**National Institute for Health and Care Excellence**

# Diabetic Retinopathy: management and monitoring

**Economic model report for evidence reviews E and G**

*NICE Guideline <TBC>*

*July 2023*

*Report developed by the Guideline Updates Team*

**Disclaimer**
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

**Copyright**
<Please insert your copyright statement - one line of text entry only>

**Funding**
<Please insert your statement here

<Please insert your copyright statement - one line of text entry only>

# Contents

# HE1  Introduction

## HE1.1  Decision problem

An economic model was developed to support the decision making of the review questions (RQs) in Table 1. Both RQs were identified as high priorities for model-based economic analysis by the guideline committee. Two separate models were developed using the same model structure defined by best corrected visual acuity (BCVA) intervals and a death state, but to allow for different interventions, subpopulations and efficacy parameters to be used given diabetic retinopathy and diabetic macular oedema follow different natural histories of disease. The BCVA-based model structure was informed by previous economic models, which allowed for the main outcome data reported from clinical trials to be incorporated into the model and for model results to be validated against previously published analyses.

Throughout this report, the model structure and inputs such as adverse event costs are discussed together where these are the same across both conditions, while only the differences between the two populations are discussed separately.

**Table 1:  Review questions informed by new economic modelling**

| | |
|---|---|
| **RQ5** | What is the effectiveness of anti-vascular endothelial growth factor agents and laser photocoagulation (alone or in combination) for the treatment of non-proliferative and proliferative diabetic retinopathy without macular oedema? |
| **RQ7** | What is the effectiveness of intravitreal steroids, laser photocoagulation and anti-vascular endothelial growth factor agents for treating diabetic macular oedema? |

<Please insert your copyright statement - one line of text entry only>

# HE2 Methods

## HE2.1 Model overview

The objective of these analyses was to compare the expected benefits, harms, and costs of treatments for people with proliferative diabetic retinopathy (RQ5) and for people with diabetic macular oedema (RQ7).

### HE2.1.1 Population(s)

The populations of interest are consistent with the review protocols for each review question.

#### Review question 5 – Proliferative diabetic retinopathy

Review question 5 includes the population for both people with non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) who do not have a diagnosis of diabetic macular oedema (DMO). However, there was not sufficient clinical evidence available for the NPDR population to populate an economic model, and therefore the population of interest for the cost-effectiveness analysis for RQ5 was PDR only.

#### Review question 7 – Diabetic macular oedema

The population of interest is people with a diagnosis of DMO. Due to the heterogeneity of the population, it was not considered appropriate to model centre involving DMO and non-centre involving DMO together. However, there was a lack of publicly available data in non-centre involving DMO, meaning a network could not be constructed for a network meta-analysis (NMA) in this subset of patients, and therefore only the centre involving population was modelled.

Another area of heterogeneity was around central retinal thickness (CRT) given the recommendations for anti-VEGFs (at the time of analysis) from NICE technology appraisals (TA) were in people with a CRT of at least 400µm. Again, due to a lack of publicly available data in people with DMO and a CRT<400µm, it was not possible to inform an economic analysis in this subgroup. As such, the subgroup analysis was only in people with centre involving DMO with a CRT≥400µm. The lack of publicly available patient level data meant that the inclusion criteria for the NMA for the population of centre involving DMO with a CRT≥400µm was based on the clinical trial having a mean CRT of at least 400µm. By relying on the mean value, it is possible that the trials in DMO with a mean CRT≥400µm would have included people with a CRT<400µm, which may lead to the subgroup population not being substantially different to the overall centre involving population.

Clinical trials included within the NMA generally had an inclusion criterion of people with visual impairment as assessed by 78 letters or less. Additionally, whilst not specified within the NMA protocol, analysis was undertaken for the clinical effectiveness for this population. However, a formal NMA was not undertaken for this subgroup in order to populate the economic model due to a lack of publicly available data to split the population by those with visual impairment.

### HE2.1.2 Interventions

The model assessed the following treatment regimens separated by the condition of interest for each review question.

<Please insert your copyright statement - one line of text entry only>

### Review question 5 – Diabetic retinopathy

- Anti-VEGF treatments:
  - Ranibizumab* (Lucentis) 500µg

    *Ranibizumab biosimilar (Ongavia) 500µg (only as a scenario assuming the same efficacy, safety and resource use as ranibizumab)
  - Aflibercept 2mg
  - Bevacizumab (off-label) 1.25mg
- Panretinal photocoagulation (PRP)

Anti-VEGF treatments that are available through the NHS including ranibizumab, aflibercept and bevacizumab were considered as part of this review. The market authorisation for ranibizumab and aflibercept includes for the treatment of people with proliferative diabetic retinopathy, however neither of these treatments have completed a health technology appraisal with NICE. It should be noted that bevacizumab is a licensed treatment but does not have a market authorisation for use in ophthalmology conditions, which we have referred to as "off-label use". PRP was considered either as monotherapy or in combination with an anti-VEGF treatment. The treatment efficacy of all anti-VEGF treatments, both monotherapy and in combination with PRP, were compared with PRP alone based on the mean difference in BCVA as assessed by logMAR within clinical trials. Treatments were compared with both PRP (as the current standard of care) and with each other.

### Review question 7 – Diabetic macular oedema

- Anti-VEGF treatments:
  - Ranibizumab* (Lucentis) 500µg

    *Ranibizumab biosimilar (Ongavia) 500µg (only as a scenario assuming the same efficacy, safety and resource use as ranibizumab)
  - Aflibercept 2mg
  - Faricimab 6mg
  - Brolucizumab 6mg
  - Bevacizumab (off-label) 1.25mg
- Intravitreal steroids:
  - Dexamethasone 700µg
  - Fluocinolone acetonide (pseudo phakic lens only) 190µg
- Macular laser therapies:
  - Standard threshold laser
  - Subthreshold micropulse laser

Anti-VEGFs that are available through the NHS, with positive recommendations in a NICE TA, were considered as part of this review. Anti-VEGFs considered in the analysis include: ranibizumab (TA274), aflibercept (TA346), faricimab (TA799) and brolucizumab (TA820). Bevacizumab, an off-label treatment, was also considered as part of the review.

Macular laser therapy delivered using either a standard threshold or a subthreshold micropulse laser, either as monotherapy or in combination with an anti-VEGF was included in the analysis. Although macular laser may not be suitable for everyone with DMO, it was considered to be a relevant comparator by the committee when the macular oedema does not involve the centre, or in people without visual impairment (TA824). Additionally, macular laser treatment was demonstrated to be safe within the DIAMOND study (Lois et al, 2022) for people with centre involving DMO with a CRT less than 400µm.

<Please insert your copyright statement - one line of text entry only>

Intravitreal steroid treatments considered in the analysis include: dexamethasone (TA824) and fluocinolone (TA301). It should be noted that fluocinolone is only recommended for patients with a pseudo phakic lens. Dexamethasone may be considered as first line for patients whom the other first line treatments are not suitable. Combination treatment of intravitreal steroids plus anti-VEGF agents was not considered a comparator of interest for the committee since they felt it was unlikely that the combination would be used over either type of treatment alone, and therefore was not included in the economic analysis. Treatment efficacy is measured by mean difference in BCVA compared with no treatment, and the cost effectiveness of these treatments were compared to each other.

### HE2.1.3 Type of evaluation, time horizon, perspective, discount rate

A lifetime cost-utility analysis was conducted to reflect all important differences in costs and health outcomes between the interventions compared. Health outcomes were valued in terms of quality adjusted life years (QALYs) estimated by weighting the years of life remaining with a quality of life (utility) score, and the results were presented using incremental cost-effectiveness ratios (ICERs) that express the cost per QALY gained. Net monetary benefits (NMBs) at a threshold of £20,000 per QALY gained were also presented to provide greater interpretability of the model outputs.

The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) in the United Kingdom.

All costs and QALYs were discounted at a rate of 3.5% per year in line with the NICE reference case.

## HE2.2 Model structure

A cohort Markov model was developed with a cycle length of 3 months and a lifetime horizon. The cycle length was consistent with previous published economic models (Régnier et al 2015, Pochopien et al 2019, Haig et al 2016, Mitchell et al 2012) and was considered a suitable length of time by the committee for changes in eyesight to occur due to disease progression or regression. A half-cycle correction was applied to account for patients moving between health states within each model cycle, not necessarily at the start or end of each cycle.

A systematic literature review and a review of published NICE TAs was conducted to find relevant economic evidence. No positive TAs were identified for diabetic retinopathy, but six positive TAs (TA824, TA820, TA799, TA346, TA301, TA274) were identified for DMO. All TAs which evaluated the cost-effectiveness of DMO used a Markov model structure with six to eight health states based on categories of BCVA in addition to a separate death state. BCVA refers to the vision after being corrected by glasses as needed. Only one published study (Hutton et al 2019) was identified for diabetic retinopathy which did not include details of an economic model, however, the study stated BCVA as the outcome of interest and used a mapping from BCVA to determine utility values. Given the lack of previous models available for diabetic retinopathy, the committee agreed that it would be reasonable to adopt a similar model structure as used for DMO. Although a model based on BCVA may not fully capture all outcomes associated with disease progression for either DMO or PDR, it is the outcome most consistently reported within the clinical trial literature. Maintaining consistency with previous economic model structures allowed for the model results to be validated against previously published models.

Shown in Figure HE001, the Markov model structure consisting of nine health states (eight levels of BCVA and death) was informed by previously published models (Régnier et al 2015, Haig et al 2016, Mitchell et al 2012). These models allowed people to move by up to two health states each model cycle (maximum of 20 letters). However, due to a lack of publicly available evidence informing these transitions of up to 20 letters, this analysis only allowed

<Please insert your copyright statement - one line of text entry only>

for transitions by one health state in each 3-month cycle. This was modelled as an increase or decrease in BCVA by between 5 and 15 letters because natural history data was only available for movements of up to one health state. The committee discussed that transitions by one health state is more reflective of what they would expect to see in clinical practice.

NICE TAs used either a model based on the costs and outcomes associated with one eye (TA274) or two eyes (TA346, TA824), and costs only considered for both eyes in TA799 and TA820. Additionally, a systematic literature search was conducted for relevant economic evidence for this review question, a further ten studies were identified for the economic evaluation of treatments for DMO which were used to inform the choice of model structure. Again, the main model structure used was a Markov structure using a mixture of one or two eye-based models. A two-eye model would allow for the most accurate capturing of benefits and costs given it is common for both eyes to be affected by PDR or DMO, but the relevant clinical data could not be accessed since clinical trials most commonly report data for the study eye only rather than separating outcomes by eye, and patient level data is generally not publicly available. For these reasons the model structure consisted of one eye only based on BCVA of the study eye, aligned with previously published models (Régnier et al 2015, Mitchell et al 2012, Haig et al 2016). However, the costs associated with treatment of the second eye were included by allowing a proportion of patients to have the disease in the fellow eye at baseline and allowing for more patients to develop disease in the second eye over the duration of the model based on the proportions reported within the RESTORE trial as reported by Régnier et al (2015).

Transitions between the BCVA states were informed by 3-monthly transition probabilities, which were derived from an NMA that used the mean change in BCVA reported in relevant clinical trials. The methods and results of the NMA are detailed in Section HE2.4.2. By using a mean BCVA change treatment effect obtained from the NMA for each treatment, and assuming it to be normally distributed, it was possible to estimate the probability that an eye would gain any given number of letters. This assumption was also used in the NICE guideline NG82 for age-related macular degeneration (AMD), which was informed by the cost-utility analysis of aflibercept and ranibizumab (Claxton et al 2016) using evidence from the VIEW trial that mean changes in BCVA are approximately normally distributed. This assumption was used to estimate the probability of transitioning between the different BCVA health states. Subsequently, these probabilities were weighted according to the baseline BCVA of an eye, as detailed in HE2.4.1.1.1.

<Please insert your copyright statement - one line of text entry only>
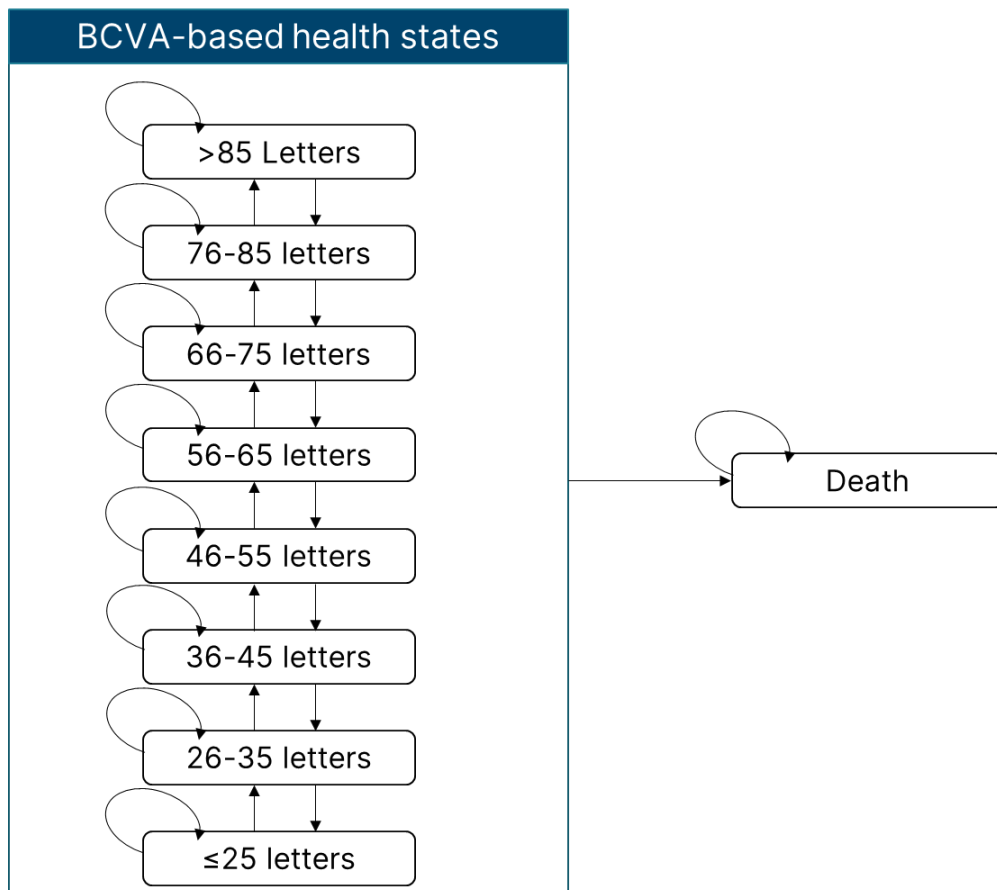
**Figure HE001: Markov model structure showing possible health state transitions**

The model included costs associated with treatment, administration, monitoring, management of adverse events and the costs associated with low vision, where low vision was considered as a visual acuity of less than or equal to 35 letters in the best seeing eye. Further information on costs is provided in Section HE2.4.4.

QALYs were accrued by weighting the time spent in a health state by the corresponding utility value for that state, and adjusting for the utility losses (disutilities) due to adverse events associated with treatment. Further information on QALYs is provided in Section HE2.4.2.2.3.

# HE2.3  Model parameterisation

**Identifying sources of parameters**

The main sources of quality of life, resource use and cost parameters were existing NICE TAs and published cost-effectiveness studies of the modelled treatments, and publicly available sources such as the National Cost Collection for the NHS and the British National Formulary (BNF).

For data on the modelled treatments, including treatment frequency and the proportion of patients remaining on treatment over time and subsequent therapies, the clinical trial publications associated with each treatment and the NICE TAs were used. All parameters and any assumptions made were informed and agreed by the committee.

Where possible, resource use information was sourced from published economic evaluations and the NICE TAs of the relevant treatments. Where the necessary data were unavailable, estimates from the experts on the guideline committee helped fill the gaps.

<Please insert your copyright statement - one line of text entry only>

The approach to identifying unit costs for each of the resource use elements was from a number of national sources, detailed as follows:

- Drugs included as interventions used prices from the BNF (February 2023). For drugs prescribed in secondary care, prices were taken from the NHS Commercial Medicines Unit's Electronic Market Information Tool (eMIT; November 2022), where available.

- NHS National Cost Collection data (2019/2020; previously known as NHS Reference Costs) was used as the source of unit costs for inpatient and outpatient procedures as well as hospital stay information and for the cost of PRP for the treatment of diabetic retinopathy. Cost year 2019/2020 was used rather than 2020/2021 due to the COVID-19 outbreak and it was thought that the 2020/2021 data was less likely to represent usual care in the NHS, for example only more severe treatments were likely to be completed and therefore, higher costs as a result.

- Where an appropriate unit cost from these sources could not be sourced, values were taken from a relevant published study, in which case they were inflated to current prices using HCIS inflation indices from Unit Costs for Health and Social Care (PSSRU; 2021).

## HE2.3.1  Network meta-analysis for treatment effects

NMAs were conducted to synthesise the treatment effects for the treatments in all economic models. The outputs of the NMAs were in the form of mean difference in LogMAR, with an improvement in vision characterised by a negative mean difference (i.e., a decrease in LogMAR).

The mean and standard deviation of the reference treatment and the mean difference were then used to calculate the treatment specific probabilities of improving or declining by one health state (between 5 and 15 letters, equal to a +/- 0.1 to 0.3 change in LogMAR) using a method assuming a normal distribution around the mean.

### HE2.3.1.1  RQ5 NMA – diabetic retinopathy

The NMA for proliferative diabetic retinopathy was conducted by Simmonds et al (2023) at the University of York. The systematic review informing the NMA aimed to identify all published randomised controlled trials (RCTs) comparing anti-VEGF treatment to PRP in people with diabetic retinopathy. Fifteen trials were included, 13 of which were in patients with PDR. The methods used for this analysis are consistent with NICE methods. Heterogeneity and network consistency were checked, and the authors found little heterogeneity across studies. Simmonds et al (2023) also conducted threshold analyses to investigate robustness of the NMA results with respect to changes in reported evidence.

Further information on this NMA is available in the published study by Simmonds et al (2023). The results of the NMA used in the economic model are in terms of mean difference in BCVA over one year comparative to PRP and are reported in HE2.4.2.1.1.

### HE2.3.1.2  RQ7 NMA - DMO

The economic model for DMO used results from two NMAs on change in BCVA at 12 months, one for each of the population groups considered. Forty-two studies were included in the analysis for all centre involving DMO, and 33 studies were included in the analysis of those with centre involving DMO and a CRT≥400μm. The NMAs were run using the WinBUGS code provided in the appendices of the NICE Decision Support Unit's Technical Support Documents (TSD 2). Both fixed and random effects models were run, and goodness of fit analysed using total residual deviance and deviance information criteria (DIC), with random effects models preferred for both the all centre involving population and the CRT≥400μm subgroup.

Further information on this NMA is available in Evidence Review G. The results of the NMAs used in the economic model were in terms of mean difference in BCVA over one year comparative to no treatment, and are reported in HE2.4.2.2.1.

# HE2.4    Parameters

## HE2.4.1    Cohort parameters

### HE2.4.1.1    Starting demographics and characteristics

Age and gender were included in the economic model to estimate general population mortality. Age and gender used were specific to the clinical trials for the relevant population for each review question.

**RQ5: Proliferative diabetic retinopathy**

The cohort of patients in the model started at 56 years of age and 57.6% of them were male, which were the average baseline characteristics of the participants in the protocol W clinical trial for aflibercept (Maturi et al 2021). This source was selected to align with the natural history estimates.

**RQ7: Diabetic macular oedema**

The cohort of patients in the model started at 63 years of age and 58.0% of them were male, which were the average baseline characteristics of the participants in the RESTORE clinical trial of the modelled treatments from Mitchell et al (2012). These characteristics are broadly consistent with the published NICE TAs.

#### HE2.4.1.1.1    *Baseline clinical data*

The model required a distribution of patients across BCVA-related health states at baseline. This was to present a reasonable reflection of the expected BCVA profile of people with either PDR (RQ5) or DMO (RQ7) at diagnosis. Shown in Table 2, the model assumed a starting distribution of BCVA reported by Régnier et al (2015) from the RESTORE clinical trial for DMO. In the absence of publicly available data in the PDR population, the baseline distribution of BCVA was assumed to be the same as for DMO which, despite there likely being differences in the two conditions, the committee agreed was a reasonable proxy given the scarcity of available data.

The proportion of patients treated in both eyes and the proportion of patients treated in either the best seeing eye (BSE) or worst seeing eye (WSE) for those with treatment in one eye were also informed by the RESTORE clinical trial for DMO (Régnier et al 2015, Mitchell et al 2012). The committee agreed that whilst it would be preferred for data from a PDR population to be used for RQ5, in the absence of data the proportions from RESTORE trial would be a reasonable assumption for PDR. The model assumed 22% of patients had treatment in both eyes at baseline. For those with treatment in one eye, 67.2% had treatment in their WSE and 32.8% had treatment in their BSE.

The probability of developing disease in the fellow eye was 5.4% per 3-monthly cycle as estimated from the ICE-UK study on fluocinolone acetonide, and reported by Pochopien et al 2019.

**Table 2: Baseline distribution of visual acuity**

| Treated eye BCVA health state | Percentage of patients starting in the health state |
|---|---|
| BCVA 86-100 ETDRS letters | 0% |
| BCVA 76-85 ETDRS letters | 11% |
| BCVA 66-75 ETDRS letters | 39% |
| BCVA 56-65 ETDRS letters | 27% |
| BCVA 46-55 ETDRS letters | 15% |
| BCVA 36-45 ETDRS letters | 8% |
| BCVA 26-35 ETDRS letters | 0% |
| BCVA ≤ 25 ETDRS letters | 0% |

*ETDRS: Early Treatment Diabetic Retinopathy Study; BCVA: Best corrected visual acuity*

### HE2.4.1.1.2 *Natural history*

**Natural history: Review question 5 – Proliferative diabetic retinopathy**

Data from a sham arm of a trial was considered an acceptable proxy for no treatment, representative of the natural history. Clinical trials within the PDR population did not have a no treatment or sham arm and so treatment effects for all interventions were relative to PRP; however, the model allowed for natural history based on the sham arm in a non-proliferative population to be used after the efficacy duration assumed for treatments had ended in scenario analyses. Treatment efficacy was assumed to sustain over a lifetime in the base-case.

The sham arm from protocol W (Maturi et al 2021) for NPDR was used to inform the 3-monthly probability of moving up or down one health state after treatment efficacy of treatment was assumed to have ended. Although this population may not be fully representative of proliferative disease given it is before changes in vision are expected, the committee agreed to this data source to inform natural history in the absence of other sources, and this was explored as a scenario only. Maturi et al (2021) reported a mean 1-year change in BCVA of -1.30 ETDRS letters (SD 4.90 letters) which was used to calculate a 2.57% probability of gaining one health state and 6.10% of losing one health state for the long-term natural history of PDR. The committee felt the protocol W population was more appropriate than the DMO estimate from Mitchell et al (2012) for estimating the long-term natural history for PDR.

**Natural history: Review question 7 – Diabetic macular oedema**

The NMA compared the mean difference in BCVA between each treatment arm and the no treatment or sham arm observed within clinical trials.

In the base-case analysis, the long-term natural history for DMO was informed by Mitchell et al (2012) where data from the Wisconsin epidemiologic study of diabetic retinopathy (WESDR) was used to create a transition matrix associated with the natural history of DMO. Data on patients with DMO was taken from the RESTORE trial and used by Mitchell et al (2012) to recalibrate the WESDR transitions. This resulted in 3-monthly probabilities of 3.5% of moving up one health state and 4.5% of moving down one health state (as assessed by a change of at least 10 letters of BCVA). These probabilities from Mitchell et al (2012) were used for informing the natural history in the NICE TAs and was accepted by the committee as an appropriate approximation for natural history.

A scenario analysis was conducted in which the mean change in visual acuity for the no treatment arm was informed by the pooled results from Massin et al (2010) and Sultan et al (2011) as presented in Table 3. These studies were selected from the set of studies with

<Please insert your copyright statement - one line of text entry only>

sham arms identified in the literature search for the NMA and were chosen from that set based on the time period reported, study location and study size.

**Table 3: Scenario: Sham arm natural history transitions for diabetic macula oedema**

| Natural history source | Mean change in ETDRS letters (52 weeks) | Probability of gaining a health state | Probability of losing a health state |
|---|---|---|---|
| Massin et al (2010) | -1.400 | 5.49% | 6.35% |
| Sultan et al (2011) | 1.200 | 6.29% | 5.55% |
| **Pooled** | **0.345** | **6.02%** | **5.81%** |

ETDRS: Early Treatment Diabetic Retinopathy Study

### HE2.4.1.2 Mortality

Mortality was modelled using age and gender-specific National Life Tables for England and Wales (2018-2020). An increased mortality risk associated with diabetes was applied in the analyses for both PDR and DMO. Similarly, to the TA for aflibercept (TA346), a hazard ratio of 1.95 was applied to account for the increased mortality risk associated with diabetes relative to the general population (Preis et al 2009). TA824 also included an additional mortality risk associated with poor vision in DMO for those with BCVA≤35 ETDRS letters, but this was not considered within our analysis to align with Mitchell et al (2012) and Régnier et al (2015) who did not include DMO-specific mortality risk in their analyses. Furthermore, the committee agreed that the main mortality risk associated with poor vision would be captured in the diabetes population rather than in DMO population.

## HE2.4.2 Treatment effects

In the base-case analysis, the model assumed the treatment efficacy to remain for the duration of the model (lifetime), meaning no natural history was applied in the base-case. However, scenario analyses assuming natural history after 5 years, 10 years and 20 years were explored.

The model allowed treatment effect to continue once an anti-VEGF injection is discontinued since the two main reasons for treatment discontinuation were reported to be death and early discharge due to stable disease (Dhingra et al 2022). This might have led to the overestimation of treatment effect estimates given that a small number of patients were also reported to discontinue due to further treatment deemed futile. However, assuming that a treatment benefit would stop immediately once people discontinue a treatment would be flawed since the risk that vision loss would happen in those who discontinue would happen gradually over time, but people may come back to the same treatment upon signs of vision loss. Therefore, the committee felt that allowing treatment effect to continue once a treatment is discontinued would be a conservative and reasonable approach.

### HE2.4.2.1 Review question 5 – Proliferative diabetic retinopathy

#### HE2.4.2.1.1 *Treatment specific transition probabilities*

The treatment effects generated in the NMA were of each treatment compared with PRP. The mean change in BCVA from baseline to 1 year for PRP was taken as the weighted average of that reported in the CLARITY and PRIDE trials (Sivaprasad et al 2017 and Lang et al 2020, respectively) and is presented in Table 4. The studies reported mean change in BCVA in ETDRS letters so have been converted to LogMAR since the NMA results, and therefore the model, used LogMAR. Change in LogMAR is equivalent to -0.2 times the change in ETDRS letters, with an increase in letters and decrease in LogMAR both indicating improvement in vision.

<Please insert your copyright statement - one line of text entry only>

**Table 4: Mean change over 1 year in BCVA, PRP**

| Study | Number of patients in PRP arm | Mean (SD) change in BCVA, ETDRS | Mean (SD) change in BCVA, LogMAR |
|---|---|---|---|
| CLARITY | 102 | -2.90 (7.07*) | - |
| PRIDE | 35 | -3.70 (17.10) | - |
| Weighted | - | **-3.104 (10.585)** | **0.062 (0.212)** |

*SD calculated using reported SE of 0.7*

The treatment effectiveness parameters based on mean difference in BCVA compared with PRP for the PDR population are presented in Table 5. The mean difference compared with PRP is added to the mean annual change for PRP, then converted to probabilities of moving up or down by one health state, assuming the change in BCVA is normally distributed. The probabilities are converted from annual to 3-monthly.

The point estimates and 95% CIs are shown on a forest plot in Figure 2.

**Table 5: Treatment effectiveness compared with PRP for diabetic retinopathy**

| Treatment | Mean difference at 1 year (LogMAR) (95% CI) | Mean annual change (LogMAR) | Per cycle probability of gaining a health state | Per cycle probability of losing a health state |
|---|---|---|---|---|
| PRP | - | 0.062 | 4.79% | 8.48% |
| Aflibercept | -0.088 (-0.232 to 0.042) | -0.026 | 7.42% | 5.85% |
| Ranibizumab | -0.123 (-0.237 to -0.011) | -0.061 | 8.45% | 4.83% |
| Ranibizumab plus PRP | -0.080 (-0.163 to 0.003) | -0.018 | 7.18% | 6.09% |
| Bevacizumab | -0.193 (-1.172 to 0.786) | -0.131 | 10.07% | 3.06% |
| Bevacizumab plus PRP | -0.172 (-0.282 to -0.065) | -0.110 | 9.66% | 3.54% |
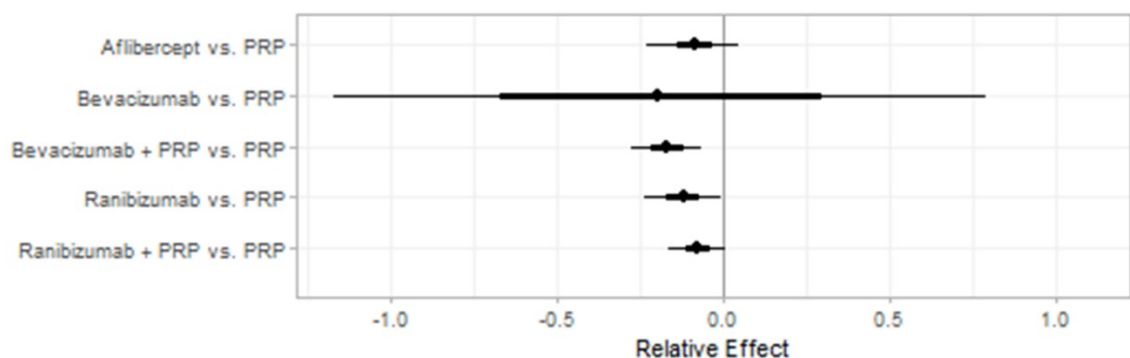


**Figure 2: Forest plot of mean difference in BCVA for PDR (LogMAR)**

Table 5 and Figure 2 show that there was a very wide 95% CI around the treatment effect for bevacizumab vs PRP, indicating greater uncertainty in this estimate. In the NMA, only one small study in Jordan/Syria informed the comparison between bevacizumab with PRP, and this study was assessed to be at a high risk of bias. The 95% CIs around the treatment effects for aflibercept, bevacizumab, and ranibizumab plus PRP all include zero, indicating uncertainty in whether the treatment is more effective than PRP or not. Figure 2 also demonstrates that the confidence intervals for all comparisons overlap.

<Please insert your copyright statement - one line of text entry only>

**HE2.4.2.1.2 *Discontinuation of treatment***

The model allowed people to discontinue treatment as informed by the literature, see Table 6. Treatment discontinuation was assumed to be the same across all treatment options. It was assumed that everyone would remain on treatment for the first year to assess the response, which was agreed by the committee and aligns with the recommendations made for RQ8 on treatment switching and stopping.

**Table 6: Treatment discontinuation for diabetic retinopathy**

| Year | % Remain on treatment | Source/Notes |
|---|---|---|
| 0 to 1 | 100% | Committee consensus and aligns with RQ8 recommendations for switching or stopping treatment. Committee discussed and agreed that treatment should be allowed to continue in the first year to be able to observe an effect. |
| 1 to 3 | 87% | Gross et al (2015): weighted average across treatments 88% for ranibizumab and 86% for PRP. |
| 3 to 5 | 75% | Wykoff et al (2018): aflibercept extension study 75% patients remain on treatment between 3 and 5 years. |
| >5 | 50% | Assumption based on faricimab TA799 combined with committee consensus that 50% (base-case) of patients would remain on treatment after 5 years. Maximum 75% of patients based on Wykoff et al (2017) and minimum 25% of patients would be expected to remain on treatment long-term based on committee consensus (scenario analyses). The committee consensus was that as long as people are still getting benefit they remain on treatment. Dhingra et al (2022) reported that 53% of patients with age-related macular degeneration remained in active care at 5 years. |

**HE2.4.2.1.3 *Adverse event rates***

Adverse events associated with treatment were included where possible, although the reporting on adverse events across clinical trials is variable for diabetic retinopathy. In the absence of data for the frequency of adverse events experienced by those receiving ranibizumab combination therapy, bevacizumab monotherapy or bevacizumab in combination with PRP was assumed equivalent to ranibizumab as agreed with the committee. The proportion of patients expected to experience each adverse event by treatment is presented in Table 7.

**Table 7: Adverse events associated with treatment for diabetic retinopathy**

| Adverse events | PRP | Aflibercept | Ranibizumab | Ranibizumab plus PRP* | Bevacizumab* | Bevacizumab plus PRP* |
|---|---|---|---|---|---|---|
| Retinal detachment | 2.69% | 0.00% | 1.61% | 1.61% | 1.61% | 1.61% |
| Retinal tear | 0.00% | 0.22% | 0.00% | 0.00% | 0.00% | 0.00% |
| Vitreous haemorrhage | 4.31% | 0.00% | 7.64% | 7.64% | 7.64% | 7.64% |
| Increased intraocular pressure | 0.22% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Glaucoma | 0.75% | 0.00% | 0.40% | 0.40% | 0.40% | 0.40% |
| Endophthalmitis | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Cataracts | 0.22% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |

<Please insert your copyright statement - one line of text entry only>

| Adverse events | PRP | Aflibercept | Ranibizumab | Ranibizumab plus PRP* | Bevacizumab* | Bevacizumab plus PRP* |
|---|---|---|---|---|---|---|
| Ocular pain | 0.87% | 1.32% | 0.00% | 0.00% | 0.00% | 0.00% |
| Stroke | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Cardiovascular death | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Source | Sivaprasad et al (2017) Gross et al (2015) | Gross et al (2015) | Sivaprasad et al (2017) | Assumed same as ranibizumab | Assumed same as ranibizumab | Assumed same as ranibizumab |

*Due to a lack of data reported specifically for anti-VEGF use in PDR, adverse events for ranibizumab plus PRP, bevacizumab and bevacizumab plus PRP were assumed to be equivalent to ranibizumab based on Gross et al (2015)*

## HE2.4.2.2 Review question 7 – Diabetic macular oedema

### HE2.4.2.2.1 *Treatment specific transition probabilities*

People with DMO were separated by centre involving and non-centre involving DMO. Due to a lack of data available for non-centre involving DMO, it was not possible to conduct an NMA to inform an economic model. As such, only centre involving DMO could be modelled, which was further categorised by CRT of less than 400μm and at least 400μm due to the differences in treatment used in these subpopulations. Again, due to a lack of data to conduct an NMA, only the subpopulation of those with a CRT of at least 400μm could be explored in cost-effectiveness analysis.

**All centre involving diabetic macular oedema**

The treatment effectiveness parameters based on mean difference in BCVA for all people with centre involving DMO are presented in Table 8. For each treatment, the mean difference compared with no treatment is added to the mean annual change for no treatment, then converted to probabilities of moving up or down by one health state. The probabilities were converted from annual to 3-monthly.

The point estimates and 95% CIs are shown on a forest plot in Figure 3.

