anti-VEGFs in an attempt to dry up the macula (e.g. 9-12 treatments in 12 months). Such eyes eventually have poor outcomes unless treatment is changed to a suitable alternative. Converting treatment of such eyes to intravitreal dexamethasone implant will require 2.4 treatments per annum (c.f. anti-VEGF), with significant cost saving, as well as better vision outcomes. Economically, there will be cost saving. A recent meta-analysis indicates that response to DMO treatments are similar for anti-VEGFs and dexamethasone implants. (He Y, Ren XJ, Hu BJ et al. A meta-analysis of the effect of a dexamethasone intravitreal implant versus intravitreal anti-VEGF treatment for DME. BMC Ophthalmol 2018;18(1):121. Furthermore, the use of dexamethasone implant pre-cataract surgery may be beneficial in eyes with DMO (Barone A et al, Eur J Ophthalmol. 2021 Mar 23:11206721211004395. • No. The technology will not increase length of life. • Yes, the technology will increase HRQoL. The new treatment will lead to better resolution of DMO, and visual acuity improvements, less frequent hospital visits, and patient satisfaction compared current care.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No. However, this technology will be available to groups did not have access previously, including pregnant diabetic women, and persons with recent cardiovascular events, where anti-VEGFs are contraindicated.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology is already in use in the NHS for other indications. The only change is an expansion of number of patients eligible for, and who will benefit from the technology. No further tests are required (compared to current care), and monitoring will be similar including clinical examination, intraocular pressure measurements, and optical coherence tomography imaging. Adoption of the technology will be capacity sparing, as it will result in reduced burden of injections compared to that with intravitreal anti-VEGF therapies. This has been highlighted during the recent Covid-19 pandemic. Clinic slots will be freed-up and staff resources re-directed.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment is indicated in eyes with DMO. Response to treatment is important. Eyes that are not sufficiently responsive to treatment (i.e. insufficient response to treatment) will have discontinued, and considered for alternative therapies. The rules will be similar to that used for eyes that are pseudophakic. Treatment paradigms are summarised in the DMO Consensus document (Amoaku et al, 2020).
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. This should be supported by health economic assessments.

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes. It represents a step-change in DMO management. QoL - Management of patients with Retinal disease during COVID pandemic: • The RCOphth guidance on Management of Ophthalmology Services during the COVID pandemic recommends that treatment changes that can reduce the frequency of required attendances for the next few months e.g. changes in intravitreal treatment regime or longer-acting drug or procedure that would result in a lower number of hospital visits (RCOphth 2020, COVID-19 Clinical Guidance and National Information. RCOphth Management of Ophthalmology Services during the Covid pandemic dated 28th March 2020. https://www.rcophth.ac.uk/about/rcophth-covid-19-response/on 3rd August 2020). • During this unprecedented time of COVID-19, there is a stronger need for a therapy in phakic DMO with a predictable, extended treatment duration that would result in fewer hospital visits versus Anti-VEGF thus minimizing the risk of exposure to COVID for both the patients and healthcare worker. • Diabetes is strongly associated with COVID-19 mortality. A nationwide analysis in England demonstrated that a ⅓ of all in-hospital deaths with COVID-19 in England occurred in people with diabetes (Barron E et al. Lancet Diabetes Endocrinol 2020; 8:813-822). **Yes**: the **unmet need** as described above. The use of the technology addresses the unmet need for non-eligible patients and non-responders to current intravitreal injection treatments. It addresses a patients' right to treatment. It is known that up to 50% patients do not respond optimally to anti-VEGF treatments. Clinical trials: RESTORE, VIVID and VISTA have shown that 50% eyes (pseudophakic or phakic) still have fluid, requiring other interventions. If patients are insufficiently responsive to anti-VEGF then dexamethasone implant will be recommended as per licence.

	Access to dexamethasone implant in phakic DMO will provide physicians the opportunity to switch non/sub-optimal responding patients from anti-VEGF treatment to dexamethasone implant earlier, and hence likely avoid irreversible damage to the retina and improve patient outcomes.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main adverse events are cataract development/progression, and increased IOP (which applies to use of the technology in eyes that are already pseudophakic). Patients with cataract progression will, however, benefit from cataract surgery such that effects on patient's quality of life are limited. The clinical trials of the technology included eyes that are phakic and pseudophakic. Current UK use is restricted because of the recommendations of NICE TA 349, which this current appraisal is aimed to address. Data are summarised below. The MEAD Study (Boyer DS et al. Ophthalmology 2014; 121(10):1904-14). Three-year, pooled data from 2 randomised, multicentre, masked, sham controlled phase III clinical trials with identical protocols MEAD) showed that 22.2% of Ozurdex treated patients gain ≥15 letters over three years from an average of 4.1 injections. However, these VA results were significantly skewed by cataract progression amongst the phakic cohort in the study (75.5%). Cataract typically developed at 18+ months after initiation of Ozurdex (i.e. after the third implant). Prior to cataract development the visual improvements matched the pseudophakic cohort. For patients who underwent cataract surgery, visual improvements were typically re-gained by the end of the study (available @ http://dx.doi.org/10.1016/j.ophtha.2014.04.024) Other reports include: i)The BEVORDEX Study. http://dx.doi.org/10.1016/j.ophtha.2014.07.002 ii) Pacella E. Clin Ophthalmol 2013: 7 1423-1428; iii) NICE TA 349 • Dexamethasone implant is an intraocular steroid for which there is a class effect of an increased intraocular pressure (IOP) in some patients. Increased IOP is a risk factor for glaucoma. The clinical safety of dexamethasone implant has shown incidence of elevated IOP and cataract (Bilgic A et al. Ophthalmology Retina 2019;3: 929-937; Rajesh B et al. Br J Ophthalmol 2020; 104:39-46). • The SAFODEX studies (Malclès A et al. Retina 2017; 37:1352–9; Rezkallah A et al. Retina 2021; 41:1438-1445) reported that DMO patients were least likely to develop ocular hypertension (ONT) compared with RVO or uveitis patients. Approximately 90% of eyes with raised IOP were managed medically with topical drops (Rajesh et al, 2020); Malclès et al, 2017), while 0.5% eyes required filtering surgery. Endophthalmitis (0.07%), retinal detachment (0.03%) and vitreous haemorrhage (0.03%) were rare. Phakic status of the eye did not affect the risk of OHT compared to pseudophakic patients (Rajesh et al, 2020).

	• Rajesh et al (2020), reported 31% required cataract surgery while 14.3% saw a progression in their cataract requiring surgery. However, 25% of these patients had cataract at baseline (Rajesh et al, 2020). Similarly, in Bilgic et al (2019), at 24 months, 29/153 patients (19%) underwent cataract surgery, however, 26/29 (90%) of these patients had pre-existing cataract. (Bilgic A et al, 2019).
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials on the technology included eyes that are phakic and pseudophakic. Current UK use of the technology is restricted to largely pseudophakic eyes because of NICE TA 349. The UK Consensus Working Group (Amoaku et al, 2020), recommendations if implemented would reflect clinical trials data. The current appraisal is aimed to address this situation. As such, current UK practice does not currently reflect the clinical trial data. These clinical trial data are summarised in Section 19 (above). In addition, the technology is used in phakic eyes elsewhere, as supported by the literature, including: *1. Rosenblatt A et al. A collaborative retrospective study on the efficacy and safety of intravitreal dexamethasone implant (Ozurdex) in patients with DME: The European DME Registry Study. Ophthalmology 2020;127:377-393; 2. Mishra SK et al. Intravitreal dexamethasone implant versus intravitreal ranibizumab injection for treatment of non-proliferative DME. Curr Drug Deliv 2021;18:825-832. 3. Udaondo P et al. Impact of different clinical baseline characteristics on intravitreal dexamethasone implant (Ozurdex) outcomes. Clin Ophthalmol 2021;15:4153-4162. 4. Wei W et al. Multicenter, prospective, randomized study of dexamethasone intravitreal implant in patients with center-involved diabetic macular edema in the Asia-Pacific Region. Clin Ophthalmol 2021;15:4097-4108. 5. Ehlers JP et al. Intravitreal pharmacotherapies for DME: A Report by the AAO. Ophthalmology 2022;129(1):88-99. 6. Pacella E et al. Effects of repeated intravitreal injections of dexamethasone implants on intraocular pressure: A 4-Year Study. Clin Ophthalmol 2020;14:3611-3617. 7. Kaldırım H et al. Comparison of anatomical and functional outcomes of intravitreal dexamethasone implant between phakic and pseudophakic eyes with DME. Korean J Ophthalmol 2020;34:383-391. 8. Nair U et al. Postmarketing safety surveillance of dexamethasone intravitreal implant in the treatment of visual impairment due to DME in India. BMC Ophthalmol 2020;20:405. 9. Furino C et al. DME and cataract surgery: Phacoemulsification combined with dexamethasone intravitreal implant compared with standard phacoemulsification. Retina 2021;41(5):1102-1109. 10. Ratra D, Sharma U, Dalan D. Efficacy and safety of intravitreal dexamethasone implant in treatment naive eyes with DME: Real world experience. Eur J Ophthalmol 2021;31(4):1899-1906.*
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes: some of the recent real world data cited in other sections.
22. Are you aware of any other relevant new evidence apart from that from the MEAD trials?	Yes. Wei W et al. Multicentre prospective randomised study of dexamethasone intravitreal implant in patients with centre-involved diabetic macular edema in the Asia-Pacific region. Clin Ophthalm 2021:15 4097–4108.

23. How do data on real-world experience compare with the trial data?

Real world data outcomes are comparable, and reported less frequent adverse events compared to clinical trial data.

Since the NICE Technology appraisal guidance for Ozurdex (NICE TA 349) there is evolving evidence including real-world data (RWD) demonstrating similar outcomes between phakic and pseudophakic eyes with DMO (Macles et al, 2017; Singer et al, 2018), with as few injections as possible (Table 1). There is comparable mean improvement in BCVA in phakic eyes having undergone cataract surgery vs pseudophakic eyes, with no reduction in treatment benefit observed because of cataract surgery (Bilgic A et al. Br J Ophthalmol 2019; doi:10.1136/bjophthalmol-2019-313991; Malclès A et al. Retina 2017;37(4):753-760; Singer MA et al. Ophthalmic Surg Lasers Imaging Retina 2018;49(6):425-435. Menezo M et al. Current Med Res Opinion 35;12: 2111-2116). Existing practice positions intravitreal injections of anti-VEGF drugs before dexamethasone implant in phakic patients. However, recent real-world data have shown broadly equivalent outcomes (Callanan DG et al, Graefes Arch Clin Exp Ophthalmol 2017;255:463-473; Comet A et al, INVICTUS. Eur J Ophthalmol 2021;31(2):754-758). Patients who had a sub-optimal response to anti-VEGF when switched to dexamethasone implant (Ozurdex) had better visual and anatomical outcomes (Busch C et al. Acta Diabetol 2018;55(8):789-796; Ruiz-Medrano J et al. Eur J Ophthalmol 2021;31(3):1135-1145; Busch C et al. Acta Diabetol 2019;56(12):1341-1350.

Table 1: RWD with Ozurdex in phakic DMO vs. pseudophakic DMO

Table 1: RWD with Ozurdex in phakic DMO vs. pseudophakic DMO

Study	Follow-up (months)	BCVA from baseline (letters)		Mean number of injections
Reldex	36	Phakic +9.5	Pseudophakic +9.5	3.6
REINFORCE	12	Phakic +12.2	Pseudophakic +11.5	2.0

Guidelines for the management of DME by EURETINA. *Recommendation for Steroids: 'In non-responders who have already been treated with anti-VEGF (after 3–6 injections, depending on the specific response of each patient), it is reasonable to switch to a steroid. First-line considered in patients who have a history*

	of a major cardiovascular event, patients who are not willing to come for monthly injections (and/or monitoring) in the first 6 months of therapy, Dexamethasone shall be the first steroid used. Phakic patients have to be informed about the high risk for cataract surgery. The IOP has to be monitored frequently in all cases.' • UK Consensus Pathway (Amoaku et al, 2020) describes the pathway. • Summary from RCOphth response to NICE TA349. *"The NICE guidance, which covers NHS England and Wales, contrasts with guidance for NHS Scotland by the Scottish Medicines Consortium which recommends Ozurdex® not only for pseudophakic patients but also for phakic patients who are considered insufficiently responsive to, or unsuitable for non-cortico-steroid therapy (published April 2015). Ophthalmologists responsible for patients in NHS England and Wales will have to apply to their local Clinical Commissioning Group (CCG) or Local Health Board (LHB) respectively as an individual funding request if they wish to use Ozurdex® in a phakic patient with DMO. Alternatively, they could work closely with their CCG or LHB to develop local funding arrangements for selected groups of individuals meeting certain predefined criteria".* • Scottish - Scottish Medicines Consortium No.1046/15 – which allows for Ozurdex in phakic eyes.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership,	Yes. Pregnant women with DMO. Such patients cannot be treated with intravitreal injections of anti-VEGFs because of risks to the foetus.

pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Clinical expert statement

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Uncertainty around the generalisability of the results from the MEAD trials Are results from the MEAD trials generalisable to people seen in UK clinical practice? Are you aware of other clinical evidence in the correct population for	The results of the MEAD trial are generally applicable to the UK population. The sham treatment arm of MEAD served to give a natural history. Participants only received treatment after exiting the study (Yoon et al, 2019). However, there are differences in the MEAD inclusion criteria, and current clinical practice. In particular, the treatment paradigm for DMO has changed significantly since the inception and completion of the MEAD study. Treatment paradigms are currently summarised in the UK DR and DMO Consensus document (Amoaku et al, 2020), and the NICE TAs (NICE TA274 [for ranibizumab], TA346 [aflibercept], and TA613 [fluocinolone]).

the required comparators?	The NICE Clinical Guidelines for Diabetic Retinopathy [GID-NG10256] is now in development and due for publication in April 2024.
Time horizon considered for the economic analysis The company adopted a lifetime horizon (40 years) in the model. The ERG considered the time horizon should be reduced to 5 or 10 years in the absence of data on treatment waning. Is a lifetime horizon appropriate? Would you expect visual acuity across all treatments to converge during the off-treatment period? How long could this take in your opinion?	The different NICE TAs on DMO have adopted different time horizons. The most recent was the NICE TA613 adopted 30-years' time horizon. A similar time horizon would have been expected for this TA. The rationale for the different time horizon suggested by the ERG on this occasion needs to be more clearly articulated. I cannot find that clarity in the ERG report. Previous TAs have been based on 2-year studies (including registration studies). The lack of long-term data should not be the basis for shorter time horizon for this appraisal. It is expected that treatments for DMO would have modified the natural history of the disease. Such modification would have shifted the natural history including visual acuity changes. As such, although some convergence may occur, the exact timings are difficult to predict. Rossi et al (2020) reported a 20.4% prevalence of diabetes in people undergoing cataract surgery. DR and DMO worsened after cataract surgery. 27.9% had DR including 7.1%had previous laser photocoagulation; 19% had NPDR, and 14% PDR. Macular oedema occurred in 27.5%, and clinically significant macular oedema in 6.5%. (Rossi et al, 2020).
Changes in BCVA resulting from DEX700 treatment in Years 4 and 5 The company obtained the 3-	Maintenance of visual acuity in DMO is dependent on optimal treatment. It is expected that DMO eyes that are optimally treated will maintain vision, and the earlier visual gains. However, the vision will deteriorate in eyes that receive suboptimal treatment with DEX or other therapies. Specifically, it is expected that BCVA should not decline in years 4 and 5 if optimally treated. (Any deterioration due to cataract would have been corrected previously by cataract surgery.)

monthly transition probabilities in Years 1 to 3 from MEAD. The 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. The ERG considered assuming vision is maintained more appropriate, if conservative for Years 4 and 5. Would the last transition matrix provide the most relevant data available from MEAD?	The continuation of anti-VEGF in eyes responding to treatment are known to be maintained with optimal treatment, whilst suboptimal treatment results in visual decline. In DMO eyes that are not responsive to anti-VEGF treatment, visual decline will continue over time. Continuation of anti-VEGF therapies in these eyes may be adopted by clinicians in the absence of appropriate alternative treatments, with the resultant progressive vision loss. Real world experience arms may be used as proxy. In the DRCRNet Protocol U, a significantly higher % of eyes gained 15L improvement in the group treated dexamethasone implant (11%) compared to ranibizumab (2%) alone.
Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5 The company used the sham arm of the MEAD trials as a proxy for continued anti-VEGF use.	Clinical management of DMO, including UK practice have evolved since commencement of the MEAD study. As such the MEAD study criteria should not be the main reference point. There is significant real life studies available to guide clinical decision making as summarised elsewhere. The continuation of anti-VEGF therapy regardless of benefit is adopted by clinicians where there is no alternative therapies available. This has significant impact on repeated clinical risks vrs benefits.

The ERG disagreed with the company's argument that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF. Do you agree that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF?	
Subsequent treatment following discontinuation of DEX700 The company assumed patients receive no further treatment following discontinuation of DEX700. The ERG disagreed with this assumption. Would re-treatment with an anti-VEGF be offered in clinical practice?	When treatment is discontinued, a wait and see option is adopted by some clinicians until the CRT reaches the minimum 400 microns allowed by NICE TAs for anti-VEGF therapies in DMO. This unless these eyes have been previously treated with anti-VEGFs. Generally, continuation of treatment may not benefit most eyes that were previously unresponsive to anti-VEGF. Some eyes may be re-assigned to anti-VEGF therapies, although there is no evidence for effectivity. However, the majority may not be. As such, the option of no further treatment is a valid option. There remains the current unmet need for DMO unresponsive to or unsuitable for treatment with anti-VEGF therapies.

