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Economic Evaluation

Anti–Vascular Endothelial Growth Factor Drugs Compared With Panretinal Photocoagulation for the Treatment of Proliferative Diabetic Retinopathy: A Cost-Effectiveness Analysis

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ABSTRACT

Objectives: This study aimed to evaluate the cost-effectiveness of anti–vascular endothelial growth factor drugs (anti-VEGFs) compared with panretinal photocoagulation (PRP) for treating proliferative diabetic retinopathy (PDR) in the United Kingdom.

Methods: A discrete event simulation model was developed, informed by individual participant data meta-analysis. The model captures treatment effects on best corrected visual acuity in both eyes, and the occurrence of diabetic macular edema and vitreous hemorrhage. The model also estimates the value of undertaking further research to resolve decision uncertainty.

Results: Anti-VEGFs are unlikely to generate clinically meaningful benefits over PRP. The model predicted anti-VEGFs be more costly and similarly effective as PRP, generating 0.029 fewer quality-adjusted life-years at an additional cost of £3688, with a net health benefit of −0.214 at a £20 000 willingness-to-pay threshold. Scenario analysis results suggest that only under very select conditions may anti-VEGFs offer potential for cost-effective treatment of PDR. The consequences of loss to follow-up were an important driver of model outcomes.

Conclusions: Anti-VEGFs are unlikely to be a cost-effective treatment for early PDR compared with PRP. Anti-VEGFs are generally associated with higher costs and similar health outcomes across various scenarios. Although anti-VEGFs were associated with lower diabetic macular edema rates, the number of cases avoided is insufficient to offset the additional treatment costs. Key uncertainties relate to the long-term comparative effectiveness of anti-VEGFs, particularly considering the real-world rates and consequences of treatment nonadherence. Further research on long-term visual acuity and rates of vision-threatening complications may be beneficial in resolving uncertainties.

Keywords: aflibercept, anti-VEGF, diabetic retinopathy, discrete event simulation, IPD meta-analysis, ranibizumab.

VALUE HEALTH. 2024; 27(7):907–917

Highlights

- Proliferative diabetic retinopathy (PDR) is a leading cause of visual impairment and blindness in the United Kingdom and worldwide. Anti–vascular endothelial growth factor (anti-VEGF) drugs aflibercept and ranibizumab are recommended by the National Institute for Health and Care Excellence for the treatment of various eye conditions, including diabetic macular edema, and have shown promise as an alternative treatment for PDR.
- There is limited evidence on the cost-effectiveness of anti-VEGFs for the treatment of diabetic retinopathy. This study reports discrete event simulation–based cost-effectiveness analysis in which we evaluate the cost-effectiveness of anti-VEGFs compared with panretinal photocoagulation for the treatment of diabetic retinopathy in a UK setting. The analysis leveraged evidence from the AVID individual participant data meta-analysis, which synthesized data from 3 randomized controlled trials evaluating the effectiveness of anti-VEGFs for diabetic retinopathy.
- The results of this analysis suggest that anti-VEGFs are unlikely to be a cost-effective treatment option compared with panretinal photocoagulation for treating early PDR in the United Kingdom. This holds across a variety of scenarios, with anti-VEGFs generally associated with higher costs and similar health outcomes over a lifetime time horizon. Important uncertainties remain around the consequences of loss to follow-up, the comparative long-term effectiveness of treatments, and the rates of vision-threatening complications.

Introduction

The rising prevalence of diabetes globally presents an increasing challenge to healthcare systems worldwide because of the burden of diabetic complications. The total costs to the United Kingdom of treating sight-threatening diabetic retinopathy (DR) was estimated to be £57 million in 2010-2011. This is projected to increase to £97 million by 2035-2036.[1] DR is a progressive complication of diabetes mellitus, and in its most severe form, proliferative diabetic retinopathy (PDR), remains a leading cause of visual impairment and blindness in the United Kingdom and worldwide.[2,3]

The primary treatment for PDR is currently panretinal photocoagulation (PRP), an effective and long-lasting treatment that can be associated with a range of side effects, requiring specialist staff and equipment to administer.[4,5] The anti–vascular endothelial growth factor (anti-VEGF) drugs, aflibercept and ranibizumab, are recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of eye conditions, including diabetic macular edema (DME)—a common complication of PDR. These drugs have also shown promise as a treatment for PDR itself and have been studied in a number of

randomized controlled trials (RCTs).[6,7] However, they are not currently recommended for this use in the National Health Service (NHS).

Anti-VEGFs are administered via injection directly into the eye (intravitreal injection) at regular intervals, inhibiting the excessive growth of abnormal blood vessels, thereby preventing many associated complications and the resulting vision loss. However, these drugs are expensive, and there are concerns about their long-term effectiveness.[8,9] It is unclear whether they could represent a cost-effective option for treating early PDR, where few patients are at immediate risk of sight loss, and anti-VEGFs are available to treat DME if it arises.