**Table 8: Treatment effectiveness compared with no treatment for diabetic macular oedema**

| Treatment | Mean difference at 1 year (LogMAR) (95% CI) | Mean annual change (LogMAR) | Per cycle probability of gaining a health state | Per cycle probability of losing a health state |
|---|---|---|---|---|
| No treatment | - | -0.007 | - | - |
| Standard threshold laser | -0.103 (-0.211 to 0.006) | -0.110 | 7.30% | 4.13% |
| Aflibercept | -0.284 (-0.394 to -0.173) | -0.291 | 7.29% | 1.69% |
| Ranibizumab | -0.234 (-0.339 to -0.129) | -0.241 | 7.61% | 2.25% |
| Ranibizumab plus standard laser | -0.218 (-0.326 to -0.108) | -0.225 | 7.67% | 2.44% |
| Bevacizumab | -0.222 (-0.332 to -0.112) | -0.229 | 7.66% | 2.39% |
| Bevacizumab plus standard laser | -0.264 (-0.443 to -0.086) | -0.271 | 7.45% | 1.91% |
| Brolucizumab | -0.308 | -0.315 | 7.06% | 1.47% |

<Please insert your copyright statement - one line of text entry only>

| Treatment | Mean difference at 1 year (LogMAR) (95% CI) | Mean annual change (LogMAR) | Per cycle probability of gaining a health state | Per cycle probability of losing a health state |
|---|---|---|---|---|
| | (-0.440 to -0.176) | | | |
| Faricimab | -0.301 (-0.421 to -0.181) | -0.308 | 7.13% | 1.53% |
| Fluocinolone acetonide* | -0.203 (-0.319 to -0.087) | -0.210 | 7.70% | 2.65% |
| Dexamethasone | -0.203 (-0.319 to -0.087) | -0.210 | 7.70% | 2.65% |
| Subthreshold laser | -0.100 (-0.220 to -0.020) | -0.106 | 7.27% | 4.19% |

*Assumed fluocinolone acetonide has the same efficacy as dexamethasone as agreed with the committee because of a lack of data*
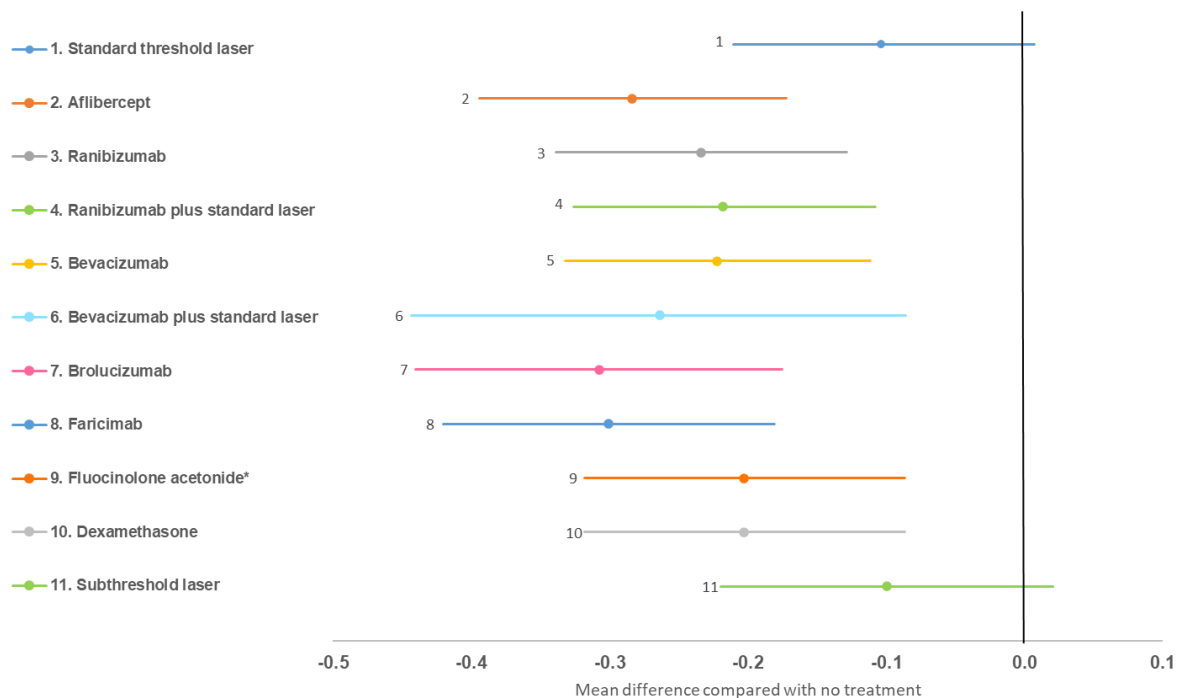


**Figure 3: Forest plot of mean difference in BCVA for DMO (LogMAR)**

Figure 3 demonstrates the overlap in the confidence intervals of all treatments, particularly the anti-VEGF options, indicating uncertainty in difference in clinical effect between these treatments. The confidence intervals around the estimates for both laser treatments include zero, indicating uncertainty in effectiveness of laser compared with no treatment.

**Centre involving diabetic macular oedema with a CRT≥400µm**

The treatment effectiveness parameters based on mean difference in BCVA for people with centre involving DMO population and CRT≥400µm are presented in Table 9. Per cycle probabilities were calculated in the same way as for the all centre involving DMO analysis.

Due to a lack of data for subthreshold laser in this subgroup, the efficacy was assumed equivalent to standard threshold laser for this population given how similarly they performed in the DIAMOND clinical trial (Lois et al 2022).

The point estimates and 95% CIs are shown on a forest plot in Figure 4.

<Please insert your copyright statement - one line of text entry only>

**Table 9: Treatment effectiveness for DMO with a CRT≥400μm**

| Treatment | Mean difference at 1 year (LogMAR) (95% CI) | Mean annual change (LogMAR) | Per cycle probability of gaining a health state | Per cycle probability of losing a health state |
|---|---|---|---|---|
| No treatment | - | -0.007 | - | - |
| Standard threshold laser | -0.087 (-0.202 to 0.030) | -0.094 | 7.15% | 4.40% |
| Aflibercept | -0.286 (-0.404 to -0.167) | -0.293 | 7.27% | 1.67% |
| Ranibizumab | -0.234 (-0.343 to -0.123) | -0.240 | 7.62% | 2.25% |
| Ranibizumab plus standard laser | -0.222 (-0.339 to -0.104) | -0.228 | 7.66% | 2.40% |
| Bevacizumab | -0.220 (-0.336 to -0.103) | -0.227 | 7.66% | 2.42% |
| Bevacizumab plus standard laser | -0.222 (-0.339 to -0.104) | -0.228 | 7.66% | 2.40% |
| Brolucizumab | -0.285 (-0.417 to -0.153) | -0.292 | 7.28% | 1.68% |
| Faricimab | -0.303 (-0.431 to -0.173) | -0.310 | 7.11% | 1.51% |
| Fluocinolone acetonide* | -0.204 (-0.327 to -0.079) | -0.210 | 7.70% | 2.64% |
| Dexamethasone | -0.204 (-0.327 to -0.079) | -0.210 | 7.70% | 2.64% |
| Subthreshold laser** | -0.087 (-0.202 to 0.030) | -0.094 | 7.15% | 4.40% |

*Assumed fluocinolone acetonide has the same efficacy as dexamethasone as agreed with the committee because of a lack of data*

**Assumed subthreshold laser has the same efficacy as standard threshold laser due to a lack of data for this comparator within this population, based on Lois et al (2022) which found subthreshold laser and standard threshold laser to have similar efficacy within the centre involving DMO population with a CRT<400μm*

Figure 4 demonstrates the overlap in the confidence intervals of all treatments, particularly the anti-VEGF options, indicating uncertainty in difference in clinical effect between these treatments. The confidence intervals around the estimates for laser treatment include zero, indicating uncertainty in effectiveness of laser compared with no treatment.

<Please insert your copyright statement - one line of text entry only>
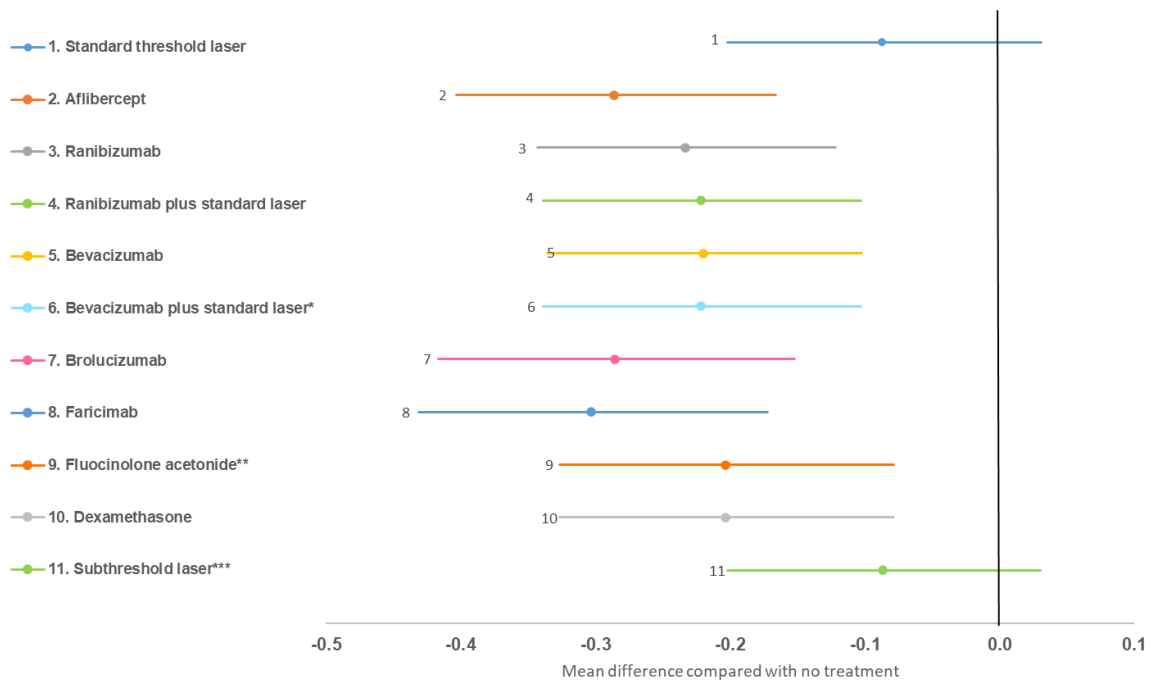
**Figure 4: Forest plot of mean difference in BCVA for DMO with CRT≥400µm (LogMAR)**

**HE2.4.2.2.2**   *Discontinuation of treatment*

Treatment discontinuation was assumed to be the same for all those with centre involving DMO regardless of central retinal thickness across all treatment options. It was assumed that everyone would remain on treatment for the first year to assess the response, which was agreed by the committee and aligns with the recommendations made for RQ8 on treatment switching and stopping. Unlike previous TAs, the model allowed some patients to continue treatment beyond 5 years to be aligned with current clinical practice. Only TA799 allowed 50% of patients to remain on treatment beyond 5 years as part of a scenario analysis. The assumptions for the proportion of patients remaining on treatment are presented in Table 10 and the treatment specific discontinuation for DMO is in Table 11. Treatment specific discontinuation (Table 11) was applied in addition to the fixed treatment discontinuation (Table 10).

**Table 10: Treatment discontinuation for diabetic macular oedema**

| Year | % Remain on treatment | Treatment specific discontinuation | Source/Notes |
|---|---|---|---|
| 0 to 1 | 100% | No | Committee consensus and aligns with RQ8 recommendations for switching or stopping treatment.<br><br>Committee discussed and agreed that treatment should be allowed to continue in the first year to be able to observe an effect. |
| 1 to 3 | Treatment specific | Yes | Based on published HTAs for DMO |
| 3 to 5 | 75% | Yes | Wykoff et al (2018) |
| >5 | 50% (base-case)<br>75% (scenario)<br>25% (scenario) | Yes | TA799 scrutiny panel<br>Wykoff et al (2018)<br>Minimum value expected |

<Please insert your copyright statement - one line of text entry only>

**Table 11: Treatment specific discontinuation for diabetic macular oedema**

| Resource | Probability of discontinuation (every 3 months) | Source |
|---|---|---|
| Standard threshold laser | 2.52% | Aflibercept TA346 |
| Aflibercept | 2% | Aflibercept TA346 |
| Ranibizumab | 1.9% | Aflibercept TA346 |
| Ranibizumab plus standard laser | 1.9% | Assumed same as ranibizumab |
| Bevacizumab | 2% | Assumed same as aflibercept |
| Bevacizumab plus standard laser | 2% | Assumed same as aflibercept |
| Brolucizumab | 3.5% | Brolucizumab TA820 |
| Faricimab | 2% | Assumed same as aflibercept |
| Fluocinolone acetonide | 2.3% | Aflibercept TA346 |
| Dexamethasone | 1.8% | Aflibercept TA346 |
| Subthreshold laser | 2.52% | Assumed same as standard threshold laser |

### HE2.4.2.2.3 *Adverse event rates*

Adverse events associated with treatment were included in the economic model. The proportion of patients expected to experience adverse events by each treatment strategy are presented in Appendix A: (Table 55).

## HE2.4.3 Quality of life

### HE2.4.3.1 Health state utility values

Similarly to the NICE AMD (NG82) and cataracts (NG77) guidelines, there is considerable debate as to the best strategy for capturing health related quality of life (HRQoL) in patients with diabetic retinopathy and DMO. The committee considered the most appropriate outcome to be used for evaluating clinical benefit of treatment and HRQoL. Although regression of diabetic retinopathy is assessed by the absence of new blood vessels and the regression of DMO is assessed by the absence of fluid and reduction in retinal thickness, these are measures unlikely to be captured within RCTs. Given the available data for modelling disease progression was in terms of BCVA, and that previous models in vision-related conditions have used BCVA levels to assign utility values, the committee agreed to use utility values based on BCVA, aligning with the modelled health states. Although BCVA does not capture all elements of the disease, for example progression in severity can happen without a change in BCVA, it is an important outcome to patients and is the most commonly reported outcomes in clinical trials.

EQ-5D is known to be insensitive to changes in a patient's quality of life associated with changes in vision (Haig et al 2016, Malkin et al 2013, Kay et al 2014). Several studies estimated utility values by mapping from BCVA in diabetic retinopathy and other eye conditions. The committee considered these studies and provided rationale for which of these would be most appropriate for the populations of PDR and DMO.

- Brown et al (1999) interviewed patients with visual loss due to diabetic retinopathy who had a BCVA of 20/40 or worse (70 letters or fewer) in at least one eye using the modified VF-14 questionnaire using time trade-off and standard gamble methods for estimating utility values. The utility values by Brown et al (1999) have frequently been used for populating economic models within the literature (and in TAs) for DMO. These values were used in the NICE AMD guideline (NG82), and in TA301 (base-case) and in TA824 (sensitivity analysis).

<Please insert your copyright statement - one line of text entry only>

- Sharma et al (2000) used a similar approach as Brown et al (1999), interviewing patients with either diabetic retinopathy or AMD to estimate values using the time trade-off method. A regression analysis was estimated to map BCVA to utility values. The committee considered the population to be applicable and similar to Brown et al (1999). However, the committee were cautious over the particularly high utility value for the best vision category (86-100) of 0.991.

- Czoski-Murray et al (2009) used contact lenses of varying central opacity to represent the different stages of AMD for members of the general public who then valued the health states. The committee discussed the limitation of this study being a simulated study, which could lead to underestimating the utility values for the lower vision health states and may overestimate treatment effect. The utility values associated with visual acuity have been used in multiple TAs (TA824, TA346, TA301). The method is aligned with the NICE reference case and was also used within the NICE AMD guideline (NG82).

- Pennington et al (2020) developed a utility calculator using utility data collected within a clinical trial for the treatment of macular oedema due to central retinal vein occlusion (CRVO). The committee did not feel these utility values were reflective of the DR or DMO populations due to the specific nature of CRVO. The committee agreed to include this utility source as a scenario only.

- Lloyd et al (2008) used standard gamble over five BCVA categories in patients with diabetic retinopathy. These values were adapted by Mitchell et al (2012) to fit eight health states, but due to the concerns in the adaption from five levels to eight levels, the committee preferred to use this utility source as a scenario only.

- Mitchell et al (2012) collected EQ-5D at four time points in the RESTORE trial for patients with visual impairment due to DMO. The health states were estimated based on the BCVA of the treated eye. Although the committee were cautious that the utility values were based on the EQ-5D, it was felt adding these values as an additional scenario would add value because this is the only utility source which considered patients with DMO over other similar eye conditions.

The utility values associated with each BCVA-based health state for BSE are presented in Table 12. The committee decided that it was most appropriate to use different utility value sets for each population and use studies that were in the modelled population, as they agreed that the impact of each indication on vision was slightly different so wanted to capture those differences as best as possible.

Based on the population in the RESTORE trial (Régnier et al 2015), the model assumed that 22% of patients had treatment in both eyes, and for those (78%) with treatment in one eye, 67.2% had treatment in their WSE and 32.8% had treatment in their BSE. Some previous analyses modelled the quality of life in the fellow eye; however, due to a lack of publicly available data, it was not possible to model the visual acuity in the fellow eye and therefore assumptions were made to capture utility of two eyes. To estimate the health state utility values in the WSE, an approach used by Régnier et al (2015) was taken, where a utility difference of 0.1 was assumed between the best (BCVA: 86-100) and worst (BCVA: ≤25) possible health states, and a linear decline was assumed for calculation of the utility values for the remaining health states (Table 30). The utility value in the best vision state for the WSE was set equal to the value in the best state for the BSE. Similarly to Haig et al (2016), utility values for BSE were used in the base-case for patients who had treatment in both eyes since BSE is the major driver of overall quality of life and patient functioning (Mitchell et al 2012, Bressler 2010). However, as part of a scenario analysis, a weighted average of BSE and WSE was also used for treatment in both eyes. Age-adjusted utility values were not included in the models as it was found to have a minimal impact on the cost effectiveness results in TA824.

<Please insert your copyright statement - one line of text entry only>

**Table 12: Health state utility values for BSE**

| Health state: BCVA letters | Brown et al (1999) (Mitchell et al 2012) | Lloyd et al (2008) (Mitchell et al 2012) | Sharma et al (2000) | RESTORE (Mitchell et al 2012) | Czoski-Murray et al (2009) | Pennington et al (2020) |
|---|---|---|---|---|---|---|
| | PDR base-case | | | | DMO base-case | |
| 86-100 | 0.839 | 0.830 | 0.991 | 0.860 | 0.850 | 0.760 |
| 76-85 | 0.839 | 0.750 | 0.818 | 0.860 | 0.758 | 0.690 |
| 66-75 | 0.783 | 0.750 | 0.666 | 0.813 | 0.685 | 0.622 |
| 56-65 | 0.783 | 0.715 | 0.636 | 0.802 | 0.611 | 0.554 |
| 46-55 | 0.732 | 0.680 | 0.591 | 0.770 | 0.537 | 0.491 |
| 36-45 | 0.681 | 0.680 | 0.563 | 0.760 | 0.464 | 0.439 |
| 26-35 | 0.630 | 0.530 | 0.544 | 0.681 | 0.390 | 0.399 |
| ≤25 | 0.579 | 0.340 | 0.537 | 0.547 | 0.353 | 0.360 |

*BCVA: Best corrected visual acuity; DMO: Diabetic macular oedema; PDR: Proliferative diabetic retinopathy*

### Review question 5 – Proliferative diabetic retinopathy

The committee felt that given the Brown et al (1999) study looked into patients with diabetic retinopathy, the utility values from this study were most applicable to this review question. The committee were concerned by the high value reported in Sharma et al (2000) of 0.991 for the best health state of 86-100 letters. This contributed to the utility values from Brown et al (1999) to be used in the base-case analysis and the utility values from Sharma et al (2000) to be used in a scenario analysis. All other utility sources discussed above explored in scenario analyses.

### Review question 7 – Diabetic macular oedema

The committee discussed the use of utility values from Pennington et al (2020) as the most recently published source; however, the committee were concerned about the population being too different compared with DMO and felt that given the similarity in utility values for the lowest health states, the utility values from Czoski-Murray et al (2009) would be more appropriate to allow for alignment with the NICE TAs. The committee discussed that whilst there were some concerns about the use of simulated population in Czoski-Murray et al (2009) in estimating the utility values, it was nevertheless felt that this source was most suitable overall, given how widely this approach has been used in previous NICE TAs for DMO, and the utility values associated with each BCVA health state appeared reasonable to the committee. Due to the uncertainty around the most appropriate utility source to be used, all those sources listed above were used in scenario analyses.

### HE2.4.3.2 Disutilities associated with adverse events

In addition to the health state utility values, utility losses associated with adverse events (Table 13) were included in the models. The adverse event utility losses were not expected to differ by the two different conditions.

**Table 13: Utility losses associated with adverse events**

| Resource | Utility decrement | Event duration | Source |
|---|---|---|---|
| Retinal detachment | 0.270 | 3 months | NG82 |
| Retinal tear | 0.000 | Immediate repair | NG82 |
| Vitreous haemorrhage | 0.020 | - | TA346 |

<Please insert your copyright statement - one line of text entry only>

| Resource | Utility decrement | Event duration | Source |
|---|---|---|---|
| | | | Pochopien et al (2019) |
| Increased intraocular pressure | 0.000 | - | TA346 Pochopien et al (2019) |
| Glaucoma | 0.000 | - | TA346 Pochopien et al (2019) |
| Endophthalmitis | 0.300 | 20% experience long term HRQoL effect (1 year), 80% (1.5 months) | NG82 |
| Cataracts | 0.142 | 1 month | NG82 |
| Stroke | 0.000 | - | No information identified |
| Cardiovascular death | 0.000 | - | No information identified |
| Myocardial infarction | 0.000 | - | No information identified |
| Injection related anxiety | 0.071 | 1 day | TA613 Dolan et al (1997) |

## HE2.4.4    Resource use and costs

### HE2.4.4.1    Administration costs

The costs associated with the administration of anti-VEGF treatments are presented in Table 14, and these were applied in both models (RQ5 and RQ7). It was assumed that treatment administration includes an optical coherence tomography (OCT) scan in addition to an administration visit. The committee discussed that approximately 95% of patients would have an outpatient administration appointment, with approximately 5% of patients requiring a day case appointment which is usually due to accessibility needs. A weighted cost of £257.98 per administration visit was applied for all anti-VEGF administrations, this cost was also applied for steroid injections for the treatment of DMO. It was assumed that the administration of laser treatments was captured within the cost of the laser treatment itself. When a patient was treated for bilateral disease, it was assumed that treatment for both eyes was administered in the same visit.

**Table 14: Administration costs for anti-VEGFs**

| Resource | Cost | Proportion of visits applied | Source |
|---|---|---|---|
| Optical coherence tomography | £101.80 | 100% | NHS Reference Costs 2019/2020. Consultant led non-admitted face-to-face attendance, follow-up. Code 130 (ophthalmology). Assumption in NICE TA294 for wet AMD. |
| Administration visit – outpatient | £129.62 | 95% | NHS Reference Costs 2019/2020. Outpatient procedure. HRG code BZ87A. Minor Vitreous Retinal Procedures. Assumption in NICE TA294. |
| Administration visit - day case | £660.84 | 5% | NHS Reference Costs 2019/20. Day case procedure. HRG code BZ87A, Minor vitreous retinal procedures. Assumption in NICE TA294. |
| **Anti-VEGF injection administration per visit** | **£257.98** | **100%** | **Calculation based on above inputs** |

<Please insert your copyright statement - one line of text entry only>

## HE2.4.4.2    Monitoring costs

The costs associated with treatment monitoring (Table 15) were assumed to be the value of an OCT scan whilst patients were still receiving treatment. The committee discussed that once treatment is completed, patients would usually receive one to two more monitoring visits before being referred back to the diabetic eye screening service, should no further progression of disease be identified. Scanlon et al (2015) estimated the cost of screening within the diabetic eye screening service to be £32, which was inflated to align with the other cost values. The committee agreed that despite this price needing to be inflated it was roughly the price they would expect to incur.

**Table 15: Monitoring costs**

| Resource | Costs (£) | Source |
|---|---|---|
| Monitoring visit during treatment | £101.80 | NHS Reference Costs 2019/2020. Consultant led non-admitted face-to-face attendance, follow-up. Code 130 (ophthalmology). Assumption used in TA294. |
| Monitoring visit post treatment | £38.34 | Scanlon et al (2015): £32 (2012/2013 prices) inflated to 2019/2020 prices. |

### HE2.4.4.2.1    *Monitoring visits – proliferative diabetic retinopathy*

The number of monitoring visits for each treatment strategy are presented in Table 16**Error! Reference source not found.**. Where possible the number of monitoring visits was sourced from the literature for diabetic retinopathy. The number of monitoring visits for anti-VEGF treatments was assumed to be equivalent to the average number of monitoring visits observed in the literature for DMO for years two onwards due to a lack of data for the PDR population. In the base case analysis, monitoring visits were assumed to occur in the same visit as for treatment.

**Table 16: Number of monitoring visits for diabetic retinopathy**

| Treatment | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 onwards |
|---|---|---|---|---|---|
| PRP | 3.063 | 2.625 | 1.000 | 1.000 | 1.000 |
| Aflibercept | 12.000 | 7.755 | 4.518 | 2.909 | 2.182 |
| Ranibizumab | 12.000 | 7.755 | 4.518 | 2.909 | 2.182 |
| Ranibizumab plus PRP | 12.000 | 7.755 | 4.518 | 2.909 | 2.182 |
| Bevacizumab | 12.000 | 7.755 | 4.518 | 2.909 | 2.182 |
| Bevacizumab plus PRP | 12.000 | 7.755 | 4.518 | 2.909 | 2.182 |
| Source | PRP: average of Royale et al (2015), Maredza et al (2022), Lois et al (2021) and Gross et al (2015) Anti-VEGFs: Gross et al (2015) | PRP: average of Lois et al (2021) and Gross et al (2015) Anti-VEGFs: average of DMO literature* | PRP: Lois et al (2021) 6-12 monthly intervals Anti-VEGFs: average based on DMO literature* | PRP: Lois et al (2021) 6-12 monthly intervals Anti-VEGFs: average based on DMO literature* | PRP: Lois et al (2021) 6-12 monthly intervals Anti-VEGFs: average based on DMO literature* |

*Assumed average of anti-VEGF visits across ranibizumab and aflibercept based on DMO literature for year two onwards as reported in Table 57*

### HE2.4.4.2.2  *Monitoring visits – diabetic macular oedema*

The frequency of monitoring visits expected each year for each treatment strategy is presented in Table 17. Due to a large number of alternative sources available on the frequency of monitoring visits for some treatments, the average across sources was considered in the base-case analysis. The number of monitoring visits each year was further explored in scenario analyses by taking the minimum and maximum reported values in addition to assuming the same number of treatments across all treatments. In the base case analysis, monitoring visits were assumed to occur in the same visit as for treatment.

**Table 17: Number of monitoring visits for diabetic macular oedema**

| Treatment | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 onwards | Source |
|---|---|---|---|---|---|---|
| No treatment | 4.00 | 4.00 | 4.00 | 2.00 | 2.00 | Committee consensus |
| Standard threshold laser | 4.00 | 3.33 | 2.80 | 2.60 | 2.45 | Average across sources (Table 57 in Appendix) |
| Aflibercept | 10.17 | 7.63 | 4.52 | 4.00 | 3.20 | Average across sources (Table 57 in Appendix) |
| Ranibizumab | 10.89 | 7.81 | 4.94 | 4.00 | 3.20 | Average across sources (Table 57 in Appendix) |
| Ranibizumab plus standard threshold laser | 12.00 | 8.00 | 4.00 | 4.00 | 4.00 | TA274 |
| Bevacizumab | 10.89 | 7.81 | 4.94 | 4.00 | 3.20 | Assumed same as ranibizumab |
| Bevacizumab plus standard threshold laser | 12.00 | 8.00 | 4.00 | 4.00 | 4.00 | Assumed same as ranibizumab plus standard laser |
| Brolucizumab | 6.91 | 4.11 | 4.00 | 4.00 | 2.00 | TA820 |
| Faricimab | 7.58 | 4.35 | 4.00 | 4.00 | 4.00 | Average across sources (Table 57 in Appendix) |
| Fluocinolone acetonide | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 | TA271 |
| Dexamethasone | 4.50 | 4.00 | 4.00 | 4.00 | 4.00 | Average across sources (Table 57 in Appendix) |
| Subthreshold laser | 4.00 | 3.00 | 2.80 | 2.60 | 2.45 | Lois et al (2022) |

### HE2.4.4.3  Treatment costs

**Review question 5 – Proliferative diabetic retinopathy**

Drug costs used for the PDR model were taken from the BNF and are presented in  Whilst there is a Patient Access Scheme (PAS) price available for bevacizumab, this is for a vial size of 100mg/4ml. Given there is large uncertainty in the costs involved of repackaging to the 1.25mg vial size, the cost of £50 per 1.25mg dose was used based on committee agreement since this is around the price clinics would pay and is also aligned with previous technology appraisals. The list prices presented in**Error! Not a valid bookmark self-reference.** are publicly available, but confidential PAS and commercial medicines unit discounts were available for aflibercept, ranibizumab (Lucentis) and ranibizumab biosimilar (Ongavia). The results produced using these confidential prices were used for decision making and guideline recommendations but cannot be presented in any publicly available documents.

Table 18. The cost of PRP was informed by the NICE TAs and the NHS national cost collection (2019/2020). Ranibizumab biosimilar (Ongavia) was used in a scenario assuming the same efficacy, safety and resource use as ranibizumab. Whilst there is a Patient Access

<Please insert your copyright statement - one line of text entry only>

Scheme (PAS) price available for bevacizumab, this is for a vial size of 100mg/4ml. Given there is large uncertainty in the costs involved of repackaging to the 1.25mg vial size, the cost of £50 per 1.25mg dose was used based on committee agreement since this is around the price clinics would pay and is also aligned with previous technology appraisals. The list prices presented in**Error! Not a valid bookmark self-reference.** are publicly available, but confidential PAS and commercial medicines unit discounts were available for aflibercept, ranibizumab (Lucentis) and ranibizumab biosimilar (Ongavia). The results produced using these confidential prices were used for decision making and guideline recommendations but cannot be presented in any publicly available documents.

**Table 18: List prices per treatment for diabetic retinopathy**

| Resource | Unit costs (£) | Source |
|---|---|---|
| Aflibercept 4.0mg/0.1ml | £816.00 | BNF 13/02/2023 |
| Ranibizumab (Lucentis) 2.3mg/0.23ml | £551.00 | BNF 13/02/2023 |
| Ranibizumab biosimilar (Ongavia) 2.3mg/0.23ml | £523.45 | BNF 28/03/2023 |
| Bevacizumab 1.25mg | £50.00 | NICE TA824 |
| PRP | £126.77 | NHS national cost collection 2019/2020 BZ87A: Minor vitreous retinal procedures. Total HRG. Assumption used in NICE TA346 |

The number of annual injections per year for anti-VEGF treatments are presented in Table 19. The number of injections per year assumed for each treatment strategy including an anti-VEGF was based on Gross et al (2015) for the first two years. The committee advised it would be reasonable to assume the same number of injections for all anti-VEGFs in the absence of other data on the number of treatments expected. The number of treatments expected for year three onwards were based on the percentage decrease seen within the DMO literature for the number of treatments over time.

**Table 19: Number of injections for diabetic retinopathy**

| Treatment | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 onwards |
|---|---|---|---|---|---|
| PRP | 0 | 0 | 0 | 0 | 0 |
| Aflibercept | 6.900* | 3.300* | 1.650 | 1.238 | 1.176 |
| Ranibizumab | 6.900 | 3.300 | 1.650 | 1.238 | 1.176 |
| Ranibizumab plus PRP | 6.900* | 3.300* | 1.650 | 1.238 | 1.176 |
| Bevacizumab | 6.900* | 3.300* | 1.650 | 1.238 | 1.176 |
| Bevacizumab plus PRP | 6.900* | 3.300* | 1.650 | 1.238 | 1.176 |
| Source | Gross et al (2015) | Gross et al (2015) | Assumed 50% decrease from previous year** | Assumed 25% decrease from previous year** | Assumed 5% decrease from previous year** |

*Assumed same number of injections for all anti-VEGFs as ranibizumab based on committee consensus for years one and two*

**Assumed a percentage decrease in injection frequency from the previous year for year three onwards based on the relationship identified in decrease over time from anti-VEGF use in DMO*

The number of annual PRP treatments for each strategy are presented in Table 20. The number of treatments expected for the first two years was from the literature and assumed to be the same as year two carried forwards. Due to an absence of publicly available data for the combination regimens, it was assumed all treatment strategies have the same number of PRP treatments, this assumption was agreed with the committee.

<Please insert your copyright statement - one line of text entry only>

**Table 20: Number of laser treatments for diabetic retinopathy**

| Treatment | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 onwards |
|---|---|---|---|---|---|
| PRP | 1.815 | 0.689 | 0.689 | 0.689 | 0.689 |
| Aflibercept | - | - | - | - | - |
| Ranibizumab | - | - | - | - | - |
| Ranibizumab plus PRP* | 1.815 | 0.689 | 0.689 | 0.689 | 0.689 |
| Bevacizumab | - | - | - | - | ]- |
| Bevacizumab plus PRP* | 1.815 | 0.689 | 0.689 | 0.689 | 0.689 |
| Source | Average of Sivaprasad et al (2017) and Gross et al (2015) | Gross et al (2015) 45% of patients required additional PRP | Assumed same as year 2 | Assumed same as year 2 | Assumed same as year 2 |

*Assumed the same number of laser treatments across all treatments with PRP*

### Review question 7 – Diabetic macular oedema

Drug costs were taken from the BNF and are presented in Table 21 for DMO. The list prices presented in Table 21 are publicly available, but confidential PAS and commercial medicines unit discounts were available for aflibercept, ranibizumab (Lucentis), ranibizumab biosimilar (Ongavia), brolucizumab, faricimab and fluocinolone acetonide. The results produced using these confidential prices were used for decision making and guideline recommendations but cannot be presented in any publicly available documents.

**Table 21: List prices per treatment for diabetic macular oedema**

| Resource | Unit costs (£) | Source |
|---|---|---|
| Aflibercept 4.0mg/0.1ml | £816.00 | BNF 13/02/2023 |
| Ranibizumab (Lucentis) 2.3mg/0.23ml | £551.00 | BNF 13/02/2023 |
| Ranibizumab biosimilar (Ongavia) 2.3mg/0.23ml | £523.45 | BNF 28/03/2023 |
| Bevacizumab 1.25mg | £50.00 | NICE TA824 |
| Brolucizumab 19.8mg/0.165ml | £816.00 | BNF 13/02/2023 |
| Faricimab 28.8mg/0.24ml | £857.00 | BNF 13/02/2023 |
| Fluocinolone acetonide 190µg | £5,550.00 | BNF 13/02/2023 |
| Dexamethasone 700µg | £870.00 | BNF 13/02/2023 |
| Standard threshold laser | £41.16 | Lois et al (2022) |
| Subthreshold laser | £47.11 | Lois et al (2022) |

The number of treatments each year for those administered by injection (anti-VEGF) or intravitreal steroid treatments are presented in Table 22 and Table 23. Due to a large number of alternative sources available on the frequency of some of the anti-VEGFs, the average across sources was considered appropriate in the base-case analysis. The number of treatments each year was further explored in scenario analyses by taking the minimum and maximum reported values in addition to assuming the same number of treatments across all anti-VEGFs.

<Please insert your copyright statement - one line of text entry only>

**Table 22: Number of injections for diabetic macular oedema**

| Treatment | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 onwards | Source |
|-----------|--------|--------|--------|--------|----------------|--------|
| No treatment | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | N/A |
| Standard threshold laser | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | N/A |
| Aflibercept | 8.16 | 4.34 | 2.88 | 2.13 | 2.06 | Average across sources (Table 56 in Appendix) |
| Ranibizumab | 8.28 | 4.48 | 2.28 | 1.71 | 1.63 | Average across sources (Table 56 in Appendix) |
| Ranibizumab plus standard threshold laser | 7.00 | 3.50 | 2.50 | 1.71 | 1.63 | Haig et al (2016) |
| Bevacizumab | 8.28 | 4.48 | 2.28 | 1.71 | 1.63 | Assumed same as ranibizumab |
| Bevacizumab plus standard threshold laser | 7.00 | 3.50 | 2.50 | 1.71 | 1.63 | Assumed same as ranibizumab plus standard laser |
| Brolucizumab | 6.91 | 4.11 | 2.30 | 1.20 | 1.00 | TA820 |
| Faricimab | 7.06 | 4.24 | 1.97 | 1.97 | 1.97 | Average across sources (Table 56 in Appendix) |
| Fluocinolone acetonide | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | N/A |
| Dexamethasone | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | N/A |
| Subthreshold laser | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | N/A |

**Table 23: Number of steroid implants for diabetic macular oedema**

| Treatment | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 onwards | Source |
|-----------|--------|--------|--------|--------|----------------|--------|
| Fluocinolone acetonide | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | TA271 Annual based on committee feedback |
| Dexamethasone | 1.78 | 1.25 | 1.08 | 1.00 | 1.00 | TA824 |

The frequency of laser treatments for each treatment strategy are presented in Table 24. The number of laser treatments was assumed the same between standard threshold laser and the combination therapies because of a lack of data available for the combination regimens.