Would this treatment be unlikely to be effective? Are you aware of any evidence that could support this?	
The natural history of vision in eyes with DMO The company estimated a 3-month probability of gaining or losing at least 10 letters of BCVA (moving up or down one health state) of 3.5% and 4.5%, using WESDR data to inform the estimates. The ERG considered the 3-month probability of gaining at least 10 letters of BCVA of 3.5% to be too high. Furthermore, the ERG considered data from WESDR could represent a less severe set of patients than the population for this appraisal and are	The natural history was well documented previously in pivotal studies. However, clinical practice has changed significantly since the introduction of new therapies. Natural history studies after discontinuation treatments are limited. The Danish retrospective study of Hodzic-Hadzibjovic et al (2018) reported a 25.4% switch of anti-VEGF to other treatments. Treatment was discontinued in 31.6% due to disease stability, and 1.4% because of significant vision reduction, whilst 3.2% died. Switching from ranibizumab to aflibercept did not result in a change in VA, and CST only reduced by <10% compared to baseline. Nine percent (9%) of 566 eyes originally treated with anti-VEGF drugs were switched to dexamethasone implant (Ozurdex). The probabilities seem correct. The lower ICER thresholds suggested by the TAG seems arbitrary, especially if confidential discount for anti-VEGFs are counted in this appraisal.

likely to reflect outdated practice. Is a 3-month probability of gaining at least 10 letters of BCVA of 3.5% to be too high? What would be the most appropriate source of natural history data?	
Are there any important issues that have been missed in ERG report?	Section 3.2.3 French RWD. The 'concern that the French RWD does not reflect UK population for this characteristic is inconsequential, as in the UK only DMO eyes with CRT>400microns would have received treatment with intravitreal anti-VEGFs (non-corticosteriod pharmacotherapy). Furthermore, laser photocoagulation would not be beneficial (and not recommended) in centre-involving DMO. The baseline VA in the French study is more reflective of VA in naïve UK DMO eyes. Section 3.2.4 UK RWE. Missing data in the laser treated group (in 50%) is irrelevant as the majority if not all cases of centre-involving DMO are not treated with laser photocoagulation. Section3.3.2. The difference may also be due to timing of cataract surgery. Section 3.4.1.1. Timing of cataract surgery Section 4.2.2.1. This point is irrelevant as it is the efficacy of Dexamethasone implant vrs anti-VEGFs being considered, and in all types of DMO. Section 4.2.6.1.1 RWE sham arm can be used as proxy Pg 96. LOCF. The high discontinuation in sham group can be explained by progressive deterioration requiring rescue. Pg 66. UK practice. Comments are unjustified as anti-VEGF will still be low when NICE criterion of 400 microns is taken into account.

	Pg 67. Data on laser photocoagulation vrs Dex is not available and will be inappropriate as laser is only used in non-centre involving DMO. A retrospective study from Turkey (Kaldirim et al, 2020) compared outcomes in phakic vrs pseudophakic DMO eyes unresponsive to anti-VEGF therapy treated with dexamethasone implant. In this study, the Dex was equally effective in reducing the DMO in both phakic and pseudo phakic eyes. (Kaldrim H et al. Comparison of anatomical and functional outcomes of intravitreal dexamethasone Implant between phakic and pseudophakic eyes with diabetic macular edema. Korean J Ophthalmol 2020;34(5):383-391. https://doi.org/10.3341/kjo.2019.0142). A phase III prospective multicentre randomised study of intravitreal Dex implant given at 5 monthly intervals vrs laser photocoagulation given 3-monthly in CI-DMO in the Asia-Pacific region (Wei W et al, 2021) recently reported a significantly better improvement in BCVA (4.3L with Dex vrs 1.4L laser; p = 0.001), CRT (−209.5 µm with DEX versus −120.3 µm with laser (P <0.001), and total leakage area from baseline (−8.367 mm^2 with DEX versus −0.637 mm^2 with laser (p < 0.001) at 12 months. Wei W et al. Multicenter, prospective, randomized study of dexamethasone intravitreal implant in patients with center-involved diabetic macular edema in the Asia-Pacific Region. Clin Ophthalmol 2021;15: 4097–4108.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is an unmet need for use of this technology in eyes that are phakic and unresponsive to intravitreal anti-VEGF therapies, and in patients where intravitreal injections of anti-VEGF therapies as treatment for DMO are unsuitable.
- The efficacy of dexamethasone implants in DMO is not affected by the lens status (i.e. pseudophakic or phakic), and a significant proportion of eyes in diabetics have cataracts at baseline (pre-treatment with the technology) as reflected in clinical trial and real world data.
- Outcomes of cataract surgery in phakic eyes treated with dexamethasone implants are excellent and comparable eyes that have not been treated with the technology.
- The adverse event of intraocular pressure increases after dexamethasone implants in diabetics are less frequent than in non-diabetic eyes.
- Treatment of DMO eyes that are phakic is capacity sparing, clinically effective and cost-effective.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with Diabetic macular oedema (DMO) or caring for a patient with DMO. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **11 May 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with DMO

Table 1 About you, DMO, current treatments and equality

1. Your name	Stephen Scowcroft
2. Are you (please tick all that apply)	☐ A patient with DMO? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with DMO? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Macular Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with DMO? **If you are a carer (for someone with DMO) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for DMO on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for DMO (for example, how dexamethasone 700 µg (DEX700) is given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of DEX700 over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does DEX700 help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	

10. If there are disadvantages of DEX700 over current treatments on the NHS please describe these. For example, are there any risks with DEX700? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from DEX700 or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering DMO and DEX700? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	

13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Uncertainty around the generalisability of the results from the MEAD trials Are results from the MEAD trials generalisable to people seen in UK clinical practice? Are you aware of other clinical evidence in the	It is worth noting that the treatment paradigm has changed since the MEAD trial was undertaken. At the time there was mainly laser use and a low usage of anti-VEGF. This has now changed and there are more options available to clinicians. This highlights the area of unmet need as despite an increase in options there is still a group of patients who do not have access to a wider variety of treatment options when they no longer respond to the treatment they have been on.

Patient expert statement

correct population for the required comparators?	
Time horizon considered for the economic analysis The company adopted a lifetime horizon (40 years) in the model. The ERG considered the time horizon should be reduced to 5 or 10 years in the absence of data on treatment waning. Is a lifetime horizon appropriate? Would you expect visual acuity across all treatments to converge during the off-treatment period? How long could this take in your opinion?	It is worth noting that there should be a comparable lifetime horizon to other HTAs for similar treatment areas. If this is not the case then is may not be a fair and reasonable comparison. From the a patient's point of view the longer the lifetime horizon the more realistic this is as DMO is a life long condition.
Changes in BCVA resulting from DEX700 treatment in Years 4 and 5	No comment

Patient expert statement

The company obtained the 3-monthly transition probabilities in Years 1 to 3 from MEAD. The 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. The ERG considered assuming vision is maintained more appropriate, if conservative for Years 4 and 5. Would the last transition matrix provide the most relevant data available from MEAD?	
Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5 The company used the sham arm of the MEAD trials as a proxy for continued anti-VEGF use. The ERG disagreed with the company's	No comment

Patient expert statement

argument that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF. Do you agree that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF?	
Subsequent treatment following discontinuation of DEX700 The company assumed patients receive no further treatment following discontinuation of DEX700. The ERG disagreed with this assumption. Would re-treatment with an anti-VEGF be offered in clinical practice? Would this treatment be unlikely to be effective? Are you aware of any evidence that could support this?	From a patient's point of view – if there is no alternative treatment available (which there currently is not for this group of patients) then it is most likely that the same treatment is continued without any further positive impact. This has the additional patient burden of all of the issues/ challenges with having a treatment (time, expenses, and anxieties) without any positives. As highlighted in our submission this can lead to sub optimal outcomes.

Patient expert statement

The natural history of vision in eyes with DMO The company estimated a 3-month probability of gaining or losing at least 10 letters of BCVA (moving up or down one health state) of 3.5% and 4.5%, using WESDR data to inform the estimates. The ERG considered the 3-month probability of gaining at least 10 letters of BCVA of 3.5% to be too high. Furthermore, the ERG considered data from WESDR could represent a less severe set of patients than the population for this appraisal and are likely to reflect outdated practice. Is a 3-month probability of gaining at least 10 letters of BCVA of 3.5% to be too high? What would be the most appropriate	No comment

Patient expert statement

source of natural history data?	
Are there any important issues that have been missed in ERG report?	No comment

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with Diabetic macular oedema (DMO) or caring for a patient with DMO. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Patient expert statement

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **11 May 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the

comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with DMO

Table 1 About you, DMO, current treatments and equality

1. Your name	Bernadette Warren
2. Are you (please tick all that apply)	☒ A patient with DMO? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with DMO? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Macular Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible)

	☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: My other experience comes from conversations that have been had on a one to one basis or with groups of others with DMO through the facebook group 'Diabetic retinopathy Uk support group' as well as the Macular Society DMO support group

	which met on line in September- December 2021 and January-May 2022. These people reside all across the UK ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with DMO? **If you are a carer (for someone with DMO) please share your experience of caring for them**	I was diagnosed with DMO (CSMO) in 2011 at the time I was in my early 40's working as a teacher in a primary school I am married and at the time of diagnosis my children were aged 12 and 14. Little did I know the severe impact that this condition would have not only on myself but on my family and friends too. Below I describe the treatment I have had for DMO and the impact the condition has had on myself and my family. **Treatment** Once I had been diagnosed treatment started promptly with injections in both eyes but it soon became apparent that my left

	eye which was my best seeing eye then was not responding. A Fluorescein angiogram was performed in 2015 and it was found I had ischemia in that eye and so all treatment for that eye stopped. My vision in that eye at the start of treatment was 6/9 it is now 1/60 (snellen). We were able to carry on treatment with my right eye and to date I have had over 90 injections in that eye. My vision at the start of treatment was 6/12 and it is now 6/24-30 Unfortunately with the injections I developed cataracts that then caused ocular hypertension for which I had bilateral iridotomies in 2016. My injections have generally caused no short term issues however in September 2021 and November of the same year I developed corneal abrasions after my injections these were extremely painful and far worse than the injection itself. On examination I was found to have very dry eyes and now take Clinitas 4 times a day as well as Carbomer eye gel at night. At a recent appointment I was told the dry eye syndrome could well be a complication of diabetes as well as having the injections. Not many clinicians I have seen know of many (if any) patients that have had so many injections. We have tried all 3 drugs available, unfortunately I could not try any steroid implants as I have been found to be a steroid

	responder (someone who experiences raised intraocular pressure while taking steroid medication). This means the only drug available to me are VEG-F drugs. **Impact** The impact on DMO has been huge not only on my physical life but at times my mental health too. As already stated when diagnosed I was starting middle age and was working as well as driving and very much enjoying life. Within 14 months of diagnosis I lost my beloved job and the following year my driving license. The loss was so quick and sudden it took me 6 months to regain any feeling of self worth. Feelings of guilt and shame overwhelmed me and I honestly did not know what I would do with my life whilst trying to set a good example to my children and supporting my husband financially as well as with all the practical issues bringing up children bring. My eldest daughter started to blame herself because at that time it was thought my diabetes had been gestational. It has been a really hard few years. I have attended appointments every month for DMO since 2011. I have great difficulty with my sight and was registered sight impaired in 2016. Difficulties include recognising peoples faces, colours, reading of text and contrast. As someone with poor sight I have missed out on clearly seeing some of the things I would

	normally see without issue such as the recent graduation of both my daughters, and last year the funerals of my father and father in law. Everyday life is a challenge with many forgetting or not realising I have a sight issue, though more often than not I do use a long cane now which helps. On a day to day basis life with DMO has been a struggle, not being able to drive has left me dependent on public transport or family or friends giving me a lift. My husband has recently been away for six weeks and so the onus has been on my daughter to take me and collect me from places I want to go and to be honest the embarrassment of asking for a lift or the effort to go by public transport is sometimes too much to bear and I stay at home. When going out socially with my husband he can never enjoy a drink because he will always be the driver and that has made me feel guilty. Recently my hospital appointments for diabetes have changed to a hospital I cannot get to by public transport and it has made me feel annoyed that my needs have not been met especially as my appointments used to be at a hospital just down the road from me. it was only when I pointed this out and said I might need to change hospitals that they gave me an appointment more easily accessible.

	Things I used to enjoy doing are now difficult and my hobbies and interests have had to adapt. I have however tried to remain positive and concentrate on things I can do not things I can't but I miss the things I so enjoyed doing such as driving to garden centres and walking around on my own for a couple of hours having some 'me' time or being able to nip down to supermarket to get the items I have run out of. I now struggle to recognise friends as I go about my business I just don't see them and unless they say 'Hello' I just don't know who they are. As mentioned earlier people often forget I have sight loss and because they can see well they forget I cannot. I often end up confused and left out of conversations because I can't see what others are referring too, this is particularly the case when watching television. Both my lenses are phackic and although I have posterior subcapsular cataracts surgery is not planned as yet.
7a. What do you think of the current treatments and care available for DMO on the NHS? **7b. How do your views on these current treatments compare to**	At the moment the main treatment option is injection therapy. Those with diabetes not just myself are told many a time that diabetes can sometimes complicate the way we respond to treatments whether that be for the eyes or any other part of the body. Many for example are given 5 loading injections for DMO instead of the usual 3 as

those of other people that you may be aware of?	'Diabetics sometimes take longer to respond to treatment' I am an active Facebook user and often see posts on 'Diabetic retinopathy UK support group' page and it does seem to be a difference in care and treatment for DMO around the country which can lead to confusion and misunderstanding. I also found this when taking part and helping to lead the Macular Society DMO support group. One example of this involves after care. Once an injection has been administrated some are given chloramphenicol antibiotic eye drops to be taken for 4 days after an injection some are not. When I questioned why these were not given at a hospital I was told that they did not want someone to build up an immunity to it in case it was really needed for an actual infection yet my hospital give them to me each month and it leads me to wonder should I take them or not. Another example is that some hospitals have a 'One stop shop' appointment system but some do not. A friend of mine has to attend one appointment for the assessment and another for the injection this not only takes up a lot of time but also costs twice as much to attend by public transport. Lastly I have felt myself that at times we with DMO are being left behind as far as drugs and research go and that those with AMD are given priority over us. It is only in the last two months that I

	have heard of any research for DMO. Through conversations I found I am not the only one who has felt this way. The role out of ranibizumab helped to fuel this thought as it was offered for AMD many months before it was offered to myself. I had to sit next to patients receiving the very drug I and my opthalmologist were desperate for me to try.
8. If there are disadvantages for patients of current NHS treatments for DMO (for example, how dexamethasone 700 µg (DEX700) is given or taken, side effects of treatment, and any others) please describe these	There are some disadvantages of the current treatments for DMO some of these are relevant to me some to others I have communicated with over the years. The disadvantages are listed below **Time** - some even take the day off work not just themselves but a career too so that they can attend an appointment without using public transport. One employer insisted that a patient took time off for treatment as part of her annual leave. **Complications** - Like me the injections can lead to other complications such as *cataracts* then ocular hypertension. I have cataracts (posterior subcapsular as well as nuclear) in my right eye which is the one having injection therapy. It is my best seeing eye and causes many issues with contrast and glare. short term complications such as *corneal abrasions* are very painful and *dry eyes* need careful and time consuming management.

	Many I have heard directly from have a *reaction to the iodine* administrated this can be very painful leading to anxiety for following appointments. Many have eyes washed out afterwards which can help but takes extra time and can be stressful. *Infection* is also a risk though I have never had this happen to me **Aftercare** -The taking of antibiotics for some can be an issue these need to be kept in the fridge but if taking them 4 times a day if away from home this can be problematic. After an injection vision can remain blurred for many hours for me I have to get 2 buses home and my sight is very blurred this is even more difficult if appointments are in the afternoon when it can get dark quickly in the winter.
9a. If there are advantages of DEX700 over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do**	DEX700 is not an anti veg f drug it is instead a steroid this would be an advantage over the other drugs which are anti-veg f drugs. Studies have shown that some patients who were treated were able to go 2-3 months before further treatment if that were the case then that would be a further 4 weeks perhaps for some over other treatments which would be an advantage for those patients who work and have other responsibilities Another advantage involves aftercare I for example am given a bottle of antibiotic eye dops after each injection 4

you consider to be the most important, and why? **9c. Does DEX700 help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	times a day for 4 days this is to prevent infection these have to be kept refrigerated which can be an issue if away from home or a fridge. Another advantage is that patients are often advised not to wash their hair for a week after an injection for some this is an issue and so reducing this to only 1 week in eight will be a great benefit over the 1 in 4 scenerio. Another advantage is that if it is given 12 weeks it will lessen the risk of complications such as infection to the injected eye Much discussion that I have heard recently also involves contact lens wearers if a person wears these the advice is is that they avoid wearing them for a period of time after an injection this would obviously only affect a few days within perhaps a 12 weeks time frame with DEX700 The fact that this is not an anti veg f is an important factor as it would be another option for those who have not responded to anti veg f treatment .