Previous economic analyses have indicated that anti-VEGFs may be superior to PRP in terms of efficacy as a treatment for DR,[5,10-15] based on short-term trial evidence, but they question whether the substantial additional costs are justified. Forthcoming NICE Guidelines on DR also include an economic model with an NHS perspective. However, no existing cost-effectiveness analyses fully account for the full value of anti-VEGFs, in terms of avoiding exacerbations and complications, such as DME and vitreous hemorrhage (VH).

The objective of this study was to evaluate the cost-effectiveness of anti-VEGF treatments compared with PRP for PDR from a UK perspective as part of a National Institute for Health Research (NIHR) health technology assessment: "Anti-VEGF drugs compared with laser photocoagulation for the treatment of diabetic retinopathy: A systematic review and economic analysis" (AVID). AVID comprised a systematic review and meta-analysis of aggregate and individual participant data (IPD), using data from several large RCTs comprising 72% of trial data on aflibercept and ranibizumab in PDR, to evaluate the clinical and cost-effectiveness of anti-VEGF treatments for the treatment of DR within a UK NHS setting.[6,7] AVID represents the most comprehensive review of the use of anti-VEGFs for the treatment of DR and is the first to use IPD to investigate the relationships between patient characteristics and effectiveness over time.

This study presents the results of the AVID cost-effectiveness analysis and explores the potential value of further primary research to resolve decision uncertainty.

Methods

A de novo model was designed, developed, and interpreted in collaboration with UK clinical and patient experts, drawing on existing cost-effectiveness analyses in DR, identified through a systematic review. Detailed information on the review methods and findings are presented in Hodgson et al.[16] The economic analysis sought to evaluate whether anti-VEGF drugs represent a cost-effective option for the treatment of PDR compared with PRP within the UK NHS context.

The primary source of clinical inputs used in the model was the AVID IPD meta-analysis,[6,7] comprising 3 RCTs:

- CLARITY, UK-based trial of aflibercept versus PRP, n = 232, 1 year of follow-up.
- DRCR.net Protocol S, US-based trial of ranibizumab versus PRP, n = 305, 5 years of follow-up.
- PROTEUS, Europe-based trial of ranibizumab plus PRP versus PRP alone, n = 87, 1 year of follow-up.

Methods and results from the AVID IPD meta-analysis are reported in Simmonds et al.[6,7]

Model Structure

The model comprised a discrete event simulation (DES). DES models allow an individual patient's journey through the healthcare system to be represented by different possible events or processes over time.[17] This approach facilitates the independent modeling of best corrected visual acuity (BCVA) in both eyes, utilizing known information about individual patients' disease characteristics. DES accommodates essentially unlimited permutations of health state combinations without the need for large numbers of discretely modeled health states, as in a state transition model. The model was coded in Microsoft Excel using Visual Basic for Applications. It was built in alignment with the general principles of patient-level simulation modeling specified in the NICE DSU Technical Support Document 15, using the basic DES structure presented in the report.[18]

Meta-analytic evidence on non-proliferative PDR (NPDR) is limited, with no evidence of any BCVA benefit.[6,7] The model therefore considered PDR only, as there may be limited scope for cost-effective use of anti-VEGFs in NPDR. Network meta-analysis found no clinically important differences in efficacy between different anti-VEGFs.[6,7] We therefore modeled the cost-effectiveness of anti-VEGFs as a therapeutic class, followed by further anti-VEGF treatment for DME as required. The comparator arm comprises PRP followed by anti-VEGF treatment for DME as required. Figure 1 presents a schematic depicting the model structure.

The model reflects baseline heterogeneity in patient characteristics by first randomly sampling variables from the AVID IPD, including age, sex, and BCVA in each eye. Best-seeing eye and worst-seeing eye BCVA were jointly sampled using the Cholesky decomposition to capture the correlation across an individual patient's eyes. Event times (ie, DME, VH, and death) are sampled based on these data. Loss to follow-up (LTF) can occur following treatment administration or a BCVA assessment, but these patients can represent if DME or VH develops. The model executes each event in chronological order, calculating accrued discounted costs and quality-adjusted life-years (QALYs) as events occur.[18]

Repeated events, such as treatment administration and BCVA assessment visits, resample the time to event to specify the next occurrence of that event. Treatment administration visit times are sampled to align with the observed number of events for patients who remained on treatment in a given year in the AVID IPD.

The model incorporates a system of "flags" to track status effects that patients can accumulate. These flags are attached to each patient, and include the treatment they are receiving, presence of DME, previous VH, and severe visual impairment (SVI)/blindness. These flags affect ongoing monitoring and treatment costs and the probability and timing of subsequent events.

The model assumes the presence of bilateral PDR at baseline. Although most patients with unilateral PDR will develop proliferative disease in the fellow eye, there may be a multiyear lead time. This simplifying assumption captures long-term visual outcomes in both eyes, although the timing of decline in each eye runs in parallel.