**Table 24: Number of laser treatments for diabetic macula oedema**

| Treatment | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 onwards | Source |
|-----------|--------|--------|--------|--------|----------------|--------|
| No treatment | 0.00 | 0.00 | 0.000 | 0.000 | 0.000 | N/A |
| Standard threshold laser | 2.01 | 0.60 | 0.675 | 0.200 | 0.150 | Average across Haig et al (2006), TA346 and Lois et al (2022) |
| Aflibercept | 0.00 | 0.00 | 0.000 | 0.000 | 0.000 | N/A |
| Ranibizumab | 0.00 | 0.00 | 0.000 | 0.000 | 0.000 | N/A |
| Ranibizumab plus standard threshold laser | 2.01 | 0.60 | 0.675 | 0.200 | 0.150 | Assumed same as standard threshold laser monotherapy |
| Bevacizumab | 0.00 | 0.00 | 0.000 | 0.000 | 0.000 | N/A |
| Bevacizumab plus standard threshold laser | 2.01 | 0.60 | 0.675 | 0.200 | 0.150 | Assumed same as standard threshold laser monotherapy |

| Treatment | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 onwards | Source |
|---|---|---|---|---|---|---|
| Brolucizumab | 0.00 | 0.00 | 0.000 | 0.000 | 0.000 | N/A |
| Faricimab | 0.00 | 0.00 | 0.000 | 0.000 | 0.000 | N/A |
| Fluocinolone acetonide | 0.00 | 0.00 | 0.000 | 0.000 | 0.000 | N/A |
| Dexamethasone | 0.00 | 0.00 | 0.000 | 0.000 | 0.000 | N/A |
| Subthreshold laser | 1.90 | 0.50 | 0.675 | 0.200 | 0.150 | Lois et al (2022) treatment from baseline to 12 months |

### HE2.4.4.4    Subsequent treatment

#### Review question 5 – Proliferative diabetic retinopathy

The model allowed a proportion of patients (Table 25) to receive a subsequent treatment based on the literature and the committee's expertise. People initially on combination treatment were assumed to receive no further treatment. The distribution of subsequent treatment for PRP was based on committee consensus assuming only 5% of patients on PRP would require anti-VEGF treatment, of which it is assumed 70% of those having anti-VEGF would have aflibercept, 20% ranibizumab and 10% bevacizumab. The distribution of subsequent treatments for aflibercept and bevacizumab was assumed to be equivalent to that reported by Gross et al (2015) for ranibizumab. Subsequent treatment was applied to costs only and was assumed to only apply for two years. The cost of subsequent treatment based on each first line treatment strategy is presented in Table 26. These values are calculated using the weightings in Table 25, and costs included are the treatment itself, administration and treatment specific adverse events.

**Table 25: Distribution of subsequent treatment for diabetic retinopathy**

| To\From | PRP | Aflibercept | Ranibizumab | Bevacizumab |
|---|---|---|---|---|
| No treatment | 95.0% | 94.0% | 94.0% | 94.0% |
| PRP | 0.0% | 6.0% | 6.0% | 6.0% |
| Aflibercept | 3.5% | 0.0% | 0.0% | 0.0% |
| Ranibizumab | 1.0% | 0.0% | 0.0% | 0.0% |
| Ranibizumab plus PRP | 0.0% | 0.0% | 0.0% | 0.0% |
| Bevacizumab | 0.5% | 0.0% | 0.0% | 0.0% |
| Bevacizumab plus PRP | 0.0% | 0.0% | 0.0% | 0.0% |
| Source | Committee consensus | Assumed same as ranibizumab | Gross et al (2015) | Assumed same as ranibizumab |

**Table 26: Subsequent treatment cost by first line regimen**

| Resource | Cost (£) |
|---|---|
| PRP | £483.28 |
| Aflibercept | £25.34 |
| Ranibizumab | £25.34 |
| Ranibizumab plus PRP | - |
| Bevacizumab | £25.34 |
| Bevacizumab plus PRP | - |

<Please insert your copyright statement - one line of text entry only>

**Review question 7 – Diabetic macular oedema**

The model included subsequent treatment when treatment duration was assumed to end, the full distribution of subsequent treatment can be found in Appendix A:. Subsequent treatment was applied for two years only because there is large variability in reporting with long term evidence. From the committee discussion, it was understood people would commonly receive subsequent treatment if they had ended treatment due to a lack of response. The committee felt that it would be important to reflect the use of subsequent treatment to not underestimate the costs associated with each first line treatment; however, due to the limited evidence available two years of subsequent treatment was chosen so as not to overweight the cost of first line treatment by the subsequent treatment therapy where the evidence is limited. The proportion of patients receiving subsequent treatment for either faricimab or brolucizumab was assumed to be equivalent to those receiving aflibercept initially because these treatments were assumed to be equivalent in the NICE TAs ([TA820](#),[TA799](#)). No further treatments were assumed for dexamethasone or fluocinolone because these treatments are predominantly used in second line and there was no data reported on subsequent treatment options. The total cost of subsequent treatment expected for each first line treatment strategy is presented in Table 27. These values are calculated using the weightings in Table 54 and costs included are the treatment itself, administration and treatment specific adverse events.

**Table 27: Subsequent treatment cost by first line regimen**

| Resource | Cost (£) |
|---|---|
| No treatment | £0.00 |
| Standard threshold laser | £2,691.08 |
| Aflibercept | £40.45 |
| Ranibizumab | £50.28 |
| Ranibizumab plus standard laser | £0.00 |
| Bevacizumab | £61.22 |
| Bevacizumab plus laser | £0.00 |
| Faricimab | £40.45 |
| Brolucizumab | £40.45 |
| Dexamethasone | £0.00 |
| Fluocinolone | £0.00 |
| Subthreshold laser | £2,246.26 |

**HE2.4.4.5 Costs associated with adverse events**

The total cost of adverse events associated with each treatment was calculated by multiplying the proportion of patients experiencing each adverse event by the cost of each adverse event which is presented in Table 28. The same costs of adverse events were used for both models (RQ5 and RQ7) as these were not expected to change between the two conditions.

**Table 28: Adverse events costs**

| Resource | Costs (£) | Source |
|---|---|---|
| Retinal detachment | £2,314.22 | AMD guideline ([NG82](#)) assuming 75% of patients require urgent vitrectomy (weighted average of non-elective long and short stay procedures (BZ84A, BZ84B) Major vitreous retinal procedures, 19 years and over, with CC score 0-2+) and 25% of patients have elective surgery (weighted average of day case procedures (BZ84A, BZ84B) Major vitreous retinal procedures, 19 years and over, with CC score 0-2+). |

<Please insert your copyright statement - one line of text entry only>

| Resource | Costs (£) | Source |
|---|---|---|
| Retinal tear | £185.61 | BZ84A-B: Major vitreous retinal procedures. Total HRGs, weighted average of CC scores. |
| Vitreous haemorrhage | £482.84 | BZ86B: Intermediate vitreous retinal procedures, 19 years and over, with CC score 0-1, weighted average of non-elective long and short stay based on TA824. |
| Increased intraocular pressure | £1,012.24 | BZ24D-G: Non-surgical ophthalmology. Total HRGs, weighted average of CC scores, with and without interventions. |
| Glaucoma | £883.00 | Trabeculectomy BZ17B: Service code 130 ophthalmology, Major glaucoma procedures, with CC score 0 (day case) based on ERG discussion TA349 that trabeculectomy is the main procedure used. |
| Endophthalmitis | £1,520.97 | Calculated using the distributions from the AMD and cataract guidelines (NG82, NG77). Assumed 18.31% patients require vitrectomy, 38.46% require urgent vitrectomies, and 17.95% patients will require at least 1 revision, 5.13% of patients will require 2 revisions as reported by Kamalarajah et al (2004). All patients were assumed to require vitreous tap (weighted average of procedures: BZ87A) based on AMD committee guidance. Elective vitrectomy assumed to be the weighted average of elective and day case procedures for BZ84A and BZ84B Major vitreous retinal procedures, urgent vitrectomy assumed to be the weighted average of nonelective long-stay procedures: BZ84A, BZ84B. It was assumed 5.5 outpatient visits will be required (from AMD committee guidance) based on consultant led non-admitted face-to-face attendance, Follow-up. Code 130 - ophthalmology. It was assumed all patients will also require medication of Amikacin 500mg/2ml. |
| Cataracts | £1,945.47 | AMD and cataract guidelines (NG82, NG77): weighted average of non-elective short stay and day case codes for phacoemulsification cataract extraction and lens implant with CC score 4+, 2-3, 0-1: BZ34A, B and C. |
| Ocular pain | £1,012.24 | BZ24D-G: Non-surgical ophthalmology. Total HRGs, weighted average of CC scores, with and without interventions. |
| Stroke | £3,655.56 | AA35A-F: Stroke. Total HRGs, weighted average of CC scores. |
| Cardiovascular death | £598.62 | VB99Z: Emergency medicine, Patient dead on arrival. |
| Myocardial infarction | £1,596.39 | EB10A-E: Actual or suspected myocardial infarction. Total HRGs, weighted average of CC scores. |

### HE2.4.4.6 Costs associated with low vision

The models for both review questions included the costs associated with low vision for all those treated in the BSE with BCVA≤35 letters. In the base-case analysis, only those costs specific to healthcare costs were included. The additional costs associated with community and residential care were included in a scenario analysis. The costs associated with low vision are presented in Table 29.

**Table 29: Low vision costs (per 3-monthly cycle)**

| Resource | Costs (£) | Source/Notes |
|---|---|---|
| Healthcare costs associated with low vision | £421.61 | Régnier et al (2015)<br>Annual total cost of visual impairment BCVA≤35 letters (£17,326) minus the cost of residential care (£15,327), community care (£600) and low vision rehabilitation (£47), to be aligned with the NHS perspective. The costs (2010/2011) were adjusted to 2019/2020 values and to a 3-monthly cycle length. |

<Please insert your copyright statement - one line of text entry only>

| Resource | Costs (£) | Source/Notes |
|---|---|---|
| Low vision community patient costs (scenario only) | £4,966.69 | Régnier et al (2015)<br>Community care and residential care costs were adjusted for a 3-monthly cycle length. |

## HE2.4.5   Summary

All parameters used in the model are summarised in Table 30, including details of the distributions and parameters used in probabilistic sensitivity analysis (PSA).

**Table 30: All parameters in original cost-utility model**

| Parameter | Point estimate | Probabilistic analysis | | Source |
|---|---|---|---|---|
| | | Distribution | Parameters | |
| Discount rate (QALYs) | 3.5% | N/A | N/A | NICE reference case |
| Discount rate (Costs) | 3.5% | N/A | N/A | NICE reference case |
| Cycles per year | 4 | N/A | N/A | Aligns with previous models |
| Time horizon | Lifetime | N/A | N/A | NICE reference case |
| **Baseline characteristics – RQ5 (PDR)** | | | | |
| Starting age | 56 | N/A | N/A | Maturi et al (2021) |
| Sex (% male) | 57.6% | N/A | N/A | Maturi et al (2021) |
| **Baseline characteristics – RQ7 (DMO)** | | | | |
| Starting age | 63 | N/A | N/A | Mitchell et al (2012); RESTORE |
| Sex (% male) | 58.0% | N/A | N/A | Mitchell et al (2012); RESTORE |
| **Mortality hazard ratio (HR) associated with diabetes** | | | | |
| Mortality HR diabetes | 1.950 | Lognormal | $\mu=0.668$, $\sigma=0.090$ | Preis et al (2009) |
| **Baseline natural history proportion of patients starting in each health state** | | | | |
| Treated eye BCVA: >85 | 0% | Dirichlet | N/A | Régnier et al (2015); RESTORE |
| Treated eye BCVA: 76-85 | 11% | Dirichlet | N/A | Régnier et al (2015); RESTORE |
| Treated eye BCVA: 66-75 | 39% | Dirichlet | N/A | Régnier et al (2015); RESTORE |
| Treated eye BCVA: 56-65 | 27% | Dirichlet | N/A | Régnier et al (2015); RESTORE |
| Treated eye BCVA: 46-55 | 15% | Dirichlet | N/A | Régnier et al (2015); RESTORE |
| Treated eye BCVA: 36-45 | 8% | Dirichlet | N/A | Régnier et al (2015); RESTORE |
| Treated eye BCVA: 26-35 | 0% | Dirichlet | N/A | Régnier et al (2015); RESTORE |
| Treated eye BCVA: ≤25 | 0% | Dirichlet | N/A | Régnier et al (2015); RESTORE |
| **Fellow eye involvement** | | | | |
| Patients treated in both eyes | 22.0% | Beta | $\alpha=75.900$, $\beta=269.100$ | Régnier et al (2015); RESTORE |
| Patients treated in WSE | 67.2% | Dirichlet | N/A | Mitchell et al (2012); RESTORE |
| Patients treated in BSE | 32.8% | Dirichlet | N/A | Mitchell et al (2012); RESTORE |

<Please insert your copyright statement - one line of text entry only>

| Parameter | Point estimate | Probabilistic analysis | | Source |
|---|---|---|---|---|
| | | Distribution | Parameters | |
| Probability of developing DMO in the fellow eye | 5.4% | Beta | α=7.900, β=138.397 | Pochopien et al (2019); ICE-UK |
| **Natural history – RQ5 (PDR)** | | | | |
| Mean change in ETDRS (52 weeks) | -1.300 | Normal | μ=-1.300, σ=0.364 | Maturi et al (2021) |
| Transition probability gain one health state (sham) | 2.6% | N/A | N/A | Calculated |
| Transition probability lose one health state (sham) | 6.1% | N/A | N/A | Calculated |
| Long-term natural history: gain one health state | 3.5% | Dirichlet | N/A | Mitchell et al (2012); Sample size based on RESTORE |
| Long-term natural history: lose one health state | 4.5% | Dirichlet | N/A | Mitchell et al (2012); Sample size based on RESTORE |
| **Natural history – RQ7 (DMO)** | | | | |
| Mean change in ETDRS (52 weeks): Massin et al (2010) | -1.400 | Normal | μ=-1.400, σ=2.029 | Massin et al (2010) |
| Mean change in ETDRS (52 weeks): Sultan et al (2011) | 1.200 | Normal | μ=1.200, σ=1.420 | Sultan et al (2011) |
| Mean change in ETDRS (52 weeks): Pooled | 0.345 | Normal | μ=0.345, σ=1.168 | Calculated |
| Transition probability gain one HS (sham) | 6.02% | N/A | N/A | Calculated |
| Transition probability lose one HS (sham) | 5.81% | N/A | N/A | Calculated |
| Long-term natural history: gain one HS | 3.50% | Dirichlet | N/A | Mitchell et al (2012); Sample size based on RESTORE |
| Long-term natural history: lose one HS | 4.50% | Dirichlet | N/A | Mitchell et al (2012) |
| **Treatment effects at one year (mean difference, LogMAR) – PDR** | | | | |
| Aflibercept (vs PRP) | -0.088 | Normal | μ=-0.088, σ=0.070 | Simmonds et al. (2023) |
| Ranibizumab (vs PRP) | -0.123 | Normal | μ=-0.123, σ=0.058 | Simmonds et al. (2023) |
| Ranibizumab plus PRP (vs PRP) | -0.080 | Normal | μ=-0.080, σ=0.042 | Simmonds et al. (2023) |
| Bevacizumab (vs PRP) | -0.193 | Normal | μ=-0.193, σ=0.499 | Simmonds et al. (2023) |

<Please insert your copyright statement - one line of text entry only>

| Parameter | Point estimate | Probabilistic analysis | | Source |
|---|---|---|---|---|
| | | Distribution | Parameters | |
| Bevacizumab plus PRP (vs PRP) | -0.172 | Normal | μ=-0.172, σ=0.055 | Simmonds et al. (2023) |
| **Treatment effects at one year (mean difference, LogMAR) – DMO, all centre involving** | | | | |
| Standard laser (vs sham) | -0.103 | Normal | μ=-0.103, σ=0.055 | NMA conducted for evidence review G |
| Aflibercept (vs sham) | -0.284 | Normal | μ=-0.284, σ=0.056 | NMA conducted for evidence review G |
| Ranibizumab (vs sham) | -0.234 | Normal | μ=-0.234, σ=0.053 | NMA conducted for evidence review G |
| Ranibizumab plus standard laser (vs sham) | -0.218 | Normal | μ=-0.218, σ=0.056 | NMA conducted for evidence review G |
| Bevacizumab (vs sham) | -0.222 | Normal | μ=-0.222, σ=0.056 | NMA conducted for evidence review G |
| Bevacizumab plus standard laser (vs sham) | -0.264 | Normal | μ=-0.264, σ=0.091 | NMA conducted for evidence review G |
| Brolucizumab (vs sham) | -0.308 | Normal | μ=-0.308, σ=0.068 | NMA conducted for evidence review G |
| Faricimab (vs sham) | -0.301 | Normal | μ=-0.301, σ=0.061 | NMA conducted for evidence review G |
| Fluocinolone Acetonide (vs sham) | -0.203 | Normal | μ=-0.203, σ=0.059 | Assumed same as dexamethasone based on committee consensus |
| Dexamethasone (vs sham) | -0.203 | Normal | μ=-0.203, σ=0.059 | NMA conducted for evidence review G |
| Subthreshold laser (vs sham) | -0.100 | Normal | μ=-0.100, σ=0.061 | NMA conducted for evidence review G |
| **Treatment effects at one year (mean difference, LogMAR) – DMO, centre involving CRT≥400** | | | | |
| Standard laser (vs sham) | -0.087 | Normal | μ=-0.087, σ=0.059 | NMA conducted for evidence review G |
| Aflibercept (vs sham) | -0.286 | Normal | μ=-0.286, σ=0.060 | NMA conducted for evidence review G |
| Ranibizumab (vs sham) | -0.234 | Normal | μ=-0.234, σ=0.056 | NMA conducted for evidence review G |
| Ranibizumab plus standard laser (vs sham) | -0.222 | Normal | μ=-0.222, σ=0.060 | NMA conducted for evidence review G |
| Bevacizumab (vs sham) | -0.220 | Normal | μ=-0.220, σ=0.059 | NMA conducted for evidence review G |
| Bevacizumab plus standard laser (vs sham) | -0.222 | Normal | μ=-0.222, σ=0.060 | Assumed same as ranibizumab plus standard laser |
| Brolucizumab (vs sham) | -0.285 | Normal | μ=-0.285, σ=0.067 | NMA conducted for evidence review G |
| Faricimab (vs sham) | -0.303 | Normal | μ=-0.303, σ=0.066 | NMA conducted for evidence review G |
| Fluocinolone Acetonide (vs sham) | -0.204 | Normal | μ=-0.204, σ=0.063 | Assumed same as dexamethasone based on committee consensus |
| Dexamethasone (vs sham) | -0.204 | Normal | μ=-0.204, σ=0.063 | NMA conducted for evidence review G |
| Subthreshold laser (vs sham) | -0.087 | Normal | μ=-0.087, σ=0.059 | Assumed same as standard threshold laser |
| **Treatment discontinuation** | | | | |

<Please insert your copyright statement - one line of text entry only>

| Parameter | Point estimate | Probabilistic analysis | | Source |
| --- | --- | --- | --- | --- |
| | | Distribution | Parameters | |
| Patients on treatment up to 1 year | 100% | N/A | N/A | Committee consensus |
| Patients continuing treatment from 1 to 3 years – PDR only | 87% | N/A | N/A | Gross et al (2015): weighted average across treatments (88% ranibizumab; 86% PRP) |
| Patients continuing treatment between 1 to 3 years – DMO only | - | Beta | - | Treatment specific (detailed in Table 11) |
| Patients continuing treatment from 3 to 5 years | 75% | N/A | N/A | Wykoff et al (2017): aflibercept extension study |
| Patients continuing treatment after 5 years | 50% | N/A | N/A | Assumption based on faricimab TA799 combined with committee consensus |
| **Treatment costs** | | | | |
| Aflibercept 4.0mg/0.1 ml | £816.00 | Gamma | μ=96.036, σ=8.497 | BNF 13/02/2023 |
| Ranibizumab (Lucentis) 2.3mg/0.23ml | £551.00 | Gamma | μ=96.036, σ=5.737 | BNF 13/02/2023 |
| Ranibizumab biosimilar (Ongavia) 2.3mg/0.23ml | £523.45 | Gamma | μ=96.036, σ=5.451 | BNF 28/03/2023 |
| Bevacizumab 1.25mg | £50.00 | Gamma | μ=96.036, σ=0.521 | NICE TA824 |
| Brolucizumab 19.8mg/0.165 | £816.00 | Gamma | μ=96.036, σ=8.497 | BNF 13/02/2023 |
| Faricimab 28.8mg/0.24ml | £857.00 | Gamma | μ=96.036, σ=8.924 | BNF 13/02/2023 |
| Fluocinolone acetonide 190 microgram | £5,500.00 | Gamma | μ=96.036, σ=57.270 | BNF 13/02/2023 |
| Dexamethasone 700 microgram | £870.00 | Gamma | μ=96.036, σ=9.059 | BNF 13/02/2023 |
| Standard threshold laser | £41.16 | Gamma | μ=96.036, σ=0.429 | Lois et al (2022) |
| Subthreshold laser | £47.11 | Gamma | μ=96.036, σ=0.491 | Lois et al (2022) |
| PRP | £126.77 | Gamma | μ=96.036, σ=1.320 | NICE TA346: NHS national cost collection 2019/2020 BZ87A: Minor vitreous retinal procedures. Total HRG. |
| **BCVA health state utilities for BSE – RQ5 (PDR) base-case** | | | | |
| Treated eye BCVA: >85 | 0.839 | Beta | α=42.697, β=8.193 | Brown et al (2000) |
| Treated eye BCVA: 76-85 | 0.839 | Beta | α=42.697, β=8.193 | |
| Treated eye BCVA: 66-75 | 0.783 | Beta | α=141.181, β=39.127 | |

<Please insert your copyright statement - one line of text entry only>

| Parameter | Point estimate | Probabilistic analysis | | Source |
|-----------|----------------|------------------------|---|--------|
| | | Distribution | Parameters | |
| Treated eye BCVA: 56-65 | 0.783 | Beta | α=141.181, β=39.127 | |
| Treated eye BCVA: 46-55 | 0.732 | Beta | α=44.858, β=16.423 | |
| Treated eye BCVA: 36-45 | 0.681 | Beta | α=46.286, β=21.682 | |
| Treated eye BCVA: 26-35 | 0.630 | Beta | α=45.992, β=27.011 | |
| Treated eye BCVA: ≤25 | 0.579 | Beta | α=3.604, β=2.621 | |
| **BCVA health state utilities for WSE – RQ5 (PDR) base-case** | | | | |
| Treated eye BCVA: >85 | 0.839 | Beta | α=42.697, β=8.193 | |
| Treated eye BCVA: 76-85 | 0.839 | Beta | α=42.697, β=8.193 | |
| Treated eye BCVA: 66-75 | 0.822 | Beta | α=45.330, β=9.794 | Brown et al (2000), assuming a utility decrement of 0.1 between the best and worst health states (and a linear decline in utility for the other states) based on the approach used by Régnier et al (2015) |
| Treated eye BCVA: 56-65 | 0.806 | Beta | α=47.651, β=11.494 | |
| Treated eye BCVA: 46-55 | 0.789 | Beta | α=49.669, β=13.283 | |
| Treated eye BCVA: 36-45 | 0.772 | Beta | α=51.396, β=15.150 | |
| Treated eye BCVA: 26-35 | 0.756 | Beta | α=52.841, β=17.085 | |
| Treated eye BCVA: ≤25 | 0.739 | Beta | α=54.016, β=19.077 | |
| **BCVA health state utilities for BSE – RQ7 (DMO) base-case** | | | | |
| Treated eye BCVA: >85 | 0.850 | Beta | α=56.772, β=10.019 | |
| Treated eye BCVA: 76-85 | 0.758 | Beta | α=92.205, β=29.438 | |
| Treated eye BCVA: 66-75 | 0.685 | Beta | α=120.321, β=55.330 | |
| Treated eye BCVA: 56-65 | 0.611 | Beta | α=148.822, β=94.749 | |
| Treated eye BCVA: 46-55 | 0.537 | Beta | α=177.323, β=152.887 | Czoski-Murray (2009) |
| Treated eye BCVA: 36-45 | 0.464 | Beta | α=205.438, β=237.317 | |
| Treated eye BCVA: 26-35 | 0.390 | Beta | α=233.939, β=365.905 | |
| Treated eye BCVA: ≤25 | 0.353 | Beta | α=248.189, β=454.897 | |
| **BCVA health state utilities for WSE – RQ7 (DMO) base-case** | | | | |
| Treated eye BCVA: >85 | 0.850 | Beta | α=56.772, β=10.019 | |
| Treated eye BCVA: 76-85 | 0.836 | Beta | α=62.274, β=12.242 | Czoski-Murray (2009), assuming a utility decrement of 0.1 between the best and worst health states (and a linear decline in utility for the other states) based on the approach used by Régnier et al (2015) |
| Treated eye BCVA: 66-75 | 0.821 | Beta | α=67.776, β=14.734 | |
| Treated eye BCVA: 56-65 | 0.807 | Beta | α=73.278, β=17.509 | |
| Treated eye BCVA: 46-55 | 0.793 | Beta | α=78.780, β=20.582 | |

<Please insert your copyright statement - one line of text entry only>

| Parameter | Point estimate | Probabilistic analysis | | Source |
| | | Distribution | Parameters | |
|---|---|---|---|---|
| Treated eye BCVA: 36-45 | 0.779 | Beta | α=84.282, β=23.970 | |
| Treated eye BCVA: 26-35 | 0.764 | Beta | α=89.784, β=27.691 | |
| Treated eye BCVA: ≤25 | 0.750 | Beta | α=95.286, β=31.762 | |

## HE2.5  Summary of key assumptions

A summary of the key assumptions used for the economic models is presented in Table 31. The assumptions were applied to the economic models for both RQ5 (diabetic retinopathy) and RQ7 (DMO) unless otherwise specified.

**Table 31: Summary of key assumptions**

| Category | Assumption | Justification |
|---|---|---|
| Treatment effects | The mean change in BCVA was characterised by a normal distribution, from which it is possible to estimate the probability of gaining or losing any given number of letters | NMAs used the mean difference in BCVA based on the data reported within clinical trials. This was then transformed into transition probabilities based on normal distribution to more accurately account for the average eye rather than simply using the midpoint and assuming a 10-letter increase or decrease from that point. The probability of the average eye moving up or down one health state (10-letter range) was equal to the probability of gaining or losing between 5 and 15 letters. |
| Fellow eye involvement | Costs associated with the treatment of a second eye were included based on the percentage of patients expected to require treatment in both eyes at baseline and the proportion of patients expected to require treatment in the second eye in each 3-monthly cycle | Whilst it was difficult to obtain the health state associated with the second eye, given the high costs of treatment and the high chance of disease developing in the second eye, it was considered important to at least capture the costs associated with treatment in the second eye. It was assumed the same treatment would be used in both eyes and the BCVA health state was based on the BSE since gains in vision and associated utility are driven by the BSE. Although data on the proportion of patients expected to require treatment for the second eye were based on the DMO population, the committee agreed that, in the absence of data available for the PDR population, it would be reasonable to assume the same proportions across both conditions. |
| Subsequent treatment | Subsequent treatment costs were included | Subsequent treatment has not always been included in previous economic analyses in PDR and DMO; however, the committee noted that in clinical practice a proportion of patients would be expected to switch to a different treatment after discontinuing the previous treatment due to a lack of response rather than the condition stabilising and felt that it was important to include these costs. |
| Patient costs | Patient costs were not included in the base-case analysis | Patient costs were not included in the base-case analysis to align with the NICE reference case of NHS and PSS perspective. The committee noted the importance of considering patient costs in the analysis because these can represent a large burden to patients. Given the lack of appropriate data, the committee discussed patient costs qualitatively alongside the model results when considering the patient perspective. |

<Please insert your copyright statement - one line of text entry only>

| Category | Assumption | Justification |
|---|---|---|
| Cost associated with low vision | Direct health care related costs associated with low vision were applied to patients with BCVA≤35 ETDRS letters in the base-case analysis | This aligns with previous TAs and published economic models. However, the base-case analysis for both review questions only included healthcare specific costs to align with the NICE reference case. |
| Adverse events | Treatment-related adverse events were included | Although adverse event reporting is sporadic across studies, the committee discussed that whilst adverse events within treatment classes are similar, they vary considerably across treatment classes which may impact a patient's choice of treatment type. It was therefore considered important to include adverse events where possible. |
| Subsequent treatment | Subsequent treatment was applied to a proportion of patients for a duration of two years | In clinical practice, it would be expected that patients would likely switch onto another treatment if they have ended treatment due to a lack of response. There is a large variability in reporting on subsequent treatment in the literature, and there is no data for the duration of subsequent treatment. Due to the limited evidence available, two years of subsequent treatment was chosen so as not to overweight the cost of first line treatment by the subsequent treatment where the evidence is limited. |
| Duration of treatment effect | Lifetime | The committee agreed that they would expect treatment to continue working for as long as it is being given. Uncertainty around this assumption was explored in scenario analysis, with treatment effect durations of 20, 10, and 5 years. |
| **RQ5: PDR specific assumption** | | |
| Treatment effect: PDR | Treatment effect relative to PRP applied for all other interventions | No treatment or sham arm only available in clinical trials for the NPDR population. The committee did not feel this was appropriate to use because it would underestimate the true treatment effect because NPDR is associated with less change in vision than in PDR. |
| Duration of treatment: PDR | Assumed all patients remain on treatment for the first year, 87% of patients remain on treatment from 1 to 3 years, 75% of patients remain on treatment from 3 to 5 years and 50% of patients remain on treatment from year 5 onwards | The percentage of patients continuing treatment were informed by the literature and in discussion with the committee. Due to a lack of treatment specific data, all treatments were assumed to have the same probability of remaining on treatment. The first year was based on RQ8 recommendations to wait a full year before considering treatment switching to allow sufficient time for treatment response. The proportion remaining on treatment from 1 to 3 years was informed by Gross et al (2015). The committee discussed given the nature of anti-VEGFs, it would be expected for a large number of patients to remain on treatment. Given the clinical trials for diabetic retinopathy lasted for a maximum of 2 years, data beyond this period was taken from DMO studies. Wykoff et al (2017) observed 75% of patients were still on treatment at the end of the aflibercept extension study for DMO. The committee agreed with the assumption that 50% of patients would be expected to remain on treatment after 5 years. This was made by the scrutiny panel for the NICE TA for the treatment of DMO which the committee felt was aligned with clinical practice in DMO and would be a reasonable assumption for the long-term use of anti-VEGFs in PDR. The proportion of patients expected to remain on treatment after 5 years was explored in scenarios of 75% and 25%. |

<Please insert your copyright statement - one line of text entry only>

| Category | Assumption | Justification |
|---|---|---|
| Natural history: PDR | Natural history was not applied in the base-case as it would only be applied after the treatment effect was assumed to have ended. In scenarios, natural history was based on the no treatment arm from protocol W for NPDR | The committee discussed treatment effect would be expected to decrease over time whilst people were still being treated. The committee were initially concerned over the use of a non-proliferative population for the source of natural history; however, no study on proliferative disease included either a sham or no treatment arm to allow for comparison. Given the natural history is only applied in scenario analyses, the committee accepted this data source in the absence of data specific to the PDR population. |
| **RQ7: DMO specific assumption** | | |
| Treatment effect: DMO | Treatment effect relative to no treatment | Mean difference in BCVA for each treatment was compared to no treatment or sham arms within clinical trials. |
| Duration of treatment: DMO | Assumed all patients remain on treatment for the first year, proportion of patients assumed to discontinue treatment from 1 to 3 years was based on treatment specific discontinuation. In addition to treatment specific discontinuation, 75% of all patients were assumed to remain on treatment from 3 to 5 years and 50% of patients assumed to remain on treatment from year 5 onwards | The percentage of patients continuing treatment were informed by the literature and in discussion with the committee. The assumption that all patients remain on treatment in the first year was based on RQ8 recommendations to wait a full year before considering treatment switching to allow sufficient time for treatment response. The proportion remaining on treatment from 1 to 3 years was informed by treatment specific discontinuation based on the literature and the TAs. The committee discussed that based on the nature of anti-VEGFs, it would be expected for a large number of patients to remain on treatment. Data from 3 to 5 years was informed by Wykoff et al (2017) which observed 75% of patients were still on treatment at the end of the aflibercept extension study for DMO. The committee agreed with the assumption that 50% of patients would be expected to remain on treatment after 5 years. This was made by the scrutiny panel for the NICE TA for the treatment of DMO which the committee felt was aligned with clinical practice in DMO and would be a reasonable assumption for the long-term use of anti-VEGFs. In addition to these proportions remaining on treatment, the model allowed for treatment specific discontinuation. The proportion of patients expected to remain on treatment after 5 years was explored in scenarios of 75% and 25%. |
| Natural history: DMO | When natural history was applied in scenarios, the 3-month probability of moving up one health state was 3.5% and moving down one health state was 4.5% (as assessed by a change of at least 10 letters of BCVA) (Mitchell et al 2012). Natural history was applied to the no treatment arm and other interventions when treatment efficacy was assumed to have ended | Mitchell et al (2012) used data from WESDR to create a transition matrix associated with the natural history of DMO. This source has been widely used within the TAs and the committee felt the population from this analysis best suited this population given a lack of alternative data sources and the values reflected natural history seen in clinical practice. The source of natural history was explored by using the pooled no treatment data from the NMA. |

<Please insert your copyright statement - one line of text entry only>

# HE2.6 Subgroup analyses

### RQ5: Proliferative diabetic retinopathy

The treatment of NPDR was discussed; however, only the PDR population was modelled due to the limited data availability for the NPDR population.

### RQ7: Diabetic macular oedema

Due to the large variation in the characteristics across the DMO population, the clinical evidence was separated by centre involving DMO and non-centre involving DMO. The centre involving DMO population was further separated by CRT of less than 400µm and CRT of at least 400µm at the start of treatment because of the different treatment strategies currently reimbursed by NICE for these subgroups. It was only possible to conduct health economic analyses for the populations where there was sufficient evidence to inform a network for NMA; as such, only the following populations were included within the economic modelling:

- All centre involving DMO
- Centre involving DMO with a CRT≥400µm

# HE2.7 Sensitivity analyses

## HE2.7.1 Deterministic sensitivity analyses

Deterministic sensitivity analyses in the form of scenario analyses were conducted to identify which model parameters had the greatest impact on the overall results. Scenarios included were chosen based on the parameters the committee felt had the greatest uncertainty.

### RQ5: Proliferative diabetic retinopathy

**Table 32: Scenarios considered in the analysis for PDR**

| Category | Base-case | Scenarios |
|---|---|---|
| Monitoring and treatment frequency | • Average across sources, or as reported in case of limited evidence | • Minimum value: assumed monitoring and treatment visits reduced by 20%<br>• Maximum value: assumed monitoring and treatment visits increased by 20% |
| Treatment to occur at the same visit as monitoring | • Yes | • No (assumed separate monitoring visits) |
| Utility for treatment in both eyes | • BSE | • Weighted across BSE and WSE based on the distribution reported by Régnier et al (2015) |
| Utility source | • Brown et al (2000) | • Czoski-Murray et al (2009)<br>• Sharma et al (2002)<br>• Lloyd et al (2008)<br>• Mitchell et al (2012)<br>• Pennington et al (2020) |
| Proportion of patients receiving treatment after year 5 | • 50% | • 75% (maximum)<br>• 25% (minimum) |
| Year in which natural history efficacy assumed | • Lifetime | • 20 years<br>• 10 years<br>• 5 years |

<Please insert your copyright statement - one line of text entry only>

| Category | Base-case | Scenarios |
|----------|-----------|-----------|
| Patient costs included | • No | • Patient costs associated with only low vision were included as a scenario |

*BSE: Best seeing eye; WSE: Worst seeing eye*

**RQ7: Diabetic macular oedema**

**Table 33: Scenarios considered in the analysis for DMO**

| Category | Base-case | Scenarios |
|----------|-----------|-----------|
| Monitoring and treatment frequency | • Average across sources for each treatment | • Minimum frequency reported<br>• Maximum frequency reported<br>• Assumed same frequency across all anti-VEGFs |
| Treatment to occur at the same visit as monitoring | • Yes | • No (assumed separate monitoring visits) |
| Utility for treatment in both eyes | • BSE | • Weighted across BSE and WSE based on the distribution reported by Régnier et al (2015) |
| Utility source | • Czoski-Murray et al (2009) | • Brown et al (2000)<br>• Sharma et al (2002)<br>• Lloyd et al (2008)<br>• Mitchell et al (2012)<br>• Pennington et al (2020) |
| Proportion of patients receiving treatment after year 5 | • 50% | • 75% (maximum)<br>• 25% (minimum) |
| Year in which natural history efficacy assumed | • Lifetime | • 20 years<br>• 10 years<br>• 5 years |
| Natural history source | • No treatment: Mitchell et al (2012)<br>• After treatment: Mitchell et al (2012) | • No treatment: sham<br>After treatment: Mitchell et al (2012)<br>• No treatment: sham<br>After treatment: sham |
| Source of sham arm BCVA changes from baseline | • Pooled sham arm across Massin et al (2010) and Sultan et al (2011) | • Massin et al (2010)<br>• Sultan et al (2011) |
| Patient costs included | • No | • Patient costs associated with only low vision were included as a scenario |

*BSE: Best seeing eye; WSE: Worst seeing eye*

## HE2.7.2    Probabilistic sensitivity analyses

The models were configured to perform PSA to quantify uncertainty in the true values of input parameters. The PSA was run for 1,000 iterations. Probability distributions were specified for all input variables. The type of distribution used was based on the properties of data of that type (for example, beta distributions were used for probabilities that are bounded between 0 and 1 and gamma distributions were used for cost parameters that are right skewed and cannot be negative). Where possible, each distribution was parameterised using dispersion data from the source from which the value was obtained; where no such data were available, consideration was given to ensuring plausible ranges were applied based on

<Please insert your copyright statement - one line of text entry only>

the committee advice and the usual properties of similar data. Costs were varied by ±20% and utilities were varied by ±10% when no other information was available.

