National Institute for Health and Care Excellence

Final

Diabetic retinopathy: management and monitoring

Economic model report for evidence reviews E and G

NICE guideline NG242

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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?

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 included the population for both people with non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) who did 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 was 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 formed 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 (TAs) 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.

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 the 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
- 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 this 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.

Intravitreal steroids are also treatments of interest in DMO, namely: dexamethasone (TA824) and fluocinolone (TA301). Intravitreal steroids are predominantly used as second line therapies and are only considered as first line treatments for patients in whom other first line treatments are not suitable or who had not responded to previous treatments (mainly laser), which would be a different population to that considered in this economic analysis. It was

therefore decided that these treatments would not be included in the economic model. In health economic analysis, it is imperative to justify the choice of alternative interventions to make appropriate comparisons. Consequently, the focus of this economic analysis was first line therapies only. Combination treatment of intravitreal steroids plus anti-VEGF agents was also not considered a comparator of interest as the committee 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 all 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 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. 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 for transitions by one health state in each 3-monthly 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.

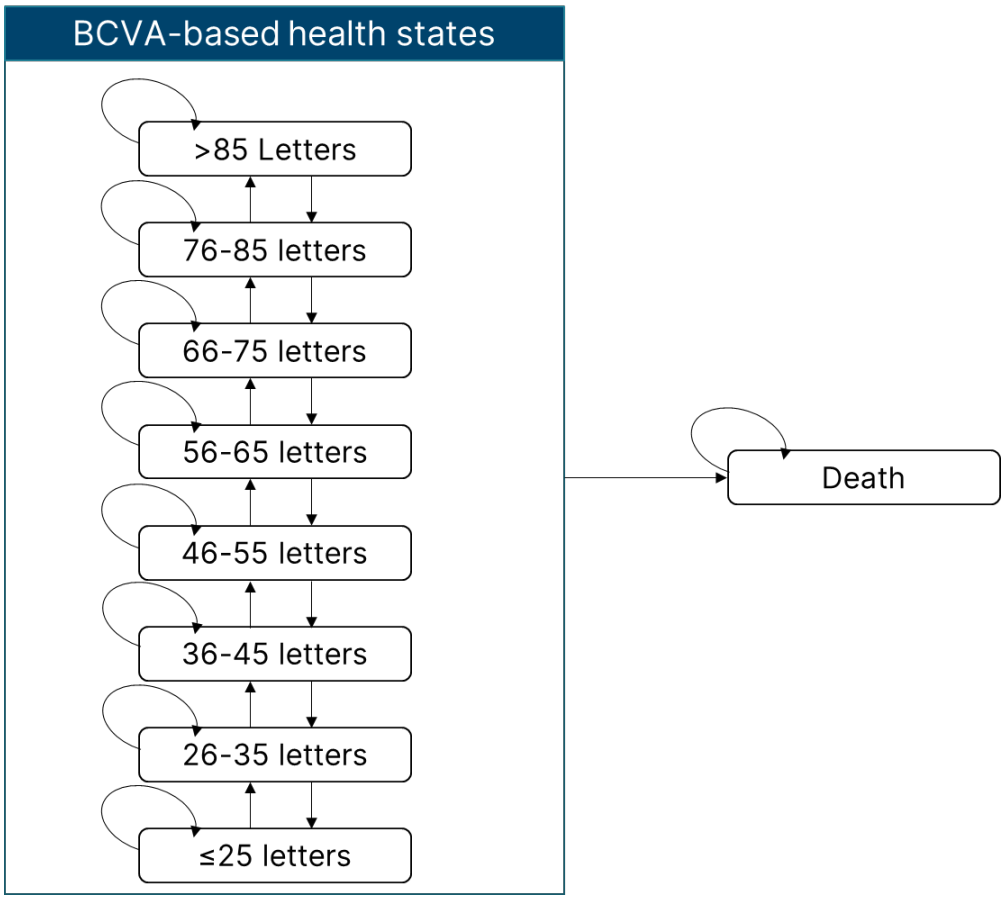

Figure HE001: Markov model structure showing possible health state transitions

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.

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). 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.

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 This study included patients on fluocinolone, but it was deemed to be the best available evidence.

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 and reported by Pochopien et al 2019. This study included patients on fluocinolone, but it was deemed to be the best available evidence.

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

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 effects from the NMA in the first year 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. In the PDR model, an important scenario was also explored around assuming stability of visual acuity following the application of the initial treatment effects.

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 (Sivaprasad et al 2017) and PRIDE (Lang et al 2020) trials 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.

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%

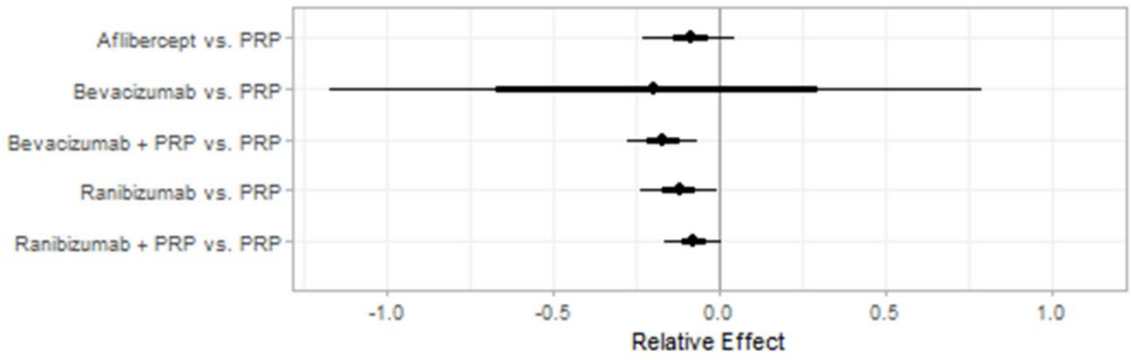

Figure 2: Forest plot of mean difference in BCVA for PDR (LogMAR)

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.