	Also the greater distance between further treatments would be advantageous to those that have work commitments or other repsponsibilities. If a patient only has to attend only every 12 weeks then this would be advantageous as it would reduce the amount of time away from work or other commitments.
10. If there are disadvantages of DEX700 over current treatments on the NHS please describe these. For example, are there any risks with DEX700? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Dexamethasone is a steroid treatment and steroids come with added risks and thus disadvantages to patients over ant veg f treatment, for example cataracts might ocular with more patients and the inter ocular pressure may also increase . I myself am a steroid responder and cannot take such treatments as it would negatively affect my ocular pressure. Another disadvantage maybe that since the appointments maybe every 12 weeks eye issues that have no side affects such as an increased ocular pressure may not be noticed until the next

	appointment which may cause further issues to the eyes
11. Are there any groups of patients who might benefit more from DEX700 or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	In order to receive this treatment you need to be fit and able without having had any of the conditions mentioned above this will mean that its benefits will only be experienced by those who are fit and well. I myself has to miss an injection due to being an inpatient with Covid in March 2022 because I missed one injection my sight went from 6/30 in my best seeing eye to 6/60 I only retuned to 6/30 after my injection in April. This treatment also needs to be given in hospital and therefore only those with means of transport will be able to have it. The antibiotic eye drop bottle can be difficult to open and the bottle can be hard to squeeze to release the eye drop this might be an issue for some with dexterity issues.
12. Are there any potential equality issues that should be	

taken into account when considering DMO and DEX700? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	

Patient expert statement

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	DMO in its very nature combines 2 chronic conditions. I have found during the last ten years that my diabetes team know very little about DMO and what causes it. **I** believe that better communication is needed between diabetes experts/consultants and opthalmologists so that each can learn from each other about the challenges of both diabetes and DMO and in particular what causes DMO.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Uncertainty around the generalisability	

Patient expert statement

of the results from the MEAD trials Are results from the MEAD trials generalisable to people seen in UK clinical practice? Are you aware of other clinical evidence in the correct population for the required comparators?	
Time horizon considered for	

the economic analysis The company adopted a lifetime horizon (40 years) in the model. The ERG considered the time horizon should be reduced to 5 or 10 years in the absence of data on treatment waning.	

Is a lifetime horizon appropriate? Would you expect visual acuity across all treatments to converge during the off-treatment period? How long could this take in your opinion?	
Changes in BCVA resulting from DEX700 treatment in Years 4 and 5	

The company obtained the 3-monthly transition probabilities in Years 1 to 3 from MEAD. The 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. The ERG considered	

assuming vision is maintained more appropriate, if conservative for Years 4 and 5. Would the last transition matrix provide the most relevant data available from MEAD?	
Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5 The company used the sham	

arm of the MEAD trials as a proxy for continued anti-VEGF use. The ERG disagreed with the company's argument that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF. Do you agree that the sham arm of the MEAD trials	

likely overestimates the efficacy of continued anti-VEGF?	
Subsequent treatment following discontinuation of DEX700 The company assumed patients receive no further treatment following discontinuation of DEX700. The ERG disagreed	

with this assumption. Would re-treatment with an anti-VEGF be offered in clinical practice? Would this treatment be unlikely to be effective? Are you aware of any evidence that could support this?	
The natural history of vision in eyes with DMO	

Patient expert statement

The company estimated a 3-month probability of gaining or losing at least 10 letters of BCVA (moving up or down one health state) of 3.5% and 4.5%, using WESDR data to inform the estimates. The ERG considered the 3-month probability of gaining at least 10 letters of	

BCVA of 3.5% to be too high. Furthermore, the ERG considered data from WESDR could represent a less severe set of patients than the population for this appraisal and are likely to reflect outdated practice. Is a 3-month probability of gaining at least 10 letters of	

BCVA of 3.5% to be too high? What would be the most appropriate source of natural history data?	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

1) DMO can have a huge negative impact on a persons life leading to job loss and the ability to drive
2) DMO can lead to further eye complications such as dry eye syndrome and cataracts which can cause further sight loss
3) DMO treatment and after care is not the same across the UK
4) DEX700 is a steroid treatment and thus different from many of the other drugs given for DMO due to the chance of a greater rise in eye pressure and formation and progression of cataracts it may be unsuitable for some patients.
5) The length of time between treatment with Dexamethasone would be beneficial to those who work and have other commitments..

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **11 May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating Diabetic macular oedema (DMO) and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Faruque Ghanchi
2. Name of organisation	Bradford Teaching Hospitals NHS Foundation Trust
3. Job title or position	Consultant Ophthalmologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with DMO? ☐ A specialist in the clinical evidence base for DMO or technology? ☐ Other (please specify): Clinical expert - Company
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for DMO? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Controlling macular exudation for improving and maintaining vision.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in vision with resolution of macular oedema, maintaining macula in driest possible state.
10. In your view, is there an unmet need for patients and healthcare professionals in DMO?	Yes, phakic DMO patients, who have suboptimal response to antiVEGF treatment, do not have access to steroid treatment.
11. How is DMO currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	RCOphth Guidelines, NICE guidance for antiVEGF and steroid implants guide clinical practice in the NHS centres. Generally, Well defined care pathways for initiation of treatment, though there are variation as to choice of antiVEGF at initiation; Unmet need in guidance for poorly responsive patients on current therapies, especially phakic DMO patients DMO care is essentially provided in secondary care.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Ozurdex usage and care pathway are well known in the NHS. Ozurdex in DMO would help reduce treatment burden for the patients and the NHS Secondary care Existing set up is sufficient for incorporating Ozurdex in clinical practice for DMO.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, Ozurdex has same biological effects and hence functions as well as in phakic

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	eyes as in pseudophakic eyes with macular oedema. It has proven longer treatment effect than current antiVEGF in NHS practice. Yes, especially in patients who are poorly responsive to current treatment options for DMO.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	See above
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Ozurdex has been in clinical practice for other indications including pseudophakic DMO, RVO and Uveitis – so wide clinical experience with the technology. NHS services are already providing this care so very little – if any impact on its practical implications.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	Submitted evidence captures this well.

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes Longer duration of action, dual mechanism of action –anti-inflammatory + antiVEGF
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	AEs are few, 2 with clinical impact Glaucoma and Cataract – are clinically managed usually drops (for glaucoma) and surgery for cataract when indicated.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	YES, Pivotal studies (MEAD I &II) included DMO populations, Ozurdex is effective in DMO Yes, improving visual acuity and drying macula No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any other relevant new evidence apart from that from the MEAD trials?	A number of Real Life Studies have concurred with MEAD studies for efficacy and safety of Ozurdex.

Clinical expert statement

23. How do data on real-world experience compare with the trial data?	As above-
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	The phakic DMO patients currently cannot access Ozurdex treatment, though their macular oedema may not respond to other available options. Thus they are – unlike psedophakic DMO patients are at a disadvantage of not getting treatment benefit from Ozurdex and with persistent macula oedema at risk of losing opportunity to improve visual function as well as losing further vision. Younger DMO patients are more likely to be phakic patients and hence more at a disadvantage.

Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Uncertainty around the generalisability of the results from the MEAD trials Are results from the MEAD trials generalisable to people seen in UK clinical practice? Are you aware of other clinical evidence in the correct population for the required	YES MEAD included DMO patients in randomised fashion. It had group of patients who had suboptimal response to prevailing therapies. The FINAL outcome of eye with persistent macular oedema is that there will be irreversible loss of vision (due to structural changes in retina that become irreversible). MEAD showed positive impact of Ozurdex on eyes in subgroup that has poor response to other interventions. This is transferrable to current clinical practice where DMO patients have poor response to other injections treatment. Real life studies (RELDEX, SAFODEX etc. and clinical experience / audits have shown Ozurdex to be effective after suboptimal response to antiVEGF injections.

Clinical expert statement

comparators?	
Time horizon considered for the economic analysis The company adopted a lifetime horizon (40 years) in the model. The ERG considered the time horizon should be reduced to 5 or 10 years in the absence of data on treatment waning. Is a lifetime horizon appropriate? Would you expect visual acuity across all treatments to converge during the off-treatment period? How long could this take in your opinion?	Modelling is used as a surrogate marker which for condition affecting relatively younger population would need to be long duration unlike ERG's consideration of 5 (or 10)years which would be too short. A lifetime horizon would be more appropriate. NICE has used longer time horizon in previous appraisals. With time it is expected that visual acuity will converge over time after active treatment is discontinued.
Changes in BCVA resulting from DEX700 treatment in Years 4 and 5 The company obtained the 3-	The impact of resolving macular oedema on visual function is long lasting. With continued treatment and maintenance of dry state of macula, visual acuity improves over time and this is observed in clinical practice too beyond first 3 years, at modest rate. As observed in MEAD phakic population the visual acuity trend turns up in year 3 and thus extrapolation

Clinical expert statement

monthly transition probabilities in Years 1 to 3 from MEAD. The 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD. The ERG considered assuming vision is maintained more appropriate, if conservative for Years 4 and 5. Would the last transition matrix provide the most relevant data available from MEAD?	that there will be modest vision improvement in years 4 /5 is entirely plausible.
Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5 The company used the sham arm of the MEAD trials as a proxy for continued anti-VEGF use.	MEAD studies had patients who were receiving treatment as per the Standard of Care that prevailed at that time. The eventual retinal changes that take place with 'suboptimal' response to (any) treatment are disorganisation of retinal tissue. Hence the data from previous studies (MEAD in particular) are relevant for comparison on 'poor responders'. Whilst MEAD protocol mandated removal of subjects from trial for poor response, thus the population distribution is skewed. The SHAM population who continued on MEAD would therefore be with 'better' outcome than those who left the study and hence this population is not comparable to patients who have

Clinical expert statement

The ERG disagreed with the company's argument that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF. Do you agree that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF?	suboptimal response to antiVEGF treatment. Furthermore, Fame study, where control group was allowed rescue treatment demonstrates clinically meaningful improvement after rescue intervention.
Subsequent treatment following discontinuation of DEX700 The company assumed patients receive no further treatment following discontinuation of DEX700. The ERG disagreed with this assumption. Would re-treatment with an anti-VEGF be offered in clinical practice? Would this treatment	The discontinuation of treatment is usually for 1. Meeting success criteria 2. Futility or rarely 3.Adverse events. Thus- following success of therapy there should not be need for further treatment. Where there is futility of treatment (failure) which was used to substitute another treatment, there would be no further treatment except for an exceptional cases. Withdrawal of treatment for Adverse event cases (rare) would merit consideration of alternative. Real impact of use of antiVEGF injections as 3rd line rescue option is not known.

be unlikely to be effective? Are you aware of any evidence that could support this?	
The natural history of vision in eyes with DMO The company estimated a 3-month probability of gaining or losing at least 10 letters of BCVA (moving up or down one health state) of 3.5% and 4.5%, using WESDR data to inform the estimates. The ERG considered the 3-month probability of gaining at least 10 letters of BCVA of 3.5% to be too high. Furthermore, the ERG considered data from WESDR could represent a less severe set of patients than the population for this appraisal and are	Patients' visual function change with DMO, WESDR data are relevant as it provides longitudinal data. Current UK practice offers best possible management of DMO, thus there will be a small proportion of patients (as in WEDR) who would gain vision, and despite this SoC in UK, the natural course of diabetic retinal changes (including maculopathy) would cause loss of vision in small proportion. It is unlikely to be 'no change'. Patients with optimised control of macular oedema can continue to gain vision with continued treatment beyond 3 years.

likely to reflect outdated practice. Is a 3-month probability of gaining at least 10 letters of BCVA of 3.5% to be too high? What would be the most appropriate source of natural history data?	
Are there any important issues that have been missed in ERG report?	Almost half the patients receiving treatment for DMO are less than 60 years (UK RLE) – working age, phakic who need optimum control of DMO to help improve and then maintain vision with optimum therapy. The benefits of the treatment would be lifelong – for many years.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

1. Current unmet need for phakic DMO patients who are unresponsive to not corticosteroid treatments: leaving such patients on ‘wait and watch’ approach is detrimental to vision and overall health status. Similarly not offering rescue and continuing with antiVEGF (where efficacy is poor) is poor patient management and poor use of resources.
2. The current practice of using AnitVEGF injections for DMO, has significant treatment burden- especially where treatment response is suboptimal.
3. Majority of DMO patients have ‘cataract’ present at the time of first treatment (UK RLE, MEAD). Vision degradation from persistent macular oedema (unresponsive cases) compounds issues for phakic patients who have ‘cataracts’.
4. Dexamethasone is as effective in pseudophakic eyes as is in phakic eyes. There is clinical evidence that early normalisation of retinal structure (resolution of macular oedema) results in better visual function, where rescue – is delayed the visual recovery is modest.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **11 May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Alimera Science** Digital Office Centre, Balheary Demense, Balheary Road, Swords, Dublin, K67 E5A0, Ireland.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None to declare.**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Uncertainty around the generalisability of the results from the MEAD trials	Yes/**No**	**We recognise the uncertainties around the generalisability of the results of the MEAD trials as do the CS. However, there remains a significant unmet need in phakic patient population and the RW evidence provided by the CS demonstrates the effectiveness of DEX700 in the phakic population in clinical practice.** *We consider the ERG argument from the perspective of the use of RW data in the HTA process, the limitation of the comparator treatment in clinical practice, key clinical issues, lack of clinical guidance for stopping rules for the comparator treatment and model assumptions*. We recognise the importance of the process implemented by decision makers in using real-world (RW) data in coverage and reimbursement. The salience of supportive RW data is that it can provide valuable information on treatment practices and patient characteristics among unselected patients. The provision of RW data as supportive evidence in the company submission (CS) is a highly integrative approach and lends credence and plausibility to

		the true effectiveness of DEX700 in clinical practice. Conversely, the RW evidence of anti-VEGF treatment demonstrates that it fails to achieve the reported BCVA outcomes from its pivotal clinical trials, due to a number of factors: (i) in the real world the strict anti-VEGF treatment regimen is difficult to achieve, it comes with a high patient burden, clinic burden and resourcing issues. (ii) Up to 40% of patients have insufficient response to anti-VEGF. (Gonzalez et al, 2016). Nearly 75% of DME patients are phakic and are currently treated with anti-VEGF or laser therapy (UK Macular Society). In cases of insufficient response, treatment with anti-VEGF is continued, often with another anti-VEGF agent introduced as second line therapy for which there is clinical benefit is not substantiated in terms of vision gains or sufficiently addressing retinal oedema. Retinal oedema must be considered relative to visual preservation and improvement. The goal of treatment is therefore the preservation or improvement in retinal function by reducing retinal thickening and oedema. (Downey et al 2021) The sequencing of anti-VEGF agents in cases of insufficient response was in fact noted during the TA613 review "*The committee was aware that most people who initially have anti-VEGFs and that in phakic eyes they might be continued even if they do not work well*." Limitations of the use of the RW data were highlighted by both the CS and the ERG (non-comparative data, heterogeneity with low ESS in MAIC). Using the MEAD mITT sham population as a proxy for anti-VEGF failure had limitations and biases and the underlying assumptions were rejected by the

		ERG. The CS was however transparent in presenting their underlying assumptions as it relates to the use of the sham-arm of the MEAD trial as a proxy for anti-VEGF use. The unique risks, costs, and benefits in this phakic sub-population are accounted for by the CS and they acknowledged the uncertainty which were largely mediated by prevailing treatments approved for DMO at the time of the MEAD trial conduct. The MEAD trial was started at a timepoint where the prevailing first-line treatment in DME was laser photocoagulation. Anti-VEGF was not authorised by the regulatory authorities for the treatment of DMO at that time, in the intervening years anti-VEGFs have become first line treatment in DME. "*The MEAD study began in 2004, and the high rate of patient discontinuations was a consequence of the study design requirement for patients to exit before receiving any escape treatment. The discontinuation rate was substantially higher, and patients discontinued earlier in the sham group than in the DEX implant groups because of lack of efficacy. Long-term studies of medical treatment in DME that were designed more recently have permitted patients to receive escape treatment and remain in the study. For example, in the 2-year RISE/RIDE study of DME patients treated with ranibizumab, which began in 2009, patients who met predefined criteria were treated with adjunctive macular laser as well as ranibizumab or sham. The significant percentage of patients (72% in the sham group, 38% in the ranibizumab 0.3 mg group, and 27% in the ranibizumab 0.5 mg group) who were treated with macular laser during RISE/RIDE would have been exited from the MEAD study. Also, anti-VEGF became available during the MEAD study, allowing some patients a good escape*" (Boyer et al 2014)

		The benefits, limitations, and methodological challenges of using RW data in their submission was discussed by the CS • The UK RWE Audit is considered relevant as it provides important information about anti-VEGF use and outcomes in the clinical setting. Notably, the overall context and evidence-base from the RW data matter greatly in determining the true value of the intervention. In clinical practice anti-VEGFs do not deliver the same results reported in clinical trials and a significant proportion of patients remain non-responsive to treatment (Kiss et al, 2014). The EARLY trial analysis clearly identified that up to 40% of patients had a <5 letter-change at 3 months following anti-VEGF treatment., notably these changes were identified after 3 months of treatment and predictive of responses over the duration of the study.(Gonzalez et al, 2016); In DME, patients with phakic eyes and an insufficient response to first-line therapy, and those with phakic eyes with a CRT >400μm continue to receive anti-VEGF injections despite no visual (BCVA) benefit and deterioration of important retinal architecture. This comes at an increased cost for anti-VEGFs vs decreased letters gained which does not represent good value for the NHS England and Wales. • The totality of the real-world evidence demonstrates that treatment with DEX-700 leads to improvements in health outcomes in DMO patient eyes for which aVEGF is inappropriate or unsuitable, irrespective of the status of the lens DEX700 therefore fills an unmet therapeutic need in protecting the retina and avoiding vision loss in the phakic population for whom there are currently no alternative treatment options in the face of insufficient response to anti-VEGF.