<Please insert your copyright statement - one line of text entry only>

# HE3 Results

Throughout this section only results of the list price analyses are presented in full. All of the anti-VEGF treatments (except bevacizumab) and fluocinolone acetonide had confidential price discounts, and analyses using these prices were the results that the committee used for decision making. However, results based on confidential prices cannot be reported in full due to their commercially sensitive nature but have been described qualitatively alongside the list price results in the following sections.

Several scenario analyses were conducted by changing key parameters anticipated to have the greatest uncertainty. The committee were presented with the three treatments that had the highest NMB in each scenario, and these results are presented in sections HE3.1.3 (PDR), HE3.2.3 (all centre involving DMO), and 0 (DMO with CRT≥400µm). The full scenario analysis results can be found in Appendix B:.

## HE3.1 Results – proliferative diabetic retinopathy

### HE3.1.1 Base-case cost-utility results

The results of the base-case deterministic analysis using the list prices are presented in Table 34 and Table 35. Bevacizumab had the lowest ICER of £2,704 compared with PRP alone. It should be noted that these list price results were not used by the committee when drafting recommendations as they do not take into account the confidential prices associated with each treatment.

When the confidential prices were used, both aflibercept and ranibizumab monotherapy had ICERs below the £20,000 per QALY gained threshold. When the confidential cost of the ranibizumab biosimilar (Ongavia) was considered as monotherapy in a scenario, it had the third highest NMB after bevacizumab and bevacizumab plus PRP; however, it was dominated by bevacizumab with or without PRP. Table 36 shows the ranking of treatments by NMB at £20,000 per QALY under the confidential prices.

The committee considered the probabilistic results presented in section 0 when drafting recommendations because of the large confidence intervals associated with the NMA outputs for the mean difference in visual acuity, discussed in HE2.4.2.1.1.

**Table 34: PDR base-case deterministic cost-utility results compared with PRP (list price)**

| Strategy | Absolute | | Incremental | | | NMB |
| --- | --- | --- | --- | --- | --- | --- |
| | Costs | QALYs | Costs | QALYs | ICER | £20K/ QALY |
| PRP | £8,486 | 11.015 | - | - | - | £211,820 |
| Bevacizumab | £11,015 | 11.951 | £2,529 | 0.935 | £2,704 | £227,997 |
| Bevacizumab plus PRP | £15,213 | 11.909 | £6,726 | 0.893 | £7,529 | £222,960 |
| Ranibizumab | £25,522 | 11.754 | £17,035 | 0.739 | £23,052 | £209,564 |
| Ranibizumab plus PRP | £30,072 | 11.539 | £21,586 | 0.524 | £41,214 | £200,709 |
| Aflibercept | £31,096 | 11.623 | £22,610 | 0.608 | £37,181 | £201,372 |

*NMB: Net monetary benefit*

<Please insert your copyright statement - one line of text entry only>

**Table 35: PDR base-case deterministic fully incremental cost-utility results (list price)**

| Strategy | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER |
| PRP | £8,486 | 11.015 | - | - | - |
| Bevacizumab | £11,015 | 11.951 | £2,529 | 0.935 | £2,704 |
| Bevacizumab plus PRP | £15,213 | 11.909 | £4,198 | -0.042 | Dominated |
| Ranibizumab | £25,522 | 11.754 | £14,506 | -0.196 | Dominated |
| Ranibizumab plus PRP | £30,072 | 11.539 | £19,057 | -0.412 | Dominated |
| Aflibercept | £31,096 | 11.623 | £20,081 | -0.327 | Dominated |

**Table 36: PDR treatments ranked by NMB at £20,000 per QALY (deterministic, confidential prices)**

| NMB rank | Treatment |
|---|---|
| 1: Highest NMB | Bevacizumab |
| 2 | Bevacizumab plus PRP |
| 3 | Ranibizumab biosimilar* |
| 4 | Aflibercept |
| 5 | Ranibizumab |
| 6 | PRP |
| 7 | Ranibizumab biosimilar* plus PRP |
| 8: Lowest NMB | Ranibizumab plus PRP |

*Ranibizumab biosimilar (Ongavia) was included as a scenario only*

## HE3.1.2 Probabilistic sensitivity analysis

In the base-case probabilistic analysis using list prices for the anti-VEGF therapies, it was found that bevacizumab plus PRP had the lowest ICER (£8,947 per QALY) and bevacizumab monotherapy had the second lowest ICER (£9,883 per QALY), compared with PRP alone. Bevacizumab plus PRP had the highest NMB (£221,374), bevacizumab monotherapy had the second highest NMB (£216,410) and PRP alone had the third highest NMB (£212,190) at the £20,000 per QALY gained threshold. These results were fairly congruent with the deterministic results, with probabilistic results having slightly higher costs in all treatments, and small differences in absolute QALYs. The only exception to this was for bevacizumab monotherapy, where the probabilistic results reported 0.5 fewer QALYs, and therefore resulting in bevacizumab monotherapy being ranked lower on NMB than bevacizumab plus PRP. In the NMA results, bevacizumab had the largest confidence interval around the treatment effect, and this is likely where the variation in QALYs stemmed from. The probabilistic base-case results are presented in Table 37. It should be noted that these results were not used by the committee when drafting recommendations for this review question, as they do not take into account the confidential discounts associated with each of the anti-VEGF treatments.

The committee was also presented with the results of the probabilistic base-case and scenario analyses when the confidential PAS and commercial medicines unit discounts were applied in the model and these results were used as the basis for their recommendations. These results are not presented here because they are commercially sensitive, so are described qualitatively and treatments were ranked in order of NMB at £20,000 per QALY. When these discounts were applied, bevacizumab plus PRP and bevacizumab monotherapy still had the lowest and second lowest ICERs, respectively, with both below NICE's £20,000 per QALY gained threshold. Aflibercept and ranibizumab had ICERs between £20,000 and

<Please insert your copyright statement - one line of text entry only>

£25,000 per QALY. When the confidential price of the ranibizumab biosimilar (Ongavia) was considered, this had an ICER below £20,000 per QALY and produced the second highest NMB. Table 38 shows the ranking of treatments by NMB at £20,000 per QALY under the confidential prices.

**Table 37: PDR base-case probabilistic cost-utility results (list price)**

| Strategy | Absolute (95% CI) | | Incremental | | | NMB |
| --- | --- | --- | --- | --- | --- | --- |
| | Costs | QALYs | Costs | QALYs | ICER | £20K/QALY (95% CI) |
| PRP | £8,493 (£7,102 to £10,078) | 11.034 (10.268 to 11.702) | - | - | - | £212,190 (£196,602 to £225,597) |
| Bevacizumab | £12,615 (£8,808 to £17,655) | 11.451 (9.990 to 12.578) | £4,122 | 0.417 | £9,883 | £216,410 (£183,744 to £239,858) |
| Bevacizumab plus PRP | £15,926 (£11,895 to £20,494) | 11.865 (11.066 to 12.686) | £7,433 | 0.831 | £8,947 | £221,374 (£203,941 to £238,388) |
| Ranibizumab | £26,435 (£21,442 to £32,483) | 11.673 (10.805 to 12.514) | £17,942 | 0.639 | £28,099 | £207,018 (£188,241 to £224,329) |
| Ranibizumab plus PRP | £30,870 (£24,617 to £38,010) | 11.515 (10.643 to 12.315) | £22,377 | 0.481 | £46,538 | £199,430 (£180,774 to £215,929) |
| Aflibercept | £32,114 (£25,757 to £39,837) | 11.565 (10.510 to 12.482) | £23,621 | 0.531 | £44,523 | £199,180 (£176,962 to £218,849) |

NMB: Net monetary benefit

**Table 38: PDR treatments ranked by NMB at £20,000 per QALY (probabilistic, confidential prices)**

| NMB rank | Treatment |
| --- | --- |
| 1: Highest NMB | Bevacizumab plus PRP |
| 2 | Ranibizumab biosimilar* |
| 3 | Bevacizumab |
| 4 | PRP |
| 5 | Aflibercept |
| 6 | Ranibizumab |
| 7 | Ranibizumab biosimilar* plus PRP |
| 8: Lowest NMB | Ranibizumab plus PRP |

*Ranibizumab biosimilar (Ongavia) was included as a scenario only*

A scatter plot of the expected costs and QALYs for each of the 1,000 simulations is presented in Figure HE005. The graph shows that whilst the number of QALYs generated are similar across treatment strategies, PRP is associated with the lowest costs, followed by bevacizumab.

A cost-effectiveness acceptability curve (CEAC) was generated from the PSA and is presented in Figure HE006. The graph shows that if the willingness-to-pay threshold is below approximately £7,000 per QALY, PRP is the strategy most likely to be cost-effective.

<Please insert your copyright statement - one line of text entry only>

Between a threshold of £7,000 and £17,000 per QALY, bevacizumab monotherapy may be considered the most cost-effective strategy, and at thresholds above £17,000 bevacizumab plus PRP is likely to be most cost-effective strategy. The CEAC followed a very similar shape and order of treatments when the confidential prices were considered.
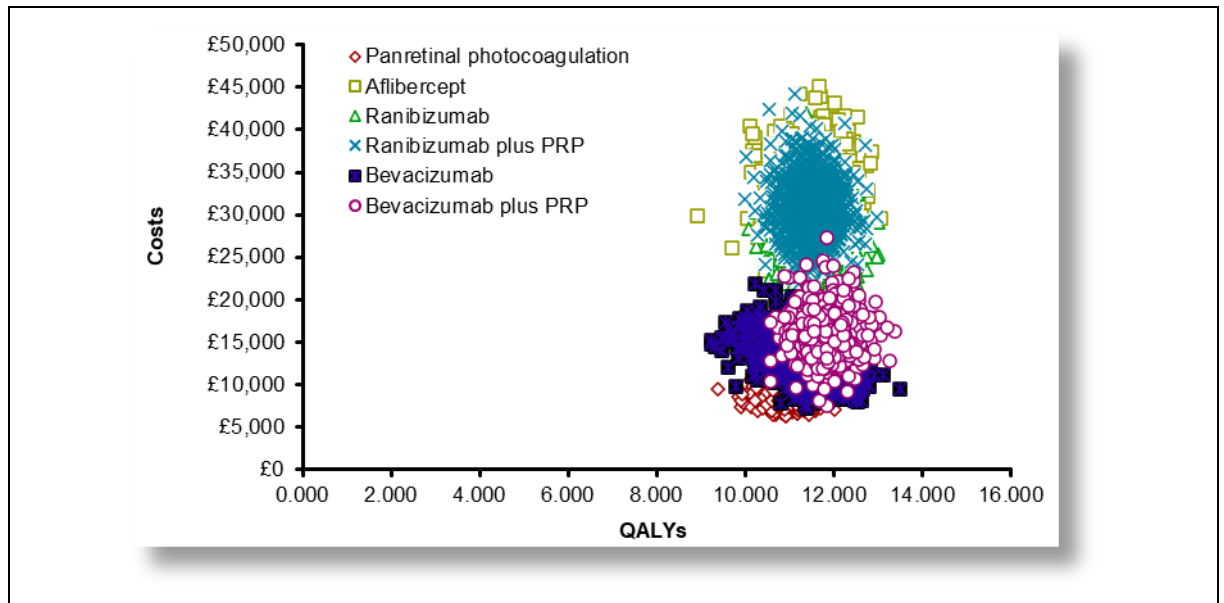


**Figure HE005: PDR base-case probabilistic results (list price) – scatter plot of expected costs and QALYs obtained from PSA**
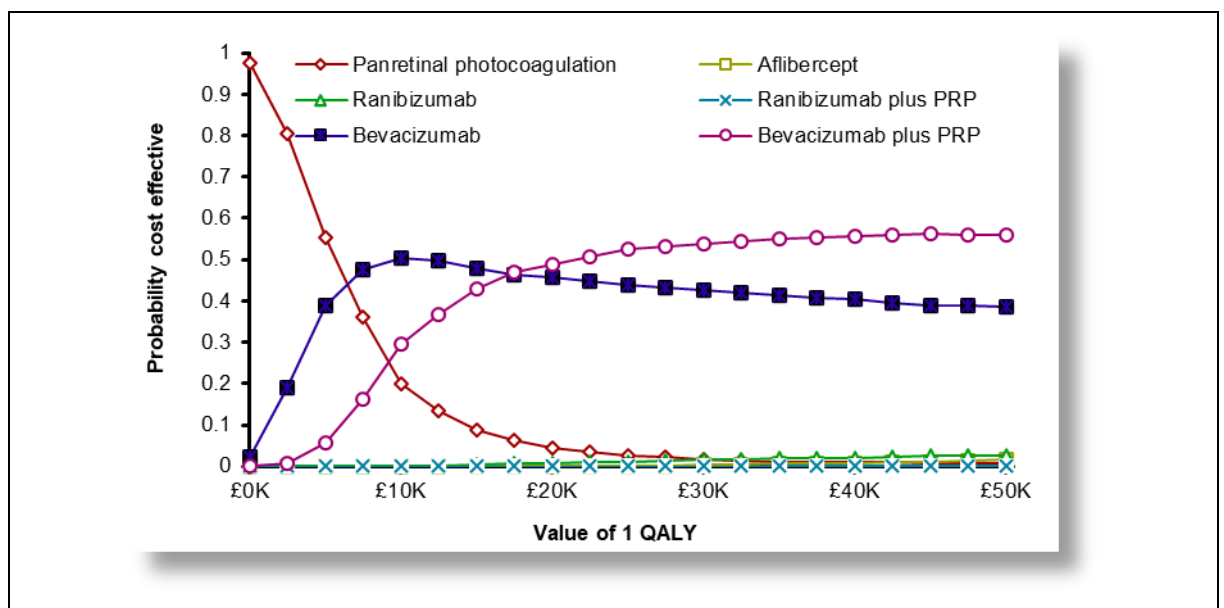


**Figure HE006: PDR base-case probabilistic results (list price) – cost-effective acceptability curve**

### HE3.1.3   Scenario analysis

Table 39 contains a summary of the probabilistic scenario analysis results at list price for the PDR population, including the three treatments with the highest NMBs for each scenario at the £20,000 per QALY gained threshold. Bevacizumab plus PRP had the highest NMB for all scenarios, this remained true when the confidential prices were also considered. Bevacizumab was found to have the second highest NMB in most scenarios at list price

<Please insert your copyright statement - one line of text entry only>

except for when treatment efficacy was assumed to end after five years, and the natural history was applied beyond that point in time. In that scenario, PRP became the second highest ranked based on NMB. When the confidential prices were considered ranibizumab became the second highest ranked based on NMB and when the confidential cost of the ranibizumab biosimilar (Ongavia) was considered bevacizumab dropped to the third highest ranked by NMB.

PRP was the third highest ranked based on NMB except for some of the scenarios when alternative utility sources were used, which highlights that the model was sensitive to changes in the utility source used. When the number of monitoring and treatment visits were reduced and when patient costs were included ranibizumab again became the third highest ranked by NMB because ranibizumab and other anti-VEGF treatments were sensitive to the changes in assumptions around the frequency of treatments and monitoring visits as this was a large driver of costs associated with anti-VEGF treatments. When the confidential prices were considered ranibizumab became the third highest ranked when the proportion of patients expected to continue treatment beyond five years is reduced to five years and when the utility source by Lloyd et al (2008) was used. Aflibercept became the third highest ranked by NMB when the monitoring and treatment visit frequency was assumed to be 20% lower.

**Table 39: Summary of scenario analysis results at list price – PDR**

| Scenario | Treatment ranking best (NMB) | Treatment ranking second best (NMB) | Treatment ranking third best (NMB) |
|---|---|---|---|
| Base-case | Bevacizumab plus PRP (£221,374) | Bevacizumab (£216,410) | PRP (£212,190) |
| Treatment and monitoring visits are separate | Bevacizumab plus PRP (£219,093) | Bevacizumab (£214,408) | PRP (£211,118) |
| Utility for treatment in both eyes: weighted average of BSE and WSE | Bevacizumab plus PRP (£222,041) | Bevacizumab (£218,208) | PRP (£214,760) |
| Utility source: Sharma et al (2002) | Bevacizumab plus PRP (£243,463) | Bevacizumab (£231,480) | Ranibizumab (£225,346) |
| Utility source: Lloyd et al (2008) | Bevacizumab plus PRP (£213,001) | Bevacizumab (£206,330) | PRP (£198,558) |
| Utility source: Mitchell et al (2012) | Bevacizumab plus PRP (£228,150) | Bevacizumab (£223,568) | PRP (£218,905) |
| Utility source: Czoski-Murray et al (2009) | Bevacizumab plus PRP (£210,503) | Bevacizumab (£199,020) | Ranibizumab (£193,835) |
| Utility source: Pennington et al (2020) | Bevacizumab plus PRP (£187,396) | Bevacizumab (£178,702) | Ranibizumab (£171,439) |
| 25% of patients receive treatment after year 5 | Bevacizumab plus PRP (£224,514) | Bevacizumab (£218,404) | PRP (£213,377) |
| 75% of patients receive treatment after year 5 | Bevacizumab plus PRP (£217,847) | Bevacizumab (£214,647) | PRP (£210,364) |
| Natural history assumed at 20 years | Bevacizumab plus PRP (£220,706) | Bevacizumab (£216,369) | PRP (£212,110) |
| Natural history assumed at 10 years | Bevacizumab plus PRP (£216,778) | Bevacizumab (£214,660) | PRP (£211,747) |
| Natural history assumed at 5 years | Bevacizumab plus PRP (£212,037) | PRP (£211,822) | Bevacizumab (£211,592) |
| Monitoring and treatment visits reduced by 20% | Bevacizumab plus PRP (£224,801) | Bevacizumab (£218,518) | Ranibizumab (£212,690) |

<Please insert your copyright statement - one line of text entry only>

| Scenario | Treatment ranking best (NMB) | Treatment ranking second best (NMB) | Treatment ranking third best (NMB) |
|---|---|---|---|
| Monitoring and treatment visits increased by 20% | Bevacizumab plus PRP (£219,818) | Bevacizumab (£215,819) | PRP (£211,628) |
| Patient costs included | Bevacizumab plus PRP (£219,186) | Bevacizumab (£203,427) | Ranibizumab (£201,969) |
| Biosimilar price for ranibizumab (Ongavia) | Bevacizumab plus PRP (£221,416) | Bevacizumab (£216,000) | PRP (£212,028) |

# HE3.2  Results – diabetic macular oedema, all centre involving

## HE3.2.1  Base-case cost-utility results

The results of the base-case deterministic analysis using the list prices for the treatment of centre involving DMO compared with no treatment are presented in Table 40. The fully incremental results are presented in Table 41. In the base-case analysis, subthreshold laser had the lowest ICER of £1,580 per QALY. From the incremental analysis, bevacizumab had an ICER of £16,256 per QALY. It should be noted that these results were not used by the committee when drafting recommendations for this review question as they do not take into account the confidential prices associated with each treatment.

When the confidential prices for treatments were used, brolucizumab, aflibercept and dexamethasone had ICERs below £20,000 per QALY compared with no treatment. Both ranibizumab and faricimab had ICERs between £20,000 and £25,000 per QALY compared with no treatment. Both types of laser treatment had higher NMBs at £20,000 per QALY than all anti-VEGF treatments except bevacizumab. When the confidential price of ranibizumab biosimilar (Ongavia) was used, the ICERs were below £20,000 per QALY for both monotherapy and in combination with standard threshold laser. Table 42 shows the ranking of treatments by NMB at £20,000 per QALY under the confidential prices.

The probabilistic results were considered by the committee when drafting recommendations to account for the uncertainty based on the confidence intervals from the NMA outputs of the mean difference in visual acuity compared with no treatment. Whilst these were smaller than those in the PDR population for RQ5, for consistency within the guideline, recommendations were based on the probabilistic results.

**Table 40: DMO (all centre involving): base-case deterministic cost-utility results compared with no treatment (list price)**

| Strategy | Absolute | | Incremental | | | NMB |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | £20K/ QALY |
| No treatment | £3,662 | 8.495 | - | - | - | £166,235 |
| Subthreshold laser | £4,453 | 8.996 | £791 | 0.501 | £1,580 | £175,460 |
| Standard threshold laser | £4,908 | 9.007 | £1,247 | 0.512 | £2,434 | £175,233 |
| Bevacizumab | £8,339 | 9.235 | £4,677 | 0.740 | £6,322 | £176,355 |
| Bevacizumab plus standard laser | £10,608 | 9.277 | £6,946 | 0.782 | £8,883 | £174,929 |
| Dexamethasone | £17,536 | 9.214 | £13,875 | 0.719 | £19,304 | £166,735 |
| Ranibizumab | £23,022 | 9.248 | £19,361 | 0.753 | £25,695 | £161,944 |
| Brolucizumab | £23,952 | 9.304 | £20,290 | 0.809 | £25,087 | £162,121 |

<Please insert your copyright statement - one line of text entry only>

| Strategy | Absolute | | Incremental | | | NMB |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | £20K/QALY |
| Ranibizumab plus standard laser | £24,083 | 9.231 | £20,421 | 0.736 | £27,743 | £160,535 |
| Aflibercept | £33,120 | 9.287 | £29,458 | 0.792 | £37,194 | £152,617 |
| Faricimab | £33,440 | 9.296 | £29,779 | 0.801 | £37,160 | £152,484 |
| Fluocinolone acetonide | £58,032 | 9.223 | £54,370 | 0.728 | £74,643 | £126,433 |

*NMB: Net monetary benefit*

**Table 41: DMO (all centre involving): fully incremental base-case deterministic cost-utility results (list price)**

| Strategy | Absolute | | Incremental | | | NMB |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | £20K/QALY |
| No treatment | £3,662 | 8.495 | - | - | - | £166,235 |
| Subthreshold laser | £4,453 | 8.996 | £791 | 0.501 | £1,580 | £175,460 |
| Standard threshold laser | £4,908 | 9.007 | £455 | 0.011 | Extendedly dominated | £175,233 |
| Bevacizumab | £8,339 | 9.235 | £3,886 | 0.239 | £16,256 | £176,355 |
| Bevacizumab plus standard laser | £10,608 | 9.277 | £2,269 | 0.042 | £53,879 | £174,929 |
| Dexamethasone | £17,536 | 9.214 | £6,928 | -0.063 | Dominated | £166,735 |
| Ranibizumab | £23,022 | 9.248 | £12,414 | -0.029 | Dominated | £161,944 |
| Brolucizumab | £23,952 | 9.304 | £13,344 | 0.027 | £497,826 | £162,121 |
| Ranibizumab plus standard laser | £24,083 | 9.231 | £131 | -0.073 | Dominated | £160,535 |
| Aflibercept | £33,120 | 9.287 | £9,168 | -0.017 | Dominated | £152,617 |
| Faricimab | £33,440 | 9.296 | £9,489 | -0.007 | Dominated | £152,484 |
| Fluocinolone acetonide | £58,032 | 9.223 | £34,080 | -0.080 | Dominated | £126,433 |

*NMB: Net monetary benefit*

**Table 42: DMO (all centre involving) treatments ranked by NMB at £20,000 per QALY (deterministic, confidential prices)**

| NMB rank | Treatment |
|---|---|
| 1: Highest NMB | Bevacizumab |
| 2 | Subthreshold laser |
| 3 | Standard threshold laser |
| 4 | Bevacizumab plus standard laser |
| 5 | Ranibizumab biosimilar* |
| 6 | Brolucizumab |
| 7 | Ranibizumab biosimilar* plus standard laser |
| 8 | Dexamethasone |
| 9 | Aflibercept |
| 10 | No treatment |

<Please insert your copyright statement - one line of text entry only>

| NMB rank | Treatment |
|---|---|
| 11 | Ranibizumab |
| 12 | Faricimab |
| 13 | Ranibizumab plus standard laser |
| 14: Lowest NMB | Fluocinolone acetonide |

*Ranibizumab biosimilar (Ongavia) was included as a scenario only*

## HE3.2.2 Probabilistic sensitivity analysis

In the base-case probabilistic analysis using list prices for the anti-VEGF therapies and fluocinolone acetonide, subthreshold laser had the lowest ICER of £1,248 per QALY compared with no treatment. The probabilistic base-case fully incremental results are presented in Table 43. The probabilistic results were fairly similar to the deterministic results, with dexamethasone, ranibizumab plus standard laser, faricimab, aflibercept and fluocinolone acetonide remaining dominated, and the two macular lasers and bevacizumab had the three highest NMB values. Macular laser treatments are not suitable for all people within this population, for example those with thicker retinas or with visual impairment, and for this reason the probabilistic base-case results compared with no treatment are also presented in Table 44. Whilst subthreshold laser treatment still had the lowest ICER compared with no treatment (and standard threshold laser had the second lowest ICER), bevacizumab monotherapy also had an ICER of £7,741 per QALY in people for whom laser therapy is not suitable. It should be noted that these results were not used by the committee when drafting recommendations for this review question, as they do not take into account the confidential discounts associated with each of the anti-VEGF treatments and for fluocinolone acetonide.

The committee was also presented with the results of the probabilistic base-case and scenario analyses when the confidential PAS discounts were applied in the model, and these results were used as the basis for their recommendations. These results cannot be presented here because they are commercially sensitive but are discussed qualitatively. When these discounts were applied, the two types of macular laser had the highest NMBs. Bevacizumab and brolucizumab could also be considered cost effective compared with no treatment in people for whom laser treatment is not suitable, with an ICER below £20,000 per QALY. Additionally, when the confidential PAS discounts were applied, the cost-effectiveness conclusions for the other anti-VEGF therapies remained unchanged at the £20,000 per QALY gained threshold. When the confidential price of ranibizumab biosimilar (Ongavia) was considered, it became cost effective as both monotherapy and in combination with standard threshold laser with an ICER below £20,000 per QALY. However, dexamethasone, aflibercept, ranibizumab and faricimab all had ICERs below £25,000 per QALY, whilst fluocinolone had an ICER above £30,000 per QALY. Table 45 shows the ranking of treatments by NMB at £20,000 per QALY under the confidential prices.

**Table 43: DMO (all centre involving) base-case probabilistic fully incremental cost-utility results (list price)**

| Strategy | Absolute (95% CI) | | Incremental | | | NMB |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | £20K/QALY (95% CI) |
| No treatment | £3,843 (£2,651 to £5,329) | 8.485 (7.841 to 9.150) | - | - | - | £165,850 (£152,520 to £179,419) |
| Subthreshold laser | £4,431 (£3,271 to £6,065) | 8.956 (8.274 to 9.666) | £588 | 0.471 | £1,248 | £174,682 (£160,969 to £188,956) |

<Please insert your copyright statement - one line of text entry only>

| Strategy | Absolute (95% CI) | | Incremental | | | NMB |
| | Costs | QALYs | Costs | QALYs | ICER | £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| Standard threshold laser | £4,823 (£3,565 to £6,483) | 8.976 (8.322 to 9.640) | £392 | 0.020 | £19,272 | £174,697 (£161,500 to £188,126) |
| Bevacizumab | £9,385 (£6,342 to £14,401) | 9.201 (8.581 to 9.841) | £4,562 | 0.225 | £20,318 | £174,625 (£161,698 to £188,032) |
| Bevacizumab plus standard laser | £11,408 (£7,685 to £15,946) | 9.216 (8.577 to 9.881) | £2,023 | 0.015 | £133,549 | £172,905 (£159,025 to £186,478) |
| Dexamethasone | £17,780 (£14,541 to £21,450) | 9.177 (8.570 to 9.829) | £6,372 | -0.038 | Dominated | £165,767 (£152,852 to £178,340) |
| Ranibizumab | £23,920 (£19,178 to £30,419) | 9.220 (8.599 to 9.882) | £12,511 | 0.004 | Extendedly dominated | £160,471 (£147,567 to £173,477) |
| Brolucizumab | £24,360 (£19,554 to £29,514) | 9.266 (8.640 to 9.903) | £12,952 | 0.051 | £256,445 | £160,963 (£147,392 to £174,636) |
| Ranibizumab plus standard laser | £24,693 (£19,590 to £30,771) | 9.199 (8.582 to 9.840) | £333 | -0.067 | Dominated | £159,295 (£146,028 to £173,040) |
| Faricimab | £33,947 (£27,031 to £41,474) | 9.266 (8.644 to 9.915) | £9,587 | 0.000 | Dominated | £151,368 (£137,455 to £166,067) |
| Aflibercept | £34,388 (£26,890 to £43,154) | 9.258 (8.637 to 9.903) | £10,028 | -0.008 | Dominated | £150,771 (£136,228 to £165,577) |
| Fluocinolone acetonide | £51,400 (£40,190 to £64,645) | 9.186 (8.578 to 9.838) | £27,040 | -0.080 | Dominated | £132,319 (£114,734 to £148,611) |

NMB: Net monetary benefit

**Table 44: DMO (all centre involving) base-case probabilistic cost-utility results compared with no treatment**

| Strategy | Absolute | | Incremental | | |
| | Costs | QALYs | Costs | QALYs | ICER |
|---|---|---|---|---|---|
| No treatment | £3,843 | 8.485 | - | - | - |
| Subthreshold laser | £4,431 | 8.956 | £588 | 0.471 | £1,248 |
| Standard threshold laser | £4,823 | 8.976 | £980 | 0.491 | £1,994 |
| Bevacizumab | £9,385 | 9.201 | £5,542 | 0.716 | £7,741 |
| Bevacizumab plus standard laser | £11,408 | 9.216 | £7,565 | 0.731 | £10,349 |
| Dexamethasone | £17,780 | 9.177 | £13,937 | 0.693 | £20,121 |
| Ranibizumab | £23,920 | 9.220 | £20,076 | 0.735 | £27,319 |
| Brolucizumab | £24,360 | 9.266 | £20,517 | 0.781 | £26,253 |
| Ranibizumab plus standard laser | £24,693 | 9.199 | £20,849 | 0.715 | £29,172 |

<Please insert your copyright statement - one line of text entry only>

| Strategy | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER |
| Faricimab | £33,947 | 9.266 | £30,104 | 0.781 | £38,541 |
| Aflibercept | £34,388 | 9.258 | £30,545 | 0.773 | £39,500 |
| Fluocinolone acetonide | £51,400 | 9.186 | £47,557 | 0.701 | £67,813 |

**Table 45: DMO (all centre involving) treatments ranked by NMB at £20,000 per QALY (probabilistic, confidential prices)**

| NMB rank | Treatment |
|---|---|
| 1: Highest NMB | Standard threshold laser |
| 2 | Subthreshold laser |
| 3 | Bevacizumab |
| 4 | Bevacizumab plus standard laser |
| 5 | Ranibizumab biosimilar* |
| 6 | Brolucizumab |
| 7 | Ranibizumab biosimilar* plus standard laser |
| 8 | No treatment |
| 9 | Dexamethasone |
| 10 | Aflibercept |
| 11 | Ranibizumab |
| 12 | Faricimab |
| 13 | Ranibizumab plus standard laser |
| 14: Lowest NMB | Fluocinolone acetonide |

*Ranibizumab biosimilar (Ongavia) was included as a scenario only*

A scatter plot of the expected costs and QALYs for each of the 1,000 simulations is presented in Figure HE007. The graph shows the QALY gains are similar across most treatments, but they are lowest for no treatment and both standard threshold laser and subthreshold laser. The main differences between treatments are the costs with no treatment and both laser treatments having the lowest costs. Bevacizumab was found to be the anti-VEGF with the lowest costs and fluocinolone acetonide was associated with the highest costs and found to be the least cost effective across all treatments included within the analysis.

<Please insert your copyright statement - one line of text entry only>
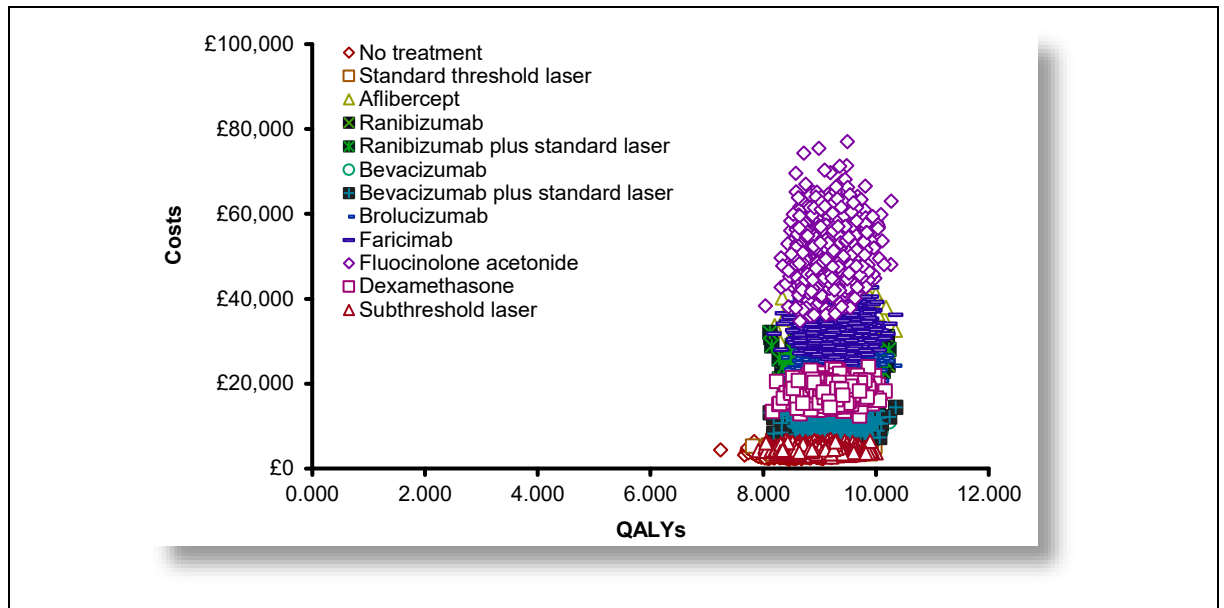
**Figure HE007: DMO (all centre involving) base-case probabilistic results (list price) – scatter plot of expected costs and QALYs obtained from PSA**

A cost-effectiveness acceptability curve was generated from the PSA for all centre involving DMO and is presented in Figure HE008. The graph shows that if the willingness-to-pay threshold is below £27,000 per QALY, then subthreshold laser is likely to be the most cost-effective strategy. If the willingness-to-pay threshold is above £27,000, then bevacizumab is likely to be the most cost-effective strategy. These results did not change when the confidential prices were considered.
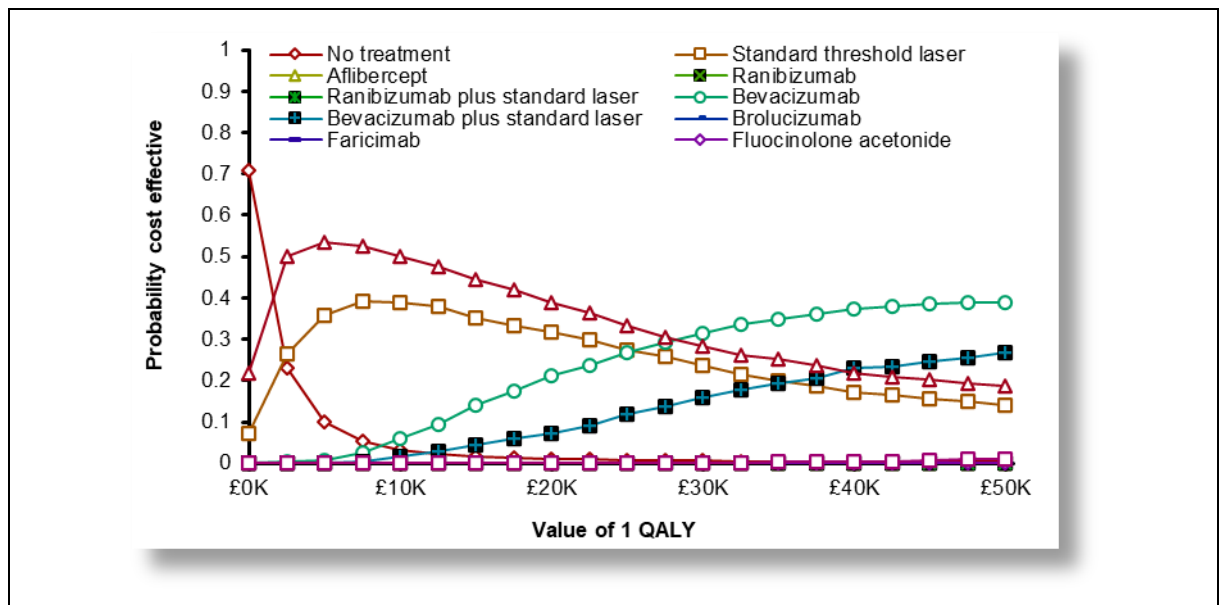


**Figure HE008: DMO (all centre involving) base-case probabilistic results – cost-effective acceptability curve**

## HE3.2.3   Scenario analysis

Table 46 contains a summary of the probabilistic scenario analysis results at list price for all centre involving DMO population, including the three treatments with the highest NMBs for each scenario at the £20,000 per QALY gained threshold. Subthreshold laser had the highest ranking based on NMB and standard threshold laser had the second highest ranking

<Please insert your copyright statement - one line of text entry only>

across most scenarios, with very little difference between the two macular laser types. Bevacizumab was found to be the third most cost effective based on NMB in the majority of scenarios.