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%

Adverse events	PRP	Aflibercept	Ranibizumab	Ranibizumab plus PRP*	Bevacizumab*	Bevacizumab plus PRP*
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%
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 efficacy 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%

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
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 (-0.440 to -0.176)	-0.315	7.06%	1.47%
Faricimab	-0.301 (-0.421 to -0.181)	-0.308	7.13%	1.53%
Subthreshold laser	-0.100 (-0.220 to -0.020)	-0.106	7.27%	4.19%

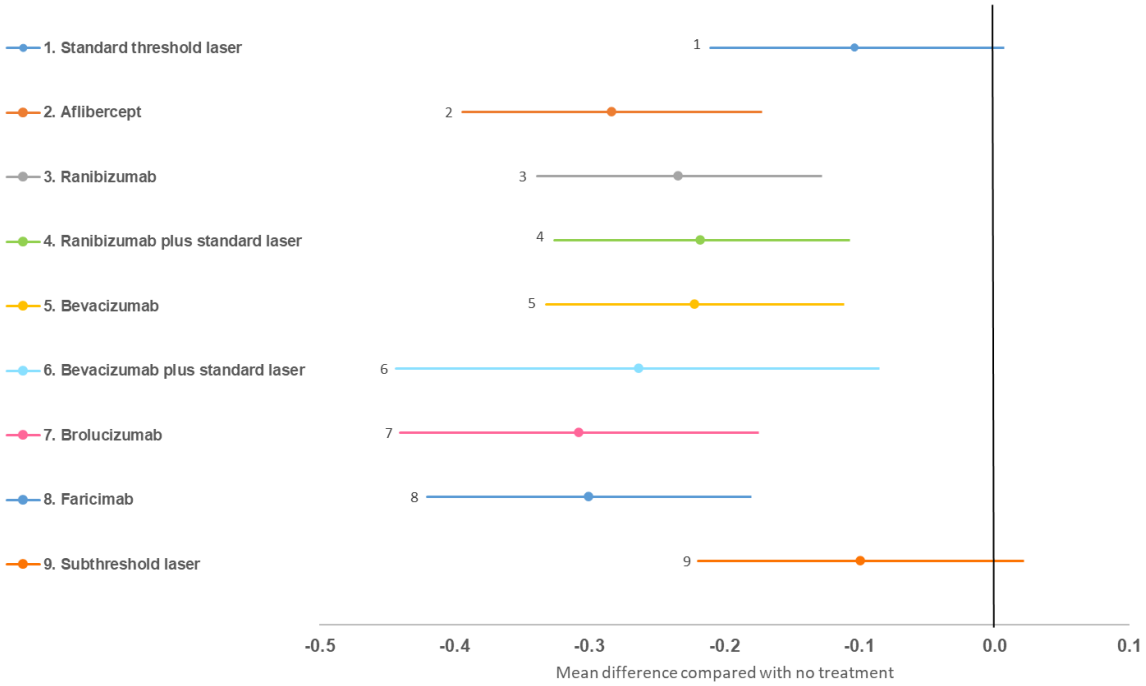

Figure 3: Forest plot of mean difference in BCVA for DMO (LogMAR)

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.

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%
Subthreshold laser*	-0.087 (-0.202 to 0.030)	-0.094	7.15%	4.40%

**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.

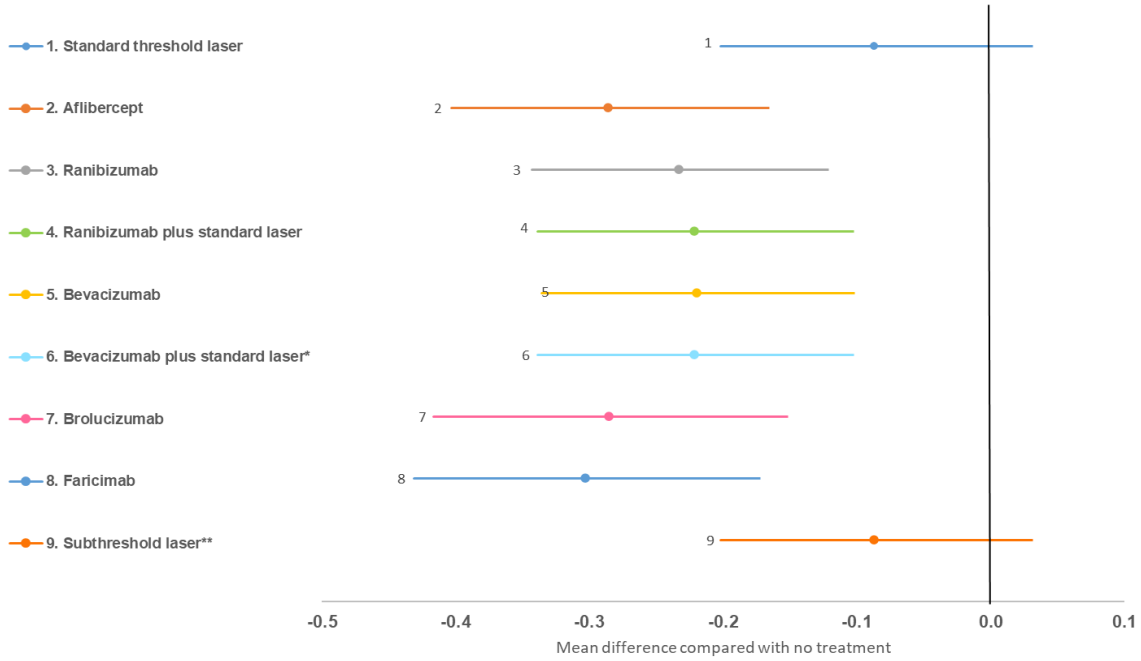

Figure 4: Forest plot of mean difference in BCVA for DMO with CRT≥400µm (LogMAR)

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. 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) 75% (scenario) 25% (scenario)	Yes	TA799 scrutiny panel Wykoff et al (2018) Minimum value expected

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
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 54).