		In the context of clinical practice in clinics across the UK, no effective guidance exists on the cessation of insufficient anti-VEGF therapy which would stop the wasteful use of NHS resources. Ideally, physicians would have the option to switch to a second-line therapy. Given current NICE guidance, this treatment escalation is not possible in the phakic DMO population whereby in-class switch (i.e., switch to another anti-VEGF agent) is the mainstay option despite lack of effect in as many as 40% of patients. A recent publication looking at consensus on when patients should be moved from a-VEGF to corticosteroids acknowledges that first-line treatment with an anti-VEGF is not an optimal treatment for a sizeable proportion of the DME population and acknowledges that many continue to receive anti-VEGF therapy despite insufficient response. The consensus group highlighted how it "*imposes a treatment burden on both patients and clinicians and, most importantly of all, can be sight threatening. Changing treatment to an intravitreal corticosteroid implant at the appropriate time may help optimise patient outcomes and reduce injection frequency, thereby reducing treatment burden*." (Downey et al 2021) Within the medical community there is a consensus on the acceptability of treating phakic eyes at risk of vision loss due to DMO with corticosteroids, in patients with an insufficient response to anti-VEGF. "*Phakic patients are as likely to have a suboptimal response to anti-VEGF treatments, and I would like the freedom to treat such patients with ILUVIEN irrespective of their lens status, in order that the retina can be effectively managed*" (Mr. Fahd Quhill, Sheffield Hallamshire Hospital). The case made is applicable to all corticosteroid intravitreal implants including DEX-700

		Patient access to corticosteroid treatment following insufficient anti-VEGF response in the phakic eye is thus considered a relevant and important change to the overall reimbursement decision in addressing this need. The acceptability of the CS model (with some modification) must therefore be considered despite its limitations; it is relevant and albeit contingent on the specific context, limitations, rational and reasons that frames the underlying assumptions relative to the unmet need of the phakic patient population in DME. In conclusion, we recognise the uncertainties around the generalisability of the results of the MEAD trials that have been acknowledged by both the CS and the ERG. However, there remains a significant unmet need in phakic patients and the RW evidence provided by the CS demonstrates the effectiveness of DEX700 in the phakic population in clinical practice.
Time horizon considered for the economic analysis	Yes/**No**	The assumption of treatment waning is a reasonable proposition. This however is subject to high levels of uncertainty. There is a dearth of longitudinal, prospective cohort studies of DMO (phakic and pseudophakic) beyond a three-year timepoint which collects data on the natural course of disease response and disease progression. Reducing the time horizon to either 5 or 10 years would itself be uncertain. As per the TA349 ERG response it was considered that a time horizon of less than 10 years was too short of a period to allow for the long-term impact of treatment on outcomes to be considered. Additionally, the ERG acknowledged that several assumptions would need to be made to consider a time horizon of longer than 10 years as the data were only available for up to 3 years. It is not clear how

		influential a parameter of waning of treatment effect would be on the model nor what impact they would have on the ICERs.
Changes in BCVA resulting from DEX700 treatment in Years 4 and 5	Yes/No	
Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5	Yes/**No**	The inherent limitations of the real-world data are accepted have been discussed in Issue 1 relative to the unmet need of the phakic patient population, who, with continued use of anti-VEGF when there is incomplete response are at higher risk of BCVA vison loss and damage to the retina. It is not clear that the sham arm in the MEAD trials does in fact overestimate the efficacy of the sham treatment arm. As noted by the ERG; "*suboptimal responders from the UK-RWE audit maintained reasonable stable vision between months 6 and 29…. none of the observed changes in Figure 10 would be considered clinically meaningful*". We would contend that the observed changes are clinically meaningful. It is important to point out that the pathophysiological and clinical consequences are most salient here and warrant careful consideration for this phakic population and the overarching unmet need. The retina exposure to risk is potentiated through insufficient response; prolonged and untreated oedema will cause irreversible damage to the photoreceptors, predisposing to blindness. Vison loss due to retinal photoreceptor degeneration has a deleterious impact on patient quality of life. (Himawan et al 2019). Recurrence of edema, i.e., repeated cycles of retina expansion and contraction damage the retina and have been linked with worse vision outcomes. (Starr et al 2021) If the retina is never dry, deterioration in function is to be expected.

		Second-line intravitreal corticosteroid treatments are very important to consider as DMO pathology is often multi-factorial including anti-inflammatory and anti-VEGF mediators in its aetiology. Anti-VEGF treatments only address the latter mediator. A recent independent publication highlighted that "*30 to 40% of optimally treated DME patients respond poorly to anti-VEGF with transient or incomplete resolution of fluid. This can be partly explained by the pro-inflammatory state present since the beginning of the disease that plays a pivotal role in the pathophysiology of early DR. As the disease progresses, studies have shown that the expression and secretion of inflammatory cytokines and chemokines increase accordingly, causing inflammation to play a major role in the pathogenesis of chronic DME inducing further resistance to anti-VEGF treatment. Therefore, steroids appear effective at all stages of DME*." (Kodjikian et al. 2022) Physicians are constrained by the current NICE restriction on corticosteroid therapy in the phakic DMO patient population. Phakic patient outcomes are impacted where patients persist on anti-VEGF treatment which it is not addressing the underlying mediators of their DMO. The full consequences of insufficient response should therefore be considered clinically meaningful. Additionally, cataract develops faster and earlier in people with diabetes, compared with those with normal glycemia (Panozzo et al 2021). Cataract progression is accelerated in DME: "*According to our study, diabetes is associated with an approximately two-fold increased detection rate of cataract. The risk of cataract associated with diabetes is highest at younger ages. Patients with diabetic macular edema are at an increased risk for cataract as well as patients with long-standing diabetes.* " (Becker et al 2015)

		Patients with DMO who are treated with an anti-VEGF agent are not immune to cataract development. 25% of diabetic patients undergoing cataract surgery have preoperative DMO (Panozzo et al 2021); this confers a high risk of the macula worsening, and potentially eliminating the vision benefits of cataract extraction; intravitreal corticosteroid immediately before or immediately post-op is effective in reducing this complication. However, current reimbursement restrictions to the phakic population prohibit its prescription. For those who develop a cataract as a natural progression of the DMO and the absence of pre-operative intravitreal corticosteroid treatment will not be eligible for cataract removal as a wet macula presents as a surgical risk. Intravitreal corticosteroid treatment therefore represents an important pre-operative intervention in the clinical management of the phakic population with pre-existing DMO as the CRT can change from <400 µm to >400 µm. This is acknowledged by the Royal College of Ophthalmologists whose evaluation of the evidence base that supports the treatment of such eyes with the intravitreal corticosteroid treatment in the perioperative period, where effect is optimised. "*Currently, some clinicians resort to IFRs to treat patients with DMO and CRT <400 µm who are not pseudophakic. However, this can be cumbersome and challenging on account of rejection due to financial constraints or poor appreciation of the clinical need. Clinicians believe that agreed national guidelines would streamline processes for offering the best care to such patients*". (Amoaku et al 2020). It must be highlighted, for those who fail the IFR process, these patients are consigned to wait and watch with continued DMO progression and sequela. One clinical expert for the CS noted the lack of evidence that the sham arm from MEAD undermines its applicability as a good proxy for the efficacy of continued anti-VEGF use. In the absence of a robust head-to-head RCT

		(DEX700 v anti-VEGF) the broader data limitations and assumptions which underpin the rationale for inclusion of the MEAD sham arm need to be considered in addressing the overall decision problem. There are several conditions for establishing good HTA process which include both transparency and relevance. The CS are transparent in the underlying assumptions as it relates to the use of the sham-arm of the MEAD trial as a proxy for anti-VEGF use. The point of relevance is substantiated through the supportive evidence of the real-world dataset provided. The benefits, limitations, and methodological challenges in using RW data are acknowledged. However, the overall context and evidence-base from the RW data matter greatly in determining the true value of the intervention. To that end, the MEAD trial design must be contextualized to the time when it was conducted, prior to the introduction of anti-VEGFs and where the prevailing first-line treatment in DMO was laser photocoagulation. Evaluation of the decision problem rests on both the empirical and pragmatic in the face of unmet need for the phakic patient population.
Subsequent treatment following discontinuation of DEX700	Yes/**No**	The assumption made by the CS presents as rational, there is no clinical evidence to support the use of anti-VEGF after DEX700. Is it plausible that following anti-VEGF failure and DEX700 discontinuation when DMO is driven by inflammation and not by VEGF that it would be clinically expedient and cost-effective practice to recommence anti-VEGF treatment for which there is a known insufficient response? Patient outcomes are impacted where patients have persisted on anti-VEGF treatment which is not addressing the underlying mediators of their DMO. This comes at a significant cost for suboptimal patient outcomes.
The natural history of vision in eyes with DMO	Yes/No	No response.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Clinical Pathway and Positioning of Technology	2.2.1	No	Occasionally a decision taken by NICE can have unintended consequences. This has happened with the restrictions for dexamethasone intravitreal implant in TA349 and fluocinolone acetonide intravitreal implant in TA301 to restrict access to these treatments only if a DMO patient has a pseudophakic lens. Clinicians faced with individual patients who are insufficient responders to, or unsuitable for, non-corticosteroid therapies but who do not have sufficient lens opacity to justify a cataract procedure, report they occasionally choose to perform the cataract procedure (with the patient's consent) so that the patient becomes eligible for these steroid treatments. Usually the patient will undergo the procedure, and then immediately receive the steroid intravitreal injection "on the table". Additionally, in current times, post COVID-19, the NHS cataract surgery backlog position is such that these patients have not only to deal with the problem that they are losing vision due to their cataract progression but also retina damage due to DMO. By the time they reach cataract surgery (which reverses the sight loss to cataract) with all the backlogs in place then the retina is so damaged that it no longer functions. Thus, allowing Clinician discretion to use a steroid in Phakic patients allows preservation of the underlying retina function balanced v the formation or worsening of cataract (which can be reversed).

Additional issue 2: Resource use and costs.	4.2.14	Yes/**No**	Existing backlogs in UK ophthalmology services have been exacerbated by COVID-19. Ophthalmology is a resource-heavy NHS service, and recorded the highest level of outpatient activity of all NHS services in 2019-20 with 7.9 million attendances.[i] Chronic conditions (e.g. cataract development, glaucoma, neovascular age related macular oedema (nAMD) and DMO) have been severely delayed during this prolonged pandemic period leading NHS England leadership to request that all healthcare systems aim for top quartile performance in productivity in high-volume clinical pathways systems with the greatest COVID-19 patient backlogs. Patient access to corticosteroid treatment following insufficient anti-VEGF response in the phakic eye is thus considered a relevant and important change to the overall reimbursement decision in addressing this need. Ophthalmology is a key focus for NHS England as it is one of the top 4 priority areas.[ii] *"Even prior to the pandemic, ophthalmology was the busiest specialty in England with the highest number of attendances for outpatient appointments and delays in hospital eye care services were resulting in permanently reduced vision in some patients. As the most common cause of delay is regarding follow-up appointments, it is clear that this is an area where improvement needs to be a priority, particularly as an intensive intravitreal regimen has a considerable effect on patients'*

			quality of life and increases the risk of patient non-adherence." (Downey et al 2021) Considering COVID-19 backlogs, reducing the clinical burden associated with the administration of a non-corticosteroid therapy with insufficient response to the phakic patient population will reduce clinic burden, free up resources, and optimize patient outcomes.
Additional issue 3: Insert additional issue		Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

[i] Hospital Outpatient Activity 2019-20, https://digital.nhs.uk/data-and-information/publications/statistical/hospital-outpatient-activity/2019-20/summary-report---treatment-specialities, accessed 3/3/21
[ii] NHS England, Winter pressures and 2021/22 Planning letter available at: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/12/important-for-action-operational-priorities-winter-and-2021-22-sent-23-december-2020.pdf, accessed 3/3/21

1. Amoaku WM, Ghanchi F, Bailey C, Banerjee S, Banerjee S, Downey L, Gale R, Hamilton R, Khunti K, Posner E, Quhill F, Robinson S, Setty R, Sim D, Varma D, Mehta H**. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group**. Eye (Lond). 2020 Jun;34(Suppl 1):1-51. doi: 10.1038/s41433-020-0961-6. Erratum in: Eye (Lond). 2020 Oct;34(10):1941-1942. PMID: 32504038; PMCID: PMC7337227.
2. Becker C, Schneider C, Aballéa S, Bailey C, Bourne R, Jick S, Meier C. **Cataract in patients with diabetes mellitus-incidence rates in the UK and risk factors.** Eye (Lond). 2018 Jun;32(6):1028-1035. doi: 10.1038/s41433-017-0003-1. Epub 2018 Feb 1. PMID: 29386666; PMCID: PMC5997651.
3. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, Li XY, Cui H, Hashad Y, Whitcup SM; **Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema**. Ophthalmology. 2014 Oct;121(10):1904-14. doi: 10.1016/j.ophtha.2014.04.024. Epub 2014 Jun 4. PMID: 24907062.
4. Downey L, Acharya N, Devonport H, Gale R, Habib M, Manjunath V, Mukherjee R, Severn P. **Treatment choices for diabetic macular oedema: a guideline for when to consider an intravitreal corticosteroid, including adaptations for the COVID-19** era. BMJ Open Ophthalmol. 2021 Apr 27;6(1):e000696. doi: 10.1136/bmjophth-2020-000696. PMID: 34192155; PMCID: PMC8088120.
5. Gonzalez VH, Campbell J, Holekamp NM, Kiss S, Loewenstein A, Augustin AJ, Ma J, Ho AC, Patel V, Whitcup SM, Dugel PU. **Early and Long-Term Responses to Anti-Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema: Analysis of Protocol I Data**. Am J Ophthalmol. 2016 Dec;172:72-79. doi: 10.1016/j.ajo.2016.09.012. Epub 2016 Sep 17. PMID: 27644589.

6. Himawan E, Ekström P, Buzgo M, Gaillard P, Stefánsson E, Marigo V, Loftsson T, Paquet-Durand F. **Drug delivery to retinal photoreceptors**. Drug Discov Today. 2019 Aug;24(8):1637-1643. doi: 10.1016/j.drudis.2019.03.004. Epub 2019 Mar 13. PMID: 30877076; PMCID: PMC6715772
7. Kiss S, Liu Y, Brown J, Holekamp NM, Almony A, Campbell J, Kowalski JW. **Clinical utilization of anti-vascular endothelial growth-factor agents and patient monitoring in retinal vein occlusion and diabetic macular edema.** Clin Ophthalmol. 2014 Aug 26;8:1611-21. doi: 10.2147/OPTH.S60893. PMID: 25210429; PMCID: PMC4155807.
8. Kodjikian L, Bandello F, de Smet M, et al. **Fluocinolone acetonide implant in diabetic macular edema: International experts' panel consensus guidelines and treatment algorithm**. *European Journal of Ophthalmology*. February 2022. doi:10.1177/11206721221080288
9. Panozzo G, Mura GD, Franzolin E, Giannarelli D, Albano V, Alessio G, Arrigo A, Casati S, Cassottana P, Contardi C, D'Aloisio R, Fasce F, Gusson E, Marchini G, Mastropasqua L, Niccolò M, Palmisano C, Pastore MR, Saviano S, Tognetto D, Bandello F. **Early DMO: a predictor of poor outcomes following cataract surgery in diabetic patients.** The DICAT-II study. Eye (Lond). 2021 Aug 3:1–7. doi: 10.1038/s41433-021-01718-4. Epub ahead of print. PMID: 34345028; PMCID: PMC8330474.
10. Starr MR, Salabati M, Mahmoudzadeh R, Patel LG, Ammar MJ, Hsu J, Garg S, Ho AC, Kuriyan AE. Fluctuations in Central Subfield Thickness Associated With Worse Visual Outcomes in Patients With Diabetic Macular Edema in Clinical Trial Setting. Am J Ophthalmol. 2021 Dec;232:90-97. doi: 10.1016/j.ajo.2021.06.030. Epub 2021 Jul 17. PMID: 34283986.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **11 May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Novartis Pharmaceuticals Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Beezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD)) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with LABA/ICS. Phillip Morris International (a tobacco company) has acquired or received valid acceptances for 74.77% shares in Vectura Group plc.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Uncertainty around the generalisability of the results from the MEAD trials	Yes	There are a number of limitations regarding the generalisability of the results from the MEAD trials that should be considered. Of note, more recent sponsored studies such as the MAGGIORE study[1], as well as RW papers[2,3], show DEX700 is injected at intervals between 4-6 months rather ≥6 months (as in the MEAD studies). The ≥6-month interval is unlikely representative of current UK practice and may underestimate frequency of treatment. 1. Callanan, D. G., Loewenstein, A., Patel, S. S., Massin, P., Corcóstegui, B., Li, X. Y., Jiao, J., Hashad, Y., & Whitcup, S. M. (2017). A multicenter, 12-month randomized study comparing dexamethasone intravitreal implant with ranibizumab in patients with diabetic macular edema. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie, 255(3), 463–473. https://doi.org/10.1007/s00417-016-3472-1 2.García-Layana, A., Figueroa, M. S., Arias, L., Adán, A., Cabrera, F., Abraldes, M., Fernández-Vega, Á., Navarro, R., Cervera, E., Silva, R., Armadá, F., Donate, J., & Ruiz-Moreno, J. M. (2018). Clinical Decision-Making when Treating Diabetic Macular Edema Patients with Dexamethasone Intravitreal Implants. Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde, 240(2), 61–72. https://doi.org/10.1159/000486800

		3.Epstein, D., Mirabelli, P., & Lövestam Adrian, M. (2020). Treatment algorithm with dexamethasone intravitreal implant in patients with diabetic macular edema. Acta ophthalmologica, 98(4), e528–e529. https://doi.org/10.1111/aos.14339
Time horizon considered for the economic analysis	No	As identified by the submitting company in the factual accuracy check of the ERG report, NICE TA613, TA346 and NG82, all adopted a lifetime horizon. This is also the most recently adopted time horizon that was accepted by NICE in an appraisal for DMO. This is in line with NICE guidance 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. It is, however, a limitation that the assumptions used in the company base case introduce uncertainty to such a long time-horizon.
Changes in BCVA resulting from DEX700 treatment in Years 4 and 5	No	Given the follow-up time of 3 years in the MEAD trials, it should not be assumed that transition probabilities in Years 4 and 5 are equal the last transition probability matrix estimated from MEAD. The ERG scenario where efficacy is assumed to be maintained in Years 4 and 5 is more reasonable than the company base case.
Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5	No	No comment.
Subsequent treatment following discontinuation of DEX700	No	No comment.
The natural history of vision in eyes with DMO	No	No comment.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Technical engagement response form

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **11 May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Roche Products Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None.**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Uncertainty around the generalisability of the results from the MEAD trials	No	No comment
Time horizon considered for the economic analysis	No	No comment
Changes in BCVA resulting from DEX700 treatment in Years 4 and 5	No	No comment
Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5	No	No comment
Subsequent treatment following discontinuation of DEX700	No	No comment
The natural history of vision in eyes with DMO	No	No comment

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: N/A	N/A	No	No additional comments

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Not applicable.			