Bevacizumab became the highest ranked by NMB when the utility source was changed to Sharma et al (2002), although it should be noted that there was very little difference between the top three highest ranked by NMB. Bevacizumab became the highest ranked by NMB when a lower proportion (25%) of patients were assumed to remain on treatment after five years, as well as when the scenarios assuming fewer monitoring and treatment visits were applied.

When the confidential prices were considered, the results in terms of highest ranked by NMB were largely unchanged. Subthreshold laser remained the treatment with the highest NMB in most scenario analyses, but the cost-effectiveness difference was very small between the two macular laser types.

Additionally, bevacizumab became the highest ranked by NMB when patient costs were included, and the source of the sham arm used was restricted to Massin et al (2010).

**Table 46: Summary of scenario analysis results at list price – DMO (all centre involving)**

| Scenario | Treatment ranking best (NMB) | Treatment ranking second best (NMB) | Treatment ranking third best (NMB) |
|---|---|---|---|
| Base-case | Standard laser (£174,697) | Subthreshold laser (£174,682) | Bevacizumab (£174,625) |
| Treatment and monitoring visits are separate | Subthreshold laser (£174,667) | Standard laser (£174,473) | Bevacizumab (£173,055) |
| Utility for treatment in both eyes: weighted average of BSE and WSE | Subthreshold laser (£180,152) | Standard laser (£179,711) | Bevacizumab (£178,748) |
| Utility source: Sharma et al (2002) | Bevacizumab (£199,834) | Subthreshold laser (£199,308) | Standard laser (£199,183) |
| Utility source: Lloyd et al (2008) | Subthreshold laser (£179,086) | Standard laser (£179,082) | Bevacizumab (£177,280) |
| Utility source: Mitchell et al (2012) | Subthreshold laser (£192,663) | Standard laser (£192,512) | Bevacizumab (£189,670) |
| Utility source: Brown et al (2000) | Subthreshold laser (£186,786) | Standard laser (£186,422) | Bevacizumab (£184,019) |
| Utility source: Pennington et al (2020) | Subthreshold laser (£156,816) | Standard laser (£156,523) | Bevacizumab (£155,871) |
| 25% of patients receive treatment after year 5 | Bevacizumab (£175,744) | Subthreshold laser (£174,745) | Standard laser (£174,586) |
| 75% of patients receive treatment after year 5 | Subthreshold laser (£174,788) | Standard laser (£174,623) | Bevacizumab (£174,231) |
| Natural history assumed at 20 years | Subthreshold laser (£174,837) | Standard laser (£174,543) | Bevacizumab (£174,258) |
| Natural history assumed at 10 years | Subthreshold laser (£172,872) | Standard laser (£172,662) | Bevacizumab (£171,836) |
| Natural history assumed at 5 years | Subthreshold laser (£169,685) | Standard laser (£169,321) | Bevacizumab (£167,047) |
| Monitoring and treatment frequency: minimum reported | Bevacizumab (£177,306) | Standard laser (£175,591) | Subthreshold laser (£175,520) |
| Monitoring and treatment frequency: maximum reported | Subthreshold laser (£174,250) | Standard laser (£173,689) | Bevacizumab (£172,726) |

<Please insert your copyright statement - one line of text entry only>

| Scenario | Treatment ranking best (NMB) | Treatment ranking second best (NMB) | Treatment ranking third best (NMB) |
|---|---|---|---|
| Monitoring and treatment frequency: assumed the same across anti-VEGFs | Bevacizumab (£176,268) | Subthreshold laser (£175,593) | Standard laser (£175,080) |
| Patient costs included | Bevacizumab (£174,021) | Bevacizumab plus standard laser (£172,661) | Standard laser (£171,991) |
| Source of sham arm change in BCVA from baseline: Massin et al (2010) | Bevacizumab (£173,321) | Subthreshold laser (£172,523) | Standard laser (£172,430) |
| Source of sham arm change in BCVA from baseline: Sultan et al (2010) | Subthreshold laser (£175,833) | Standard laser (£175,732) | Bevacizumab (£175,225) |
| Sham arm used as source of no treatment BCVA progression | Subthreshold laser (£175,273) | Bevacizumab (£175,057) | Standard laser (£175,046) |
| Sham arm used as source of long-term natural history BCVA progression | Standard laser (£175,118) | Bevacizumab (£175,024) | Subthreshold laser (£174,972) |
| Biosimilar price for ranibizumab (Ongavia) | Bevacizumab (£175,109) | Standard laser (£175,062) | Subthreshold laser (£174,979) |

## HE3.3 Results – diabetic macular oedema with a CRT≥400µm

### HE3.3.1 Base-case cost-utility results

The results of the subgroup analysis using the list prices for the treatment of centre involving DMO with a CRT≥400µm compared with no treatment are presented in Table 47 and the incremental analysis is presented in Table 48. Subthreshold laser had the lowest ICER of £1,776 per QALY; however, it should be noted that laser treatment may often be unsuitable for this subgroup. From the incremental results, bevacizumab was the only option that had an ICER below £20,000 per QALY at list price.

When the confidential prices for treatments were used, brolucizumab, aflibercept and dexamethasone had ICERs below £20,000 per QALY compared with no treatment. Both ranibizumab and faricimab had ICERs between £20,000 and £25,000 per QALY. When the confidential price of ranibizumab biosimilar (Ongavia) was used, the ICERs were below £20,000 per QALY for both monotherapy and in combination with standard threshold laser. Table 49 shows the ranking of treatments by NMB at £20,000 per QALY under the confidential prices.

The probabilistic results were considered by the committee when drafting recommendations to account for uncertainty within the parameters and for consistency across all review questions for this guideline.

**Table 47: DMO with a CRT≥400µm: deterministic cost-utility results compared with no treatment**

| Strategy | Absolute | | Incremental | | | NMB |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | £20K/ QALY |
| No treatment | £3,662 | 8.495 | - | - | - | £166,235 |
| Subthreshold laser | £4,483 | 8.957 | £821 | 0.462 | £1,776 | £174,662 |
| Standard threshold laser | £4,947 | 8.957 | £1,285 | 0.462 | £2,779 | £174,198 |
| Bevacizumab | £8,340 | 9.232 | £4,679 | 0.737 | £6,348 | £176,296 |

<Please insert your copyright statement - one line of text entry only>

| Strategy | Absolute | | Incremental | | | NMB |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | £20K/ QALY |
| Bevacizumab plus standard laser | £10,628 | 9.235 | £6,967 | 0.741 | £9,407 | £174,079 |
| Dexamethasone | £17,536 | 9.215 | £13,874 | 0.720 | £19,275 | £166,757 |
| Ranibizumab | £23,022 | 9.248 | £19,361 | 0.753 | £25,722 | £161,928 |
| Brolucizumab | £23,958 | 9.296 | £20,296 | 0.801 | £25,346 | £161,954 |
| Ranibizumab plus standard laser | £24,081 | 9.235 | £20,419 | 0.740 | £27,588 | £160,619 |
| Aflibercept | £33,119 | 9.288 | £29,458 | 0.793 | £37,141 | £152,640 |
| Faricimab | £33,440 | 9.297 | £29,778 | 0.802 | £37,127 | £152,498 |
| Fluocinolone acetonide | £58,031 | 9.224 | £54,370 | 0.729 | £74,536 | £126,454 |

**Table 48: DMO with a CRT≥400μm: fully incremental deterministic cost-utility results**

| Strategy | Absolute | | Incremental | | | NMB |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | £20K/ QALY |
| No treatment | £3,662 | 8.495 | - | - | - | £166,235 |
| Subthreshold laser | £4,483 | 8.957 | £821 | 0.462 | £1,776 | £174,662 |
| Standard threshold laser | £4,947 | 8.957 | £464 | 0.000 | Dominated | £174,198 |
| Bevacizumab | £8,340 | 9.232 | £3,857 | 0.275 | £14,049 | £176,296 |
| Bevacizumab plus standard laser | £10,628 | 9.235 | £2,288 | 0.004 | Extendedly dominated | £174,079 |
| Dexamethasone | £17,536 | 9.215 | £9,195 | -0.017 | Dominated | £166,757 |
| Ranibizumab | £23,022 | 9.248 | £14,682 | 0.016 | Extendedly dominated | £161,928 |
| Brolucizumab | £23,958 | 9.296 | £15,617 | 0.064 | £244,956 | £161,954 |
| Ranibizumab plus standard laser | £24,081 | 9.235 | £123 | -0.061 | Dominated | £160,619 |
| Aflibercept | £33,119 | 9.288 | £9,161 | -0.008 | Dominated | £152,640 |
| Faricimab | £33,440 | 9.297 | £9,482 | 0.001 | £7,272,435 | £152,498 |
| Fluocinolone acetonide | £58,031 | 9.224 | £24,591 | -0.073 | Dominated | £126,454 |

*NMB: Net monetary benefit*

**Table 49: DMO (CRT≥400μm) treatments ranked by NMB at £20,000 per QALY (deterministic, confidential prices)**

| NMB rank | Treatment |
|---|---|
| 1: Highest NMB | Bevacizumab |
| 2 | Subthreshold laser |
| 3 | Standard threshold laser |
| 4 | Bevacizumab plus standard laser |
| 5 | Ranibizumab biosimilar* |
| 6 | Brolucizumab |
| 7 | Ranibizumab biosimilar* plus standard laser |

<Please insert your copyright statement - one line of text entry only>

| NMB rank | Treatment |
|---|---|
| 8 | Dexamethasone |
| 9 | Aflibercept |
| 10 | No treatment |
| 11 | Ranibizumab |
| 12 | Faricimab |
| 13 | Ranibizumab plus standard laser |
| 14: Lowest NMB | Fluocinolone acetonide |

*Ranibizumab biosimilar (Ongavia) was included as a scenario only*

## HE3.3.2 Probabilistic sensitivity analysis

In the base-case probabilistic analysis for those with centre involving DMO and a CRT≥400µm using list prices for the anti-VEGF therapies and fluocinolone acetonide, subthreshold laser had the lowest ICER of £1,442 per QALY compared with no treatment. The probabilistic base-case fully incremental results are presented in Table 50 and the results compared with no treatment are presented in Table 51. Whilst subthreshold laser treatment had the lowest ICER compared with no treatment (and standard threshold laser had the second lowest ICER), bevacizumab monotherapy had an ICER of £7,746 per QALY in people for whom laser therapy is not suitable. It should be noted that these results were not used by the committee when drafting recommendations for this review question, as they do not take into account the confidential discounts associated with each of the anti-VEGF treatments and for fluocinolone acetonide.

The committee was also presented with the results of the probabilistic base-case and scenario analyses when the confidential PAS discounts were applied in the model, and these results were used as the basis for their recommendations. These results cannot be presented here because they are commercially sensitive. When these discounts were applied, subthreshold laser remained the treatment with the highest NMB, while standard threshold laser remained the treatment with the next highest NMB. The difference in cost-effectiveness was very small between the two macular laser types, it should be noted that the efficacy for subthreshold laser was assumed equivalent to standard threshold laser due to a lack of data for this population which would explain the limited difference. Bevacizumab and brolucizumab had ICERs below £20,000 per QALY compared with no treatment (in people for whom laser treatment is not suitable). Additionally, when the confidential PAS discounts were applied, the cost-effectiveness conclusions for the other anti-VEGF therapies remained unchanged at a £20,000 per QALY gained threshold. When the confidential price of ranibizumab biosimilar (Ongavia) was considered, the ICERs were below £20,000 per QALY for both monotherapy and in combination with standard threshold laser. Dexamethasone, aflibercept, ranibizumab and faricimab had ICERs below £25,000 per QALY, whilst fluocinolone had an ICER above £30,000 per QALY. Table 52 shows the ranking of treatments by NMB at £20,000 per QALY under the confidential prices.

**Table 50: DMO (CRT≥400µm) probabilistic fully incremental cost-utility results (list price)**

| Strategy | Absolute (95% CI) | | Incremental | | | NMB |
|---|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER | £20K/QALY (95% CI) |
| No treatment | £3,822 (£2,674 to £5,328) | 8.503 (7.856 to 9.199) | - | - | - | £166,238 (£152,957 to £180,234) |

<Please insert your copyright statement - one line of text entry only>

| Strategy | Absolute (95% CI) | | Incremental | | | NMB |
| | Costs | QALYs | Costs | QALYs | ICER | £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| Subthreshold laser | £4,458 (£3,291 to £5,881) | 8.944 (8.265 to 9.586) | £635 | 0.441 | £1,442 | £174,414 (£160,952 to £187,227) |
| Standard threshold laser | £4,919 (£3,661 to £6,453) | 8.928 (8.218 to 9.608) | £462 | -0.015 | Dominated | £173,646 (£159,605 to £187,244) |
| Bevacizumab | £9,308 (£6,168 to £14,365) | 9.211 (8.578 to 9.819) | £4,850 | 0.268 | £18,125 | £174,916 (£161,429 to £187,533) |
| Bevacizumab plus standard laser | £11,325 (£7,510 to £16,050) | 9.211 (8.558 to 9.828) | £2,017 | 0.000 | Extendedly dominated | £172,899 (£159,168 to £186,269) |
| Dexamethasone | £17,867 (£14,749 to £21,569) | 9.180 (8.514 to 9.814) | £8,559 | -0.031 | Dominated | £165,730 (£152,352 to £178,782) |
| Ranibizumab | £24,039 (£18,906, £30,678) | 9.224 (8.579, 9.846) | £14,731 | 0.012 | Extendedly dominated | £160,434 (£146,828 to £174,059) |
| Brolucizumab | £24,348 (£19,503 to £30,034) | 9.268 (8.621 to 9.881) | £15,040 | 0.057 | £263,607 | £161,016 (£147,669 to £173,755) |
| Ranibizumab plus standard laser | £24,904 (£19,416 to £31,299) | 9.209 (8.569 to 9.833) | £556 | -0.060 | Dominated | £159,268 (£145,571 to £172,882) |
| Faricimab | £33,979 (£27,159 to £41,856) | 9.271 (8.626 to 9.873) | £9,630 | 0.003 | £3,116,792 | £151,448 (£137,073 to £164,968) |
| Aflibercept | £34,522 (£27,494 to £43,642) | 9.267 (8.625 to 9.867) | £544 | -0.005 | Dominated | £150,813 (£136,809 to £164,845) |
| Fluocinolone acetonide | £51,480 (£40,585 to £64,948) | 9.193 (8.512 to 9.781) | £17,502 | -0.078 | Dominated | £132,389 (£115,368 to £148,012) |

**Table 51: DMO (CRT≥400µm) probabilistic cost-utility results compared with no treatment**

| Strategy | Absolute | | Incremental | | |
| | Costs | QALYs | Costs | QALYs | ICER |
|---|---|---|---|---|---|
| No treatment | £3,822 | 8.503 | - | - | - |
| Subthreshold laser | £4,458 | 8.944 | £635 | 0.441 | £1,442 |
| Standard threshold laser | £4,919 | 8.928 | £1,097 | 0.425 | £2,579 |
| Bevacizumab | £9,308 | 9.211 | £5,485 | 0.708 | £7,746 |
| Bevacizumab plus standard laser | £11,325 | 9.211 | £7,502 | 0.708 | £10,593 |
| Dexamethasone | £17,867 | 9.180 | £14,044 | 0.677 | £20,751 |
| Ranibizumab | £24,039 | 9.224 | £20,216 | 0.721 | £28,054 |
| Brolucizumab | £24,348 | 9.268 | £20,526 | 0.765 | £26,824 |

<Please insert your copyright statement - one line of text entry only>

| Strategy | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER |
| Ranibizumab plus standard laser | £24,904 | 9.209 | £21,081 | 0.706 | £29,878 |
| Faricimab | £33,979 | 9.271 | £30,156 | 0.768 | £39,250 |
| Aflibercept | £34,522 | 9.267 | £30,700 | 0.764 | £40,196 |
| Fluocinolone acetonide | £51,480 | 9.193 | £47,658 | 0.690 | £69,025 |

**Table 52: DMO (CRT≥400µm) treatments ranked by NMB at £20,000 per QALY (probabilistic, confidential prices)**

| NMB rank | Treatment |
|---|---|
| 1: Highest NMB | Subthreshold laser |
| 2 | Bevacizumab |
| 3 | Standard threshold laser |
| 4 | Bevacizumab plus standard laser |
| 5 | Ranibizumab biosimilar* |
| 6 | Brolucizumab |
| 7 | Ranibizumab biosimilar* plus standard laser |
| 8 | No treatment |
| 9 | Dexamethasone |
| 10 | Aflibercept |
| 11 | Ranibizumab |
| 12 | Faricimab |
| 13 | Ranibizumab plus standard laser |
| 14: Lowest NMB | Fluocinolone acetonide |

*Ranibizumab biosimilar (Ongavia) was included as a scenario only*

### HE3.3.3 Scenario analysis

The summary of the probabilistic scenario analysis results at list price for DMO with a CRT≥400µm are presented in Table 53. Similarly to the population of all centre involving DMO, subthreshold laser was the highest ranked based on NMB in the majority of scenarios. However, bevacizumab was the highest ranked in the base case analysis in addition to the same scenarios as above and when the sham arm was used as the source for natural history progression for both no treatment and for when treatment efficacy is assumed to have ended. Bevacizumab was not found to be as sensitive to the assumptions around the long-term use of treatment for the DMO population with a CRT≥400µm, since bevacizumab remained highest ranked for both the upper and lower bound assumption for the long-term use of treatment over 5 years.

**Table 53: Summary of scenario analysis results – DMO (CRT≥400µm)**

| Scenario | Treatment ranking best (NMB) | Treatment ranking second best (NMB) | Treatment ranking third best (NMB) |
|---|---|---|---|
| Base-case | Bevacizumab (£174,916) | Subthreshold laser (£174,414) | Standard laser (£173,646) |
| Treatment and monitoring visits are separate | Subthreshold laser (£173,774) | Standard laser (£173,553) | Bevacizumab (£172,929) |
| Utility for treatment in both eyes: weighted average of BSE and WSE | Subthreshold laser (£178,972) | Standard laser (£178,835) | Bevacizumab (£178,387) |

<Please insert your copyright statement - one line of text entry only>

| Scenario | Treatment ranking best (NMB) | Treatment ranking second best (NMB) | Treatment ranking third best (NMB) |
|---|---|---|---|
| Utility source: Sharma et al (2002) | Bevacizumab (£200,132) | Subthreshold laser (£199,070) | Standard laser (£198,397) |
| Utility source: Lloyd et al (2008) | Subthreshold laser (£178,164) | Standard laser (£177,895) | Bevacizumab (£176,468) |
| Utility source: Mitchell et al (2012) | Subthreshold laser (£191,947) | Standard laser (£191,528) | Bevacizumab (£189,286) |
| Utility source: Brown et al (2000) | Subthreshold laser (£186,481) | Standard laser (£186,032) | Bevacizumab (£184,094) |
| Utility source: Pennington et al (2020) | Subthreshold laser (£156,124) | Bevacizumab (£155,896) | Standard laser (£155,621) |
| 25% of patients receive treatment after year 5 | Bevacizumab (£175,816) | Bevacizumab plus standard laser (£174,313) | Subthreshold laser (£174,172) |
| 75% of patients receive treatment after year 5 | Bevacizumab (£174,689) | Subthreshold laser (£174,617) | Standard laser (£174,151) |
| Natural history assumed at 20 years | Bevacizumab (£174,859) | Subthreshold laser (£174,238) | Standard threshold laser (£173,961) |
| Natural history assumed at 10 years | Subthreshold laser (£172,451) | Standard laser (£171,984) | Bevacizumab (£171,813) |
| Natural history assumed at 5 years | Subthreshold laser (£169,896) | Standard laser (£169,513) | Bevacizumab (£167,528) |
| Monitoring and treatment frequency: minimum reported | Bevacizumab (£177,514) | Subthreshold laser (£174,987) | Standard laser (£174,647) |
| Monitoring and treatment frequency: maximum reported | Subthreshold laser (£172,953) | Standard laser (£172,497) | Bevacizumab (£171,971) |
| Monitoring and treatment frequency: assumed the same across anti-VEGFs | Bevacizumab (£176,056) | Subthreshold laser (£174,457) | Standard laser (£173,853) |
| Patient costs included | Bevacizumab (£173,661) | Bevacizumab plus standard laser (£171,788) | Subthreshold laser (£170,707) |
| Source of sham arm change in BCVA from baseline: Massin et al (2010) | Bevacizumab (£173,028) | Subthreshold laser (£171,753) | Bevacizumab plus standard laser (£171,032) |
| Source of sham arm change in BCVA from baseline: Sultan et al (2010) | Subthreshold laser (£175,421) | Bevacizumab (£175,130) | Standard laser (£174,927) |
| Sham arm used as source of no treatment BCVA progression | Bevacizumab (£174,604) | Subthreshold laser (£173,958) | Standard laser (£173,420) |
| Sham arm used as source of long-term natural history BCVA progression | Bevacizumab (£174,499) | Subthreshold laser (£173,835) | Standard laser (£173,548) |
| Biosimilar price for ranibizumab (Ongavia) | Bevacizumab (£174,748) | Subthreshold laser (£174,281) | Standard laser (£173,817) |

<Please insert your copyright statement - one line of text entry only>

# HE3.4  Discussion

## HE3.4.1  Principal findings

### Review question 5 – Proliferative diabetic retinopathy

The principal finding of the economic model based on the deterministic results was that bevacizumab had an ICER below £20,000 per QALY compared with PRP. However, bevacizumab is currently an off-label treatment for diabetic retinopathy. When available with the current commercial agreement, all anti-VEGFs including the ranibizumab biosimilar (Ongavia) also had ICERs below the £20,000 per QALY gained threshold compared with PRP. However, bevacizumab monotherapy was a dominant treatment strategy.

The cost-effectiveness results were associated with large uncertainty due to the wide confidence intervals around the NMA outputs for mean difference in visual acuity compared with PRP, particularly that of bevacizumab which was one of the strategies with the lowest ICER. There was also uncertainty in the treatment effects for aflibercept, bevacizumab and ranibizumab plus PRP, as their confidence intervals included zero. Given this uncertainty and the uncertainty associated with frequency and duration of anti-VEGF treatments, the committee used the results from PSA to account for some of the uncertainty associated with the wide confidence intervals alongside other considerations such as patient burden when making their recommendations.

The principal finding from the probabilistic analysis was that bevacizumab with or without PRP had the lowest ICERs of the strategies considered and these ICERs were below £20,000 per QALY gained. When considering the results based on the confidential prices, aflibercept and ranibizumab (Lucentis) had ICERs between £20,000 and £25,000 per QALY compared with PRP; however, ranibizumab biosimilar (Ongavia) had an ICER below £20,000 per QALY. It should be noted that the NICE reference case values QALYs at £20,000 but consideration can be given to therapies with an ICER between £20,000 and £30,000.

Parameters associated with treatment and monitoring frequency, duration of treatment and the source of utility mapping used were found to be the most influential drivers of the model, as identified in sensitivity analyses. Bevacizumab with or without PRP and PRP alone had the highest NMBs in the majority of scenarios explored (Table 39).

### Review question 7– Diabetic macular oedema

The principal finding of the economic model based on the probabilistic results was that subthreshold laser had an ICER below £20,000 per QALY compared with no treatment for patients with centre involving DMO. For those in which laser-based treatments may be unsuitable due to the proximity to the centre of the macular, bevacizumab was the only anti-VEGF with an ICER below £20,000 per QALY compared with no treatment.

When the confidential price discounts were applied, bevacizumab, ranibizumab biosimilar (Ongavia) and brolucizumab had ICERs below £20,000 per QALY. Dexamethasone, aflibercept, ranibizumab and faricimab had ICERs between £20,000 and £25,000 per QALY. Fluocinolone acetonide had an ICER above £30,000 per QALY. It should be noted that the NICE reference case values QALYs at £20,000 but consideration can be given to therapies with an ICER between £20,000 and £30,000 if there are additional benefits not captured by the economic analysis, for example reducing health inequalities or if there are few treatment options in a population. Given the number of available treatments in DMO, it is unlikely that a treatment with an ICER nearer to £30,000 would be considered a cost-effective use of resources.

When considering only those with centre involving DMO with a CRT≥400µm, which is the population the anti-VEGFs are licensed for, the conclusions remained unchanged.

<Please insert your copyright statement - one line of text entry only>

Parameters associated with treatment and monitoring frequency, duration of treatment and the source of utility mapping used were found to be the most influential drivers of the model, as identified in sensitivity analyses.

## HE3.4.2    Strengths of the analysis

A major strength of this analysis was that the results of network meta-analyses (including many clinical trials) informed the mean difference in visual acuity. Another key strength of this analysis was that the models allowed for the comparison of all available treatments in each indication and subgroup, which had not been addressed in the published literature. The analysis built on previous models, taking into account patients treated in their WSE, their BSE or both eyes, and using a lifetime time horizon, and allowing treatment to continue beyond five years which is broadly applicable to current clinical practice. All parameters used in the analyses were informed by clinical trials, published literature or assumption, and were verified by clinical experts to ensure the analyses reflected current clinical practice. The model results were robust to the majority of parameters explored in sensitivity analyses.

Where possible the analyses included all relevant costs associated with treatment such as subsequent treatment and treatment related adverse events which may not have previously been included, to most realistically model treatment pathways seen within clinical practice. The model results accounted for the anticipated long-term usage of anti-VEGFs which have not always been considered within the TAs, particularly now it is known they are used for much longer durations than initially considered in early published TAs.

## HE3.4.3    Limitations of the analysis

Generally, the available data on DMO or PDR are separated by condition, and therefore it was not possible to reflect the reality that an eye can start with either DMO or PDR and later develop the other condition which would have an impact on the treatments a person may receive, and on costs and QALYs accumulated over a person's lifetime. However, any impact of developing either of these conditions was expected to be captured within the BCVA transition probabilities. Furthermore, this is consistent with the approach taken in previous models published for both populations.

Whilst the analyses have the strength of including adverse events, the data on these may not reflect the true patient experience because of inconsistency in the reporting of adverse events. However, the overall costs and disutilities associated with adverse events are likely to be very small, and therefore unlikely to have a large impact on the conclusions drawn. Mitchell et al (2012) did not include adverse events in their analysis as it was assumed to have a negligible impact on the cost-effectiveness. Similarly, data is poorly reported for the distributions of subsequent treatment used. Based on the evidence available, an assumption was made that treatment switched between laser-based therapies and anti-VEGFs only, no within class switches were included such as to an alternative anti-VEGF. The committee discussed that in general people would usually switch classes rather than between classes such as to an alternative anti-VEGF for those previously receiving an anti-VEGF treatment. No data was available for the distribution of treatments for those switching from combination regimens or steroid treatments. The duration of subsequent treatment was limited to two years for both PDR (RQ5) and DMO (RQ7) populations. This was to not overweight the costs associated with subsequent treatment where there was a lot of uncertainty around the true distribution and duration of subsequent treatments. It is likely that the costs of subsequent treatment were underestimated as a result. However, the analysis had the benefit of being more representative of clinical practice by including subsequent treatment at all.

Given the nature of both PDR and DMO, it is common for both eyes to eventually be affected and require treatment. Since most clinical studies have published results only on the study eye, it was not possible to accurately apply a two-eye model, and therefore the modelled health states were based on one eye. Where possible the costs of treatment were applied to

account for the second eye. Whilst this may not most accurately reflect the disease profile of both PDR and DMO, the Markov model structure is widely used within the literature and NICE TAs. We are aware that previous NICE TAs were able to take a more granular approach to including the fellow eye, but given the lack of publicly available data it was not possible for the guideline development team to use this type of structure. Given the considerable heterogeneity between patient pathways and outcomes, a simulation model would best be able to reflect this. However, due to a lack of publicly available data, it was not possible to develop such a model.

### Review question 5 – Proliferative diabetic retinopathy

The model used for diabetic retinopathy was also limited by the fact that due to a lack of data in PDR some parameters had to be informed by published literature on DMO, mainly those around the long-term use of anti-VEGFs. The baseline visual acuity distribution was also based on a DMO source; however, all parameters were agreed by the committee as being representative for the PDR population in the absence of published data.

It should be noted that a general limitation of modelling proliferative diabetic retinopathy is that visual acuity does not necessarily capture all important outcomes, and that clinical features such as presence of new blood vessels are important in capturing progression. The limitation with modelling is that there generally isn't available data on these clinical features, or a way of mapping those features to quality of life outcomes, so it is not possible to develop analyses without using BCVA at the current time.

### Review question 7– Diabetic macular oedema

Macular laser therapy delivered using either a standard threshold laser or a subthreshold micropulse laser was included in the analysis for people with centre involving DMO population with a CRT≥400µm. Macular laser is generally not suitable for this subpopulation, but it was considered to be a relevant comparator by the committee when someone has good vision. Some studies included macular laser even when the population of interest was centre involving, so the committee specified that all interventions should be included in the analysis to reflect the whole evidence base. A limitation of this subgroup analysis was that although some studies were reported to be in people with CRT≥400, this was the mean CRT of the population, most of the studies did not separate people by more or less than 400 microns, and it was likely that some people included within the NMA would have had thinner retinas with a CRT<400. However, the downside of removing macular laser from the CRT≥400 subgroup was that it would have removed some of the data from the NMA, whereas with the full analysis more data were available to help compare the other treatment options. The mean difference in BCVA used to inform the economic model was formed using a much larger number of trials in the NMA than was used within the TAs. The NMA results found anti-VEGFs to be clinically effective compared with macular laser therapy or no treatment; however, it is possible this effect may be smaller than demonstrated in the TAs because of the wider population considered. Although anti-VEGFs were more clinically effective than either type of laser, both lasers came out as most cost-effective options since they were very cheap even when the confidential prices for anti-VEGFs were used. This may explain any differences in conclusions of cost-effectiveness of treatments, where the anti-VEGFs are recommended currently by NICE for those with a CRT≥400µm.

## HE3.4.4   Comparison with other cost-utility analyses

### Review question 5 – Proliferative diabetic retinopathy

One study (Hutton et al 2019) was identified for RQ5 and was considered partially applicable given it was conducted in a US setting. Hutton et al (2019) estimated that over a 10-year time horizon ranibizumab would be associated with a cost of £517,315 per QALY (converted to

GBP from USD) for the treatment of PDR without DMO, compared with PRP. The analysis for this guideline found a much lower cost per QALY compared with the results from Hutton et al (2019). This may be driven partly by the difference in time horizon and the treatment setting, although treatment duration was not found to be a key driver of results based on the sensitivity analysis.

**Review question 7– Diabetic macular oedema**

The economic model results are consistent with Mitchell et al (2012) which found ranibizumab monotherapy and ranibizumab in combination with laser therapy to be cost effective compared with standard threshold laser based on an ICER threshold of £30,000 per QALY. The results are also consistent with Haig et al (2016) which found ranibizumab monotherapy and ranibizumab in combination with laser therapy to be cost effective compared with standard threshold laser based on an ICER threshold of CA$50,000 per QALY. Furthermore, the results are consistent with Sharma et al (2000) which found standard threshold laser to be cost effective compared with no treatment based on a QALY being valued at $20,000, given the ICER for standard threshold laser compared with no treatment was much lower than this.

Lois et al (2022) found that whilst subthreshold laser did have slightly better efficacy compared with standard threshold laser, the differences were very small and the confidence intervals overlapped, hence the authors considered both treatments to be cost effective. The NMA results were informed by the DIAMOND clinical trial which the analysis by Lois et al (2022) was based on, whilst the standard threshold laser arm was informed by multiple studies including the DIAMOND study which may explain the very small differences in results between the two treatments. Overall, the differences in NMB were generally very small between the two laser types which is consistent with the findings from Lois et al (2022).

The Hutton et al (2023) analysis evaluated the cost-effectiveness of aflibercept monotherapy compared with bevacizumab as first line treatment followed by aflibercept if needed. The results from Hutton et al (2023) found aflibercept monotherapy not to be cost effective compared with bevacizumab as first line treatment, which, despite the slightly different comparison, is still consistent with the results from this current analysis that found aflibercept to be dominated by bevacizumab in the fully incremental analysis.

Régnier et al (2015) found both ranibizumab monotherapy as needed or as a treat and extend regimen to be both less expensive and more effective compared with aflibercept. Although at list price ranibizumab was less expensive, aflibercept had greater QALY gains both for the all centre involving population and the subgroup restricted to those with a CRT≥400μm. This difference may be explained by the BCVA efficacy; Régnier et al (2015) analysis was informed by the RESTORE trial only, whereas this current analysis was informed by a much larger number of clinical trials. Holekamp et al (2020) also found aflibercept could not be considered cost effective compared with the ranibizumab based on a US study setting. Whilst this analysis using the list prices aligns with the results, this cannot be extended to when the confidential prices are used, unless the ranibizumab biosimilar is used rather than ranibizumab. This is likely due to the difference in drug prices used within the analysis.

Pochopien et al (2019) found fluocinolone acetonide to be cost effective compared with dexamethasone for the treatment of vision impairment in people with DMO who had not responded to previous treatment and who had a psuedophakic lens. The analysis conducted for this guideline did not find fluocinolone to be cost effective; however, the population included within this analysis was not separated by lens type. Additionally, due to a lack of efficacy data for fluocinolone acetonide at 12 months, equal efficacy was assumed between dexamethasone and fluocinolone acetonide as agreed by the committee. These assumptions likely explain the difference in results between this analysis and Pochopien et al (2019).

Brown et al (2015) found ranibizumab to be cost effective compared with sham with an ICER of $4,587 (£3,186) per QALY, whereas this current analysis found ranibizumab to only be cost effective below an ICER threshold of £25,000 per QALY. When the ranibizumab biosimilar price was used then it became cost effective below an ICER of £20,000 per QALY.

# HE3.5    Conclusions

## HE3.5.1    Review question 5 – Diabetic retinopathy

Bevacizumab with or without PRP had the highest net monetary benefit at a threshold of £20,000 per QALY gained for people with PDR. Due to the limited availability of long-term clinical evidence on the effectiveness of anti-VEGF treatments for the treatment of PDR and the large confidence intervals associated with the NMA outputs which were based on small studies, PRP alone could not be ruled out as an option for first line therapy with the third highest net monetary benefit in both the base-case and across all probabilistic scenarios.

## HE3.5.2    Review question 7– Diabetic macular oedema

Subthreshold micropulse laser had the highest net monetary benefit at a threshold of £20,000 per QALY gained compared with no treatment for the treatment of centre involving DMO and in a subgroup analysis of those with DMO with a CRT of at least 400µm. Subthreshold laser remained the treatment option with the highest net monetary benefit in most scenarios, but the difference between the subthreshold and standard threshold laser types was very small. When considering the treatment for those whom laser therapies would not be suitable, for example those with thicker retinas, bevacizumab was found to be the dominant treatment strategy.

<Please insert your copyright statement - one line of text entry only>

# HE4  References

Kaltenthaler E, Tappenden P, Paisley S, Squires H. NICE DSU technical support document 13: identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. 2011. Available from www.nicedsu.org.uk.

National Institute for Health and Care Excellence (NICE). Developing NICE guidelines: the manual. 2018. Available from: www.nice.org.uk/process/pmg20.