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. 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).

- 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 29). 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.

Table 12: Health state utility values for best seeing eye

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

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. 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**

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. 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 Royle 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 56*

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	TA349, reported in TA824
Standard threshold laser	4.00	3.33	2.80	2.60	2.45	Average across sources (Table 56 in Appendix)
Aflibercept	10.17	7.63	4.52	4.00	3.20	Average across sources (Table 56 in Appendix)
Ranibizumab	10.89	7.81	4.94	4.00	3.20	Average across sources (Table 56 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 56 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 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 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 Table 18 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

Resource	Unit costs (£)	Source
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.

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)	Assumed same as year 2	Assumed same as year 2	Assumed same as year 2

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5 onwards
	Gross et al (2015)	45% of patients required additional PRP			

**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 and faricimab. 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
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) are presented in Table 22. 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.

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 55 in Appendix)
Ranibizumab	8.28	4.48	2.28	1.71	1.63	Average across sources (Table 55 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

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5 onwards	Source
Faricimab	7.06	4.24	1.97	1.97	1.97	Average across sources (Table 55 in Appendix)
Subthreshold laser	0.00	0.00	0.00	0.00	0.00	N/A

The frequency of laser treatments for each treatment strategy are presented in Table 23. 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 23: 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
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
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 24) 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 25. These values are calculated using the weightings in Table 24, and costs included are the treatment itself, administration and treatment specific adverse events.

Table 24: 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%

To\From	PRP	Aflibercept	Ranibizumab	Bevacizumab
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 25: Subsequent treatment cost by first line regimen

First line regimen	Cost of subsequent treatment (£)
PRP	£483.28
Aflibercept	£25.34
Ranibizumab	£25.34
Ranibizumab plus PRP	-
Bevacizumab	£25.34
Bevacizumab plus PRP	-

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). The total cost of subsequent treatment expected for each first line treatment strategy is presented in Table 26. These values are calculated using the weightings in Table 53 and costs included are the treatment itself, administration and treatment specific adverse events.

Table 26: Subsequent treatment cost by first line regimen

First line regimen	Cost of subsequent treatment (£)
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
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 27. 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 27: 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+).
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 28.

Table 28: Low vision costs (per 3-monthly cycle)

Resource	Costs (£)	Source/Notes
Healthcare costs associated with low vision	£421.61	Régnier et al (2015) 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.
Low vision community patient costs (scenario only)	£4,966.69	Régnier et al (2015) 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 29, including details of the distributions and parameters used in probabilistic sensitivity analysis (PSA).

Table 29: 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	μ=0.668, σ=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

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
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	α=75.900, β=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
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

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
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)
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
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

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
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
Subthreshold laser (vs sham)	-0.087	Normal	μ=-0.087, σ=0.059	Assumed same as standard threshold laser
Treatment discontinuation				
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
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				

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
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	
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	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: 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	
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	Czoski-Murray (2009)
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	
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	Czoski-Murray (2009), assuming a utility decrement of 0.1 between the best and worst health states (and a
Treated eye BCVA: 76-85	0.836	Beta	α=62.274, β=12.242	

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Treated eye BCVA: 66-75	0.821	Beta	α=67.776, β=14.734	linear decline in utility for the other states) based on the approach used by Régnier et al (2015)
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	
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 30. The assumptions were applied to the economic models for both RQ5 (diabetic retinopathy) and RQ7 (DMO) unless otherwise specified.

Table 30: 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

Category	Assumption	Justification
		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.
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

Category	Assumption	Justification
		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%.
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 in 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-monthly 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.

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 31: 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% • 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) • Sharma et al (2002) • Lloyd et al (2008) • Mitchell et al (2012) • Pennington et al (2020)
Proportion of patients receiving treatment after year 5	• 50%	• 75% (maximum) • 25% (minimum)
Year in which natural history efficacy assumed	• Lifetime	• 20 years • 10 years • 5 years

Category	Base-case	Scenarios
Patient costs included	• No	• Patient costs associated with only low vision were included as a scenario
Treatment effect assumptions	• Treatment effects from the NMA in the first year were applied for the remainder of the lifetime	• PRP: Treatment effect from the NMA was applied for the first year followed by stable visual acuity for the remainder of the lifetime Anti-VEGFs: Treatment effects from the NMA were applied for the first year followed by a linear decline between the first and second years, and stable visual acuity after year 2

BSE: Best seeing eye; WSE: Worst seeing eye

RQ7: Diabetic macular oedema

Table 32: Scenarios considered in the analysis for DMO

Category	Base-case	Scenarios
Monitoring and treatment frequency	• Average across sources for each treatment	• Minimum frequency reported • Maximum frequency reported • 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) • Sharma et al (2002) • Lloyd et al (2008) • Mitchell et al (2012) • Pennington et al (2020)
Proportion of patients receiving treatment after year 5	• 50%	• 75% (maximum) • 25% (minimum)
Year in which natural history efficacy assumed	• Lifetime	• 20 years • 10 years • 5 years
Natural history source	• No treatment: Mitchell et al (2012) • After treatment: Mitchell et al (2012)	• No treatment: sham After treatment: Mitchell et al (2012) • No treatment: sham 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) • 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 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.