Sensitivity analyses around revised base case
Not applicable.

BMJ TAG

Dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]

Technical engagement response

May 2022

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/50/19.

1 Introduction

This document provides the Evidence Review Group's (ERG's) critique of the company's response to technical engagement (TE) for the appraisal of dexamethasone intravitreal implant for treating diabetic macular oedema in people without a pseudophakic lens [ID3951]. Each of the issues outlined in the TE report are discussed in detail in Section 2. For a summary of the ERG's judgement on each issue, see Table 1. The company's updated base case analyses are outlined in Section 3 and the ERG's analyses are reported in Section 4.

Table 1. Issues for technical engagement and current status regarding issue resolution

Key Issue	Status according to the ERG	Company approach	ERG approach
Key issue 1: Uncertainty around the generalisability of the results from the MEAD trials[1]	Unresolved	MEAD trials[1] and supportive RWE	MEAD trials[1] but consider uncertainty remains
Key issue 2: Time horizon considered for the economic analysis	Unresolved	40 years	10 years
Key issue 3: Changes in BCVA resulting from DEX700 treatment in Years 4 and 5	Unresolved	Vision improves (last transition probability matrix carried forward)	Vision maintains
Key issue 4: Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5	Resolved	Sham arm of MEAD[1]	Sham arm of MEAD[1]
Key issue 5: Subsequent treatment following discontinuation of DEX700	Resolved	Include	Include
Key issue 6: The natural history of vision in eyes with DMO	Unresolved	TA274[2] (2.5% improve and 3.5% worsen)	TA613[3] (0% improve and 3.5% worsen)

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor therapy; BCVA, best corrected visual acuity; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; TA, technology appraisal.

2 Issues for technical engagement

2.1 Key issue 1: Uncertainty around the generalisability of the results from the MEAD trials

The evidence review group (ERG) considers the uncertainty around the generalisability of the results from the MEAD trials[1] to UK clinical practice remains, although the ERG notes that the company has presented further examples of real world evidence (RWE) studies in their response to technical engagement (TE) to support their case that the MEAD trials represent the most appropriate source of evidence for dexamethasone 700 µg intravitreal implant in applicator (hereinafter referred to as DEX700, [Ozurdex®; AbbVie]) for this appraisal. The company also reported that they consider that the impact of the differences is not likely to favour the efficacy of DEX700, although the ERG does not consider it possible to accurately predict the direction of the resulting bias. The ERG, therefore, does not agree with the company that it can be concluded that outcomes presented in MEAD are a conservative estimate of the absolute and relative efficacy of DEX700 compared to continued anti-vascular endothelial growth factor (anti-VEGF) therapy.

The ERG notes that the majority of the supportive published RWE studies presented in the company response to TE assess the efficacy of DEX700 in a pooled phakic and pseudophakic population, whereas the focus of this technology appraisal is the phakic population. However, the company also cite RWE papers [4-8] that they consider demonstrate the efficacy of DEX700 is similar in both pseudophakic and phakic patients. Due to time constraints the ERG has not reviewed all of the RWE submitted by the company but the ERG does not consider it resolves the issues around the generalisability of the MEAD trials to the UK population in terms of the differences in the baseline characteristics of the patient population in MEAD compared with current clinical practice. Additionally, the ERG remains concerned about the use of last observation carried forward (LOCF) methodology to account for missing data in the MEAD trials due to the large imbalance between discontinuations for the DEX700 and sham treatment arms. The ERG also notes that the company has provided no detail on the methodology for identifying the RWE studies reported in their response to TE and the ERG is thus concerned that it is potentially not fully representative of all the relevant published RWE.

The ERG does not agree with the company that the differences in the baseline characteristics between patients in the MEAD trials and UK clinical practice, such as the low proportion of patients receiving prior anti-VEGF therapy in the MEAD trials and the higher proportion with cataract at

baseline in the MEAD trials, can be confidently predicted to result in conservative estimates for DEX700. Additionally as discussed in the ERG report, the ERG considers the 6-month timepoint from the UK RWE audit[9] suboptimal responder cohort should be used to inform the baseline assessments for insufficient responders to anti-VEGFs (non-corticosteroids) rather than the 0-month timepoint from the UK RWE audit. The ERG, therefore, does not agree with the company's argument that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF (if sham is used as a proxy for continued anti-VEGF) and therefore likely results in a conservative estimate of the relative treatment effect. The ERG instead considers the MEAD sham arm is potentially a reasonable proxy for continued anti-VEGF use and that it is not possible to predict the likely direction of any potential bias in the comparison of DEX700 versus sham.

The ERG considers that no new data were provided in the company response to TE to address the imbalance in the discontinuation rates between the DEX700 and sham arms of MEAD. As discussed in the ERG report, in the phakic-only mITT population of MEAD, [redacted]% of the sham arm discontinued (mostly due to a lack of efficacy or receipt of rescue therapy), whereas only [redacted]% of the DEX700 arm discontinued (most frequently due to adverse events).[10] The ERG considers that assuming no change in BCVA for patients with missing data is optimistic given the natural history of DMO is for vision to decline. The ERG is therefore concerned that the LOCF approach used in the analyses of the MEAD trials biases both the sham and DEX700 arms and does not consider it possible to predict the direction of the resulting bias.

2.2 Key issue 2: Time horizon considered for the economic analysis

In the company's base case analysis, the time horizon of the model is 40 years, which is considered to cover a lifetime. As noted in the ERG report, the ERG considers the company's long-term modelling assumptions to be too simplistic to accurately capture the costs and consequences over a lifetime time horizon. This is because patients may experience comorbidities of DMO which have important costs and consequences, more treatment options may become available to patients when they become pseudophakic (for example, fluocinolone acetonide) and no treatment waning assumptions have been modelled, which means DEX700 maintains a benefit in visual acuity above anti-VEGFs beyond the 5-year treatment period and throughout the remaining time horizon (Figure 1). Shorter time horizons (10 and 15 years) have also been adopted in other DMO appraisals, including the NICE ranibizumab appraisal (TA274)[2] and the previous NICE DEX700 appraisal (TA349)[11].

Figure 1. Mean BCVA in treated eye(s) over the modelled time horizon: original company base case (generated by the ERG)

Additionally, the ERG considers it important to highlight that the mean BCVA curves changed shape in the company's revised analysis. As shown in Figure 2, the mean [redacted] for unilateral DMO in the best-seeing eye (BSE) and bilateral DMO. The ERG considered the company's revised assumptions and found that this change is driven by the additional mortality due to blindness applied to patients in whom the BSE is in the worst health state (see revised assumption in Section 2.7.2). In consequence, there are [redacted] health state contributing to the mean BCVA, which is reasonable.

The ERG also notes that when the natural history of improving vision is reduced from a 3-monthly probability of 2.5% to 0%, as per TA613, the curves for unilateral DMO in the BSE demonstrate a [redacted] and the curves for bilateral DMO demonstrate [redacted]. The curves for each treatment arm are also generally closer together when natural history estimates from TA613 are used (

Figure 3). For these reasons, the natural history of vision according to TA613 may be considered more clinically plausible than the natural history of vision according to TA274 (Figure 2).

However, as noted in the ERG report, the ERG's clinical experts expressed concerns that the same probability of improving or worsening vision was applied irrespective of where a patient's vision starts. Thus, as a patient's vision changes over time the natural history of vision is also likely to change over time. In consequence neither of the natural history estimates from TA274 or TA613 are likely to be accurate over a lifetime time horizon which further supports using a shorter time horizon for the economic analysis. For a greater discussion of the natural history of vision, see Key Issue 6 in Section 2.6.

Figure 2. Mean BCVA in treated eye(s) over the modelled time horizon: revised company base case (generated by the ERG)

Figure 3. Mean BCVA in treated eye(s) over the modelled time horizon: natural history (NH) as per

TA613 (generated by the ERG)

In response to TE, the company reiterated that lifetime time horizons were adopted and accepted in the NICE fluocinolone acetonide appraisal (TA613)[3], NICE aflibercept appraisal (TA346)[12] and NICE age-related macular degeneration (AMD) guideline (NG82)[13]. The company also noted that TA346 was based on primary trial evidence with three years of follow-up (equal to the follow-up of MEAD) and NG82 was based on two years of comparative efficacy data (shorter than the follow-up of MEAD).

Stakeholders responding to this issue also supported a lifetime time horizon to ensure consistency with these appraisals (Table 2).

However, the company did not acknowledge in their TE response that a 15-year time horizon was accepted in TA349.[11] The TA349 Final Appraisal Determination (FAD) also states that, "*The ERG acknowledged that the company would have to make a number of assumptions to consider a time horizon of longer than 10 years, because the data were only available for up to 3 years*".

In response to the ERG's concerns on the absence of treatment effect waning, the company explained that no further treatment effect is assumed after the 5-year treatment duration, as the same natural history estimates for the proportion of patients whose vision improves and worsens at each time point are applied equally between the treatment arms. Therefore, it could be argued that treatment effect waning is applied from 5 years, as although the absolute change in BCVA outcomes does not become equalised at this point in time, the rates of improvement and worsening vision are set to be equal. Using survival modelling for an oncology NICE appraisal as a comparative example, this approach would be akin to setting the hazards for the survival curves to be equal between the treatment arms at cessation of treatment, which in this setting would be interpreted as an application of treatment effect waning.

The company also noted that although the mean change in BCVA is never equal between the treatment arms, the absolute difference between the treatment arms does decline over time. Further feedback elicited from the company's multiple UK clinical experts during TE does align with the ERG's clinical expert's assertion that there would be convergence over time, but the clinicians noted there was considerable uncertainty regarding the form this would take. In a separate consultation, a UK clinician also highlighted to the company that although there would likely be no ongoing treatment effect after discontinuation, there was no reason to expect the rate of improvement and worsening would be different between a patient who received DEX700 and a patient who received anti-VEGFs, from the point of discontinuation.

The ERG reviewed the feedback[14] received by the company during TE (Figure 4) and adds that some experts suggested [redacted].

Figure 4. Conversation 4 reproduced from Allergan's HTA Digital Advisory Board Interim Report (May 2022)[14]

The ERG agrees with the company that, if a DEX700 patient has better vision than an anti-VEGF patient at 5 years, it makes sense for it to take a while for the DEX700 patient to have the same vision as the anti-VEGF patient. However, in the model, a DEX700 patient never has the same vision as an anti-VEGF patient, which doesn't align with most clinical experts opinion or committee opinion in previous appraisals. For example, the TA613 FAD[15] states, "*The committee agreed that there might be a continued treatment effect after treatment has stopped but it was uncertain how long this would last. The ERG was unable to directly explore the effect of continued treatment in the model but explored this issue by adjusting the time horizon in scenario analyses. The committee concluded that it is implausible to assume the continued treatment effect would last for a lifetime*". The ERG notes that from the end of Year 6 in TA613 it is assumed that all patients cease treatment and incur no treatment costs, and an equal probability of worsening BCVA (the natural history) is applied in both treatment arms when they cease treatment. Except for the duration of treatment (5 vs 6 years) and natural history source, this is largely in line with this appraisal.

Instead of reducing the time horizon, the ERG considered a scenario where the distribution of vision in the DEX700 arm is equal to the anti-VEFGF arm from Year 10 (as per the time point suggested by one of the clinical experts to the company at TE). However, this scenario is limited as it forces the distribution of vision to become equal in both treatment arms from one model cycle (leading to a sudden large drop in vision). As such, the scenario could be considered conservative as losses are more likely to be gradual, for example, like an exponential decay curve. Figure 5 illustrates the impact of the ERG's scenario on the modelled mean BCVA. As shown in Section 4, the inc. NMB at a £30,000 QALY threshold reduced from £10,386 to £8,539 when the ERG implemented the scenario in the model.

Figure 5. Mean BCVA in treated eye(s) over the modelled time horizon: company revised base case vs ERG scenario assuming convergence at Year 10 (generated by the ERG)

The ERG also notes that the company provided scenarios using time horizons of 30, 15 and 10 years and the incremental net monetary benefit (NMB) at a £30,000 quality-adjusted life year (QALY) threshold reduced from £10,386 (base case) to £10,367, £9,336 and £8,418 in these scenarios, respectively.

As for the company's reference to oncology appraisals for comparative examples of treatment effect waning, the ERG is of a different opinion. Based on the ERG's experience, oncology appraisals consider waning during post-progression (off-treatment) and treatment is usually given until progression. At the point of treatment waning, the overall survival curve for the new treatment would usually be made equal to standard care to remove post-progression benefits (off-treatment

benefits), which is akin to the ERG's scenario which assumes vision in the DEX700 arm is equal to the sham arm after 10 years. The ERG is unaware of any oncology appraisals that have taken the approach suggested by the company as an application of treatment effect waning and adds that the company did not provide any specific oncology appraisals to support their approach. Nevertheless, the key point for this appraisal is that while the natural history of vision is made equal, this largely maintains the difference in benefit between DEX700 and anti-VEGFs as both arms decline at the same rate from the point of discontinuation.

Overall, the ERG maintains that a shorter time horizon (10 years) should be used as the company's long-term modelling assumptions are too simplistic to accurately capture the costs and consequences over a lifetime time horizon. For completeness, the ERG will present its preferred base case assumptions using a 10-year time horizon and lifetime time horizon (see Section 4).

Table 2. Stakeholder comments on Key Issue 1 (time horizon considered for the economic analysis)

Stakeholder	Comment
Novartis	As identified by the submitting company in the factual accuracy check of the ERG report, NICE TA613, TA346 and NG82, all adopted a lifetime horizon. This is also the most recently adopted time horizon that was accepted by NICE in an appraisal for DMO. This is in line with NICE guidance 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. It is, however, a limitation that the assumptions used in the company base case introduce uncertainty to such a long time-horizon.
Alimera	The assumption of treatment waning is a reasonable proposition. This however is subject to high levels of uncertainty. There is a dearth of longitudinal, prospective cohort studies of DMO (phakic and pseudophakic) beyond a three-year timepoint which collects data on the natural course of disease response and disease progression. Reducing the time horizon to either 5 or 10 years would itself be uncertain. As per the TA349 ERG response it was considered that a time horizon of less than 10 years was too short of a period to allow for the long-term impact of treatment on outcomes to be considered. Additionally, the ERG acknowledged that several assumptions would need to be made to consider a time horizon of longer than 10 years as the data were only available for up to 3 years. It is not clear how influential a parameter of waning of treatment effect would be on the model nor what impact they would have on the ICERs.
Clinical Expert 1	The different NICE TAs on DMO have adopted different time horizons. The most recent was the NICE TA613 adopted 30-years' time horizon. A similar time horizon would have been expected for this TA. The rationale for the different time horizon suggested by the ERG on this occasion needs to be more clearly articulated. I cannot find that clarity in the ERG report. Previous TAs have been based on 2-year studies (including registration studies). The lack of long-term data should not be the basis for shorter time horizon for this appraisal. It is expected that treatments for DMO would have modified the natural history of the disease. Such modification would have shifted the natural history including visual

	acuity changes. As such, although some convergence may occur, the exact timings are difficult to predict.
Clinical Expert 2	It is worth noting that there should be a comparable lifetime horizon to other HTAs for similar treatment areas. If this is not the case then is may not be a fair and reasonable comparison. From a patient's point of view the longer the lifetime horizon the more realistic this is as DMO is a lifelong condition.

Abbreviations: DMO, diabetic macular oedema; ERG, Evidence Review Group; HTA, health technology appraisal; ICER, incremental cost-effectiveness ratio; NG, NICE guideline; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

2.3 Key issue 3: Changes in BCVA resulting from DEX700 treatment in Years 4 and 5

In the company's base case analysis, the 3-monthly transition probabilities in Years 4 and 5 were assumed to equal the last transition probability matrix estimated from MEAD[1], which the ERG considered questionable in the absence of data.

In response to TE, the company argued that last transition matrix provides the most relevant data available from MEAD as it allows for any recovery in BCVA following the development and extraction of cataracts in a significant proportion of patients to be captured.

The company highlighted in their TE response that the mean time between the last DEX700 injection and cataract surgery in the modified intention-to-treat (mITT) population of MEAD was [redacted], with exploratory analyses presented in the company submission (Figure 14, Document B) demonstrating that patients who received DEX700 at their last visit before cataract surgery experienced better outcomes than patients who did not receive DEX700 at the last visit prior to surgery. UK clinicians advising the company have stated that they treat patients with a DEX700 injection just prior to cataract surgery, which ensures the adequate control of postoperative inflammation and prevents deterioration of macular oedema. Therefore, the assumed changes in visual acuity outcomes over the treatment period in the company base case analysis include a decline in outcomes that is not expected to occur in reality.

In their TE response, the company also provided Figure 6 to demonstrate that patients who underwent cataract surgery at earlier timepoints in the trial fully recovered the initial gains in visual acuity outcomes that they had initially made after receiving treatment with DEX700. However, as noted in the ERG report, not all cataracts are deemed clinically significant or severe enough to require immediate surgery after cataract diagnosis. Additionally, the subgroup analyses presented by the company include patients with cataract at baseline and thus the analyses may be confounded

by vision improvement in patients who would naturally have received an improvement in BCVA with cataract surgery in the absence of DEX700 treatment. For these reasons, the ERG does not consider the results of this subgroup analysis suitable for drawing robust conclusions.