National Institute for Health and Care Excellence (NICE). TA274: Ranibizumab for treating diabetic macular oedema. 2013. Available from: https://www.nice.org.uk/guidance/ta274

National Institute for Health and Care Excellence (NICE). TA301: Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy. 2013. Available from: https://www.nice.org.uk/guidance/ta301

National Institute for Health and Care Excellence (NICE). TA346: Aflibercept for treating diabetic macular oedema. 2015. Available from: https://www.nice.org.uk/guidance/ta346

National Institute for Health and Care Excellence (NICE). TA799: Faricimab for treating diabetic macular oedema. 2022. Available from: https://www.nice.org.uk/guidance/ta799

National Institute for Health and Care Excellence (NICE). TA820: Brolucizumab for treating diabetic macular oedema. 2022. Available from: https://www.nice.org.uk/guidance/ta820

National Institute for Health and Care Excellence (NICE). TA824: Dexamethasone intravitreal implant for treating diabetic macular oedema. 2022. Available from: https://www.nice.org.uk/guidance/ta824

Haig, Jennifer; Barbeau, Martin; Ferreira, Alberto (2016) Cost-effectiveness of ranibizumab in the treatment of visual impairment due to diabetic macular edema. Journal of medical economics 19(7): 663-71

Mitchell, Paul, Annemans, Lieven, Gallagher, Meghan et al. (2012) Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial. The British journal of ophthalmology 96(5): 688-93

Pochopien, Michal, Beiderbeck, Annette, McEwan, Phil et al. (2019) Cost-effectiveness of fluocinolone acetonide implant (ILUVIEN R) in UK patients with chronic diabetic macular oedema considered insufficiently responsive to available therapies. BMC health services research 19(1): 22

Regnier, S.A., Malcolm, W., Haig, J. et al. (2015) Cost-effectiveness of ranibizumab versus aflibercept in the treatment of visual impairment due to diabetic macular edema: A UK healthcare perspective. ClinicoEconomics and Outcomes Research 7: 235-247

Hutton, David W, Stein, Joshua D, Glassman, Adam R et al. (2019) Five-Year Cost-effectiveness of Intravitreous Ranibizumab Therapy vs Panretinal Photocoagulation for Treating Proliferative Diabetic Retinopathy: A Secondary Analysis of a Randomized Clinical Trial. JAMA ophthalmology 137(12): 1424-1432

National Institute for Health and Care Excellence (NICE). NG82 Age-related macular degeneration: diagnosis and management. 2018. Available from: https://www.nice.org.uk/guidance/ng82

Claxton, L., Hodgson, R., Taylor, M., Malcolm, B., & Pulikottil Jacob, R. (2017). Simulation Modelling in Ophthalmology: Application to Cost Effectiveness of Ranibizumab and Aflibercept for the Treatment of Wet Age-Related Macular Degeneration in the United Kingdom. PharmacoEconomics, 35(2), 237–248. https://doi.org/10.1007/s40273-016-0459-z

<Please insert your copyright statement - one line of text entry only>

National Institute for Health and care Excellence (NICE). British National Formulary (BNF). Published 2023. Accessed February, 2023. https://bnf.nice.org.uk/

Department of health and social care (2022): Drugs and pharmaceutical electronic market information tool (eMIT) [November 2022]. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

NHS England (2020) National Schedule of NHS Costs Year: 2019-20. Available from: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/

Personal Social Services Research Unit. Unit Costs of Health and Social Care 2021. Published online 2021. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/

Maturi, R. K., Glassman, A. R., Josic, K., Antoszyk, A. N., Blodi, B. A., Jampol, L. M., Marcus, D. M., Martin, D. F., Melia, M., Salehi-Had, H., Stockdale, C. R., Punjabi, O. S., Sun, J. K., & DRCR Retina Network (2021). Effect of Intravitreous Anti-Vascular Endothelial Growth Factor vs Sham Treatment for Prevention of Vision-Threatening Complications of Diabetic Retinopathy: The Protocol W Randomized Clinical Trial. JAMA ophthalmology, 139(7), 701–712. https://doi.org/10.1001/jamaophthalmol.2021.0606

Massin, P., Bandello, F., Garweg, J. G., Hansen, L. L., Harding, S. P., Larsen, M., Mitchell, P., Sharp, D., Wolf-Schnurrbusch, U. E., Gekkieva, M., Weichselberger, A., & Wolf, S. (2010). Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes care, 33(11), 2399–2405. https://doi.org/10.2337/dc10-0493

Lang, G.E., Stahl, A., Voegeler, J., Quiering, C., Lorenz, K., Spital, G. and Liakopoulos, S. (2020), Efficacy and safety of ranibizumab with or without panretinal laser photocoagulation versus laser photocoagulation alone in proliferative diabetic retinopathy – the PRIDE study. Acta Ophthalmol, 98: e530-e539. https://doi.org/10.1111/aos.14312

Sultan, M. B., Zhou, D., Loftus, J., Dombi, T., Ice, K. S., & Macugen 1013 Study Group (2011). A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. Ophthalmology, 118(6), 1107–1118. https://doi.org/10.1016/j.ophtha.2011.02.045

Office for National Statistics. National life tables: England 2018-2020. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables

Preis, S. R., Hwang, S. J., Coady, S., Pencina, M. J., D'Agostino, R. B., Sr, Savage, P. J., Levy, D., & Fox, C. S. (2009). 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, 119(13), 1728–1735. https://doi.org/10.1161/CIRCULATIONAHA.108.829176

Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross, J. G., Glassman, A. R., Jampol, L. M., Inusah, S., Aiello, L. P., Antoszyk, A. N., Baker, C. W., Berger, B. B., Bressler, N. M., Browning, D., Elman, M. J., Ferris, F. L., 3rd, Friedman, S. M., Marcus, D. M., Melia, M., Stockdale, C. R., Sun, J. K., & Beck, R. W. (2015). Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA, 314(20), 2137–2146. https://doi.org/10.1001/jama.2015.15217

Wykoff, C. C., Ou, W. C., Khurana, R. N., Brown, D. M., Lloyd Clark, W., Boyer, D. S., & ENDURANCE Study Group (2018). Long-term outcomes with as-needed aflibercept in diabetic macular oedema: 2-year outcomes of the ENDURANCE extension study. The British

<Please insert your copyright statement - one line of text entry only>

journal of ophthalmology, 102(5), 631–636. https://doi.org/10.1136/bjophthalmol-2017-310941

Brown, M. M., Brown, G. C., Sharma, S., & Shah, G. (1999). Utility values and diabetic retinopathy. American journal of ophthalmology, 128(3), 324–330. https://doi.org/10.1016/s0002-9394(99)00146-4

Sharma, S., Brown, G. C., Brown, M. M., Shah, G. K., Snow, K., Brown, H., & Hollands, H. (2000). Converting visual acuity to utilities. Canadian journal of ophthalmology. Journal canadien d'ophtalmologie, 35(5), 267–272. https://doi.org/10.1016/s0008-4182(00)80077-0

Czoski-Murray, C., Carlton, J., Brazier, J., Young, T., Papo, N. L., & Kang, H. K. (2009). Valuing condition-specific health states using simulation contact lenses. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, 12(5), 793–799. https://doi.org/10.1111/j.1524-4733.2009.00527.x

Pennington, B. M., Hernández-Alava, M., Hykin, P., Sivaprasad, S., Flight, L., Alshreef, A., & Brazier, J. (2020). Mapping From Visual Acuity to EQ-5D, EQ-5D With Vision Bolt-On, and VFQ-UI in Patients With Macular Edema in the LEAVO Trial. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, 23(7), 928–935. https://doi.org/10.1016/j.jval.2020.03.008

Lloyd, A., Nafees, B., Gavriel, S., Rousculp, M. D., Boye, K. S., & Ahmad, A. (2008). Health utility values associated with diabetic retinopathy. Diabetic medicine : a journal of the British Diabetic Association, 25(5), 618–624. https://doi.org/10.1111/j.1464-5491.2008.02430.x

National Institute for Health and Care Excellence (NICE). TA613: Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy. 2019. Available from: https://www.nice.org.uk/guidance/ta613

Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35(11):1095-108

National Institute for Health and Care Excellence (NICE). TA294: Aflibercept solution for injection for treating wet age-related macular degeneration. 2013. Available from: https://www.nice.org.uk/guidance/ta294

Scanlon, P. H., Aldington, S. J., Leal, J., Luengo-Fernandez, R., Oke, J., Sivaprasad, S., Gazis, A., & Stratton, I. M. (2015). Development of a cost-effectiveness model for optimisation of the screening interval in diabetic retinopathy screening. Health technology assessment (Winchester, England), 19(74), 1–116. https://doi.org/10.3310/hta19740

Sivaprasad, S., Prevost, A. T., Vasconcelos, J. C., Riddell, A., Murphy, C., Kelly, J., Bainbridge, J., Tudor-Edwards, R., Hopkins, D., Hykin, P., & CLARITY Study Group (2017). Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet (London, England), 389(10085), 2193–2203. https://doi.org/10.1016/S0140-6736(17)31193-5

Royle, P., et al. (2015). "Pan-retinal photocoagulation and other forms of laser treatment and drug therapies for non-proliferative diabetic retinopathy: systematic review and economic evaluation." Health Technol Assess 19(51).

Maredza M, Mistry H, Lois N on behalf of the EMERALD Study Group, et al Surveillance of people with previously successfully treated diabetic macular oedema and proliferative diabetic retinopathy by trained ophthalmic graders: cost analysis from the EMERALD study. British Journal of Ophthalmology 2022;106:1549-1554.

<Please insert your copyright statement - one line of text entry only>

Lois, N., Cook, J. A., Wang, A., Aldington, S., Mistry, H., Maredza, M., McAuley, D., Aslam, T., Bailey, C., Chong, V., Ganchi, F., Scanlon, P., Sivaprasad, S., Steel, D. H., Styles, C., Azuara-Blanco, A., Prior, L., Waugh, N., & EMERALD Study Group (2021). Evaluation of a New Model of Care for People with Complications of Diabetic Retinopathy: The EMERALD Study. Ophthalmology, 128(4), 561–573. https://doi.org/10.1016/j.ophtha.2020.10.030

Lois, Noemi, Campbell, Christina, Waugh, Norman et al. (2022) Standard threshold laser versus subthreshold micropulse laser for adults with diabetic macular oedema: the DIAMONDS non-inferiority RCT. Health technology assessment (Winchester, England) 26(50): 1-86

Wells, J. A., et al. (2016). "Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial." Ophthalmology 123(6): 1351-1359.

Simmonds, M., Llewellyn, A., Walker, R., Fulbright, H., Stewart, L., Dias, S., Lawrenson, J., Peto, T., Steel, D. (2023) Anti-VEGF drugs compared with laser photocoagulation for the treatment of diabetic retinopathy: a systematic review and meta-analysis. (Currently under peer review)

<Please insert your copyright statement - one line of text entry only>

# Appendix A:  Model parameters

**Review question 7 – Diabetic macular oedema**

**Table 54: Distribution of subsequent treatment for diabetic macular oedema**

| From/To | No treatment | Standard threshold laser | Aflibercept | Ranibizumab | Ranibizumab + standard laser | Beva cizumab | Bevacizumab + standard laser | Faricimab | Brolu cizumab | Dexamethasone | Fluocinolone | Source |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Standard threshold laser | 78% | - | 14.8% | 4.24% | - | 0.71% | - | 0.71% | 0.71% | 0.4% | 0.4% | Lois et al (2022) |
| Aflibercept | 63% | 37% | - | - | - | - | - | - | - | - | - | Wells et al (2016) |
| Ranibizumab | 54% | 46% | - | - | - | - | - | - | - | - | - | Wells et al (2016) |
| Ranibizumab plus standard laser | - | - | - | - | - | - | - | - | - | - | - | - |
| Bevacizumab | 44% | 56% | - | - | - | - | - | - | - | - | - | Wells et al (2016) |
| Bevacizumab plus standard laser | - | - | - | - | - | - | - | - | - | - | - | - |
| Brolucizumab | 63% | 37% | - | - | - | - | - | - | - | - | - | Assumed same as aflibercept |
| Faricimab | 63% | 37% | - | - | - | - | - | - | - | - | - | Assumed same as aflibercept |
| Subthreshold laser | 81.9% | - | 12.7% | 3.6% | - | 0.6% | - | 0.6% | 0.6% | - | - | Lois et al (2022) |

**Table 55: Adverse events associated with treatment for diabetic macular oedema**

| Adverse events | Standard threshold laser | Aflibercept | Ranibizumab | Ranibizumab + standard laser | Bevacizumab | Bevacizumab + standard laser | Brolucizumab | Faricimab | Fluocinolone acetonide | Dexamethasone | Subthreshold laser |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Retinal detachment | 0.03% | 0.08% | 0.05% | 0.05% | 0.13% | 0.13% | 0.00% | 0.02% | 0.00% | 0.00% | 0.03% |
| Retinal tear | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Vitreous haemorrhage | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.30% | 0.00% |
| Increased intraocular pressure | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.07% | 2.99% | 0.00% |
| Glaucoma | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Endophthalmitis | 0.03% | 0.06% | 0.14% | 0.14% | 0.07% | 0.07% | 0.07% | 0.08% | 0.00% | 0.00% | 0.03% |
| Cataracts | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 2.83% | 0.00% |
| Ocular pain | 0.06% | 0.13% | 0.03% | 0.03% | 0.13% | 0.13% | 0.69% | 0.12% | 0.00% | 0.31% | 0.06% |
| Stroke | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Cardiovascular death | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Source | Virgilli et al (2022) | Virgilli et al (2022) | Virgilli et al (2022) | Assumed same as ranibizumab | Virgilli et al (2022) | Assumed same as bevacizumab | Virgilli et al (2022) | Virgilli et al (2022) | Pochopien et al (2019) Year 1 | TA824 | Assumed same as standard laser |

**Table 56: Frequency of anti-VEGF treatments for DMO**

| Treatment | Frequency of Anti-VEGF treatments | | | | | Source |
| --- | --- | --- | --- | --- | --- | --- |
| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | |
| Standard threshold laser | - | - | - | - | - | Not applicable |
| Aflibercept | 8.50 | 5.100 | 5.10 | 0.00 | 0.00 | Régnier et al (2015) |
| | 8.00 | 4.000 | 2.30 | 1.20 | 1.00 | TA346 |
| | 8.55 | 4.000 | 4.00 | 4.00 | 4.00 | TA346 |
| | 9.20 | 5.000 | 2.37 | 2.37 | 2.37 | TA799 |
| | 8.00 | 4.000 | 2.00 | 2.00 | 2.00 | TA799 (scrutiny panel: assuming complete doses) |
| | 8.50 | 4.000 | 2.00 | 2.00 | 2.00 | TA799 (scrutiny panel: including proportions of planned doses beyond month 12) |
| | 7.70 | 5.600 | 2.30 | 1.20 | 1.00 | TA820 |
| | 6.00 | 3.000 | 3.00 | - | - | Talks et al (2021) |
| | 9.00 | - | - | - | - | Diabetic retinopathy clinical research network (2015) |
| Ranibizumab | 7.00 | 3.90 | 2.90 | 0.00 | 0.00 | Haig et al (2016) |
| | 7.93 | 4.00 | 2.30 | 1.20 | 1.00 | TA346 |
| | 9.40 | 5.40 | 2.17 | 2.17 | 2.17 | TA799 |
| | 8.00 | 4.00 | 2.00 | 2.00 | 2.00 | TA799 (scrutiny panel: assuming complete doses) |
| | 8.50 | 4.00 | 2.00 | 2.00 | 2.00 | TA799 (scrutiny panel: including proportions of planned doses beyond month 12) |
| | 7.70 | 5.60 | 2.30 | 1.20 | 1.00 | TA820 |
| | 9.40 | - | - | - | - | Diabetic retinopathy clinical research network (2015) |
| Ranibizumab plus standard laser | 7.00 | 3.50 | 2.50 | 0.00 | 0.00 | Haig et al (2016) |

| Treatment | Frequency of Anti-VEGF treatments | | | | | Source |
|---|---|---|---|---|---|---|
| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | |
| Bevacizumab | - | - | - | - | - | Assumed same as ranibizumab |
| Bevacizumab plus standard laser | 7.00 | 3.50 | 2.50 | 0.00 | 0.00 | Assumed same as ranibizumab plus standard laser |
| Brolucizumab | 6.91 | 4.11 | 2.30 | 1.20 | 1.00 | TA820 (pooled KITE and KESTREL trials for years 1 and 2), TA346 (assuming same for all treatments for year 3 onwards |
| Faricimab | 8.420 | 4.73 | 1.90 | 1.90 | 1.90 | TA799 (base-case) |
| | 6.000 | 4.00 | 2.00 | 2.00 | 2.00 | TA799 (scrutiny panel: assuming complete doses) |
| | 6.750 | 4.00 | 2.00 | 2.00 | 2.00 | TA799 (scrutiny panel: including proportions of planned doses beyond month 12) |
| Fluocinolone acetonide | 1.000 | 1.00 | 1.00 | 1.00 | 1.00 | Annual based on committee feedback, TA271 (administered every 3 years was considered unrealistic) |
| | 1.00 | 0.00 | 0.00 | 0.33 | 0.33 | TA271 (administered every 3 years) |
| Dexamethasone | 1.780 | 1.25 | 1.08 | 1.00 | 1.00 | TA349, TA824 |
| Subthreshold laser | - | - | - | - | - | Not applicable |

**Table 57: Frequency of monitoring visits for DMO**

| Treatment | Frequency of monitoring visits | | | | | Source |
|---|---|---|---|---|---|---|
| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | |
| Standard threshold laser | 4.00 | 4.00 | 2.60 | 2.20 | 1.90 | TA346 (ERG suggested laser monitoring should be 12 in year 1 to align with VIVID and VISTA trials), committee disagreed at this being reflective of clinical practice so assumed max 4 monitoring visits a year |
| | 4.00 | 3.00 | 3.00 | 3.00 | 3.00 | Maredza et al (2021): every 3 to 4 months |
| | 4.00 | 3.00 | - | - | - | Lois et al (2022): Diamond trial, followed up every 3 to 4 months |
| Aflibercept | 8.50 | 5.10 | 5.10 | 0.00 | 0.00 | Régnier et al (2015) |
| | 8.00 | 6.30 | 4.00 | 4.00 | 2.00 | TA346 |
| | 12.00 | 9.40 | 4.00 | 4.00 | 4.00 | TA799 (12.95 visits but capped to 12 based on committee feedback) |
| | 8.50 | 4.00 | 4.00 | 4.00 | 4.00 | TA799 |
| | 12.00 | 12.00 | 4.00 | 4.00 | 2.00 | TA820 (UK RWE study for years 1 and 2), TA346 (years 3 onwards), 14.2 visits but capped to 12 based on committee feedback |
| | 12.00 | 9.00 | 6.00 | 4.00 | 4.00 | Maredza et al (2021): every 1 to 3 months with anti-VEGF |
| Ranibizumab | 12.00 | 9.00 | 7.50 | 0.00 | 0.00 | Régnier et al (2015) |
| | 7.70 | 5.10 | 5.10 | 0.00 | 0.00 | Régnier et al (2015) |
| | 12.00 | 6.30 | 4.00 | 4.00 | 2.00 | TA346 |
| | 12.00 | 9.30 | 4.00 | 4.00 | 4.00 | TA799 (12.66 visits but capped to 12 based on committee feedback) |
| | 8.50 | 4.00 | 4.00 | 4.00 | 4.00 | TA799 (scrutiny panel: including proportions of planned doses) |
| | 12.00 | 12.00 | 4.00 | 4.00 | 2.00 | TA820 (UK RWE study for years 1 and 2), TA346 (years 3 onwards), 14.2 visits but capped to 12 based on committee feedback |

| Treatment | Frequency of monitoring visits | | | | | Source |
|---|---|---|---|---|---|---|
| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | |
| | 12.00 | 9.00 | 6.00 | 4.00 | 4.00 | Maredza et al (2021): every 1 to 3 months with anti-VEGF |
| Ranibizumab plus standard laser | 12.00 | 8.00 | 4.00 | 4.00 | 4.00 | TA274 |
| Bevacizumab | 4.00 | 4.00 | 4.00 | 0.00 | 2.00 | Assumed same as ranibizumab |
| Bevacizumab plus standard laser | 12.00 | 4.00 | 4.00 | 4.00 | 4.00 | Assumed same as ranibizumab plus standard laser |
| Brolucizumab | 6.91 | 4.11 | 4.00 | 4.00 | 2.00 | TA820 (assuming equal to injection freq. years 1 and 2), TA346 (for year 3 onwards) |
| Faricimab | 8.40 | 4.70 | 4.00 | 4.00 | 4.00 | TA799 |
| | 6.75 | 4.00 | 4.00 | 4.00 | 4.00 | TA799 |
| Fluocinolone acetonide | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 | TA271, TA349 |
| Dexamethasone | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 | TA349 |
| | 5.00 | - | - | - | - | TA346 |
| Subthreshold laser | 4.00 | 3.00 | 2.60 | 2.20 | 1.90 | Lois et al (2022): Diamond trial, followed up every 3 to 4 months with a total of 7 visits over 2 years, assumed same as standard threshold laser after 2 years |

# Appendix B:  Full scenario analysis results

Full results including costs, outcomes, ICERs and NMBs for each scenario are presented in this appendix, separated by population. These were probabilistic scenario analyses, so there may be small changes in absolute costs and/or QALYs in scenarios where these differences would not be expected (e.g. a change to utility source resulting in different total costs) but this is down to the probabilistic sampling.

## Scenario analysis results – PDR

**Treatment and monitoring visits are separate**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £9,244 | 11.018 | - | - | - | £211,118 (£197,342 to £225,083) |
| Aflibercept | £33,777 | 11.565 | £24,533 | 0.547 | £44,859 | £197,522 (£174,295 to £217,477) |
| Ranibizumab | £28,222 | 11.669 | £18,978 | 0.651 | £29,157 | £205,158 (£187,203 to £222,692) |
| Ranibizumab plus PRP | £32,685 | 11.495 | £23,442 | 0.477 | £49,140 | £197,217 (£178,768 to £215,020) |
| Bevacizumab | £14,431 | 11.442 | £5,187 | 0.424 | £12,238 | £214,408 (£181,942 to £238,641) |
| Bevacizumab plus PRP | £17,777 | 11.843 | £8,533 | 0.825 | £10,338 | £219,093 (£202,818 to £236,071) |

<Please insert your copyright statement - one line of text entry only>

**Utility for treatment in both eyes: weighted average of BSE and WSE**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,541 | 11.165 | - | - | - | £214,760 (£200,473 to £229,028) |
| Aflibercept | £32,009 | 11.626 | £23,468 | 0.461 | £50,862 | £200,520 (£178,946 to £220,335) |
| Ranibizumab | £26,268 | 11.752 | £17,727 | 0.587 | £30,185 | £208,779 (£190,967 to £225,953) |
| Ranibizumab plus PRP | £30,780 | 11.586 | £22,239 | 0.421 | £52,834 | £200,940 (£184,793 to £219,189) |
| Bevacizumab | £12,529 | 11.537 | £3,988 | 0.372 | £10,726 | £218,208 (£188,110 to £241,615) |
| Bevacizumab plus PRP | £15,914 | 11.898 | £7,372 | 0.733 | £10,063 | £222,041 (£206,856 to £238,651) |

**Utility source: Sharma et al (2002)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,516 | 11.503 | - | - | - | £221,535 (£208,864 to £234,154) |
| Aflibercept | £32,018 | 12.325 | £23,502 | 0.822 | £28,575 | £214,482 (£185,897 to £241,070) |
| Ranibizumab | £26,219 | 12.578 | £17,703 | 1.076 | £16,457 | £225,346 (£198,512 to £247,358) |
| Ranibizumab plus PRP | £30,643 | 12.223 | £22,127 | 0.720 | £30,732 | £213,807 (£192,733 to £236,482) |
| Bevacizumab | £12,496 | 12.199 | £3,980 | 0.696 | £5,716 | £231,480 (£200,376 to £265,413) |
| Bevacizumab plus PRP | £15,765 | 12.961 | £7,250 | 1.459 | £4,969 | £243,463 (£220,427 to £261,552) |

78

<Please insert your copyright statement - one line of text entry only>

## Utility source: Lloyd et al (2008)

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,504 | 10.353 | - | - | - | £198,558 (£186,409 to £211,103) |
| Aflibercept | £31,930 | 11.041 | £23,426 | 0.688 | £34,057 | £188,889 (£161,535 to £211,425) |
| Ranibizumab | £26,314 | 11.226 | £17,810 | 0.872 | £20,413 | £198,198 (£176,807 to £216,122) |
| Ranibizumab plus PRP | £30,745 | 10.996 | £22,241 | 0.643 | £34,591 | £189,176 (£169,771 to £207,952) |
| Bevacizumab | £12,500 | 10.942 | £3,996 | 0.588 | £6,791 | £206,330 (£169,994 to £232,436) |
| Bevacizumab plus PRP | £15,899 | 11.445 | £7,394 | 1.092 | £6,772 | £213,001 (£195,693 to £228,964) |

## Utility source: Mitchell et al (2012)

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,543 | 11.372 | - | - | - | £218,905 (£205,768 to £231,694) |
| Aflibercept | £32,135 | 11.901 | £23,591 | 0.529 | £44,635 | £205,885 (£182,905 to £225,473) |
| Ranibizumab | £26,262 | 12.048 | £17,719 | 0.676 | £26,228 | £214,698 (£196,639 to £230,409) |
| Ranibizumab plus PRP | £30,863 | 11.862 | £22,320 | 0.489 | £45,616 | £206,371 (£188,769 to £222,067) |
| Bevacizumab | £12,634 | 11.810 | £4,091 | 0.438 | £9,347 | £223,568 (£190,627 to £244,516) |
| Bevacizumab plus PRP | £15,880 | 12.201 | £7,337 | 0.829 | £8,849 | £228,150 (£212,566 to £242,951) |

<Please insert your copyright statement - one line of text entry only>

**Utility source: Czoski-Murray et al (2009)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,506 | 9.857 | - | - | - | £188,644 (£175,996 to £200,513) |
| Aflibercept | £31,954 | 10.760 | £23,448 | 0.903 | £25,971 | £183,253 (£153,381 to £208,162) |
| Ranibizumab | £26,340 | 11.009 | £17,834 | 1.151 | £15,491 | £193,835 (£167,603 to £215,639) |
| Ranibizumab plus PRP | £30,685 | 10.666 | £22,179 | 0.808 | £27,440 | £182,630 (£160,429 to £203,582) |
| Bevacizumab | £12,669 | 10.584 | £4,163 | 0.727 | £5,727 | £199,020 (£162,294 to £232,383) |
| Bevacizumab plus PRP | £15,811 | 11.316 | £7,305 | 1.458 | £5,009 | £210,503 (£188,528 to £229,279) |

**Utility source: Pennington et al (2020)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,539 | 8.912 | - | - | - | £169,692 (£159,308 to £180,647) |
| Aflibercept | £32,111 | 9.646 | £23,572 | 0.735 | £32,084 | £160,814 (£136,096 to £182,849) |
| Ranibizumab | £26,342 | 9.889 | £17,803 | 0.977 | £18,213 | £171,439 (£150,063 to £190,687) |
| Ranibizumab plus PRP | £30,867 | 9.598 | £22,329 | 0.686 | £32,545 | £161,085 (£141,485 to £179,873) |
| Bevacizumab | £12,565 | 9.563 | £4,026 | 0.652 | £6,177 | £178,702 (£147,058 to £206,539) |
| Bevacizumab plus PRP | £15,854 | 10.162 | £7,315 | 1.251 | £5,848 | £187,396 (£169,524 to £202,865) |

<Please insert your copyright statement - one line of text entry only>

**25% of patients receive treatment after year 5**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £7,189 | 11.028 | - | - | - | £213,377 (£198,440 to £227,677) |
| Aflibercept | £26,164 | 11.540 | £18,976 | 0.512 | £37,064 | £204,640 (£181,564 to £224,608) |
| Ranibizumab | £21,471 | 11.690 | £14,282 | 0.662 | £21,582 | £212,330 (£194,657 to £230,201) |
| Ranibizumab plus PRP | £24,893 | 11.524 | £17,704 | 0.496 | £35,705 | £205,589 (£187,716 to £222,871) |
| Bevacizumab | £10,684 | 11.454 | £3,496 | 0.426 | £8,203 | £218,404 (£185,334 to £241,027) |
| Bevacizumab plus PRP | £12,723 | 11.862 | £5,534 | 0.834 | £6,639 | £224,514 (£208,125 to £240,548) |

**75% of patients receive treatment after year 5**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £9,803 | 11.008 | - | - | - | £210,364 (£194,543 to £224,992) |
| Aflibercept | £37,770 | 11.551 | £27,967 | 0.542 | £51,566 | £193,244 (£168,687 to £214,392) |
| Ranibizumab | £31,121 | 11.675 | £21,318 | 0.666 | £31,996 | £202,371 (£184,007 to £221,017) |
| Ranibizumab plus PRP | £36,743 | 11.496 | £26,940 | 0.488 | £55,187 | £193,187 (£174,279 to £210,244) |
| Bevacizumab | £14,652 | 11.465 | £4,849 | 0.457 | £10,619 | £214,647 (£180,414 to £238,490) |
| Bevacizumab plus PRP | £19,115 | 11.848 | £9,312 | 0.840 | £11,089 | £217,847 (£199,641 to £234,758) |

<Please insert your copyright statement - one line of text entry only>

**Natural history assumed at 20 years**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,530 | 11.032 | - | - | - | £212,110 (£198,536 to £226,392) |
| Aflibercept | £32,031 | 11.534 | £23,501 | 0.502 | £46,816 | £198,649 (£176,664 to £218,775) |
| Ranibizumab | £26,532 | 11.664 | £18,002 | 0.632 | £28,477 | £206,751 (£188,886 to £223,687) |
| Ranibizumab plus PRP | £30,891 | 11.505 | £22,361 | 0.473 | £47,241 | £199,216 (£181,925 to £215,837) |
| Bevacizumab | £12,784 | 11.458 | £4,254 | 0.426 | £9,994 | £216,369 (£185,853 to £240,417) |
| Bevacizumab plus PRP | £15,944 | 11.832 | £7,414 | 0.800 | £9,262 | £220,706 (£205,919 to £236,027) |

**Natural history assumed at 10 years**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,531 | 11.014 | - | - | - | £211,747 (£196,766 to £224,943) |
| Aflibercept | £32,382 | 11.409 | £23,851 | 0.395 | £60,318 | £195,804 (£176,497 to £213,561) |
| Ranibizumab | £26,785 | 11.521 | £18,255 | 0.507 | £35,982 | £203,638 (£186,814 to £218,147) |
| Ranibizumab plus PRP | £31,243 | 11.362 | £22,712 | 0.348 | £65,276 | £195,993 (£179,780 to £211,143) |
| Bevacizumab | £12,750 | 11.370 | £4,219 | 0.357 | £11,831 | £214,660 (£190,535 to £233,035) |
| Bevacizumab plus PRP | £16,284 | 11.653 | £7,753 | 0.639 | £12,130 | £216,778 (£201,125 to £230,910) |

<Please insert your copyright statement - one line of text entry only>

**Natural history assumed at 5 years**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,453 | 11.014 | - | - | - | £211,822 (£196,994 to £225,765) |
| Aflibercept | £32,550 | 11.286 | £24,097 | 0.272 | £88,482 | £193,172 (£176,425 to £209,131) |
| Ranibizumab | £27,095 | 11.342 | £18,642 | 0.328 | £56,865 | £199,737 (£184,764 to £213,927) |
| Ranibizumab plus PRP | £31,501 | 11.236 | £23,048 | 0.222 | £103,745 | £193,217 (£177,775 to £207,383) |
| Bevacizumab | £13,045 | 11.232 | £4,591 | 0.218 | £21,054 | £211,592 (£191,279 to £228,238) |
| Bevacizumab plus PRP | £16,725 | 11.438 | £8,271 | 0.424 | £19,494 | £212,037 (£197,137 to £226,350) |

**Monitoring and treatment visits reduced by 20%**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £7,995 | 11.032 | - | - | - | £212,650 (£198,144 to £226,338) |
| Aflibercept | £25,314 | 11.588 | £17,318 | 0.556 | £31,147 | £206,452 (£183,977 to £224,287) |
| Ranibizumab | £21,222 | 11.696 | £13,227 | 0.663 | £19,939 | £212,690 (£192,979 to £229,497) |
| Ranibizumab plus PRP | £24,847 | 11.512 | £16,852 | 0.480 | £35,117 | £205,395 (£186,875 to £222,054) |
| Bevacizumab | £10,421 | 11.447 | £2,425 | 0.415 | £5,849 | £218,518 (£186,100 to £242,857) |
| Bevacizumab plus PRP | £12,758 | 11.878 | £4,762 | 0.846 | £5,631 | £224,801 (£208,560 to £240,335) |

<Please insert your copyright statement - one line of text entry only>

**Monitoring and treatment visits increased by 20%**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,930 | 11.028 | - | - | - | £211,628 (£196,965 to £225,479) |
| Aflibercept | £36,956 | 11.573 | £28,027 | 0.545 | £51,435 | £194,499 (£171,936 to £214,873) |
| Ranibizumab | £29,951 | 11.670 | £21,021 | 0.642 | £32,744 | £203,447 (£182,198 to £220,435) |
| Ranibizumab plus PRP | £35,204 | 11.527 | £26,274 | 0.499 | £52,619 | £195,340 (£176,979 to £211,911) |
| Bevacizumab | £13,339 | 11.458 | £4,409 | 0.430 | £10,254 | £215,819 (£179,555 to £239,660) |
| Bevacizumab plus PRP | £17,466 | 11.864 | £8,536 | 0.836 | £10,207 | £219,818 (£203,048 to £237,042) |

**Patient costs included**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £33,517 | 11.025 | - | - | - | £186,984 (£166,070 to £205,767) |
| Aflibercept | £42,586 | 11.558 | £9,069 | 0.533 | £17,025 | £188,569 (£140,170 to £216,843) |
| Ranibizumab | £31,978 | 11.697 | -£1,539 | 0.672 | -£2,290 | £201,969 (£167,308 to £224,594) |
| Ranibizumab plus PRP | £40,670 | 11.505 | £7,153 | 0.480 | £14,890 | £189,439 (£157,696 to £212,206) |
| Bevacizumab | £25,474 | 11.445 | -£8,044 | 0.420 | -£19,151 | £203,427 (£131,780 to £239,528) |
| Bevacizumab plus PRP | £18,119 | 11.865 | -£15,399 | 0.840 | -£18,327 | £219,186 (£198,163 to £237,775) |

<Please insert your copyright statement - one line of text entry only>

**Biosimilar price for ranibizumab**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| PRP | £8,489 | 11.026 | - | - | - | £212,028 (£197,853 to £226,736) |
| Aflibercept | £31,925 | 11.580 | £23,436 | 0.554 | £42,289 | £199,676 (£177,133 to £219,746) |
| Ranibizumab | £25,528 | 11.704 | £17,039 | 0.678 | £25,125 | £208,553 (£190,578 to £224,770) |
| Ranibizumab plus PRP | £29,976 | 11.527 | £21,488 | 0.502 | £42,834 | £200,573 (£183,415 to £218,262) |
| Bevacizumab | £12,682 | 11.434 | £4,194 | 0.408 | £10,272 | £216,000 (£181,061 to £239,383) |
| Bevacizumab plus PRP | £15,980 | 11.870 | £7,492 | 0.844 | £8,877 | £221,416 (£204,771 to £238,465) |

<Please insert your copyright statement - one line of text entry only>

# Scenario analysis results – DMO (all centre involving)

**Treatment and monitoring visits are separate**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,840 | 8.488 | - | - | - | £165,921 (£152,081 to £180,060) |
| Standard threshold laser | £5,188 | 8.983 | £1,348 | 0.495 | £2,722 | £174,473 (£160,268 to £187,585) |
| Aflibercept | £36,106 | 9.270 | £32,266 | 0.782 | £41,255 | £149,298 (£133,766 to £164,782) |
| Ranibizumab | £25,902 | 9.229 | £22,062 | 0.741 | £29,780 | £158,676 (£144,662 to £172,477) |
| Ranibizumab plus standard laser | £26,450 | 9.213 | £22,610 | 0.724 | £31,209 | £157,801 (£143,904 to £171,717) |
| Bevacizumab | £11,212 | 9.213 | £7,372 | 0.725 | £10,164 | £173,055 (£158,974 to £186,252) |
| Bevacizumab plus standard laser | £13,022 | 9.228 | £9,182 | 0.740 | £12,403 | £171,545 (£157,486 to £186,115) |
| Brolucizumab | £25,797 | 9.281 | £21,957 | 0.793 | £27,702 | £159,817 (£145,451 to £173,609) |
| Faricimab | £35,708 | 9.277 | £31,868 | 0.789 | £40,408 | £149,827 (£134,636 to £164,964) |
| Fluocinolone acetonide | £51,572 | 9.198 | £47,732 | 0.710 | £67,223 | £132,391 (£114,623 to £149,029) |
| Dexamethasone | £18,413 | 9.186 | £14,573 | 0.698 | £20,870 | £165,314 (£151,002 to £177,771) |
| Subthreshold laser | £4,723 | 8.969 | £883 | 0.481 | £1,834 | £174,667 (£160,608 to £188,543) |