HE3 Results

Throughout this section only results of the list price analyses are presented in full. All of the anti-VEGF treatments (except bevacizumab) 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 33 and Table 34. 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 35 shows the ranking of treatments by NMB at £20,000 per QALY under the confidential prices.

The committee considered the probabilistic results presented in HE3.1.2 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 33: 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

Table 34: 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 35: 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; NMB: Net monetary benefit*

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 36. 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

£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 37 shows the ranking of treatments by NMB at £20,000 per QALY under the confidential prices.

Table 36: 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 37: 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; NMB: Net monetary benefit*

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.

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.

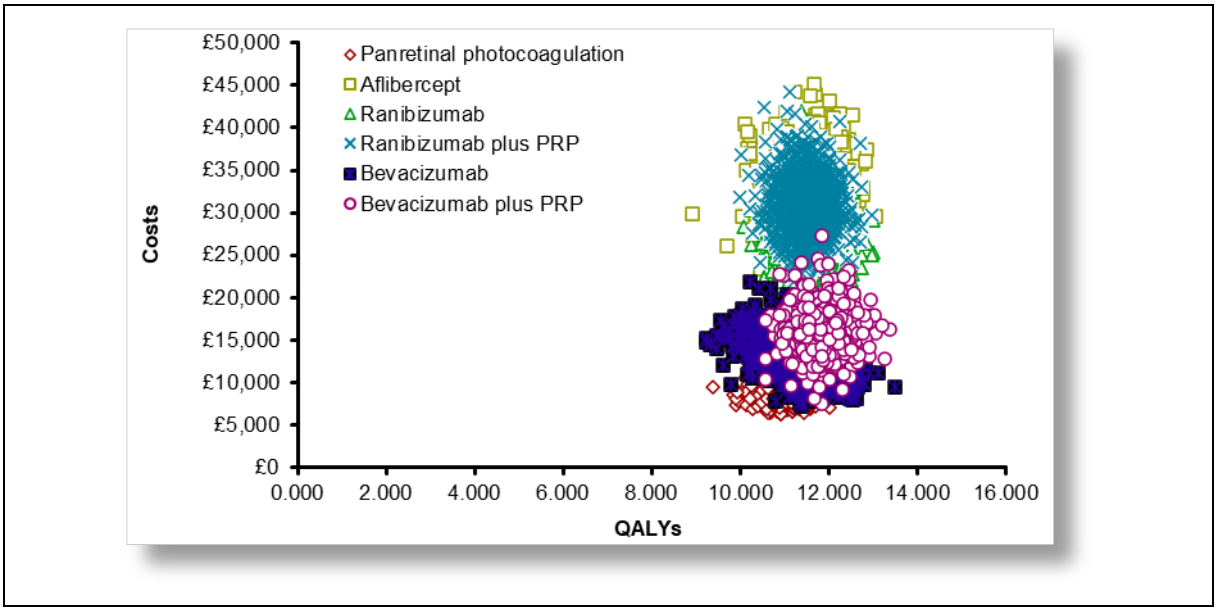

Figure HE005: PDR base-case probabilistic results (list price) – scatter plot of expected costs and QALYs obtained from PSA

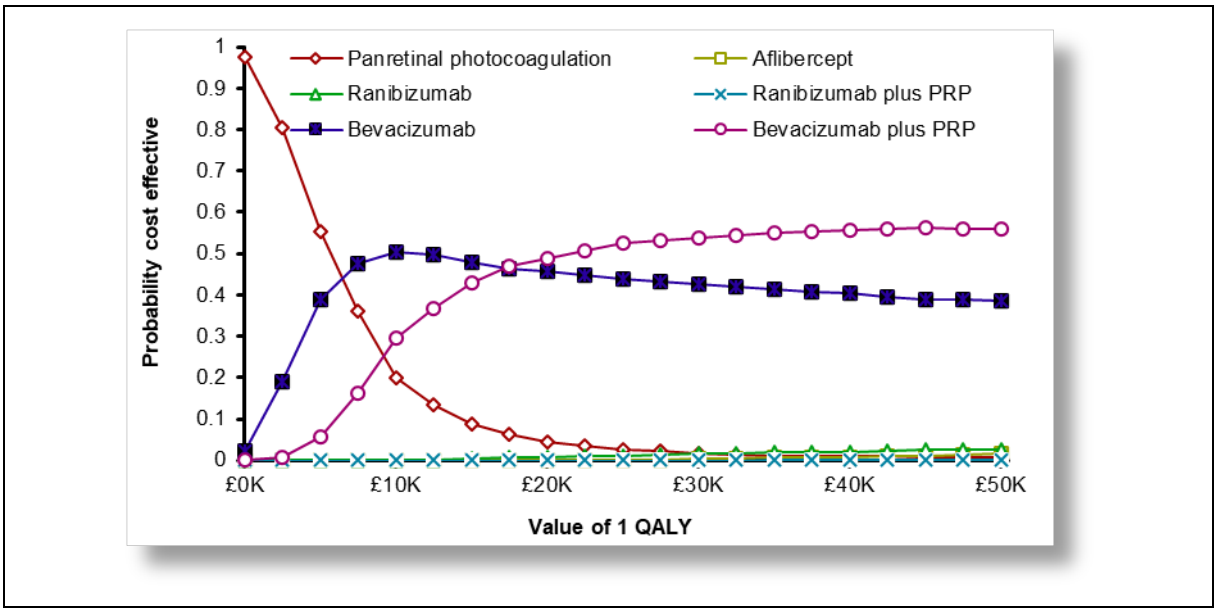

Figure HE006: PDR base-case probabilistic results (list price) – cost-effective acceptability curve

HE3.1.3 Scenario analysis

Table 38 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

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.