Figure 6. Change in mean BCVA from MEAD stratified by the timing of cataract surgery from the start of the trial (reproduced from the company's TE response)

The company also referred to a French study (Mathis 2020)[7] of DEX700 in 152 patients (227 eyes), which suggested a strong and continued treatment effect for up to five years. Half of the eyes in this study were pseudophakic at baseline (n=115) and cataract surgery was performed on 55 eyes (49% of 112 phakic eyes) during the follow-up period. Eyes previously treated by anti-VEGF treatment (n=122) showed poorer BCVA at baseline than treatment-naïve eyes (n=105, p=0.30). However, BCVA gains remained non-significantly different between the 2 groups at each time points (except for 10 months, p=0.021).

Table 3 presents the mean BCVA and VA letter gain from baseline over time reported in Mathis *et al.* 2020[7]. The ERG agrees with the company that this study provides supportive evidence that patients on DEX700 treatment in Years 4 and 5 incur benefits, but these results are based on small patient numbers which results in extremely wide 95% confidence intervals (illustrated within the study figures). The ERG also notes that better results are seen at Month 48 than Month 60. To account for this finding, the ERG considers a scenario where the transition probabilities in Years 4 are equal the

last transition probability matrix estimated from MEAD and the transition probabilities in Year 5 maintain the treatment benefit. As shown in Section 4, the inc. NMB at a £30,000 QALY threshold generated from this scenario (£8,581) is in between the company's base case (£10,386) and the scenario which assumes vision is maintained in Years 4 and 5 (£7,311). Figure 7 illustrates the impact of the ERG's scenario on the modelled mean BCVA.

Table 3. Mathis *et al.* 2020[7], key results

Month	Number of patients	BCVA	VA ETDRS letter gain
0 (baseline)	152	51.4	-
12	116	54.6	3.2
24	78	56.5	5.1
36	41	58.2	6.8
48	20	66.4	15.0
60	8	66.1	14.7

Abbreviations: BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity

Figure 7. Mean BCVA in the treated eye over 5 years: company base case vs ERG scenarios (generated by the ERG)

The company also highlighted in their TE response that [redacted] DEX700 patients had developed cataract but had not had cataract surgery during the MEAD study duration (company submission, Figure 15) and it could be expected that they would have received their cataract extraction during Year 4 or Year 5 of treatment, had the study continued. Thus, by capping the benefit at year 3, no benefits from the observed trend can be realised which in the company's opinion is an extreme and pessimistic assumption. In consequence, the ERG agrees that it may be conservative to assume vision is maintained by all patients on DEX700 treatment in Years 4 and 5.

However, the company has not commented on whether they would expect to see benefits in the sham arm of MEAD following cataract surgery or the number of sham patients who developed cataract but had not had cataract surgery during the MEAD study duration.

When the ERG sought these numbers for the sham arm, the ERG could not verify the numbers provided by the company for the DEX700 arm. In Figure 15 of the company submission (CS), two descriptions are provided for [redacted] patients: "Proportion of Patients Who Developed Cataract Without Cataract Surgery during the Study DEX700 ([redacted])" and "without Cataract Surgery during the study DEX700 ([redacted])". The numbers in Figure 6 above suggest the latter description is true as [redacted] patients ([redacted]) received surgery which suggests [redacted] patients did not ([redacted]). Following this, the ERG is unclear how many of these [redacted] patients developed cataracts.

If the ERG had access to reliable numbers, the ERG would consider a scenario where patients who had developed cataract, but had not had cataract surgery during the MEAD study, to experience the last transition probability matrix estimated from MEAD, while patients who had cataract surgery during the MEAD study maintain their benefits. However, this scenario would be limited as the last transition probability matrix includes all patients on treatment (the ERG does not have access to transition probability matrices according to lens status). The ERG also notes that the cost of cataract surgery should be incurred by the patients that are yet to undergo surgery.

Furthermore, if the company is concerned that vision depends on lens status and that this is inappropriately captured in the model, the company should revisit their model structure and consider health states according to lens status, as per the suggestion in clarification question B3.

An additional and related area concern in the ERG report related to the number of DEX700 injections in Years 4 and 5. In response to TE, the company updated the costing assumptions in its revised base case to assume the number of DEX700 injections administered in Year 3 of MEAD is applied in Year 4

and 5 (patients will continue to receive the same number of injections in Year 4 and 5 as in Year 3). The company noted that increasing the number of injections patients are assumed to receive ([redacted] per year instead of 1.0) aligns with the ERG's base case and helps mitigate against uncertainty by more closely aligning treatment costs with the assumptions related to efficacy. The ERG accepts this revision and adds that its clinical experts considered 1.0 injections per year to be too low to maintain or improve vision.

During the TE stage, the company further consulted with UK clinical experts. The ERG reviewed the feedback[14] received by the company during TE (

Figure 8) and adds that one expert questioned the legitimacy of the company's assumption (capturing the upward trend in Years 4 and 5 by using the last transition probability matrix from MEAD) without long-term data and noted that worsening vision due to damage to the retina may be counteracted by improvements in vision due to cataract surgery. The ERG also notes that stakeholders responding suggested vision on DEX700 treatment in Years 4 and 5 is more likely to be maintained than improve or worsen (Table 4).

Overall, the ERG considers the changes in BCVA resulting from DEX700 treatment in Years 4 and 5 to still be a key area of uncertainty and therefore the ERG maintains its preferred assumption that DEX700 maintains vision in Years 4 and 5 (see Section 4). The ERG models maintenance using a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.0%, as per TA274[2] (see Key Issue 4). No changes have been made to the anti-VEGF arm in Years 4 and 5 (the last transition probability matrix from the sham arm of MEAD is applied, leading to a small decline in vision, on average).

Table 4. Stakeholder comments on Key Issue 3 (changes in BCVA resulting from DEX700 treatment in Years 4 and 5)

Stakeholder	Comment
Novartis	Given the follow-up time of 3 years in the MEAD trials, it should not be assumed that transition probabilities in Years 4 and 5 are equal the last transition probability matrix estimated from MEAD. The ERG scenario where efficacy is assumed to be maintained in Years 4 and 5 is more reasonable than the company base case.
Clinical expert 1	Maintenance of visual acuity in DMO is dependent on optimal treatment. It is expected that DMO eyes that are optimally treated will maintain vision, and the earlier visual gains. However, the vision will deteriorate in eyes that receive suboptimal treatment with DEX or other therapies. Specifically, it is expected that BCVA should not decline in years 4 and 5 if optimally treated. (Any deterioration due to cataract would have been corrected previously by cataract surgery.)

	The continuation of anti-VEGF in eyes responding to treatment are known to be maintained with optimal treatment, whilst suboptimal treatment results in visual decline. In DMO eyes that are not responsive to anti-VEGF treatment, visual decline will continue over time. Continuation of anti-VEGF therapies in these eyes may be adopted by clinicians in the absence of appropriate alternative treatments, with the resultant progressive vision loss.

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor therapy; BCVA, best corrected visual acuity; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ERG, Evidence Review Group.

Figure 8. Conversation 3 reproduced from Allergan's HTA Digital Advisory Board Interim Report (May 2022)[14]

2.4 Key issue 4: Changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5

In the CS, the company explained that there is limited evidence that directly compares the DEX700 with anti-VEGF treatments in the group of patients who are insufficiently responsive to anti-VEGF treatment. Additionally, there is limited relevant randomised controlled trial (RCT) evidence on the use of anti-VEGF or laser in insufficient responders. As a result, the company used the sham arm of the MEAD trials as a proxy for continued anti-VEGF use in the CS. In the CS, it was also noted that this approach is consistent with TA613[3], in which the committee considered it appropriate, in the absence of suitable alternative evidence, to assume that the relative efficacy of fluocinolone acetonide vs sham in FAME[15] was a reasonable proxy for the relative efficacy of fluocinolone acetonide vs continued use of anti-VEGF or laser.

In the CS, the company provided a scenario where anti-VEGF treatment resulted in zero net impact on vision (assuming a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.5%). The ERG considered this scenario to be important given that the goal of anti-VEGF treatment in insufficient responders is usually to preserve the retinal architecture. The ERG also considered the scenario to be more transparent than the company's other analyses in terms of the likely bias that exist (for example, the company is not comparing heterogenous populations or using one treatment as a proxy for another). However, this scenario favoured anti-VEGF treatment (total quality-adjusted life years [QALYs] increased compared to using the sham arm of MEAD) which is somewhat counterintuitive when the sham arm of MEAD, results, on average, in a small net gain in vision. Moreover, when a zero net impact on vision for anti-VEGF treatment was assumed in TA613, this did not favour anti-VEGF treatment (total QALYs decreased compared to assuming the sham arm of FAME).

In response to TE, the company noted that the ERG's approach (assuming a 3-month probability of gaining or losing at least 10 letters of BCVA of 0%, which is consistent with the probability applied in the TA613 scenario) does not account for the fact that individual patients within the cohort in the UK RWE experienced gains and losses of letters. For example, a proportion of patients in the UK RWE gained and lost at least 10 letters from baseline to month 12, month 12 to month 24 and month 24 to month 36. These data demonstrated that a meaningful proportion of patients experienced changing vision throughout the study and that a higher proportion of patients lost at least 10 letters ([redacted]) than gained at least 10 letters ([redacted]) at each timepoint.

The company also noted that the ERG's approach results in significant bias related to the costs associated with severe vision loss. In the company base case analysis, patients on both the DEX700 and anti-VEGF treatment arms could transition to the most severe vision related health state and incur costs associated with the management of severe vision loss. The ERG's approach (assuming a 3-month probability of gaining or losing at least 10 letters of BCVA of 0%) artificially stops patients on the anti-VEGF arm from transitioning to the most severe health state. In response to TE the company also acknowledged that a slightly greater proportion of patients in the DEX700 arm transitioned into this health state relative to the sham arm in MEAD given the higher rate of cataract development. However, according to the company's clinical experts, patients with cataract will undergo surgery more promptly than they did in MEAD and therefore adding severe vision loss costs to DEX700 is conservative.

In response to TE, the company provided an additional scenario analysis which assumes a 3-month probability of gaining or losing at least 10 letters of BCVA of 3.0%, which is consistent with the estimates applied in the NICE appraisal of ranibizumab (TA274)[2], where they modelled a period of stable vision during the on-treatment period. As shown in Section 3, this scenario reduced the inc. NMB from £10,386 to £7,768. When implementing this scenario, the company applied a restricted set of MEAD transition probabilities to the DEX700 arm, whereby the transitions were restricted to a maximum of one health state improvement or worsening to ensure there was consistency in the approach between the two treatment arms. The company noted that use of a restricted set of transition probabilities is associated with limitations, but for the purposes of this scenario analysis this is required to ensure a consistent approach between the arms to minimise the risk of bias. For completeness, the ERG has provided results using an unrestricted set of transition probabilities in Section 4.

The company also referred to the scenario presented in response to clarification question B5, assuming no movement up or down health states within the anti-VEGF arm but excluding severe vision loss costs in both treatment arms to reduce the risk of bias.

The company then concluded that their base case assumption, which uses the sham arm of MEAD is a more appropriate yet conservative proxy for the efficacy of continued anti-VEGFs in insufficient responders as this allows us to model the individual variations in vision losses and gains, while on average resulting in a small gain in vision.

The ERG considers that the company has been transparent in its TE response regarding the higher number of patients that enter the severe vision loss health state in the DEX700 arm compared to the anti-VEGF arm. The ERG also agrees with the company that fewer patients (in both treatment arms) will enter the severe vision loss health state in clinical practice if patients with cataract undergo surgery more promptly than they did in MEAD and that restricting the movements in the anti-VEGF arm introduces bias against DEX700.

The ERG, however, does not agree with the company's argument that the sham arm of the MEAD trials likely overestimates the efficacy of continued anti-VEGF and therefore likely results in a conservative estimate of the relative treatment effect. The ERG instead considers the MEAD sham arm is potentially a reasonable proxy for continued anti-VEGF use and that it is not possible to

predict the likely direction of any potential bias in the comparison of DEX700 versus sham (largely due to the use of LOCF in the company analyses of MEAD).

Stakeholder comments on this issue are provided in Table 5. In summary, they suggest that UK practice has evolved since commencement of the MEAD study, RWE should supplement decision making, anti-VEGF treatment is continued when patients demonstrate an incomplete response, damage to the retina is clinically meaningful and clinicians find the current reimbursement restrictions on steroid use in the phakic population difficult.

Overall, the ERG accepts the company's base case assumption. However, given the large assumptions needed to model continued anti-VEGF treatment, the ERG considers that committee may want to account for this uncertainty by using the lower threshold for cost-effectiveness (that is, an ICER below £20,000 per QALY gained).

Table 5. Stakeholder comments on Key Issue 4 (changes in BCVA resulting from anti-VEGF treatment in Years 1 to 5)

Stakeholder	Comment
Alimera	[…] unmet need of the phakic patient population, who, with continued use of anti-VEGF when there is incomplete response are at higher risk of BCVA vison loss and damage to the retina. It is not clear that the sham arm in the MEAD trials does in fact overestimate the efficacy of the sham treatment arm. […] The retina exposure to risk is potentiated through insufficient response; prolonged and untreated oedema will cause irreversible damage to the photoreceptors, predisposing to blindness. Vison loss due to retinal photoreceptor degeneration has a deleterious impact on patient quality of life. (Himawan et al 2019). Recurrence of edema, i.e., repeated cycles of retina expansion and contraction damage the retina and have been linked with worse vision outcomes. (Starr et al 2021) If the retina is never dry, deterioration in function is to be expected. Physicians are constrained by the current NICE restriction on corticosteroid therapy in the phakic DMO patient population. Phakic patient outcomes are impacted where patients persist on anti-VEGF treatment which it is not addressing the underlying mediators of their DMO. The full consequences of insufficient response should therefore be considered clinically meaningful. […] Patients with DMO who are treated with an anti-VEGF agent are not immune to cataract development. 25% of diabetic patients undergoing cataract surgery have preoperative DMO (Panozzo et al 2021); this confers a high risk of the macula worsening, and potentially eliminating the vision benefits of cataract extraction; intravitreal corticosteroid immediately before or immediately post-op is effective in reducing this complication. However, current reimbursement restrictions to the phakic population prohibit its prescription. For those who develop a cataract as a natural progression of the DMO and the absence of pre-operative intravitreal corticosteroid treatment will not be eligible for cataract removal as a wet macula presents as a surgical risk. Intravitreal corticosteroid treatment therefore represents an important

	pre-operative intervention in the clinical management of the phakic population with pre-existing DMO as the CRT can change from <400 µm to >400 µm. […] The benefits, limitations, and methodological challenges in using RW data are acknowledged. However, the overall context and evidence-base from the RW data matter greatly in determining the true value of the intervention. To that end, the MEAD trial design must be contextualized to the time when it was conducted, prior to the introduction of anti-VEGFs and where the prevailing first-line treatment in DMO was laser photocoagulation. […]
Clinical expert 1	Clinical management of DMO, including UK practice have evolved since commencement of the MEAD study. As such the MEAD study criteria should not be the main reference point. There is significant real life studies available to guide clinical decision making as summarised elsewhere. The continuation of anti-VEGF therapy regardless of benefit is adopted by clinicians where there is no alternative therapies available. This has significant impact on repeated clinical risks vrs benefits.

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor therapy; BCVA, best corrected visual acuity; CRT, central retinal thickness; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; NICE, National Institute for Health and Care Excellence; RW, real world.

2.5 Key issue 5: Subsequent treatment following discontinuation of DEX700

As noted in the ERG report, the ERG's clinical experts disagreed with the company's assumption in the CS that patients receive no treatment when they discontinue DEX700 due to either adverse events (AEs) and other non-efficacy related reasons or due to lack (or loss) of efficacy of treatment . According to the ERG's clinical experts, these patients would be offered re-treatment with an anti-VEGF in clinical practice.

During the TE stage, the company further consulted with UK clinical experts who confirmed that some patients would likely receive anti-VEGF again following discontinuation from DEX700 in the absence of other options. The company therefore accept that there could be a proportion of patients who would receive subsequent treatment with anti-VEGFs following DEX700. However, the feedback received also highlighted that this treatment would be given for a short period of time and would likely be ineffective, consistent with the ERG's clinical expert opinion. The UK clinical experts consulted by the company also indicated that not all patients would receive treatment, estimating that approximately 80% of patients who discontinue DEX700 would likely receive subsequent treatment. Therefore, the company's base case analysis has been updated to reflect this, assuming 80% of patients who discontinue treatment with DEX700 will receive subsequent anti-VEGFs for 1 year. A one-off cost was estimated, assuming 5.0 injections would be administered, consistent with the number assumed to be administered in Year 1 for patients on the anti-VEGF arm in the company's revised base case, giving an additional one-off cost of £4,009.85 (£5,012.32*0.8) for

DEX700 patients. However, as is noted in the ERG report, there is no evidence that could inform the efficacy of subsequent treatment in patients who have received prior DEX700, and therefore although these costs have been included in the revised base case, no changes have been made to the efficacy assumptions for the DEX700 arm.

Stakeholder comments on this issue are summarised in Table 6 and suggest that anti-VEGFs may be given once DEX700 is discontinued, but this may depend on what is driving their loss of response. Stakeholders also suggested that once a patient becomes pseudophakic, more options become available to them.

The ERG accepts the company's revised assumption and notes that patients do not discontinue DEX700 in the model when they become pseudophakic.