86

<Please insert your copyright statement - one line of text entry only>

**Utility for treatment in both eyes: weighted average of BSE and WSE**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,858 | 8.843 | - | - | - | £172,996 (£159,475 to £186,612) |
| Standard threshold laser | £4,852 | 9.228 | £994 | 0.385 | £2,578 | £179,711 (£166,500 to £192,176) |
| Aflibercept | £34,315 | 9.454 | £30,457 | 0.611 | £49,858 | £154,757 (£139,154 to £169,531) |
| Ranibizumab | £24,168 | 9.420 | £20,310 | 0.577 | £35,178 | £164,233 (£150,023 to £177,933) |
| Ranibizumab plus standard laser | £24,867 | 9.409 | £21,008 | 0.566 | £37,086 | £163,318 (£150,224 to £176,794) |
| Bevacizumab | £9,365 | 9.406 | £5,507 | 0.563 | £9,782 | £178,748 (£165,348 to £191,327) |
| Bevacizumab plus standard laser | £11,413 | 9.417 | £7,554 | 0.574 | £13,153 | £176,929 (£163,436 to £189,625) |
| Brolucizumab | £24,366 | 9.463 | £20,507 | 0.620 | £33,055 | £164,897 (£151,240 to £177,862) |
| Faricimab | £34,217 | 9.458 | £30,359 | 0.615 | £49,345 | £154,942 (£139,501 to £169,031) |
| Fluocinolone acetonide | £51,246 | 9.400 | £47,387 | 0.557 | £85,031 | £136,755 (£118,971 to £153,459) |
| Dexamethasone | £17,850 | 9.386 | £13,992 | 0.544 | £25,735 | £169,878 (£156,572 to £182,364) |
| Subthreshold laser | £4,440 | 9.230 | £582 | 0.387 | £1,504 | £180,152 (£166,746 to £193,150) |

<Please insert your copyright statement - one line of text entry only>

**Utility source: Sharma et al (2002)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,864 | 9.688 | - | - | - | £189,896 (£177,099 to £204,447) |
| Standard threshold laser | £4,856 | 10.202 | £992 | 0.514 | £1,931 | £199,183 (£184,314 to £213,994) |
| Aflibercept | £34,572 | 10.529 | £30,709 | 0.841 | £36,534 | £175,998 (£161,890 to £190,547) |
| Ranibizumab | £24,337 | 10.480 | £20,473 | 0.792 | £25,857 | £185,258 (£170,430 to £198,898) |
| Ranibizumab plus standard laser | £25,055 | 10.458 | £21,191 | 0.770 | £27,524 | £184,103 (£168,911 to £199,744) |
| Bevacizumab | £9,534 | 10.468 | £5,671 | 0.780 | £7,266 | £199,834 (£185,445 to £212,896) |
| Bevacizumab plus standard laser | £11,473 | 10.481 | £7,609 | 0.793 | £9,595 | £198,147 (£184,123 to £212,542) |
| Brolucizumab | £24,591 | 10.536 | £20,727 | 0.848 | £24,437 | £186,132 (£171,998 to £200,212) |
| Faricimab | £34,391 | 10.537 | £30,528 | 0.849 | £35,962 | £176,346 (£161,826 to £191,060) |
| Fluocinolone acetonide | £51,408 | 10.446 | £47,545 | 0.758 | £62,692 | £157,519 (£138,857 to £173,267) |
| Dexamethasone | £17,833 | 10.440 | £13,970 | 0.752 | £18,585 | £190,959 (£176,631 to £204,201) |
| Subthreshold laser | £4,464 | 10.189 | £600 | 0.501 | £1,199 | £199,308 (£183,974 to £214,482) |

<Please insert your copyright statement - one line of text entry only>

**Utility source: Lloyd et al (2008)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,843 | 8.869 | - | - | - | £173,537 (£160,780 to £185,808) |
| Standard threshold laser | £4,839 | 9.196 | £996 | 0.327 | £3,046 | £179,082 (£166,133 to £192,070) |
| Aflibercept | £34,351 | 9.362 | £30,508 | 0.493 | £61,905 | £152,886 (£137,071 to £167,459) |
| Ranibizumab | £23,971 | 9.335 | £20,128 | 0.466 | £43,213 | £162,725 (£147,707 to £175,917) |
| Ranibizumab plus standard laser | £24,693 | 9.325 | £20,850 | 0.456 | £45,752 | £161,801 (£147,991 to £175,182) |
| Bevacizumab | £9,327 | 9.330 | £5,484 | 0.461 | £11,887 | £177,280 (£163,902 to £190,229) |
| Bevacizumab plus standard laser | £11,378 | 9.335 | £7,535 | 0.466 | £16,186 | £175,313 (£161,926 to £189,045) |
| Brolucizumab | £24,429 | 9.371 | £20,586 | 0.502 | £41,047 | £162,982 (£148,837 to £175,532) |
| Faricimab | £34,188 | 9.367 | £30,345 | 0.498 | £60,885 | £153,160 (£138,280 to £167,025) |
| Fluocinolone acetonide | £51,599 | 9.324 | £47,755 | 0.455 | £104,902 | £134,887 (£116,399 to £151,306) |
| Dexamethasone | £17,714 | 9.315 | £13,871 | 0.446 | £31,090 | £168,589 (£155,905 to £181,062) |
| Subthreshold laser | £4,421 | 9.175 | £578 | 0.306 | £1,886 | £179,086 (£166,177 to £192,721) |

89

<Please insert your copyright statement - one line of text entry only>

**Utility source: Mitchell et al (2012)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,835 | 9.627 | - | - | - | £188,711 (£177,247 to £200,401) |
| Standard threshold laser | £4,832 | 9.867 | £997 | 0.240 | £4,156 | £192,512 (£181,156 to £204,599) |
| Aflibercept | £34,352 | 9.978 | £30,517 | 0.350 | £87,085 | £165,203 (£150,790 to £179,609) |
| Ranibizumab | £24,032 | 9.961 | £20,197 | 0.334 | £60,526 | £175,188 (£162,771 to £187,191) |
| Ranibizumab plus standard laser | £25,020 | 9.956 | £21,185 | 0.328 | £64,493 | £174,096 (£161,420 to £186,632) |
| Bevacizumab | £9,405 | 9.954 | £5,570 | 0.326 | £17,062 | £189,670 (£177,876 to £201,528) |
| Bevacizumab plus standard laser | £11,355 | 9.960 | £7,520 | 0.333 | £22,585 | £187,851 (£175,944 to £200,057) |
| Brolucizumab | £24,601 | 9.988 | £20,766 | 0.360 | £57,632 | £175,152 (£162,525 to £187,413) |
| Faricimab | £34,313 | 9.982 | £30,478 | 0.354 | £85,992 | £165,322 (£152,221 to £179,554) |
| Fluocinolone acetonide | £51,925 | 9.959 | £48,090 | 0.332 | £144,774 | £147,265 (£131,164 to £163,089) |
| Dexamethasone | £17,812 | 9.948 | £13,977 | 0.321 | £43,579 | £181,149 (£170,154 to £192,610) |
| Subthreshold laser | £4,442 | 9.855 | £607 | 0.228 | £2,663 | £192,663 (£181,589 to £205,078) |

<Please insert your copyright statement - one line of text entry only>

**Utility source: Brown et al (2000)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,819 | 9.305 | - | - | - | £182,284 (£169,983 to £194,588) |
| Standard threshold laser | £4,799 | 9.561 | £979 | 0.256 | £3,828 | £186,422 (£173,087 to £199,863) |
| Aflibercept | £34,212 | 9.693 | £30,392 | 0.388 | £78,386 | £159,646 (£144,572 to £175,633) |
| Ranibizumab | £24,168 | 9.675 | £20,349 | 0.370 | £55,040 | £169,330 (£155,623 to £183,679) |
| Ranibizumab plus standard laser | £24,829 | 9.668 | £21,010 | 0.363 | £57,957 | £168,525 (£155,205 to £183,257) |
| Bevacizumab | £9,328 | 9.667 | £5,509 | 0.362 | £15,211 | £184,019 (£170,422 to £198,177) |
| Bevacizumab plus standard laser | £11,431 | 9.675 | £7,612 | 0.370 | £20,599 | £182,063 (£167,859 to £196,341) |
| Brolucizumab | £24,454 | 9.703 | £20,635 | 0.398 | £51,829 | £169,612 (£155,151 to £184,663) |
| Faricimab | £34,096 | 9.698 | £30,277 | 0.393 | £77,138 | £159,858 (£144,859 to £175,355) |
| Fluocinolone acetonide | £51,430 | 9.670 | £47,611 | 0.364 | £130,680 | £141,960 (£123,345 to £159,078) |
| Dexamethasone | £17,694 | 9.659 | £13,875 | 0.353 | £39,267 | £175,476 (£163,207 to £189,030) |
| Subthreshold laser | £4,389 | 9.559 | £570 | 0.254 | £2,246 | £186,786 (£173,824 to £200,429) |

<Please insert your copyright statement - one line of text entry only>

**Utility source: Pennington et al (2020)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,861 | 7.659 | - | - | - | £149,310 (£136,926 to £163,245) |
| Standard threshold laser | £4,833 | 8.068 | £972 | 0.409 | £2,375 | £156,523 (£144,858 to £168,688) |
| Aflibercept | £34,320 | 8.318 | £30,459 | 0.659 | £46,218 | £132,031 (£117,512 to £145,446) |
| Ranibizumab | £24,119 | 8.284 | £20,258 | 0.625 | £32,393 | £141,560 (£128,394 to £154,589) |
| Ranibizumab plus standard laser | £24,781 | 8.267 | £20,920 | 0.609 | £34,358 | £140,568 (£128,972 to £153,828) |
| Bevacizumab | £9,425 | 8.265 | £5,564 | 0.606 | £9,178 | £155,871 (£144,315 to £169,188) |
| Bevacizumab plus standard laser | £11,410 | 8.283 | £7,549 | 0.624 | £12,098 | £154,240 (£141,682 to £167,428) |
| Brolucizumab | £24,331 | 8.328 | £20,470 | 0.669 | £30,575 | £142,230 (£129,805 to £155,497) |
| Faricimab | £34,265 | 8.325 | £30,404 | 0.666 | £45,649 | £132,227 (£118,558 to £144,952) |
| Fluocinolone acetonide | £51,499 | 8.262 | £47,638 | 0.604 | £78,912 | £113,745 (£96,435 to £130,517) |
| Dexamethasone | £17,807 | 8.248 | £13,946 | 0.589 | £23,676 | £147,145 (£135,778 to £159,934) |
| Subthreshold laser | £4,423 | 8.062 | £562 | 0.403 | £1,394 | £156,816 (£143,957 to £170,192) |

<Please insert your copyright statement - one line of text entry only>

**25% of patients receive treatment after year 5**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,839 | 8.484 | - | - | - | £165,838 (£152,464 to £180,344) |
| Standard threshold laser | £4,932 | 8.976 | £1,094 | 0.492 | £2,223 | £174,586 (£160,312 to £187,087) |
| Aflibercept | £30,046 | 9.265 | £26,208 | 0.781 | £33,570 | £155,244 (£141,011 to £169,068) |
| Ranibizumab | £21,260 | 9.226 | £17,422 | 0.743 | £23,459 | £163,269 (£149,609 to £175,982) |
| Ranibizumab plus standard laser | £21,463 | 9.204 | £17,624 | 0.720 | £24,490 | £162,607 (£149,667 to £175,513) |
| Bevacizumab | £8,436 | 9.209 | £4,597 | 0.725 | £6,340 | £175,744 (£162,706 to £187,923) |
| Bevacizumab plus standard laser | £9,909 | 9.222 | £6,071 | 0.739 | £8,220 | £174,538 (£161,143 to £186,765) |
| Brolucizumab | £22,632 | 9.273 | £18,793 | 0.789 | £23,828 | £162,819 (£149,931 to £175,787) |
| Faricimab | £29,134 | 9.271 | £25,296 | 0.787 | £32,143 | £156,282 (£142,670 to £169,422) |
| Fluocinolone acetonide | £39,114 | 9.195 | £35,275 | 0.711 | £49,582 | £144,792 (£129,824 to £159,055) |
| Dexamethasone | £14,352 | 9.185 | £10,513 | 0.701 | £14,989 | £169,353 (£156,529 to £181,110) |
| Subthreshold laser | £4,474 | 8.961 | £636 | 0.477 | £1,333 | £174,745 (£161,359 to £188,301) |

<Please insert your copyright statement - one line of text entry only>

**75% of patients receive treatment after year 5**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,843 | 8.491 | - | - | - | £165,976 (£152,486 to £179,348) |
| Standard threshold laser | £4,773 | 8.970 | £930 | 0.479 | £1,943 | £174,623 (£160,349 to £188,167) |
| Aflibercept | £36,935 | 9.258 | £33,092 | 0.767 | £43,166 | £148,216 (£133,621 to £162,636) |
| Ranibizumab | £25,782 | 9.217 | £21,939 | 0.726 | £30,202 | £158,565 (£144,089 to £171,656) |
| Ranibizumab plus standard laser | £26,840 | 9.199 | £22,998 | 0.708 | £32,468 | £157,144 (£142,324 to £170,240) |
| Bevacizumab | £9,824 | 9.203 | £5,981 | 0.712 | £8,403 | £174,231 (£161,033 to £186,792) |
| Bevacizumab plus standard laser | £12,299 | 9.219 | £8,457 | 0.728 | £11,613 | £172,083 (£158,066 to £186,206) |
| Brolucizumab | £24,726 | 9.267 | £20,884 | 0.776 | £26,900 | £160,619 (£147,311 to £174,143) |
| Faricimab | £36,972 | 9.265 | £33,130 | 0.774 | £42,784 | £148,333 (£132,959 to £163,222) |
| Fluocinolone acetonide | £57,745 | 9.189 | £53,903 | 0.698 | £77,192 | £126,039 (£108,154 to £143,169) |
| Dexamethasone | £19,889 | 9.178 | £16,046 | 0.687 | £23,351 | £163,673 (£151,122 to £176,243) |
| Subthreshold laser | £4,432 | 8.961 | £589 | 0.470 | £1,254 | £174,788 (£160,276 to £188,949) |

<Please insert your copyright statement - one line of text entry only>

**Natural history assumed at 20 years**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,852 | 8.495 | - | - | - | £166,044 (£152,957 to £180,498) |
| Standard threshold laser | £4,826 | 8.968 | £974 | 0.474 | £2,057 | £174,543 (£161,827 to £188,944) |
| Aflibercept | £34,547 | 9.254 | £30,695 | 0.759 | £40,441 | £150,529 (£135,917 to £165,516) |
| Ranibizumab | £24,282 | 9.216 | £20,430 | 0.721 | £28,332 | £160,036 (£146,171 to £173,487) |
| Ranibizumab plus standard laser | £24,973 | 9.198 | £21,121 | 0.703 | £30,053 | £158,978 (£145,943 to £173,318) |
| Bevacizumab | £9,600 | 9.193 | £5,748 | 0.698 | £8,234 | £174,258 (£160,793 to £187,970) |
| Bevacizumab plus standard laser | £11,564 | 9.217 | £7,712 | 0.723 | £10,673 | £172,783 (£158,915 to £186,861) |
| Brolucizumab | £24,432 | 9.266 | £20,580 | 0.771 | £26,692 | £160,884 (£147,396 to £174,706) |
| Faricimab | £34,383 | 9.261 | £30,531 | 0.767 | £39,826 | £150,845 (£136,240 to £165,295) |
| Fluocinolone acetonide | £51,661 | 9.187 | £47,809 | 0.693 | £69,032 | £132,085 (£115,871 to £147,374) |
| Dexamethasone | £17,896 | 9.171 | £14,044 | 0.676 | £20,780 | £165,516 (£153,034 to £179,181) |
| Subthreshold laser | £4,443 | 8.964 | £591 | 0.469 | £1,259 | £174,837 (£160,689 to £188,567) |

<Please insert your copyright statement - one line of text entry only>

**Natural history assumed at 10 years**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,853 | 8.504 | - | - | - | £166,224 (£152,800 to £179,935) |
| Standard threshold laser | £4,944 | 8.880 | £1,091 | 0.376 | £2,899 | £172,662 (£159,690 to £185,909) |
| Aflibercept | £34,412 | 9.104 | £30,559 | 0.600 | £50,940 | £147,663 (£133,745 to £161,603) |
| Ranibizumab | £24,193 | 9.077 | £20,340 | 0.573 | £35,507 | £157,341 (£144,606 to £169,450) |
| Ranibizumab plus standard laser | £24,948 | 9.059 | £21,095 | 0.555 | £38,030 | £156,223 (£143,378 to £168,388) |
| Bevacizumab | £9,459 | 9.065 | £5,606 | 0.561 | £9,995 | £171,836 (£159,108 to £184,415) |
| Bevacizumab plus standard laser | £11,413 | 9.074 | £7,559 | 0.570 | £13,264 | £170,064 (£157,298 to £182,745) |
| Brolucizumab | £24,550 | 9.115 | £20,697 | 0.611 | £33,892 | £157,741 (£145,180 to £170,545) |
| Faricimab | £34,183 | 9.110 | £30,330 | 0.607 | £50,005 | £148,025 (£133,953 to £160,932) |
| Fluocinolone acetonide | £51,681 | 9.057 | £47,827 | 0.553 | £86,424 | £129,465 (£111,894 to £145,023) |
| Dexamethasone | £17,793 | 9.047 | £13,939 | 0.543 | £25,677 | £163,143 (£151,201 to £176,021) |
| Subthreshold laser | £4,536 | 8.870 | £683 | 0.367 | £1,863 | £172,872 (£160,347 to £185,844) |

<Please insert your copyright statement - one line of text entry only>

**Natural history assumed at 5 years**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,830 | 8.467 | - | - | - | £165,514 (£151,792 to £179,691) |
| Standard threshold laser | £5,071 | 8.720 | £1,241 | 0.252 | £4,917 | £169,321 (£156,161 to £181,922) |
| Aflibercept | £34,683 | 8.859 | £30,853 | 0.392 | £78,743 | £142,497 (£128,030 to £156,186) |
| Ranibizumab | £24,374 | 8.841 | £20,544 | 0.374 | £54,970 | £152,445 (£139,612 to £165,008) |
| Ranibizumab plus standard laser | £25,080 | 8.832 | £21,250 | 0.364 | £58,319 | £151,552 (£138,916 to £164,503) |
| Bevacizumab | £9,584 | 8.832 | £5,754 | 0.364 | £15,794 | £167,047 (£153,954 to £179,736) |
| Bevacizumab plus standard laser | £11,606 | 8.839 | £7,776 | 0.372 | £20,926 | £165,170 (£152,864 to £177,840) |
| Brolucizumab | £24,741 | 8.866 | £20,911 | 0.398 | £52,493 | £152,570 (£140,064 to £165,740) |
| Faricimab | £34,311 | 8.863 | £30,481 | 0.395 | £77,082 | £142,942 (£129,639 to £155,767) |
| Fluocinolone acetonide | £51,491 | 8.835 | £47,661 | 0.368 | £129,632 | £125,207 (£108,898 to £141,488) |
| Dexamethasone | £17,979 | 8.822 | £14,149 | 0.355 | £39,899 | £158,458 (£146,532 to £170,449) |
| Subthreshold laser | £4,642 | 8.716 | £812 | 0.249 | £3,259 | £169,685 (£157,452 to £181,927) |

<Please insert your copyright statement - one line of text entry only>

**Monitoring and treatment frequency: minimum reported**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,855 | 8.483 | - | - | - | £165,805 (£151,307 to £179,831) |
| Standard threshold laser | £3,965 | 8.978 | £110 | 0.495 | £223 | £175,591 (£161,764 to £189,592) |
| Aflibercept | £21,847 | 9.265 | £17,992 | 0.782 | £23,007 | £163,453 (£149,560 to £178,024) |
| Ranibizumab | £18,165 | 9.218 | £14,310 | 0.735 | £19,458 | £166,204 (£153,179 to £180,395) |
| Ranibizumab plus standard laser | £21,849 | 9.199 | £17,994 | 0.716 | £25,141 | £162,125 (£149,028 to £176,639) |
| Bevacizumab | £6,787 | 9.205 | £2,932 | 0.722 | £4,063 | £177,306 (£164,326 to £191,179) |
| Bevacizumab plus standard laser | £10,275 | 9.214 | £6,420 | 0.731 | £8,778 | £174,013 (£159,176 to £188,079) |
| Brolucizumab | £24,421 | 9.267 | £20,567 | 0.784 | £26,244 | £160,912 (£147,253 to £175,170) |
| Faricimab | £31,520 | 9.263 | £27,666 | 0.780 | £35,472 | £153,738 (£139,768 to £169,397) |
| Fluocinolone acetonide | £21,361 | 9.188 | £17,506 | 0.705 | £24,817 | £162,407 (£149,072 to £176,447) |
| Dexamethasone | £17,660 | 9.179 | £13,805 | 0.696 | £19,830 | £165,924 (£153,385 to £179,681) |
| Subthreshold laser | £3,696 | 8.961 | -£159 | 0.478 | -£333 | £175,520 (£161,005 to £189,936) |

98

<Please insert your copyright statement - one line of text entry only>

## Monitoring and treatment frequency: maximum reported

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,855 | 8.497 | - | - | - | £166,079 (£151,939 to £180,370) |
| Standard threshold laser | £5,573 | 8.963 | £1,717 | 0.466 | £3,683 | £173,689 (£160,329 to £186,708) |
| Aflibercept | £51,345 | 9.244 | £47,490 | 0.747 | £63,557 | £133,533 (£117,607 to £149,855) |
| Ranibizumab | £29,564 | 9.212 | £25,709 | 0.716 | £35,923 | £154,683 (£140,649 to £168,583) |
| Ranibizumab plus standard laser | £29,873 | 9.196 | £26,018 | 0.700 | £37,179 | £154,057 (£139,303 to £167,969) |
| Bevacizumab | £11,239 | 9.198 | £7,383 | 0.702 | £10,524 | £172,726 (£160,068 to £185,222) |
| Bevacizumab plus standard laser | £13,104 | 9.213 | £9,249 | 0.717 | £12,907 | £171,161 (£156,963 to £184,204) |
| Brolucizumab | £24,599 | 9.269 | £20,744 | 0.773 | £26,852 | £160,785 (£147,970 to £173,787) |
| Faricimab | £37,183 | 9.262 | £33,328 | 0.766 | £43,534 | £148,062 (£133,597 to £163,090) |
| Fluocinolone acetonide | £51,473 | 9.188 | £47,618 | 0.691 | £68,925 | £132,278 (£113,574 to £148,106) |
| Dexamethasone | £17,924 | 9.180 | £14,069 | 0.683 | £20,588 | £165,677 (£153,433 to £178,370) |
| Subthreshold laser | £5,035 | 8.964 | £1,180 | 0.468 | £2,524 | £174,250 (£159,983 to £187,768) |

<Please insert your copyright statement - one line of text entry only>

**Monitoring and treatment frequency: assumed the same across anti-VEGFs**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,662 | 8.509 | - | - | - | £166,527 (£152,133 to £180,231) |
| Standard threshold laser | £4,908 | 8.999 | £1,247 | 0.490 | £2,544 | £175,080 (£160,796 to £190,540) |
| Aflibercept | £33,120 | 9.286 | £29,458 | 0.777 | £37,912 | £152,609 (£140,112 to £165,624) |
| Ranibizumab | £23,022 | 9.242 | £19,361 | 0.733 | £26,415 | £161,825 (£148,808 to £175,358) |
| Ranibizumab plus standard laser | £24,083 | 9.223 | £20,421 | 0.713 | £28,634 | £160,369 (£146,770 to £174,115) |
| Bevacizumab | £8,339 | 9.230 | £4,677 | 0.721 | £6,488 | £176,268 (£162,484 to £190,305) |
| Bevacizumab plus standard laser | £10,608 | 9.243 | £6,946 | 0.734 | £9,468 | £174,254 (£160,642 to £188,215) |
| Brolucizumab | £23,952 | 9.294 | £20,290 | 0.785 | £25,857 | £161,931 (£149,057 to £174,951) |
| Faricimab | £33,440 | 9.291 | £29,779 | 0.781 | £38,117 | £152,373 (£139,882 to £165,542) |
| Fluocinolone acetonide | £58,032 | 9.220 | £54,370 | 0.710 | £76,568 | £126,358 (£113,631 to £140,111) |
| Dexamethasone | £17,536 | 9.206 | £13,875 | 0.697 | £19,919 | £166,583 (£153,093 to £180,314) |
| Subthreshold laser | £4,453 | 9.002 | £791 | 0.493 | £1,606 | £175,593 (£161,014 to £190,159) |

<Please insert your copyright statement - one line of text entry only>

**Patient costs included**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £12,245 | 8.499 | - | - | - | £157,733 (£136,077 to £177,316) |
| Standard threshold laser | £7,817 | 8.990 | -£4,428 | 0.492 | -£9,010 | £171,991 (£154,164 to £186,857) |
| Aflibercept | £34,910 | 9.274 | £22,665 | 0.775 | £29,244 | £150,568 (£135,004 to £164,831) |
| Ranibizumab | £24,837 | 9.236 | £12,592 | 0.737 | £17,084 | £159,882 (£144,974 to £173,182) |
| Ranibizumab plus standard laser | £25,853 | 9.217 | £13,608 | 0.718 | £18,956 | £158,482 (£144,386 to £172,032) |
| Bevacizumab | £10,298 | 9.216 | -£1,947 | 0.717 | -£2,715 | £174,021 (£160,573 to £186,977) |
| Bevacizumab plus standard laser | £12,142 | 9.240 | -£103 | 0.741 | -£139 | £172,661 (£158,433 to £185,722) |
| Brolucizumab | £25,046 | 9.282 | £12,801 | 0.783 | £16,352 | £160,589 (£146,501 to £175,002) |
| Faricimab | £34,416 | 9.280 | £22,171 | 0.782 | £28,367 | £151,193 (£136,082 to £166,119) |
| Fluocinolone acetonide | £52,945 | 9.203 | £40,700 | 0.704 | £57,832 | £131,108 (£111,999 to £148,151) |
| Dexamethasone | £18,891 | 9.201 | £6,646 | 0.702 | £9,462 | £165,135 (£151,019 to £178,666) |
| Subthreshold laser | £7,696 | 8.969 | -£4,549 | 0.470 | -£9,675 | £171,686 (£152,986 to £186,224) |

<Please insert your copyright statement - one line of text entry only>

**Source of sham arm change in BCVA from baseline: Massin et al (2010)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,817 | 8.487 | - | - | - | £165,932 (£153,381 to £180,480) |
| Standard threshold laser | £4,955 | 8.869 | £1,137 | 0.382 | £2,979 | £172,430 (£158,299 to £186,373) |
| Aflibercept | £34,614 | 9.228 | £30,796 | 0.741 | £41,585 | £149,947 (£134,471 to £163,980) |
| Ranibizumab | £24,283 | 9.166 | £20,466 | 0.678 | £30,181 | £159,028 (£145,446 to £172,646) |
| Ranibizumab plus standard laser | £25,021 | 9.140 | £21,203 | 0.653 | £32,482 | £157,784 (£144,012 to £170,514) |
| Bevacizumab | £9,665 | 9.149 | £5,847 | 0.662 | £8,835 | £173,321 (£159,396 to £186,509) |
| Bevacizumab plus standard laser | £11,470 | 9.169 | £7,652 | 0.681 | £11,233 | £171,905 (£157,416 to £185,555) |
| Brolucizumab | £24,546 | 9.249 | £20,729 | 0.761 | £27,224 | £160,431 (£146,538 to £172,784) |
| Faricimab | £34,151 | 9.243 | £30,334 | 0.756 | £40,148 | £150,709 (£136,073 to £164,223) |
| Fluocinolone acetonide | £51,505 | 9.121 | £47,687 | 0.633 | £75,293 | £130,912 (£113,677 to £147,958) |
| Dexamethasone | £17,769 | 9.112 | £13,951 | 0.624 | £22,343 | £164,469 (£151,346 to £177,195) |
| Subthreshold laser | £4,545 | 8.853 | £727 | 0.366 | £1,988 | £172,523 (£158,190 to £187,000) |

<Please insert your copyright statement - one line of text entry only>

**Source of sham arm change in BCVA from baseline: Sultan et al (2010)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,831 | 8.480 | - | - | - | £165,777 (£151,740 to £180,513) |
| Standard threshold laser | £4,767 | 9.025 | £937 | 0.545 | £1,720 | £175,732 (£162,719 to £189,134) |
| Aflibercept | £34,239 | 9.268 | £30,408 | 0.788 | £38,588 | £151,130 (£136,342 to £165,626) |
| Ranibizumab | £24,004 | 9.240 | £20,174 | 0.760 | £26,561 | £160,794 (£147,387 to £174,710) |
| Ranibizumab plus standard laser | £24,724 | 9.219 | £20,893 | 0.739 | £28,288 | £159,656 (£145,559 to £174,226) |
| Bevacizumab | £9,306 | 9.227 | £5,475 | 0.746 | £7,338 | £175,225 (£161,366 to £188,890) |
| Bevacizumab plus standard laser | £11,324 | 9.234 | £7,493 | 0.754 | £9,939 | £173,362 (£160,134 to £186,439) |
| Brolucizumab | £24,361 | 9.277 | £20,530 | 0.797 | £25,775 | £161,177 (£147,229 to £174,673) |
| Faricimab | £33,904 | 9.273 | £30,073 | 0.793 | £37,944 | £151,555 (£137,253 to £166,106) |
| Fluocinolone acetonide | £51,237 | 9.216 | £47,406 | 0.736 | £64,406 | £133,092 (£116,026 to £148,602) |
| Dexamethasone | £17,692 | 9.209 | £13,861 | 0.729 | £19,020 | £166,491 (£153,126 to £180,099) |
| Subthreshold laser | £4,405 | 9.012 | £574 | 0.532 | £1,081 | £175,833 (£161,696 to £189,535) |

<Please insert your copyright statement - one line of text entry only>

**Sham arm used as source of no treatment BCVA progression**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,728 | 8.648 | - | - | - | £169,242 (£158,252 to £180,102) |
| Standard threshold laser | £4,790 | 8.992 | £1,063 | 0.343 | £3,096 | £175,046 (£161,504 to £188,381) |
| Aflibercept | £34,196 | 9.279 | £30,469 | 0.631 | £48,313 | £151,387 (£136,300 to £165,869) |
| Ranibizumab | £23,963 | 9.239 | £20,236 | 0.591 | £34,251 | £160,823 (£146,875 to £173,905) |
| Ranibizumab plus standard laser | £24,682 | 9.222 | £20,955 | 0.573 | £36,568 | £159,748 (£145,669 to £172,736) |
| Bevacizumab | £9,421 | 9.224 | £5,693 | 0.575 | £9,895 | £175,057 (£161,825 to £188,812) |
| Bevacizumab plus standard laser | £11,267 | 9.235 | £7,539 | 0.587 | £12,854 | £173,434 (£158,911 to £187,026) |
| Brolucizumab | £24,365 | 9.287 | £20,638 | 0.638 | £32,344 | £161,366 (£147,388 to £174,793) |
| Faricimab | £34,003 | 9.284 | £30,275 | 0.635 | £47,675 | £151,668 (£137,788 to £166,175) |
| Fluocinolone acetonide | £51,446 | 9.206 | £47,718 | 0.557 | £85,650 | £132,667 (£115,375 to £148,457) |
| Dexamethasone | £17,795 | 9.192 | £14,067 | 0.543 | £25,903 | £166,037 (£153,155 to £179,024) |
| Subthreshold laser | £4,443 | 8.986 | £715 | 0.337 | £2,121 | £175,273 (£160,959 to £189,381) |

<Please insert your copyright statement - one line of text entry only>

**Sham arm used as source of long-term natural history BCVA progression**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,855 | 8.495 | - | - | - | £166,051 (£152,985 to £181,248) |
| Standard threshold laser | £4,807 | 8.996 | £952 | 0.501 | £1,900 | £175,118 (£161,379 to £188,605) |
| Aflibercept | £34,405 | 9.274 | £30,549 | 0.778 | £39,251 | £151,068 (£135,957 to £164,687) |
| Ranibizumab | £24,082 | 9.233 | £20,226 | 0.738 | £27,414 | £160,581 (£146,978 to £173,946) |
| Ranibizumab plus standard laser | £24,796 | 9.213 | £20,940 | 0.718 | £29,183 | £159,462 (£145,749 to £173,098) |
| Bevacizumab | £9,345 | 9.218 | £5,490 | 0.723 | £7,592 | £175,024 (£161,861 to £188,059) |
| Bevacizumab plus standard laser | £11,315 | 9.227 | £7,459 | 0.732 | £10,191 | £173,231 (£158,951 to £186,316) |
| Brolucizumab | £24,452 | 9.283 | £20,596 | 0.788 | £26,135 | £161,216 (£147,877 to £175,176) |
| Faricimab | £34,174 | 9.280 | £30,318 | 0.785 | £38,619 | £151,434 (£137,125 to £165,978) |
| Fluocinolone acetonide | £51,485 | 9.204 | £47,629 | 0.709 | £67,190 | £132,599 (£114,864 to £149,300) |
| Dexamethasone | £17,758 | 9.190 | £13,903 | 0.694 | £20,022 | £166,036 (£152,951 to £179,127) |
| Subthreshold laser | £4,458 | 8.971 | £603 | 0.476 | £1,266 | £174,972 (£161,005 to £189,033) |

<Please insert your copyright statement - one line of text entry only>

**Biosimilar price for ranibizumab**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,828 | 8.497 | - | - | - | £166,115 (£152,167 to £179,538) |
| Standard threshold laser | £4,801 | 8.993 | £973 | 0.496 | £1,961 | £175,062 (£160,977 to £188,857) |
| Aflibercept | £34,541 | 9.272 | £30,713 | 0.775 | £39,629 | £150,903 (£135,590 to £164,975) |
| Ranibizumab | £23,304 | 9.231 | £19,476 | 0.734 | £26,524 | £161,325 (£147,756 to £174,930) |
| Ranibizumab plus standard laser | £24,155 | 9.217 | £20,327 | 0.720 | £28,224 | £160,193 (£145,959 to £173,645) |
| Bevacizumab | £9,258 | 9.218 | £5,430 | 0.721 | £7,530 | £175,109 (£161,118 to £188,411) |
| Bevacizumab plus standard laser | £11,353 | 9.232 | £7,525 | 0.735 | £10,241 | £173,286 (£159,307 to £186,928) |
| Brolucizumab | £24,396 | 9.285 | £20,568 | 0.788 | £26,113 | £161,301 (£147,642 to £174,883) |
| Faricimab | £34,170 | 9.279 | £30,342 | 0.782 | £38,788 | £151,419 (£136,848 to £165,508) |
| Fluocinolone acetonide | £51,280 | 9.202 | £47,452 | 0.705 | £67,327 | £132,759 (£115,429 to £149,712) |
| Dexamethasone | £17,746 | 9.191 | £13,918 | 0.694 | £20,055 | £166,077 (£153,430 to £179,445) |
| Subthreshold laser | £4,450 | 8.971 | £622 | 0.474 | £1,311 | £174,979 (£160,180 to £188,341) |