Based on Protocol S, in the PDR model, a key scenario analysis was conducted whereby treatment effects from the NMA were applied in the first year for all interventions. For PRP, visual acuity was then assumed to stabilise beyond the first year since there is evidence of long-term stability for as long as 15 years with PRP treatment (Wells 2016). For anti-VEGFs, a linear decline of transition probabilities was assumed between the first and second years, with visual acuity stabilising from the second year onwards, since there is evidence that anti-VEGFs can stabilise vision in 90% of people (Lazarus 2020). In this scenario, patients who switched their treatment beyond one year for PRP and two years for anti-VEGFs did not receive any treatment benefit of switching, given the assumption of stability in visual acuity. Furthermore, it was assumed that the other anti-VEGFs would follow the same disease progression pattern as ranibizumab in the absence of other evidence. This scenario resulted in PRP having the highest NMB, followed by bevacizumab alone then bevacizumab plus PRP, in both the list price and PAS price analyses. Although the committee considered this scenario almost equally plausible to the base-case, it was kept as an important scenario due to the following reasons:

- PDR and DMO were modelled separately given our review questions; the risk of developing DMO in the PDR model was not included. This was a limitation, but the data was not well reported to be able to include. Even when DMO was included as an adverse event within the diabetic retinopathy trials, it was very unclear if it meant patients had DMO requiring treatment. It was assumed that any impact of developing DMO would be captured within their BCVA transition probabilities rather than having DMO as explicit health state.

- The Protocol S study compared ranibizumab 0.5mg with PRP for the treatment of PDR. In both arms of Protocol S, about 40 to 45 percent of eyes had active neovascularization at two years. The short-term outcomes thus far do not allow for confidence in the long-term stability of PDR treated with anti-VEGFs alone.

- The Protocol S study compared ranibizumab 0.5mg with PRP, and in the absence of other evidence, it may be flawed to assume that the other anti-VEGFs would follow exactly the same disease progression pattern as ranibizumab.

- It may also be flawed to assume that patients who switch their treatment beyond one year for PRP and two years for anti-VEGFs would not receive any treatment benefit of switching, given the assumption of stability in visual acuity. Treatment effect may also sustain if patients continue to receive treatment, and assuming visual acuity to stabilise so early in the disease pathway may not be a fully reasonable approach.

- The committee agreed to keep similarity between the base-case analyses of both PDR and DMO models given the review questions.

Table 38: 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)
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)
Stability of visual acuity applied after initial treatment effects	PRP (£223,416)	Bevacizumab (£219,303)	Bevacizumab plus PRP (£217,309)

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 39. The fully incremental results are presented in Table 40. 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 and aflibercept 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 41 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 39: 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
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
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

NMB: Net monetary benefit

Table 40: 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
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

NMB: Net monetary benefit

Table 41: 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	Aflibercept
9	No treatment
10	Ranibizumab
11	Faricimab
12: Lowest NMB	Ranibizumab plus standard laser

**Ranibizumab biosimilar (Ongavia) was included as a scenario only; NMB: Net monetary benefit*

HE3.2.2 Probabilistic sensitivity analysis

In the base-case probabilistic analysis using list prices for the anti-VEGF therapies, 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 42. The probabilistic results were fairly similar to the deterministic results, with ranibizumab plus standard laser, faricimab and aflibercept 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 43. 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.

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, aflibercept, ranibizumab and faricimab all had ICERs below £25,000 per QALY. Table 44 shows the ranking of treatments by NMB at £20,000 per QALY under the confidential prices.

Table 42: 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)
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)
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)

Strategy	Absolute (95% CI)		Incremental			NMB
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY (95% CI)
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)

NMB: Net monetary benefit

Table 43: DMO (all centre involving) base-case probabilistic cost-utility results compared with no treatment (list price)

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
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
Faricimab	£33,947	9.266	£30,104	0.781	£38,541
Aflibercept	£34,388	9.258	£30,545	0.773	£39,500

Table 44: 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	Aflibercept
10	Ranibizumab
11	Faricimab
12: Lowest NMB	Ranibizumab plus standard laser

**Ranibizumab biosimilar (Ongavia) was included as a scenario only; NMB: Net monetary benefit*

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.