Table 6. Stakeholder comments on Key issue 5 (subsequent treatment following discontinuation of DEX700)

Stakeholder	Comment
Alimera	The assumption made by the CS presents as rational, there is no clinical evidence to support the use of anti-VEGF after DEX700. Is it plausible that following anti-VEGF failure and DEX700 discontinuation when DMO is driven by inflammation and not by VEGF that it would be clinically expedient and cost-effective practice to recommence anti-VEGF treatment for which there is a known insufficient response? Patient outcomes are impacted where patients have persisted on anti-VEGF treatment which is not addressing the underlying mediators of their DMO. This comes at a significant cost for suboptimal patient outcomes
Alimera	Occasionally a decision taken by NICE can have unintended consequences. This has happened with the restrictions for dexamethasone intravitreal implant in TA349 and fluocinolone acetonide intravitreal implant in TA301 to restrict access to these treatments only if a DMO patient has a pseudophakic lens. Clinicians faced with individual patients who are insufficient responders to, or unsuitable for, non-corticosteroid therapies but who do not have sufficient lens opacity to justify a cataract procedure, report they occasionally choose to perform the cataract procedure (with the patient's consent) so that the patient becomes eligible for these steroid treatments. Usually the patient will undergo the procedure, and then immediately receive the steroid intravitreal injection "on the table". Additionally, in current times, post COVID-19, the NHS cataract surgery backlog position is such that these patients have not only to deal with the problem that they are losing vision due to their cataract progression but also retina damage due to DMO. By the time they reach cataract surgery (which reverses the sight loss to cataract) with all the backlogs in place then the retina is so damaged that it no longer functions. Thus, allowing Clinician discretion to use a steroid in Phakic patients allows preservation of the underlying retina function balanced v the formation or worsening of cataract (which can be reversed).
Clinical expert 1	When treatment is discontinued, a wait and see option is adopted by some clinicians until the CRT reaches the minimum 400 microns allowed by NICE TAs for anti-VEGF

	therapies in DMO. This unless these eyes have been previously treated with anti-VEGFs. Generally, continuation of treatment may not benefit most eyes that were previously unresponsive to anti-VEGF. Some eyes may be re-assigned to anti-VEGF therapies, although there is no evidence for effectivity. However, the majority may not be. As such, the option of no further treatment is a valid option. There remains the current unmet need for DMO unresponsive to or unsuitable for treatment with anti-VEGF therapies.
Clinical expert 2	From a patient's point of view – if there is no alternative treatment available (which there currently is not for this group of patients) then it is most likely that the same treatment is continued without any further positive impact. This has the additional patient burden of all of the issues/ challenges with having a treatment (time, expenses, and anxieties) without any positives. As highlighted in our submission this can lead to sub optimal outcomes.

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor therapy; BCVA, best corrected visual acuity; CRT, central retinal thickness; CS, company submission; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; NICE, National Institute for Health and Care Excellence; TA, technology appraisal

2.6 Key issue 6: The natural history of vision in eyes with DMO

As per TA349[11], natural history data were taken from Mitchell *et al*. 2012.[16] This study reported a 3-month probability of gaining or losing at least 10 letters of BCVA (moving up or down one health state) of 3.5% and 4.5%, respectively. As noted in the ERG report, the ERG considered the source to reflect outdated practice and include a population with diabetic retinopathy that may not have had DMO (i.e., WESDR population in Mitchell *et al.* 2012 may be less severe). The ERG's clinical experts also considered the 3-month probability of gaining 10 letters of 3.5% to be too high. As such, the ERG preferred the natural history data accepted in TA613 (a 3-month probability of gaining or losing at least 10 letters of BCVA of 0% or 3.5%, respectively). The ERG also noted in the ERG report that it was inferred within TA613[3] that these estimates were obtained from the ranibizumab appraisal (TA274)[2] and that this could not be verified.

In response to TE, the company conducted a detailed review to try and fully understand the source of the natural history data used in TA613 in order to assess the quality and appropriateness of the study compared with Mitchell *et al*. 2012.[16] Following this, the company found no reference to the estimates and instead identified a 3-month probability of gaining or losing at least 10 letters of BCVA of 2.5% or 3.5% in TA274, respectively.

The company also noted in their TE response that the assumption that no patients would experience any improvement in vision lacks clinical plausibility and is not consistent with what was observed in the WESDR study, what was accepted in TA274, and also data from the sham arm from MEAD and

the UK RWE. Therefore, the assumption adopted in TA274 may have greater clinical plausibility, while also addressing the concern raised by the ERG's clinical expert that the probability of 3.5% may be too high. Therefore, the company's revised base case assumes a 3-month probability of gaining or losing at least 10 letters of BCVA of 2.5% or 3.5%, respectively.

The ERG agrees with the company that patients' vision may improve with no treatment. However, the ERG still has issues with the magnitude of the improvement and the sources used to justify these improvements. According to the ERG's clinical experts, improvements in vision are likely to be smaller than 10-letters and therefore would be within one model health state. The ERG also considers it inappropriate to use the UK RWE audit and sham arm of MEAD as sources of evidence for improving vision as patients contributing to the UK RWE audit received anti-VEGF treatment and the company used a LOCF approach to account for missing data in the sham arm of MEAD, which may lead to optimistic results as vision in patients with missing data cannot worsen (see Key Issue 1). Furthermore, TA613 was conducted after TA274, and the TA613 committee accepted a 3-month probability of gaining or losing at least 10 letters of BCVA of 0% or 3.5%, respectively.

For stakeholder comments and additional clinical expert opinion to the company on this issue, see Table 7 and Figure 9. The ERG considers neither of these to provide more appropriate natural history estimates.

Overall, the ERG maintains that the most appropriate natural history estimates are those accepted in TA613 and applies these in its preferred base case (see Section 4).

Figure 9. Conversation 7 reproduced from Allergan's HTA Digital Advisory Board Interim Report (May 2022)[14]

Table 7. Stakeholder comments on Key Issue 6 (the natural history of vision in eyes with DMO)

Stakeholder	Comment
Clinical expert 1	The natural history was well documented previously in pivotal studies. However, clinical practice has changed significantly since the introduction of new therapies. Natural history studies after discontinuation treatments are limited. The Danish retrospective study of Hodzic-Hadzibjovic et al (2018) reported a 25.4% switch of anti-VEGF to other treatments. Treatment was discontinued in 31.6% due to disease stability, and 1.4% because of significant vision reduction, whilst 3.2% died. Switching from ranibizumab to aflibercept did not result in a change in VA, and CST only reduced by <10% compared to baseline. Nine percent (9%) of 566 eyes originally treated with anti-VEGF drugs were switched to dexamethasone implant (Ozurdex). The probabilities seem correct. The lower ICER thresholds suggested by the TAG seems arbitrary, especially if confidential discount for anti-VEGFs are counted in this appraisal.

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor therapy; CST, contrast sensitivity testing; DMO, diabetic macular oedema; ICER, incremental cost effectiveness ratio; TAG, technology assessment group; VA, visual acuity

2.7 Additional issues

Other cost-effectiveness issues raised by the ERG in the ERG report include:

- the assumption that patients cannot discontinue anti-VEGF treatment during the treatment period;
- the different cataract extraction rates applied to patients on and off anti-VEGF treatment;
- the company's approach to model additional mortality due to diabetes mellitus (DM) and severe vision loss;
- the raised IOP rates applied to anti-VEGFs;
- the omission of disutilities due to adverse events (AEs); and
- the number of DEX700 injections assumed in Years 4 and 5.

However, exploratory and sensitivity undertaken by the company (in the CS or at clarification) and the ERG suggest that these issues have a minimal impact on the cost-effectiveness results.

In the company's TE response, the company responded to four of the additional issues, each of these are described in turn below.

2.7.1 Cataract extraction rates applied to patients on and off anti-VEGF treatment

In the CS, cataract extraction rates for patients receiving anti-VEGF were taken from the UK RWE audit[9], while cataract extraction rates for patients no longer receiving treatment (in either treatment arm) were taken from the Blue Mountain Eye Study[17]. Clinical expert opinion sort by the ERG

indicated that the rate of cataract extraction would be similar in patients on and off anti-VEGF treatment. Therefore, like TA613[3] which used the sham arm of FAME to inform anti-VEGF cataract extraction rates, the ERG used the sham arm of MEAD to inform cataract extraction rates in patients receiving anti-VEGF treatment or no treatment (on either treatment arm) in its preferred base case analysis.

In response to TE, the company accepted that there is limited evidence to indicate that the risk of cataract extraction would differ between patients receiving anti-VEGF treatment compared with patients receiving no treatment and therefore accepted the ERG's assumption that the risk of cataract extraction for anti-VEGF would be equal to that of no treatment and therefore adopted this approach in their revised base case. The company considered the UK RWE audit (excluding Month 0-12) to be the most relevant source to estimate the risk of cataract extraction in UK patients with DMO in phakic eyes and used this data in its revised base case. The proportion of patients with phakic eyes over the duration of the model time horizon are illustrated in Figure 10.

The company excluded Month 0-12 data from the UK RWE audit given that data from Month 12–24 data provided the first full year of data following an assessment of insufficient response. However, the ERG considers response status to be independent of cataract extraction rates. Moreover, the data from MEAD was not limited to patients following an assessment of insufficient response. For these reasons, the ERG explored a scenario including Month 0-12 data, nevertheless this had a minimal impact on the results (inc. NMB reduced from £10,386 to £10,372).

The ERG also considers the source to inform anti-VEGF treatment (on and off treatment) difficult to choose. On the one hand, the sham arm of MEAD is consistent with the approach taken in TA613 (which used the sham arm of FAME) and the source used to inform DEX700. On the other hand, the UK RWE audit better reflects UK patients receiving anti-VEGF treatment. As noted in the ERG report, clinical opinion to the company and ERG has advised that nearly all patients with DMO with a phakic lens will eventually develop a cataract, which could suggest the cataract extractions rates in the sham arm of MEAD are too low.

In response to TE, the ERG sought the cataract extraction rates in the sham arm of FAME and found that 8 of 72 (14.8%) and 24 of 112 (36.4%) of patients with nonchronic and chronic DMO, respectively, underwent surgery over a 3-year period (Cunha-Vaz *et al.* 2014)[18]. The ERG is unable to compare the modelled cataract extraction rates in TA613 with the sham arm of MEAD as the rates reported in TA613 are conditional on a patient being diagnosed with cataract. Nevertheless, the estimates from Cunha-Vaz *et al.* 2014 are closer to the UK RWE audit than the sham arm of FAME

and therefore the ERG accepts the company's revised approach. For completeness, the ERG has provided a scenario using the sham arm of MEAD to inform cataract extraction rates for patients receiving anti-VEGF and no treatment (on either treatment arm) in Section 4.

Table 8 summarises the cataract extractions rates considered by the company.

Table 8. Cataract extraction rates

Source	Cataract extraction rate for phakic eyes			
	Year 1	Year 2	Year 3	Year 4+
MEAD DEX700 arm	[redacted]	[redacted]	[redacted]	[redacted]
MEAD sham arm	[redacted]	[redacted]	[redacted]	[redacted]
Blue Mountains study	2.32%	2.32%	2.32%	2.32%
UK RWE including Month 0-12	[redacted]	[redacted]	[redacted]	[redacted]
UK RWE excluding Month 0-12	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DEX700, dexamethasone 700 µg; RWE, Real World Evidence, UK, United Kingdom

Figure 10. Proportion of phakic eyes in the revised model (generated by the ERG)

2.7.2 Additional mortality due to diabetes mellitus (DM) and severe vision loss

In the CS, all-cause mortality was adjusted for the additional mortality due to diabetes mellitus (DM) (relative to the general population) and due to DMO (relative to the population with DM) and

assuming that mortality occurs equally across all BCVA states. The additional mortality hazard ratios (HRs) due to DM and due to DMO were 1.93 (Mulnier *et al.* 2006[19]) and 1.27 (Hirai *et al.* 2008[20]), consistent with the base case assumptions from TA349. The company acknowledged that there may be some double counting in the application of these two HRs as the HR derived for the additional mortality due to DM may include some patients with DMO.

To reduce the company's double counting concerns and include the evidence of increased mortality in blind patients, the ERG stated a preference for the approach adopted in TA613 where DMO related mortalities are limited to blind patients (BCVA ≤ 35 letters). However, to inform the increased mortality in blind patients, the ERG considers the multiplier associated with "severe visual impairment" (1.54) to be of more relevance than the multiplier applied in TA613 which was associated with "some visual impairment" (1.23).

In response to TE, the company accepted the ERG's approach and applied a HR of 1.95 for the additional blindness due to DM (Preis *et al*. 2009[21]) and a HR of 1.54 for the additional mortality due to blindness (Christ *et al.* 2008[22]).

The company also considered that that it may be appropriate to apply the HR due to blindness (1.54) only when both eyes experience severe vision loss, however a complex amendment to the model would be needed to implement this correctly. In consequence, the company assumed that the additional mortality due to blindness is only applied to patients in whom the BSE is in the worst health state and noted that this aligns with the approach taken for the additional costs due to blindness.

Overall, the ERG accepts the company's revised assumptions.

2.7.3 Disutilities due to adverse events (AEs)

In response to TE, the company included utility decrements due to AEs to align with the ERG's base case.

An additional and related area of concern noted by the ERG in the ERG report was that the raised IOP rate was [redacted] for anti-VEGF treatment than DEX700 treatment. However, including disutilities due to AEs does not exacerbate this issue as no disutility was assumed for raised IOP in TA613. Also, as shown in the ERG report, using lower a rate of raised IOP in the anti-VEGF arm had a minimal

impact on the results. Thus, if the company applied the appropriate rates or not, the ERG does not consider it likely to make a substantial difference to the ICER.

2.7.4 The number of DEX700 injections assumed in Years 4 and 5

In response to TE, the company updated the costing assumptions in its revised base case to assume the number of DEX700 injections administered in year 3 of MEAD is applied in Year 4 and 5 (patients will continue to receive the same number of injections in Year 4 and 5 as in Year 3). Increasing the number of injections patients are assumed to receive ([redacted] per year instead of 1.0) aligns with the ERG's base case and helps mitigate against uncertainty by more closely aligning treatment costs with the assumptions related to efficacy.

The company also picked up on clinical expert opinion to the ERG in the ERG report that the number of injections for Year 1 for anti-VEFs from the UK RWE audit[9] ([redacted] injections) was low and more likely to between the UK RWE audit and the RESTORE study[23] (5.5 injections), citing 5 injections in Year 1 to be a plausible alternative assumption. The company therefore revised their base case analysis to assume 5 injections of anti-VEGF in the first year.

The ERG accepts the company's revised assumptions.

3 Company's revised cost-effectiveness results

In response to the technical engagement (TE) report, the company presented updated base case analyses. The changes that have been made to the company's base case analyses include:

- A correction to the model regarding treatment acquisition costs in fellow eyes;
- A correction to the model regarding proportion of treated eyes at risk of cataract surgery in Year 4 and Year 5;
- Assuming 80% of patients who discontinue dexamethasone 700 µg (DEX700) during Years 1-5 receive 1 additional year of anti-vascular endothelial growth factor (anti-VEGF) treatment (Key Issue 5);
- Using TA274[2] to inform the natural history of vision: 2.5% probability of improvement and 3.5% probability of worsening per 3-month cycle (Key Issue 6);
- Using the UK Real World Evidence (RWE) audit[9] to inform the cataract rates in anti-VEGF patients (on and off treatment);
- Amending the mortality hazard ratio (HR) due to diabetes from 1.93 to 1.95;

- Including additional mortality (HR 1.54) due to blindness (best-seeing eyes in health state 1);
- Using Evidence Review Group (ERG) clinical opinion to inform the number of anti-VEGF injections in Year 1 (increased from 3.5 to 5); and,
- Including utility decrements due to adverse events (AEs).

As per the company submission (CS), the company compared DEX700 to a composite comparator based on the proportion of patients receiving ranibizumab 0.5 mg ([redacted]) and aflibercept 2 mg ([redacted]) treatment in the UK RWE audit[9].

The economic analysis also assumes a maximum duration of treatment of 5 years (for the intervention and comparator). The cost of each treatment each year, including acquisition and administration costs, and the company's revised base case assumptions, is summarised in **Error! Not a valid bookmark self-reference.**. While the unit price of DEX700 is higher than that of anti-VEGF treatments, DEX700 has a lower annual cost compared with anti-VEGF treatments due its lower frequency of administration.

Table 9. Cumulative cost of each treatment each year (list prices)

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Cost of treatment each year					
DEX700 PRN	£2,273	£1,783	£1,552	£1,446	£1,327
Anti-VEGFs	£5,012	£5,012	£2,824	£2,985	£2,985
Cumulative cost of each treatment each year					
DEX700 PRN	£2,273	£4,056	£5,608	£7,054	£8,382
anti-VEGF	£5,012	£7,901	£10,725	£13,710	£16,696

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; DEX700, dexamethasone 700 µg; PAS, patient access scheme; PRN, pro re nata.

The company's revised base case results comparing DEX700 to the composite comparator are presented in Table 10. As the company did not provide revised probabilistic results these have been generated by the ERG using 1,000 iterations, also presented in Table 10. For scenario analysis results, see

Table 11. Results including comparator patient access scheme (PAS) discounts can be found in the confidential appendix. No PAS is in place for DEX700.

Table 10. Company's base case results

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NMB (£30,000/ QALY WTP threshold)
Original base case (deterministic)						

Anti-VEGFs	£38,695	7.4815	-	-	-	-
DEX700	£31,728	7.5853	-£6,968	0.1038	Dominant	£10,080
Revised base case (deterministic)						
Anti-VEGFs	£41,799	7.942				
DEX700	£34,830	8.056	-£6,969	0.1139	Dominant	£10,386
Revised base case (probabilistic using 1,000 iterations)						
Anti-VEGFs	£42,001	7.811				
DEX700	£34,977	7.934	-£7,024	0.1233	Dominant	£10,722*

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; CS, company submission; DEX700, dexamethasone 700 µg; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

*DEX700 has a 100% chance of being cost-effective at WTP threshold of £20,000 and £30,000 per QALY.