<Please insert your copyright statement - one line of text entry only>

# Scenario analysis results – DMO (CRT≥400µm)

**Treatment and monitoring visits are separate**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,873 | 8.495 | - | - | - | £166,024 (£152,782 to £179,321) |
| Standard threshold laser | £5,253 | 8.940 | £1,381 | 0.446 | £3,099 | £173,553 (£159,898 to £187,748) |
| Aflibercept | £36,570 | 9.269 | £32,698 | 0.774 | £42,238 | £148,809 (£133,747 to £163,028) |
| Ranibizumab | £26,057 | 9.230 | £22,185 | 0.735 | £30,190 | £158,536 (£143,700 to £172,521) |
| Ranibizumab plus standard laser | £26,627 | 9.213 | £22,755 | 0.718 | £31,681 | £157,634 (£143,705 to £171,125) |
| Bevacizumab | £11,237 | 9.208 | £7,364 | 0.713 | £10,322 | £172,929 (£159,819 to £186,044) |
| Bevacizumab plus standard laser | £13,222 | 9.216 | £9,349 | 0.721 | £12,971 | £171,090 (£157,386 to £184,722) |
| Brolucizumab | £25,855 | 9.273 | £21,982 | 0.778 | £28,256 | £159,601 (£145,160 to £172,976) |
| Faricimab | £35,787 | 9.275 | £31,914 | 0.781 | £40,888 | £149,720 (£134,777 to £163,249) |
| Fluocinolone acetonide | £52,315 | 9.199 | £48,442 | 0.704 | £68,817 | £131,660 (£114,281 to £148,372) |
| Dexamethasone | £18,578 | 9.195 | £14,705 | 0.700 | £21,000 | £165,324 (£153,061 to £178,743) |
| Subthreshold laser | £4,834 | 8.930 | £9 | 0.436 | £2,207 | £173,774 (£160,234 to £187,907) |

<Please insert your copyright statement - one line of text entry only>

**Utility for treatment in both eyes: weighted average of BSE and WSE**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,824 | 8.827 | - | - | - | £172,725 (£159,535 to £185,344) |
| Standard threshold laser | £4,873 | 9.185 | £1,049 | 0.358 | £2,931 | £178,835 (£164,852 to £192,363) |
| Aflibercept | £34,338 | 9.437 | £30,514 | 0.610 | £50,050 | £154,404 (£137,616 to £168,685) |
| Ranibizumab | £23,970 | 9.406 | £20,146 | 0.579 | £34,792 | £164,159 (£149,660 to £177,233) |
| Ranibizumab plus standard laser | £24,801 | 9.393 | £20,977 | 0.566 | £37,067 | £163,066 (£149,263 to £176,567) |
| Bevacizumab | £9,449 | 9.392 | £5,625 | 0.564 | £9,966 | £178,387 (£164,000 to £191,184) |
| Bevacizumab plus standard laser | £11,402 | 9.393 | £7,578 | 0.566 | £13,392 | £176,464 (£162,349 to £189,772) |
| Brolucizumab | £24,509 | 9.440 | £20,685 | 0.613 | £33,744 | £164,300 (£150,466 to £178,616) |
| Faricimab | £34,118 | 9.441 | £30,294 | 0.613 | £49,396 | £154,696 (£139,755 to £168,646) |
| Fluocinolone acetonide | £51,608 | 9.386 | £47,784 | 0.559 | £85,528 | £136,114 (£118,558 to £152,460) |
| Dexamethasone | £17,813 | 9.368 | £13,989 | 0.541 | £25,864 | £169,553 (£155,904 to £181,902) |
| Subthreshold laser | £4,495 | 9.173 | £9 | 0.346 | £1,940 | £178,972 (£163,886 to £192,033) |

<Please insert your copyright statement - one line of text entry only>

**Utility source: Sharma et al (2002)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,841 | 9.716 | - | - | - | £190,474 (£176,092 to £204,706) |
| Standard threshold laser | £4,930 | 10.166 | £1,088 | 0.451 | £2,416 | £198,397 (£182,905 to £212,580) |
| Aflibercept | £34,454 | 10.552 | £30,613 | 0.836 | £36,604 | £176,587 (£159,932 to £191,101) |
| Ranibizumab | £24,103 | 10.500 | £20,262 | 0.784 | £25,841 | £185,894 (£171,191 to £199,487) |
| Ranibizumab plus standard laser | £24,781 | 10.484 | £20,940 | 0.768 | £27,253 | £184,901 (£169,492 to £199,603) |
| Bevacizumab | £9,384 | 10.476 | £5,542 | 0.760 | £7,292 | £200,132 (£184,422 to £213,797) |
| Bevacizumab plus standard laser | £11,319 | 10.483 | £7,478 | 0.767 | £9,745 | £198,343 (£183,773 to £211,958) |
| Brolucizumab | £24,374 | 10.547 | £20,532 | 0.831 | £24,709 | £186,561 (£171,404 to £199,880) |
| Faricimab | £34,139 | 10.556 | £30,298 | 0.840 | £36,051 | £176,985 (£160,830 to £192,007) |
| Fluocinolone acetonide | £51,549 | 10.462 | £47,708 | 0.746 | £63,963 | £157,684 (£137,742 to £174,948) |
| Dexamethasone | £17,766 | 10.461 | £13,925 | 0.745 | £18,680 | £191,458 (£176,729 to £205,020) |
| Subthreshold laser | £4,459 | 10.176 | £10 | 0.461 | £1,340 | £199,070 (£184,354 to £213,513) |

<Please insert your copyright statement - one line of text entry only>

**Utility source: Lloyd et al (2008)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,834 | 8.863 | - | - | - | £173,424 (£161,026 to £186,100) |
| Standard threshold laser | £4,881 | 9.139 | £1,046 | 0.276 | £3,794 | £177,895 (£165,246 to £190,966) |
| Aflibercept | £34,407 | 9.338 | £30,573 | 0.475 | £64,299 | £152,361 (£138,263 to £167,501) |
| Ranibizumab | £24,081 | 9.315 | £20,247 | 0.452 | £44,781 | £162,220 (£148,472 to £176,061) |
| Ranibizumab plus standard laser | £25,005 | 9.308 | £21,170 | 0.445 | £47,584 | £161,152 (£146,880 to £174,666) |
| Bevacizumab | £9,475 | 9.297 | £5,641 | 0.434 | £12,990 | £176,468 (£163,104 to £189,797) |
| Bevacizumab plus standard laser | £11,379 | 9.306 | £7,545 | 0.443 | £17,034 | £174,738 (£162,125 to £187,963) |
| Brolucizumab | £24,585 | 9.344 | £20,750 | 0.481 | £43,109 | £162,301 (£149,415 to £175,575) |
| Faricimab | £34,178 | 9.346 | £30,344 | 0.483 | £62,838 | £152,739 (£138,679 to £167,240) |
| Fluocinolone acetonide | £51,513 | 9.301 | £47,678 | 0.439 | £108,722 | £134,517 (£118,140 to £151,038) |
| Dexamethasone | £17,742 | 9.295 | £13,908 | 0.432 | £32,164 | £168,165 (£155,688 to £181,328) |
| Subthreshold laser | £4,519 | 9.134 | £9 | 0.271 | £2,522 | £178,164 (£165,266 to £191,179) |

<Please insert your copyright statement - one line of text entry only>

**Utility source: Mitchell et al (2012)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,859 | 9.602 | - | - | - | £188,174 (£176,189 to £199,795) |
| Standard threshold laser | £4,866 | 9.820 | £1,007 | 0.218 | £4,618 | £191,528 (£179,768 to £203,896) |
| Aflibercept | £34,240 | 9.956 | £30,381 | 0.355 | £85,680 | £164,885 (£150,772 to £178,610) |
| Ranibizumab | £24,070 | 9.940 | £20,211 | 0.339 | £59,671 | £174,737 (£162,190 to £187,548) |
| Ranibizumab plus standard laser | £24,720 | 9.936 | £20,861 | 0.334 | £62,462 | £173,993 (£162,321 to £187,215) |
| Bevacizumab | £9,378 | 9.933 | £5,519 | 0.332 | £16,647 | £189,286 (£176,741 to £201,790) |
| Bevacizumab plus standard laser | £11,317 | 9.935 | £7,458 | 0.334 | £22,355 | £187,388 (£174,980 to £199,400) |
| Brolucizumab | £24,412 | 9.963 | £20,553 | 0.361 | £56,934 | £174,841 (£162,310 to £187,529) |
| Faricimab | £34,071 | 9.961 | £30,212 | 0.360 | £84,038 | £165,152 (£151,318 to £178,554) |
| Fluocinolone acetonide | £51,265 | 9.935 | £47,406 | 0.333 | £142,411 | £147,425 (£131,209 to £162,689) |
| Dexamethasone | £17,750 | 9.926 | £13,891 | 0.324 | £42,815 | £180,772 (£168,641 to £192,740) |
| Subthreshold laser | £4,461 | 9.820 | £10 | 0.219 | £2,754 | £191,947 (£180,174 to £203,665) |

<Please insert your copyright statement - one line of text entry only>

**Utility source: Brown et al (2000)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,855 | 9.310 | - | - | - | £182,352 (£169,870 to £195,280) |
| Standard threshold laser | £4,898 | 9.546 | £1,043 | 0.236 | £4,417 | £186,032 (£173,036 to £199,221) |
| Aflibercept | £34,482 | 9.702 | £30,627 | 0.392 | £78,210 | £159,557 (£143,119 to £174,094) |
| Ranibizumab | £24,237 | 9.682 | £20,383 | 0.371 | £54,894 | £169,396 (£154,750 to £183,718) |
| Ranibizumab plus standard laser | £24,945 | 9.675 | £21,090 | 0.365 | £57,805 | £168,559 (£153,942 to £181,895) |
| Bevacizumab | £9,407 | 9.675 | £5,552 | 0.365 | £15,225 | £184,094 (£170,098 to £197,444) |
| Bevacizumab plus standard laser | £11,502 | 9.675 | £7,647 | 0.365 | £20,953 | £182,004 (£168,088 to £195,173) |
| Brolucizumab | £24,627 | 9.707 | £20,773 | 0.397 | £52,331 | £169,519 (£155,244 to £183,274) |
| Faricimab | £34,192 | 9.707 | £30,338 | 0.396 | £76,544 | £159,942 (£145,381 to £174,081) |
| Fluocinolone acetonide | £51,737 | 9.677 | £47,882 | 0.367 | £130,498 | £141,809 (£125,105 to £158,520) |
| Dexamethasone | £17,914 | 9.669 | £14,060 | 0.359 | £39,205 | £175,465 (£161,842 to £188,570) |
| Subthreshold laser | £4,483 | 9.548 | £10 | 0.238 | £2,641 | £186,481 (£173,584 to £199,654) |

<Please insert your copyright statement - one line of text entry only>

**Utility source: Pennington et al (2020)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,820 | 7.663 | - | - | - | £149,431 (£137,660 to £161,891) |
| Standard threshold laser | £4,886 | 8.025 | £1,066 | 0.363 | £2,938 | £155,621 (£143,840 to £167,553) |
| Aflibercept | £34,423 | 8.312 | £30,603 | 0.649 | £47,149 | £131,809 (£118,453 to £144,814) |
| Ranibizumab | £24,221 | 8.273 | £20,401 | 0.610 | £33,427 | £141,236 (£129,557 to £153,440) |
| Ranibizumab plus standard laser | £24,880 | 8.263 | £21,060 | 0.601 | £35,056 | £140,386 (£128,904 to £152,759) |
| Bevacizumab | £9,348 | 8.262 | £5,528 | 0.600 | £9,218 | £155,896 (£144,261 to £168,069) |
| Bevacizumab plus standard laser | £11,384 | 8.262 | £7,564 | 0.599 | £12,626 | £153,849 (£142,593 to £166,135) |
| Brolucizumab | £24,329 | 8.313 | £20,509 | 0.650 | £31,539 | £141,927 (£129,970 to £154,062) |
| Faricimab | £33,982 | 8.315 | £30,162 | 0.653 | £46,204 | £132,325 (£119,917 to £145,373) |
| Fluocinolone acetonide | £51,417 | 8.250 | £47,597 | 0.588 | £80,989 | £113,587 (£98,426 to £128,590) |
| Dexamethasone | £17,842 | 8.242 | £14,022 | 0.580 | £24,182 | £147,006 (£135,118 to £158,923) |
| Subthreshold laser | £4,443 | 8.028 | £8 | 0.366 | £1,704 | £156,124 (£144,077 to £168,699) |

<Please insert your copyright statement - one line of text entry only>

**25% of patients receive treatment after year 5**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,851 | 8.499 | - | - | - | £166,130 (£152,529 to £180,344) |
| Standard threshold laser | £5,034 | 8.945 | £1,183 | 0.446 | £2,654 | £173,861 (£160,407 to £187,213) |
| Aflibercept | £29,965 | 9.271 | £26,114 | 0.772 | £33,825 | £155,457 (£141,025 to £168,996) |
| Ranibizumab | £21,449 | 9.232 | £17,598 | 0.733 | £24,016 | £163,187 (£149,292 to £176,595) |
| Ranibizumab plus standard laser | £21,546 | 9.222 | £17,695 | 0.723 | £24,465 | £162,901 (£149,534 to £175,977) |
| Bevacizumab | £8,521 | 9.217 | £4,670 | 0.718 | £6,506 | £175,816 (£162,789 to £188,051) |
| Bevacizumab plus standard laser | £9,960 | 9.214 | £6,109 | 0.715 | £8,549 | £174,313 (£161,091 to £186,674) |
| Brolucizumab | £22,605 | 9.272 | £18,754 | 0.773 | £24,254 | £162,841 (£149,302 to £175,562) |
| Faricimab | £29,058 | 9.280 | £25,207 | 0.781 | £32,285 | £156,538 (£142,816 to £170,073) |
| Fluocinolone acetonide | £39,422 | 9.204 | £35,571 | 0.705 | £50,471 | £144,655 (£129,557 to £159,228) |
| Dexamethasone | £14,416 | 9.193 | £10,564 | 0.694 | £15,225 | £169,443 (£156,569 to £182,159) |
| Subthreshold laser | £4,514 | 8.934 | £9 | 0.435 | £1,524 | £174,172 (£160,535 to £188,263) |

<Please insert your copyright statement - one line of text entry only>

**75% of patients receive treatment after year 5**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,833 | 8.521 | - | - | - | £166,59 (£153,108 to £179,407) |
| Standard threshold laser | £4,857 | 8.950 | £1,024 | 0.429 | £2,387 | £174,151 (£160,186 to £188,096) |
| Aflibercept | £36,982 | 9.282 | £33,149 | 0.761 | £43,571 | £148,661 (£133,937 to £162,600) |
| Ranibizumab | £25,791 | 9.241 | £21,958 | 0.719 | £30,530 | £159,020 (£144,786 to £172,447) |
| Ranibizumab plus standard laser | £26,737 | 9.222 | £22,905 | 0.701 | £32,693 | £157,701 (£143,270 to £171,515) |
| Bevacizumab | £9,784 | 9.224 | £5,951 | 0.702 | £8,474 | £174,689 (£161,288 to £187,777) |
| Bevacizumab plus standard laser | £12,191 | 9.225 | £8,358 | 0.704 | £11,871 | £172,317 (£158,771 to £185,633) |
| Brolucizumab | £24,959 | 9.285 | £21,126 | 0.763 | £27,680 | £160,732 (£146,957 to £173,904) |
| Faricimab | £36,752 | 9.287 | £32,919 | 0.766 | £42,994 | £148,988 (£134,391 to £163,667) |
| Fluocinolone acetonide | £57,576 | 9.210 | £53,743 | 0.688 | £78,069 | £126,619 (£108,139 to £144,547) |
| Dexamethasone | £19,869 | 9.202 | £16,036 | 0.680 | £23,570 | £164,165 (£151,067 to £176,927) |
| Subthreshold laser | £4,483 | 8.955 | £9 | 0.434 | £1,500 | £174,617 (£159,793 to £187,239) |

<Please insert your copyright statement - one line of text entry only>

**Natural history assumed at 20 years**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,815 | 8.513 | - | - | - | £166,439 (£153,186 to £180,185) |
| Standard threshold laser | £4,872 | 8.942 | £1,057 | 0.429 | £2,465 | £173,961 (£160,318 to £188,203) |
| Aflibercept | £34,394 | 9.266 | £30,579 | 0.753 | £40,619 | £150,916 (£135,178 to £166,018) |
| Ranibizumab | £23,980 | 9.227 | £20,165 | 0.714 | £28,231 | £160,560 (£146,180 to £175,106) |
| Ranibizumab plus standard laser | £24,615 | 9.210 | £20,800 | 0.697 | £29,835 | £159,583 (£146,756 to £173,974) |
| Bevacizumab | £9,332 | 9.210 | £5,517 | 0.697 | £7,917 | £174,859 (£161,619 to £189,552) |
| Bevacizumab plus standard laser | £11,352 | 9.204 | £7,537 | 0.691 | £10,902 | £172,729 (£159,507 to £186,305) |
| Brolucizumab | £24,474 | 9.269 | £20,659 | 0.756 | £27,323 | £160,902 (£147,864 to £174,715) |
| Faricimab | £33,853 | 9.272 | £30,038 | 0.759 | £39,573 | £151,582 (£137,479 to £166,649) |
| Fluocinolone acetonide | £51,275 | 9.205 | £47,460 | 0.692 | £68,591 | £132,818 (£115,702 to £149,511) |
| Dexamethasone | £17,751 | 9.185 | £13,936 | 0.673 | £20,715 | £165,958 (£153,706 to £179,794) |
| Subthreshold laser | £4,469 | 8.935 | £9 | 0.423 | £1,548 | £174,238 (£160,078 to £189,540) |

116

<Please insert your copyright statement - one line of text entry only>

**Natural history assumed at 10 years**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,808 | 8.507 | - | - | - | £166,327 (£152,342 to £179,294) |
| Standard threshold laser | £4,938 | 8.846 | £1,130 | 0.339 | £3,329 | £171,984 (£158,276 to £185,321) |
| Aflibercept | £34,600 | 9.110 | £30,792 | 0.604 | £51,014 | £147,607 (£134,183 to £162,166) |
| Ranibizumab | £24,155 | 9.083 | £20,346 | 0.576 | £35,326 | £157,500 (£144,319 to £170,416) |
| Ranibizumab plus standard laser | £24,802 | 9.071 | £20,994 | 0.565 | £37,184 | £156,625 (£143,582 to £169,308) |
| Bevacizumab | £9,500 | 9.066 | £5,692 | 0.559 | £10,184 | £171,813 (£159,075 to £184,042) |
| Bevacizumab plus standard laser | £11,351 | 9.068 | £7,543 | 0.561 | £13,438 | £170,010 (£157,375 to £182,413) |
| Brolucizumab | £24,516 | 9.115 | £20,707 | 0.608 | £34,062 | £157,778 (£145,156 to £170,105) |
| Faricimab | £34,068 | 9.114 | £30,260 | 0.607 | £49,831 | £148,212 (£134,020 to £161,256) |
| Fluocinolone acetonide | £51,718 | 9.058 | £47,909 | 0.551 | £86,956 | £129,437 (£111,598 to £145,250) |
| Dexamethasone | £17,775 | 9.051 | £13,966 | 0.544 | £25,672 | £163,241 (£151,044 to £175,410) |
| Subthreshold laser | £4,574 | 8.851 | £9 | 0.344 | £2,222 | £172,451 (£159,238 to £185,078) |

<Please insert your copyright statement - one line of text entry only>

**Natural history assumed at 5 years**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,851 | 8.509 | - | - | - | £166,331 (£152,703 to £180,770) |
| Standard threshold laser | £5,064 | 8.729 | £1,213 | 0.220 | £5,519 | £169,513 (£156,438 to £182,680) |
| Aflibercept | £34,461 | 8.887 | £30,610 | 0.378 | £80,921 | £143,286 (£129,368 to £157,420) |
| Ranibizumab | £24,385 | 8.869 | £20,534 | 0.360 | £56,980 | £153,004 (£140,717 to £166,130) |
| Ranibizumab plus standard laser | £25,086 | 8.862 | £21,235 | 0.353 | £60,206 | £152,150 (£139,231 to £164,569) |
| Bevacizumab | £9,704 | 8.862 | £5,853 | 0.353 | £16,603 | £167,528 (£154,558 to £180,516) |
| Bevacizumab plus standard laser | £11,696 | 8.864 | £7,845 | 0.354 | £22,135 | £165,574 (£153,127 to £178,605) |
| Brolucizumab | £24,618 | 8.892 | £20,767 | 0.383 | £54,229 | £153,223 (£141,032 to £166,174) |
| Faricimab | £34,278 | 8.892 | £30,427 | 0.383 | £79,426 | £143,566 (£130,559 to £157,490) |
| Fluocinolone acetonide | £51,989 | 8.864 | £48,138 | 0.355 | £135,612 | £125,292 (£108,832 to £142,381) |
| Dexamethasone | £18,075 | 8.853 | £14,224 | 0.344 | £41,339 | £158,988 (£146,335 to £171,047) |
| Subthreshold laser | £4,686 | 8.729 | £9 | 0.220 | £3,796 | £169,896 (£156,990 to £182,867) |

<Please insert your copyright statement - one line of text entry only>

**Monitoring and treatment frequency: minimum reported**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,827 | 8.499 | - | - | - | £166,148 (£152,151 to £180,375) |
| Standard threshold laser | £4,028 | 8.934 | £201 | 0.435 | £462 | £174,647 (£159,315 to £189,187) |
| Aflibercept | £21,720 | 9.279 | £17,893 | 0.780 | £22,943 | £163,853 (£150,576 to £177,808) |
| Ranibizumab | £18,257 | 9.237 | £14,430 | 0.738 | £19,546 | £166,483 (£153,385 to £180,269) |
| Ranibizumab plus standard laser | £21,818 | 9.217 | £17,991 | 0.718 | £25,053 | £162,520 (£148,822 to £176,633) |
| Bevacizumab | £6,880 | 9.220 | £3,053 | 0.721 | £4,235 | £177,514 (£164,053 to £191,212) |
| Bevacizumab plus standard laser | £10,246 | 9.221 | £6,419 | 0.722 | £8,893 | £174,166 (£160,788 to £188,194) |
| Brolucizumab | £24,469 | 9.271 | £20,642 | 0.772 | £26,744 | £160,943 (£147,082 to £175,385) |
| Faricimab | £31,518 | 9.279 | £27,691 | 0.780 | £35,486 | £154,064 (£139,861 to £168,788) |
| Fluocinolone acetonide | £21,376 | 9.207 | £17,549 | 0.708 | £24,786 | £162,759 (£149,074 to £176,378) |
| Dexamethasone | £17,710 | 9.194 | £13,883 | 0.695 | £19,982 | £166,160 (£152,388 to £179,521) |
| Subthreshold laser | £3,724 | 8.936 | £9 | 0.437 | -£236 | £174,987 (£160,622 to £189,146) |

<Please insert your copyright statement - one line of text entry only>

**Monitoring and treatment frequency: maximum reported**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,815 | 8.478 | - | - | - | £165,739 (£152,087 to £179,928) |
| Standard threshold laser | £5,630 | 8.906 | £1,814 | 0.429 | £4,233 | £172,497 (£158,394 to £186,878) |
| Aflibercept | £51,147 | 9.222 | £47,331 | 0.744 | £63,623 | £133,287 (£117,755 to £149,435) |
| Ranibizumab | £29,577 | 9.186 | £25,761 | 0.709 | £36,355 | £154,150 (£140,632 to £167,735) |
| Ranibizumab plus standard laser | £29,782 | 9.172 | £25,967 | 0.694 | £37,418 | £153,652 (£140,167 to £167,390) |
| Bevacizumab | £11,298 | 9.163 | £7,483 | 0.686 | £10,912 | £171,971 (£159,158 to £185,572) |
| Bevacizumab plus standard laser | £13,119 | 9.166 | £9,304 | 0.688 | £13,523 | £170,195 (£156,746 to £183,174) |
| Brolucizumab | £24,333 | 9.237 | £20,517 | 0.760 | £27,009 | £160,415 (£147,045 to £173,832) |
| Faricimab | £36,829 | 9.235 | £33,013 | 0.757 | £43,584 | £147,875 (£133,697 to £161,778) |
| Fluocinolone acetonide | £51,642 | 9.158 | £47,827 | 0.680 | £70,338 | £131,511 (£115,019 to £147,151) |
| Dexamethasone | £17,854 | 9.151 | £14,039 | 0.673 | £20,855 | £165,164 (£151,943 to £178,703) |
| Subthreshold laser | £5,086 | 8.902 | £9 | 0.424 | £2,995 | £172,953 (£158,548 to £187,519) |

<Please insert your copyright statement - one line of text entry only>

**Monitoring and treatment frequency: assumed the same across anti-VEGFs**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,662 | 8.506 | - | - | - | £166,453 (£153,038 to £180,673) |
| Standard threshold laser | £4,947 | 8.940 | £1,285 | 0.434 | £2,960 | £173,853 (£160,259 to £187,407) |
| Aflibercept | £33,119 | 9.280 | £29,458 | 0.774 | £38,051 | £152,479 (£140,211 to £164,774) |
| Ranibizumab | £23,022 | 9.242 | £19,361 | 0.736 | £26,308 | £161,811 (£149,624 to £174,819) |
| Ranibizumab plus standard laser | £24,081 | 9.226 | £20,419 | 0.720 | £28,363 | £160,433 (£148,046 to £173,229) |
| Bevacizumab | £8,340 | 9.220 | £4,679 | 0.714 | £6,552 | £176,056 (£163,062 to £188,829) |
| Bevacizumab plus standard laser | £10,628 | 9.220 | £6,967 | 0.714 | £9,751 | £173,776 (£160,227 to £186,663) |
| Brolucizumab | £23,958 | 9.276 | £20,296 | 0.770 | £26,356 | £161,559 (£149,055 to £174,545) |
| Faricimab | £33,440 | 9.288 | £29,778 | 0.782 | £38,090 | £152,311 (£140,026 to £165,064) |
| Fluocinolone acetonide | £58,031 | 9.211 | £54,370 | 0.705 | £77,136 | £126,181 (£113,355 to £139,295) |
| Dexamethasone | £17,536 | 9.201 | £13,874 | 0.696 | £19,945 | £166,491 (£153,968 to £178,925) |
| Subthreshold laser | £4,483 | 8.947 | £9 | 0.441 | £1,861 | £174,457 (£160,331 to £189,066) |

121

<Please insert your copyright statement - one line of text entry only>

**Patient costs included**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £12,001 | 8.501 | - | - | - | £158,009 (£139,044 to £177,316) |
| Standard threshold laser | £8,345 | 8.942 | -£3,656 | 0.441 | -£8,287 | £170,490 (£151,867 to £186,084) |
| Aflibercept | £35,116 | 9.266 | £23,115 | 0.765 | £30,210 | £150,197 (£134,750 to £164,155) |
| Ranibizumab | £25,043 | 9.227 | £13,042 | 0.726 | £17,957 | £159,494 (£145,467 to £172,976) |
| Ranibizumab plus standard laser | £26,010 | 9.206 | £14,009 | 0.706 | £19,853 | £158,113 (£143,771 to £171,607) |
| Bevacizumab | £10,523 | 9.209 | -£1,478 | 0.709 | -£2,085 | £173,661 (£160,170 to £187,419) |
| Bevacizumab plus standard laser | £12,420 | 9.210 | £419 | 0.710 | £590 | £171,788 (£157,466 to £185,462) |
| Brolucizumab | £25,143 | 9.267 | £13,141 | 0.767 | £17,135 | £160,207 (£146,307 to £174,216) |
| Faricimab | £34,725 | 9.271 | £22,723 | 0.770 | £29,505 | £150,689 (£136,357 to £164,657) |
| Fluocinolone acetonide | £52,529 | 9.202 | £40,528 | 0.701 | £57,792 | £131,507 (£113,991 to £147,965) |
| Dexamethasone | £18,870 | 9.189 | £6,869 | 0.689 | £9,971 | £164,919 (£151,437 to £178,036) |
| Subthreshold laser | £7,988 | 8.935 | £9 | 0.434 | -£9,242 | £170,707 (£152,415 to £186,625) |

<Please insert your copyright statement - one line of text entry only>

**Source of sham arm change in BCVA from baseline: Massin et al (2010)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,880 | 8.472 | - | - | - | £165,557 (£152,103 to £178,968) |
| Standard threshold laser | £5,027 | 8.791 | £1,147 | 0.320 | £3,590 | £170,800 (£155,914 to £185,750) |
| Aflibercept | £34,341 | 9.216 | £30,461 | 0.744 | £40,919 | £149,984 (£134,549 to £164,073) |
| Ranibizumab | £24,128 | 9.155 | £20,248 | 0.684 | £29,618 | £158,981 (£143,815 to £172,478) |
| Ranibizumab plus standard laser | £24,853 | 9.131 | £20,973 | 0.660 | £31,796 | £157,776 (£143,262 to £171,837) |
| Bevacizumab | £9,575 | 9.130 | £5,695 | 0.658 | £8,651 | £173,028 (£157,991 to £186,991) |
| Bevacizumab plus standard laser | £11,582 | 9.131 | £7,701 | 0.659 | £11,689 | £171,032 (£156,074 to £184,657) |
| Brolucizumab | £24,501 | 9.221 | £20,621 | 0.749 | £27,529 | £159,917 (£145,988 to £173,857) |
| Faricimab | £34,351 | 9.231 | £30,470 | 0.759 | £40,145 | £150,267 (£135,994 to £163,759) |
| Fluocinolone acetonide | £51,387 | 9.113 | £47,507 | 0.641 | £74,127 | £130,867 (£113,433 to £148,075) |
| Dexamethasone | £17,863 | 9.102 | £13,983 | 0.630 | £22,206 | £164,168 (£150,012 to £177,893) |
| Subthreshold laser | £4,582 | 8.817 | £9 | 0.345 | £2,036 | £171,753 (£156,193 to £187,069) |

123

<Please insert your copyright statement - one line of text entry only>

**Source of sham arm change in BCVA from baseline: Sultan et al (2010)**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,839 | 8.499 | - | - | - | £166,142 (£153,363 to £180,159) |
| Standard threshold laser | £4,850 | 8.989 | £1,011 | 0.490 | £2,063 | £174,927 (£161,509 to £188,082) |
| Aflibercept | £34,458 | 9.274 | £30,619 | 0.775 | £39,510 | £151,023 (£136,749 to £164,034) |
| Ranibizumab | £24,138 | 9.242 | £20,299 | 0.743 | £27,320 | £160,703 (£147,138 to £173,659) |
| Ranibizumab plus standard laser | £24,922 | 9.235 | £21,083 | 0.736 | £28,640 | £159,782 (£146,042 to £172,423) |
| Bevacizumab | £9,573 | 9.235 | £5,733 | 0.736 | £7,789 | £175,130 (£161,990 to £187,953) |
| Bevacizumab plus standard laser | £11,350 | 9.230 | £7,511 | 0.731 | £10,269 | £173,259 (£161,034 to £186,245) |
| Brolucizumab | £24,490 | 9.282 | £20,651 | 0.783 | £26,377 | £161,150 (£148,576 to £174,124) |
| Faricimab | £33,988 | 9.278 | £30,148 | 0.779 | £38,701 | £151,574 (£137,791 to £164,750) |
| Fluocinolone acetonide | £51,773 | 9.222 | £47,933 | 0.723 | £66,309 | £132,666 (£114,761 to £148,195) |
| Dexamethasone | £17,660 | 9.215 | £13,820 | 0.716 | £19,295 | £166,647 (£153,968 to £179,579) |
| Subthreshold laser | £4,426 | 8.992 | £9 | 0.493 | £1,190 | £175,421 (£161,981 to £189,184) |

<Please insert your copyright statement - one line of text entry only>

**Sham arm used as source of no treatment BCVA progression**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,715 | 8.629 | - | - | - | £168,867 (£157,299 to £180,317) |
| Standard threshold laser | £4,898 | 8.916 | £1,183 | 0.287 | £4,126 | £173,420 (£158,142 to £187,465) |
| Aflibercept | £34,097 | 9.256 | £30,382 | 0.626 | £48,501 | £151,014 (£136,759 to £164,589) |
| Ranibizumab | £24,043 | 9.219 | £20,328 | 0.589 | £34,488 | £160,328 (£146,463 to £173,196) |
| Ranibizumab plus standard laser | £24,771 | 9.203 | £21,056 | 0.574 | £36,714 | £159,282 (£145,194 to £172,703) |
| Bevacizumab | £9,336 | 9.197 | £5,621 | 0.568 | £9,898 | £174,604 (£162,191 to £188,164) |
| Bevacizumab plus standard laser | £11,356 | 9.200 | £7,641 | 0.571 | £13,375 | £172,652 (£158,685 to £185,430) |
| Brolucizumab | £24,369 | 9.263 | £20,654 | 0.633 | £32,605 | £160,883 (£147,099 to £173,889) |
| Faricimab | £34,022 | 9.266 | £30,307 | 0.637 | £47,614 | £151,291 (£137,778 to £165,239) |
| Fluocinolone acetonide | £51,566 | 9.187 | £47,851 | 0.558 | £85,805 | £132,170 (£114,335 to £148,260) |
| Dexamethasone | £17,695 | 9.174 | £13,980 | 0.545 | £25,643 | £165,791 (£153,013 to £178,486) |
| Subthreshold laser | £4,474 | 8.922 | £9 | 0.292 | £2,594 | £173,958 (£160,147 to £188,034) |

<Please insert your copyright statement - one line of text entry only>

**Sham arm used as source of long-term natural history BCVA progression**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,830 | 8.487 | - | - | - | £165,913 (£151,303 to £179,973) |
| Standard threshold laser | £4,873 | 8.921 | £1,043 | 0.434 | £2,404 | £173,548 (£159,769 to £187,771) |
| Aflibercept | £34,297 | 9.250 | £30,468 | 0.763 | £39,915 | £150,711 (£135,543 to £166,072) |
| Ranibizumab | £24,178 | 9.208 | £20,348 | 0.721 | £28,216 | £159,988 (£145,533 to £173,837) |
| Ranibizumab plus standard laser | £25,056 | 9.195 | £21,226 | 0.708 | £29,979 | £158,847 (£144,077 to £172,514) |
| Bevacizumab | £9,368 | 9.193 | £5,538 | 0.706 | £7,842 | £174,499 (£160,645 to £187,647) |
| Bevacizumab plus standard laser | £11,502 | 9.195 | £7,672 | 0.708 | £10,836 | £172,401 (£158,612 to £186,257) |
| Brolucizumab | £24,530 | 9.253 | £20,700 | 0.766 | £27,017 | £160,537 (£146,116 to £174,268) |
| Faricimab | £34,129 | 9.258 | £30,299 | 0.771 | £39,318 | £151,026 (£136,424 to £165,009) |
| Fluocinolone acetonide | £51,201 | 9.178 | £47,371 | 0.691 | £68,581 | £132,357 (£114,366 to £149,369) |
| Dexamethasone | £17,702 | 9.173 | £13,872 | 0.686 | £20,219 | £165,763 (£152,092 to £179,378) |
| Subthreshold laser | £4,492 | 8.916 | £9 | 0.429 | £1,542 | £173,835 (£159,370 to £188,725) |

<Please insert your copyright statement - one line of text entry only>

**Biosimilar price for ranibizumab**

| Treatment | Absolute costs | Absolute QALYs | Incremental costs | Incremental QALYs | ICER | NMB at £20K/QALY (95% CI) |
|---|---|---|---|---|---|---|
| No treatment | £3,840 | 8.486 | - | - | - | £165,888 (£151,460 to £179,466) |
| Standard threshold laser | £4,899 | 8.936 | £1,060 | 0.449 | £2,358 | £173,817 (£160,173 to £187,803) |
| Aflibercept | £34,520 | 9.260 | £30,680 | 0.774 | £39,638 | £150,688 (£135,085 to £165,200) |
| Ranibizumab | £23,252 | 9.225 | £19,413 | 0.739 | £26,276 | £161,251 (£147,381 to £174,920) |
| Ranibizumab plus standard laser | £24,164 | 9.210 | £20,324 | 0.724 | £28,073 | £160,043 (£146,307 to £173,534) |
| Bevacizumab | £9,320 | 9.203 | £5,480 | 0.717 | £7,643 | £174,748 (£161,040 to £189,195) |
| Bevacizumab plus standard laser | £11,377 | 9.206 | £7,537 | 0.720 | £10,473 | £172,744 (£158,675 to £186,652) |
| Brolucizumab | £24,458 | 9.264 | £20,618 | 0.777 | £26,532 | £160,812 (£146,954 to £175,270) |
| Faricimab | £34,299 | 9.266 | £30,459 | 0.780 | £39,061 | £151,025 (£136,522 to £165,287) |
| Fluocinolone acetonide | £51,786 | 9.195 | £47,946 | 0.708 | £67,695 | £132,107 (£114,424 to £149,190) |
| Dexamethasone | £17,727 | 9.185 | £13,887 | 0.698 | £19,889 | £165,966 (£152,245 to £179,610) |
| Subthreshold laser | £4,468 | 8.937 | £9 | 0.451 | £1,392 | £174,281 (£159,976 to £188,273) |

<Please insert your copyright statement - one line of text entry only>