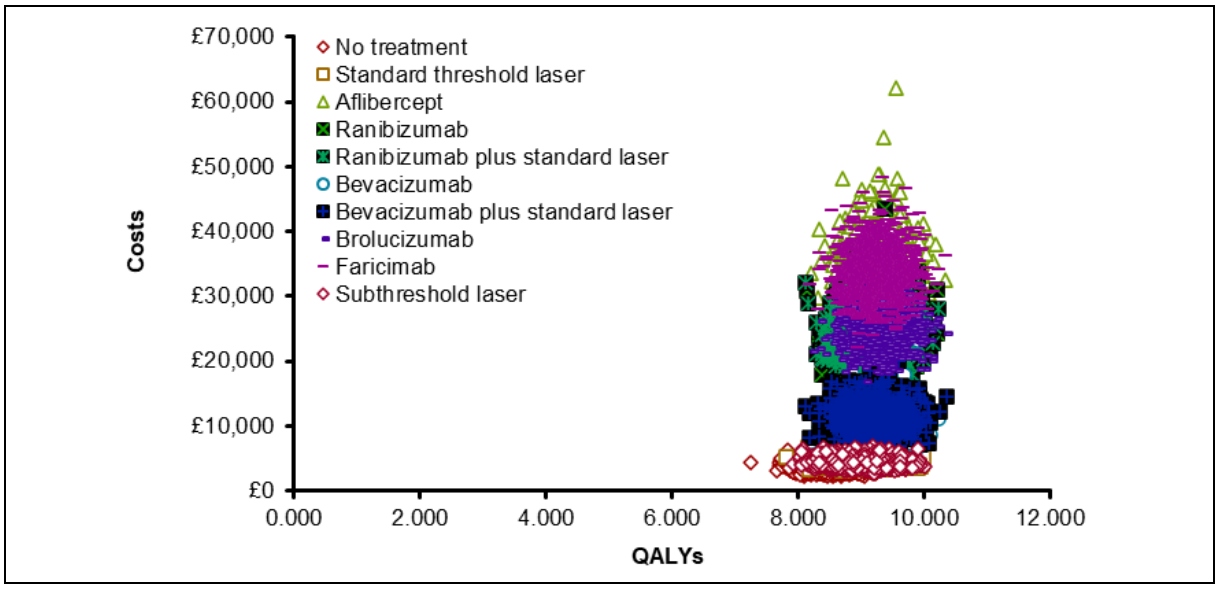

Figure HE007: DMO (all centre involving) base-case probabilistic results (list price) – scatter plot of expected costs and QALYs obtained from PSA

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.

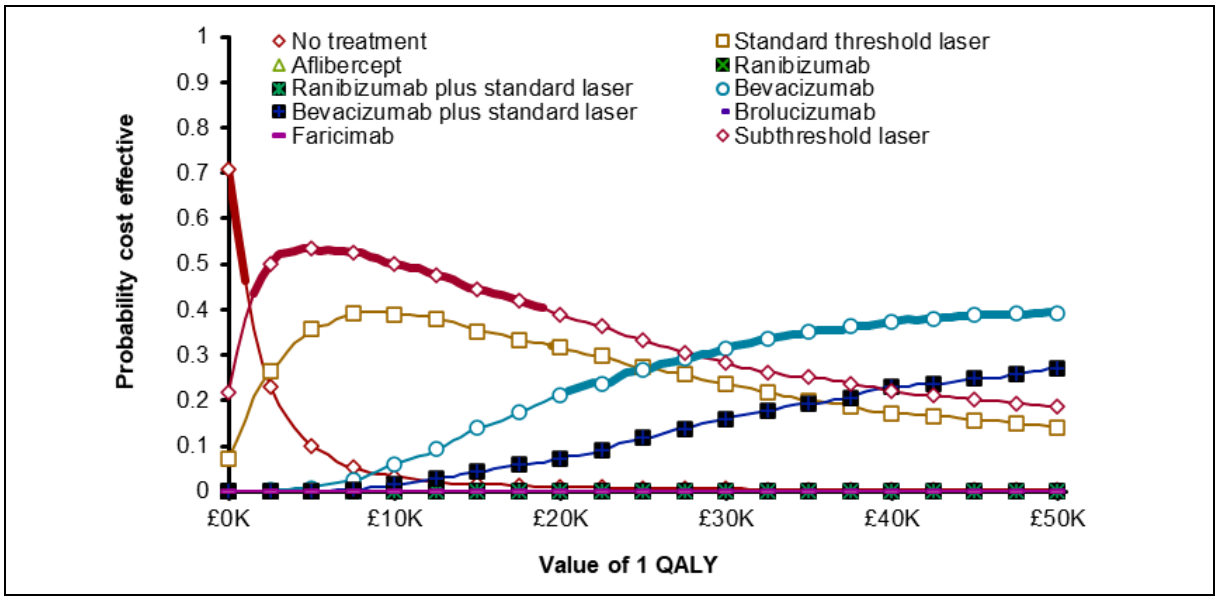

Figure HE008: DMO (all centre involving) base-case probabilistic results (list price) – cost-effective acceptability curve

HE3.2.3 Scenario analysis

Table 45 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

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 45: 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)

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 46 and the incremental analysis is presented in Table 47. 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 and 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 48 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 46: DMO with a CRT≥400µm: 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	£4,483	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
Bevacizumab plus standard laser	£10,628	9.235	£6,967	0.741	£9,407	£174,079

Strategy	Absolute		Incremental			NMB
	Costs	QALYs	Costs	QALYs	ICER	£20K/ QALY
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

Table 47: DMO with a CRT≥400µm: fully incremental 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	£4,483	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
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

NMB: Net monetary benefit

Table 48: 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
8	Aflibercept
9	No treatment
10	Ranibizumab
11	Faricimab
12: Lowest NMB	Ranibizumab plus standard laser

**Ranibizumab biosimilar (Ongavia) was included as a scenario only; NMB: Net monetary benefit*

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, 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 49 and the results compared with no treatment are presented in Table 50. 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.

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. Aflibercept, ranibizumab and faricimab had ICERs below £25,000 per QALY. Table 51 shows the ranking of treatments by NMB at £20,000 per QALY under the confidential prices.