Table 11. Sensitivity analyses around the revised base case

Scenario description	Revised base case assumption	Scenario assumption	ICER (DEX700 vs anti-VEGF)	Inc. NMB (WTP threshold £30,000/QALY)
Base case			Dominant	£10,386
Time horizon	[redacted] years	30 years	Dominant	£10,367
		15 years	Dominant	£9,336
		10 years	Dominant	£8,418
Dosing anti-VEGF	5 injections in Year 1, UK RWE thereafter	The RESTORE study[23]	Dominant	£13,468
		[redacted] injections in Year 1, UK RWE[9] thereafter (original company base case)	Dominant	£9,132
Mortality due to blindness	HR of 1.54 applied only to BSE in health state 1	HR of 1.54 applied to both BSE and WSE in health state 1	Dominant	£10,374
		No mortality due to blindness	Dominant	£10,179
Cataract extraction rate off-treatment	UK RWE (last observed year)	Blue Mountain study[17] (original company base case)	Dominant	£10,142
Off-treatment efficacy	Natural history based on NICE TA274[2] (2.5% improvement, 3.5% worsening)	Natural history based on Mitchell *et al.* 2012[16] (3.5% improvement, 4.5% worsening)	Dominant	£10,213
Efficacy DEX700	MEAD DEX700 - phakic population	MEAD pseudophakic population	Dominant	£22,552
		French RWE[24] (baseline to Month 12 probabilities recalculated into 3-month probabilities)	Dominant	£27,325

Scenario description	Revised base case assumption	Scenario assumption	ICER (DEX700 vs anti-VEGF)	Inc. NMB (WTP threshold £30,000/QALY)
Base case			Dominant	£10,386
		French RWE (baseline to Month 24 probabilities recalculated into 3-month probabilities)	Dominant	£24,560
		French RWE (baseline to Month 36 probabilities recalculated into 3-month probabilities)	Dominant	£28,302
Efficacy anti-VEGF	MEAD sham - phakic population	UK RWE (baseline to Month 12 probabilities recalculated into 3-month probabilities)	Dominant	£21,105
		UK RWE (baseline to Month 24 probabilities recalculated into 3-month probabilities)	Dominant	£13,138
		UK RWE (baseline to Month 36 probabilities recalculated into 3-month probabilities)	Dominant	£10,509
		UK RWE TPs calculated per year	Dominant	£18,035
		DMO natural history (2.5% improve / 3.5% worsen)	Dominant	£12,067
		Net-zero impact on vision (3.0% improve / 3.0% worsen)	Dominant	£7,768
		Net-zero impact on vision (3.5% improve / 3.5% worsen)	Dominant	£8,295
		No change in vision (excluding severe vision loss costs)	Dominant	£8,266

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor therapy; BCVA, best corrected visual acuity; BSE, best seeing eye; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost effectiveness ratio; NICE, National Institute for Health and Care Excellence; NMB, net monetary benefit; RWE, real world evidence; TP, transition probability; WSE, worst seeing eye; WTP, willingness to pay.

4 ERG's cost-effectiveness results

In Section 2, the ERG has described several scenarios that warrant further exploration. The scenarios that the ERG has produced are applied to the company's revised base case and include:

1. Distribution of vision in the DEX700 arm is equal to the anti-VEFGF arm from Year 10 (see Key Issue 2);

2. DEX700 transition probabilities in Years 4 are equal the last transition probability matrix estimated from MEAD and DEX700 transition probabilities in Year 5 maintain vision (see Key Issue 3);
3. Unrestricted transition probability matrices for DEX700 when a net zero impact on vision is assumed for anti-VEGFs (see Key Issue 4);
4. Natural history of vision based on TA613[3] (0% improvement, 3.5% worsening) (see Key Issue 6);
5. Cataract extraction rates for patients receiving anti-VEGF and no treatment (on either treatment arm) informed by the sham arm of MEAD (see additional issues).

Results of these scenario analyses are provided in Table 12.

Table 12. ERG's scenario analysis results

#	Results per patient	DEX700	ANTI-VEGF	Incremental value
0	Company base case			
	Total costs	£34,830	£41,799	-£6,969
	QALYs	8.06	7.94	0.11
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£10,386
1	Distribution of vision in the DEX700 arm is equal to the anti-VEFGF arm from Year 10			
	Total costs	£35,130	£41,799	-£6,669
	QALYs	8.00	7.94	0.06
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£8,539
2	DEX700 transition probabilities in Years 4 are equal the last transition probability matrix estimated from MEAD and DEX700 transition probabilities in Year 5 maintain vision			
	Total costs	£35,130	£41,799	-£6,669
	QALYs	8.01	7.94	0.06
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£8,581
3a	Unrestricted transition probability matrices for DEX700 when a net zero impact on vision (3.0%) is assumed for anti-VEGFs			
	Total costs	£34,830	£37,492	-£2,662
	QALYs	8.06	8.04	0.02
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£3,139
3b	Unrestricted transition probability matrices for DEX700 when a net zero impact on vision (0.0%) is assumed for anti-VEGFs (excluding severe vision loss costs)			

	Total costs	£20,970	£29,417	-£8,447
	QALYs	8.06	8.06	-0.01
	ICER (£/QALY)			£1,400,103 (SW)
	Inc. NMB (£30,000/QALY)			£8,266
3c	Unrestricted transition probability matrices for DEX700 when a net zero impact on vision (0.0%) is assumed for anti-VEGFs (including severe vision loss costs)			
	Total costs	£34,830	£34,688	£142
	QALYs	8.06	8.06	-0.01
	ICER (£/QALY)			Dominated
	Inc. NMB (£30,000/QALY)			-£323
4	Natural history of vision based on TA613			
	Total costs	£42,045	£48,485	-£6,440
	QALYs	7.70	7.61	0.08
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£8,876
5	Cataract extraction rates for patients receiving anti-VEGF and no treatment (on either treatment arm) informed by the sham arm of MEAD			
	Total costs	£34,523	£40,870	-£6,347
	QALYs	8.06	7.94	0.11
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£9,755

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; DEX700, dexamethasone 700 µg; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality adjusted life year; SW, south-west quadrant ICER (DEX700 if less expensive and less effective than the comparator).

In this section of the report, the ERG also presents its preferred base case ICER. The key differences between the company's base case ICER and ERG's preferred base case ICER are given in Table 13. Table 14 shows the impact of each assumption cumulatively using the composite comparator. For probabilistic results, see Table 15.

The ERG notes that when its preferred assumptions are applied, DEX700 switches from being more effective than anti-VEGFs to less effective. In consequence, the ICER switches from the south-east quadrant on the cost-effectiveness plane (dominant) to the south-west quadrant. The ERG also notes that the incremental QALYs are relatively small when its preferred assumptions are applied, resulting in extremely sensitive ICERs.

Table 13. ERG's preferred assumptions

#	Assumptions	Company approach	ERG approach
1	Changes in BCVA resulting from DEX700 treatment in Years 4 and 5 (key issue 3)	Vision improves (last transition probability matrix carried forward)	Vision maintains (3-month probability of gaining or losing at least 10 letters of BCVA of 3.0%, as per stable vision in TA274)
2	The natural history of vision in eyes with DMO (key issue 6)	TA274[2] (3-month probability of gaining or losing at least 10 letters of BCVA of 2.5% or 3.5%, respectively)	TA613[3] (3-month probability of gaining or losing at least 10 letters of BCVA of 0.0% or 3.5%, respectively)
3	Time horizon considered for the economic analysis (key issue 2)	40 years	10 years

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor therapy; BCVA, best corrected visual acuity; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; TA, technology appraisal.

Table 14. ERG's preferred base case, cumulative results (composite comparator)

#	Results per patient	DEX700	ANTI-VEGF	Incremental value
0	Company base case			
	Total costs	£34,830	£41,799	-£6,969
	QALYs	8.06	7.94	0.11
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£10,386
1	DEX700 maintains vision in Years 4 and 5			
	Total costs	£35,153	£41,799	-£6,646
	QALYs	7.96	7.94	0.02
	ICER (£/QALY)			Dominant
	Inc. NMB (£30,000/QALY)			£7,311
2	Natural history of vision as per TA613			
	Total costs	£42,868	£48,485	-£5,617
	QALYs	7.59	7.61	-0.02
	ICER (£/QALY)			£272,481 (SW)
	Inc. NMB (£30,000/QALY)			£4,999
3	10-year time horizon			
	Total costs	£25,193	£31,526	-£6,333
	QALYs	4.84	4.85	-0.01
	ICER (£/QALY)			£1,040,800 (SW)
	Inc. NMB (£30,000/QALY)			£6,150

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; DEX700, dexamethasone 700 µg; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality adjusted life year; SW, south-west quadrant ICER (DEX700 if less expensive and less effective than the comparator).

Table 15. ERG's preferred base case, deterministic vs probabilistic results

Results per patient	DEX700	ANTI-VEGF	Incremental value
ERG base case (deterministic)			
Total costs	£25,193	£31,526	-£6,333
QALYs	4.844	4.850	-0.006
ICER (£/QALY)			£1,040,800 (SW)
Inc. NMB (£30,000/QALY)			£6,150
ERG base case (probabilistic using 1,000 iterations)			
Total costs	£25,200	£31,522	-£6,322
QALYs	4.821	4.824	-0.003
ICER (£/QALY)			£2,267,457 (SW)*
Inc. NMB (£30,000/QALY)			£6,238

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; DEX700, dexamethasone 700 µg; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year; SW, south-west quadrant ICER (DEX700 if less expensive and less effective than the comparator); WTP, willingness-to-pay.
*DEX700 has a 100% chance of being cost-effective at WTP threshold of £20,000 and £30,000 per QALY.

As noted in the ERG report, amending the composite comparator ([redacted] ranibizumab and [redacted] aflibercept) to a 100% ranibizumab comparator has no impact for decision making in the company base case as DEX700 remains dominant. However, given the magnitude of the change in the inc. NMB (£10,386 vs £5,998 for the composite comparator vs ranibizumab, respectively) assessing ranibizumab as an individual comparator could be important for decision making when a number of modelling assumptions are changed. Additionally, clinical experts to the ERG have suggested that the use of aflibercept estimated based on the latest 2 years of the UK RWE audit[9] ([redacted]) is not unreasonable as the use of aflibercept appears to be increasing. For these reasons, the ERG also presents its preferred base case for a 100% aflibercept comparator (Table 16) and a 100% ranibizumab comparator (Table 17). For fully incremental results, see Table 18.

Table 16. ERG's preferred base case (aflibercept)

Results per patient	DEX700	AFILBERCEPT	Incremental value
Company base case			
Total costs	£34,830	£44,379	-£9,549
QALYs	8.056	7.942	0.114
ICER (£/QALY)			Dominant
Inc. NMB (£30,000/QALY)			£12,966
ERG base case			
Total costs	£25,139	£34,106	-£8,913
QALYs	4.844	4.850	-0.006

ICER (£/QALY)	£1,464,837 (SW)
Inc. NMB (£30,000/QALY)	£8,730

Abbreviations: DEX700, dexamethasone 700 µg; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality adjusted life year; SW, south-west quadrant ICER (DEX700 if less expensive and less effective than the comparator).

Table 17. ERG's preferred base case (ranibizumab)

Results per patient	DEX700	RANIBIZUMAB	Incremental value
Company base case			
Total costs	£34,830	£37,411	-£2,581
QALYs	8.056	7.942	0.114
ICER (£/QALY)			Dominant
Inc. NMB (£30,000/QALY)			£5,998
ERG base case			
Total costs	£25,193	£27,138	-£1,945
QALYs	4.844	4.850	-0.006
ICER (£/QALY)			£319,691 (SW)
Inc. NMB (£30,000/QALY)			£1,763

Abbreviations: DEX700, dexamethasone 700 µg; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality adjusted life year; SW, south-west quadrant ICER (DEX700 if less expensive and less effective than the comparator).

Table 18. ERG's fully incremental base case results

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
DEX700	£25,193	4.844	-	-	-
Ranibizumab	£27,138	4.850	£1,945	0.006	£319,691
Aflibercept	£34,106	4.850	£6,968	0.000	Dominated by ranibizumab

Abbreviations: DEX700, dexamethasone 700 µg; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; WTP, willingness-to-pay

5 References

1. Boyer DS, Yoon YH, Belfort R, Jr., Bandello F, Maturi RK, Augustin AJ, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology* 2014; **121**: 1904-14.
2. National Institue for Health and Care Excellence (NICE). Ranibizumab for treating diabetic macular oedema: Technology appraisal [TA274], 2013. Available from: https://www.nice.org.uk/guidance/ta274. Date accessed: May 2022.
3. National Institute for Health and Care Excellence (NICE). Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy: Technology appraisal [TA613], 2019. Available from: https://www.nice.org.uk/guidance/ta613. Date accessed: May 2022.

4. Guigou S, Pommier S, Meyer F, Hajjar C, Merite PY, Parrat E, et al. Efficacy and Safety of Intravitreal Dexamethasone Implant in Patients with Diabetic Macular Edema. *Ophthalmologica Journal international d'ophtalmologie International journal of ophthalmology Zeitschrift fur Augenheilkunde* 2015; **233**: 169-75.
5. Kaldırım H, Savur F, Kırgız A, Atalay K. Comparison of Anatomical and Functional Outcomes of Intravitreal Dexamethasone Implant between Phakic and Pseudophakic Eyes with Diabetic Macular Edema. *Korean journal of ophthalmology : KJO* 2020; **34**: 383-91.
6. Malclès A, Dot C, Voirin N, Agard É, Vié A-L, Bellocq D, et al. Real-life Study in Diabetic Macular Edema Treated with Dexamethasone Implant: The Reldex Study. *Retina* 2017; **37**.
7. Mathis T, Lereuil T, Abukashabah A, Voirin N, Sudhalkar A, Bilgic A, et al. Long-term follow-up of diabetic macular edema treated with dexamethasone implant: a real-life study. *Acta Diabetol* 2020; **57**: 1413-21.
8. Mello Filho P, Andrade G, Maia A, Maia M, Biccas Neto L, Muralha Neto A, et al. Effectiveness and Safety of Intravitreal Dexamethasone Implant (Ozurdex) in Patients with Diabetic Macular Edema: A Real-World Experience. *Ophthalmologica Journal international d'ophtalmologie International journal of ophthalmology Zeitschrift fur Augenheilkunde* 2019; **241**: 9-16.
9. AbbVie. Long-term Follow Up of anti-VEGF use in Phakic Patients with Diabetic Macular Oedema: Real World Outcomes (Data on file). 2021.
10. AbbVie. MEAD Post-Hoc Analysis: Tables for Phakic Inputs (model) (Data on file). 2021.
11. National institute for Health and Care Excellence (NICE). Dexamethasone intravitreal implant for treating diabetic macular oedema: Technology appraisal [TA349], 2015. Available from: https://www.nice.org.uk/guidance/ta349. Date accessed: May 2022.
12. National Institute for Health and Care Excellence (NICE). Aflibercept for treating diabetic macular oedema: Technology appraisal [TA346], 2015. Available from: https://www.nice.org.uk/guidance/ta346. Date accessed: May 2022.
13. National Institute for Health and Care Excellence. Age-related macular degeneration (NG82), 2018. Available from: https://www.nice.org.uk/guidance/ng82/evidence/appendix-j-health-economics-pdf-170036251093. Date accessed: May 2022.
14. AbbVie. Allergan* Ozurdex (Dexamethasone Intravitreal Implant 0.7mg) HTA Digital Advisory Board Interim Report. Date of preparation: May 2022.
15. National Institute for Health and Care Excellence (NICE). Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy: Final appraisal document [TA613], 2019. Available from: https://www.nice.org.uk/guidance/ta613/documents/final-appraisal-determination-document. Date accessed: May 2022.
16. Mitchell P, Annemans L, Gallagher M, Hasan R, Thomas S, Gairy K, et al. Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial. *Br J Ophthalmol* 2012; **96**: 688-93.
17. Tan JS, Wang JJ, Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. *Ophthalmic Epidemiol* 2008; **15**: 317-27.
18. Cunha-Vaz J, Ashton P, Iezzi R, Campochiaro P, Dugel PU, Holz FG, et al. Sustained Delivery Fluocinolone Acetonide Vitreous Implants: Long-Term Benefit in Patients with Chronic Diabetic Macular Edema. *Ophthalmology* 2014; **121**: 1892-903.e3.
19. Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA. Mortality in people with type 2 diabetes in the UK. *Diabetic medicine : a journal of the British Diabetic Association* 2006; **23**: 516-21.
20. Hirai FE, Knudtson MD, Klein BE, Klein R. Clinically Significant Macular Edema and Survival in Type 1 and Type 2 Diabetes. *Am J Ophthalmol* 2008; **145**: 700-6.

21. Preis SR, Hwang SJ, Coady S, Pencina MJ, D'Agostino RB, Sr., Savage PJ, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation* 2009; **119**: 1728-35.
22. Christ SL, Lee DJ, Lam BL, Zheng DD, Arheart KL. Assessment of the effect of visual impairment on mortality through multiple health pathways: structural equation modeling. *Invest Ophthalmol Vis Sci* 2008; **49**: 3318-23.
23. Schmidt-Erfurth U, Lang GE, Holz FG, Schlingemann RO, Lanzetta P, Massin P, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology* 2014; **121**: 1045-53.
24. AbbVie. French RWD. Real World Study in Diabetic Macular Oedema Treated with Dexamethasone Implant: phakic vs pseudophakic (Data on file). 2021.