Table 49: 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)
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)

Strategy	Absolute (95% CI)		Incremental			NMB
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY (95% CI)
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)

Table 50: DMO (CRT≥400µm) probabilistic cost-utility results compared with no treatment (list price)

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
Ranibizumab	£24,039	9.224	£20,216	0.721	£28,054
Brolucizumab	£24,348	9.268	£20,526	0.765	£26,824
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

Table 51: 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	Aflibercept

NMB rank	Treatment
10	Ranibizumab
11	Faricimab
12: Lowest NMB	Ranibizumab plus standard laser

**Ranibizumab biosimilar (Ongavia) was included as a scenario only; NMB: Net monetary benefit*

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 52. 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 52: Summary of scenario analysis results (list price) – 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)
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)

Scenario	Treatment ranking best (NMB)	Treatment ranking second best (NMB)	Treatment ranking third best (NMB)
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)

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 PRP had the lowest ICER of the strategies considered with an ICER 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.

The scenario analysis (based on Protocol S) around assuming stability of visual acuity following the application of the initial treatment effects resulted in PRP being the most dominant treatment strategy, followed by bevacizumab alone then bevacizumab plus PRP, in

both the list price and PAS price analyses. The committee considered this scenario almost equally plausible to the base-case analysis.

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 38); however, when alternative assumptions around duration of treatment effect and stability of visual acuity were explored, PRP had the highest NMB.

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. Aflibercept, ranibizumab and faricimab had ICERs between £20,000 and £25,000 per QALY. 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.

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. 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, both eyes can 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 only. 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. 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 might 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 is generally no 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 base-case 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, the way in which treatment effects were applied over time and the treatment setting.

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.

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 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. However, when key alternative assumptions around duration of treatment effect and stability of visual acuity were explored, PRP had the highest net monetary benefit.

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.

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Appendix A: Model parameters

Review question 7 – Diabetic macular oedema

Table 53: 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 54: 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	Subthreshold laser
Retinal detachment	0.03%	0.08%	0.05%	0.05%	0.13%	0.13%	0.00%	0.02%	0.03%
Retinal tear	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%
Increased intraocular pressure	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Glaucoma	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%	0.03%
Cataracts	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Ocular pain	0.06%	0.13%	0.03%	0.03%	0.13%	0.13%	0.69%	0.12%	0.06%
Stroke	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%
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)	Assumed same as standard laser

Table 55: Frequency of anti-VEGF treatments for diabetic macular oedema

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 (ERG report)
	9.20	5.000	2.37	2.37	2.37	Aflibercept in TA799
	8.00	4.000	2.00	2.00	2.00	Aflibercept in TA799 (scrutiny panel: assuming complete doses)
	8.50	4.000	2.00	2.00	2.00	Aflibercept in TA799 (scrutiny panel: including proportions of planned doses beyond month 12)
	7.70	5.600	2.30	1.20	1.00	Aflibercept in 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	Ranibizumab in TA346
	9.40	5.40	2.17	2.17	2.17	Ranibizumab in TA799
	8.00	4.00	2.00	2.00	2.00	Ranibizumab in TA799 (scrutiny panel: assuming complete doses)
	8.50	4.00	2.00	2.00	2.00	Ranibizumab in TA799 (scrutiny panel: including proportions of planned doses beyond month 12)
	7.70	5.60	2.30	1.20	1.00	Ranibizumab in TA820

Treatment	Frequency of Anti-VEGF treatments					Source
	Year 1	Year 2	Year 3	Year 4	Year 5	
	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)
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)
Subthreshold laser	-	-	-	-	-	Not applicable

Table 56: Frequency of monitoring visits for diabetic macular oedema

Treatment	Frequency of monitoring visits					Source
	Year 1	Year 2	Year 3	Year 4	Year 5	
No treatment	4.00	4.00	4.00	4.00	4.00	Non-treated patients in TA349, reported in the update TA824 The TA reported 4 monitoring visits per year but the committee agreed this would be reduced to 2 visits a year after year 3.
Standard threshold laser	4.00	4.00	2.60	2.20	1.90	Standard laser in 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	Aflibercept in TA346
	12.00	9.40	4.00	4.00	4.00	Aflibercept in TA799 (12.95 visits but capped to 12 based on committee feedback)
	8.50	4.00	4.00	4.00	4.00	Aflibercept in TA799 (scrutiny panel)
	12.00	12.00	4.00	4.00	2.00	Aflibercept in 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	Ranibizumab in TA346
	12.00	9.30	4.00	4.00	4.00	Ranibizumab in TA799 (12.66 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	
	8.50	4.00	4.00	4.00	4.00	Ranibizumab in TA799 (scrutiny panel: including proportions of planned doses)
	12.00	12.00	4.00	4.00	2.00	Ranibizumab in 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 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 (scrutiny panel)
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 – proliferative diabetic retinopathy

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)

Utility for treatment in both eyes: weighted average of best seeing eye (BSE) and worst seeing eye (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)

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)

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)

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)

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)

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)

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)

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)

Treatment effect followed by stability of visual acuity

Treatment	Absolute costs	Absolute QALYs	Incremental costs	Incremental QALYs	ICER	NMB at £20K/QALY (95% CI)
PRP	£6,517	11.497	-	-	-	£223,416 (£209,318 to £236,866)
Aflibercept	£31,457	11.601	£24,941	0.105	£238,631	£200,566 (£185,554 to £215,098)
Ranibizumab	£26,028	11.603	£19,511	0.107	£182,657	£206,041 (£191,991 to £219,855)
Ranibizumab plus PRP	£30,206	11.555	£23,690	0.058	£408,631	£200,886 (£186,711 to £215,028)
Bevacizumab	£11,677	11.549	£5,160	0.052	£98,507	£219,303 (£203,877 to £234,198)
Bevacizumab plus PRP	£15,714	11.651	£9,197	0.155	£59,517	£217,309 (£202,512 to £230,714)

Scenario analysis results – diabetic macular oedema (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)
Subthreshold laser	£4,723	8.969	£883	0.481	£1,834	£174,667 (£160,608 to £188,543)

Utility for treatment in both eyes: weighted average of best seeing eye (BSE) and worst seeing eye (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)
Subthreshold laser	£4,440	9.230	£582	0.387	£1,504	£180,152 (£166,746 to £193,150)

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)
Subthreshold laser	£4,464	10.189	£600	0.501	£1,199	£199,308 (£183,974 to £214,482)

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)
Subthreshold laser	£4,421	9.175	£578	0.306	£1,886	£179,086 (£166,177 to £192,721)

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)
Subthreshold laser	£4,442	9.855	£607	0.228	£2,663	£192,663 (£181,589 to £205,078)

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)
Subthreshold laser	£4,389	9.559	£570	0.254	£2,246	£186,786 (£173,824 to £200,429)

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)
Subthreshold laser	£4,423	8.062	£562	0.403	£1,394	£156,816 (£143,957 to £170,192)

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)
Subthreshold laser	£4,474	8.961	£636	0.477	£1,333	£174,745 (£161,359 to £188,301)

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)
Subthreshold laser	£4,432	8.961	£589	0.470	£1,254	£174,788 (£160,276 to £188,949)

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)
Subthreshold laser	£4,443	8.964	£591	0.469	£1,259	£174,837 (£160,689 to £188,567)

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)
Subthreshold laser	£4,536	8.870	£683	0.367	£1,863	£172,872 (£160,347 to £185,844)

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)
Subthreshold laser	£4,642	8.716	£812	0.249	£3,259	£169,685 (£157,452 to £181,927)

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)
Subthreshold laser	£3,696	8.961	-£159	0.478	-£333	£175,520 (£161,005 to £189,936)

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)
Subthreshold laser	£5,035	8.964	£1,180	0.468	£2,524	£174,250 (£159,983 to £187,768)

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)
Subthreshold laser	£4,453	9.002	£791	0.493	£1,606	£175,593 (£161,014 to £190,159)

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)
Subthreshold laser	£7,696	8.969	-£4,549	0.470	-£9,675	£171,686 (£152,986 to £186,224)

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)
Subthreshold laser	£4,545	8.853	£727	0.366	£1,988	£172,523 (£158,190 to £187,000)

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)
Subthreshold laser	£4,405	9.012	£574	0.532	£1,081	£175,833 (£161,696 to £189,535)

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)
Subthreshold laser	£4,443	8.986	£715	0.337	£2,121	£175,273 (£160,959 to £189,381)

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)
Subthreshold laser	£4,458	8.971	£603	0.476	£1,266	£174,972 (£161,005 to £189,033)

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)
Subthreshold laser	£4,450	8.971	£622	0.474	£1,311	£174,979 (£160,180 to £188,341)

Scenario analysis results – diabetic macular oedema (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)
Subthreshold laser	£4,834	8.930	£9	0.436	£2,207	£173,774 (£160,234 to £187,907)

Utility for treatment in both eyes: weighted average of best seeing eye (BSE) and worst seeing eye (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)
Subthreshold laser	£4,495	9.173	£9	0.346	£1,940	£178,972 (£163,886 to £192,033)

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)
Subthreshold laser	£4,459	10.176	£10	0.461	£1,340	£199,070 (£184,354 to £213,513)

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)
Subthreshold laser	£4,519	9.134	£9	0.271	£2,522	£178,164 (£165,266 to £191,179)

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)
Subthreshold laser	£4,461	9.820	£10	0.219	£2,754	£191,947 (£180,174 to £203,665)

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)
Subthreshold laser	£4,483	9.548	£10	0.238	£2,641	£186,481 (£173,584 to £199,654)

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)
Subthreshold laser	£4,443	8.028	£8	0.366	£1,704	£156,124 (£144,077 to £168,699)

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)
Subthreshold laser	£4,514	8.934	£9	0.435	£1,524	£174,172 (£160,535 to £188,263)

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)
Subthreshold laser	£4,483	8.955	£9	0.434	£1,500	£174,617 (£159,793 to £187,239)

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)
Subthreshold laser	£4,469	8.935	£9	0.423	£1,548	£174,238 (£160,078 to £189,540)

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)
Subthreshold laser	£4,574	8.851	£9	0.344	£2,222	£172,451 (£159,238 to £185,078)

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)
Subthreshold laser	£4,686	8.729	£9	0.220	£3,796	£169,896 (£156,990 to £182,867)

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)
Subthreshold laser	£3,724	8.936	£9	0.437	-£236	£174,987 (£160,622 to £189,146)

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)
Subthreshold laser	£5,086	8.902	£9	0.424	£2,995	£172,953 (£158,548 to £187,519)

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)
Subthreshold laser	£4,483	8.947	£9	0.441	£1,861	£174,457 (£160,331 to £189,066)

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)
Subthreshold laser	£7,988	8.935	£9	0.434	-£9,242	£170,707 (£152,415 to £186,625)

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)
Subthreshold laser	£4,582	8.817	£9	0.345	£2,036	£171,753 (£156,193 to £187,069)

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)
Subthreshold laser	£4,426	8.992	£9	0.493	£1,190	£175,421 (£161,981 to £189,184)

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)
Subthreshold laser	£4,474	8.922	£9	0.292	£2,594	£173,958 (£160,147 to £188,034)

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)
Subthreshold laser	£4,492	8.916	£9	0.429	£1,542	£173,835 (£159,370 to £188,725)

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)
Subthreshold laser	£4,468	8.937	£9	0.451	£1,392	£174,281 (£159,976 to £188,273)