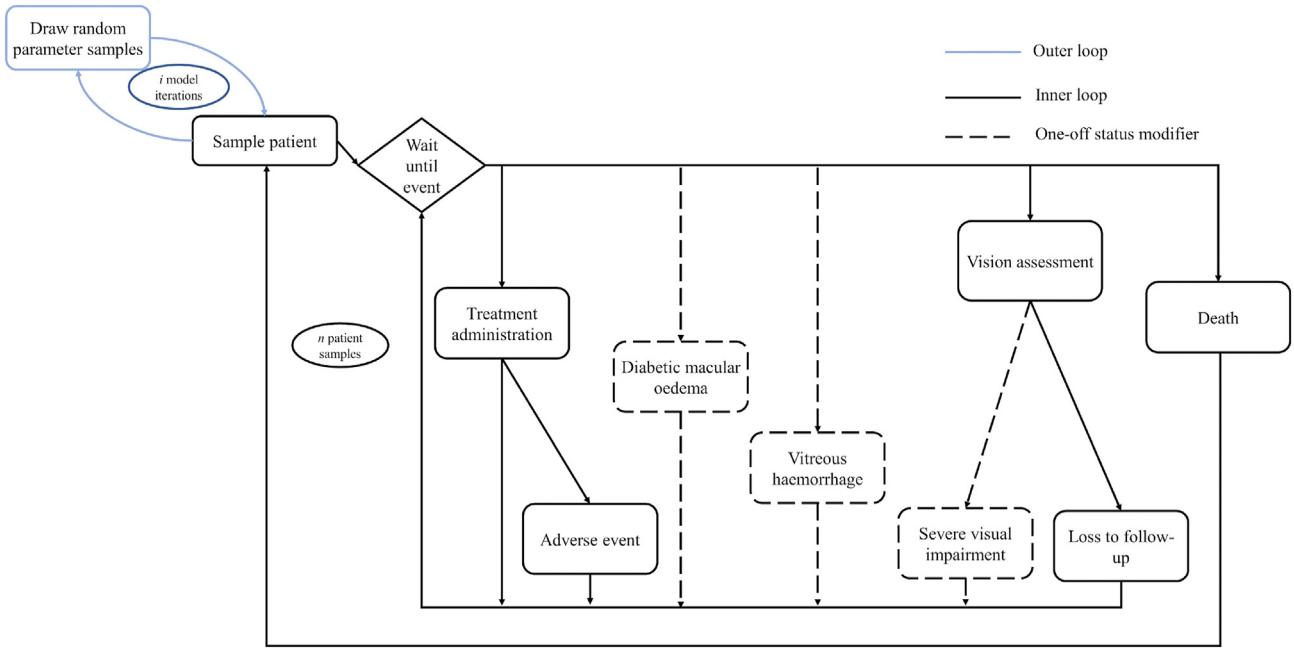
The base-case analysis uses a 50-year time horizon (ie, lifetime). Costs and benefits are discounted at 3.5% per annum. The analysis adopts a UK NHS and Personal Social Services perspective. A severity-based QALY weight multiplier would not be applicable in this indication under current NICE methods.[19]

AVID IPD Analysis

Baseline characteristics

The population considered in the economic model included all patients for whom IPD was obtained (see Appendix Table 1 in

Figure 1. Discrete event simulation model schematic.



Supplementary Materials found at https://doi.org/10.1016/j.jval.2024.03.007). Baseline characteristics were drawn from a normal distribution for each patient to allow heterogeneity to be propagated in model outcomes. Modeled patient characteristics were broadly comparable to published UK epidemiological sources. The mean age of the modeled population was 50.65 (SD 12.46) years—lower than the 58.9 (SD 14.6) years reported by Scanlon et al.[20] However, this might be expected given the early-stage PDR without baseline macular edema considered in the present study.

BCVA regression analysis

Longitudinal data on Early Treatment Diabetic Retinopathy Study (ETDRS) score in Protocol S and CLARITY were analyzed using linear mixed-effects regression (lmer) models to characterize the relationship between BCVA and key predictor variables. PROTEUS was excluded from this analysis because combination therapy may affect long-term outcomes, and DME was managed primarily using further laser in the PRP arm, which differed to the other trials. DME and VH were excluded as covariates because they had no significant impact on BCVA. This analysis used the lmer function from the lme4 package in R.[21] Methods are reported in full in Simmonds et al.[7]

The regression intercept was set at 1 year, allowing 1-year and long-term treatment response to be modeled separately. Regression coefficients are summarized in Table 1 and are depicted graphically in the supplementary material. This analysis showed that anti-VEGFs improve vision compared with PRP at 1 year, but there was evidence that BCVA improves on PRP with increasing duration of follow-up, whereas on anti-VEGFs it declines by comparison, suggesting that any BCVA benefit relative to PRP is lost within 3 years on average. Greater visual acuity at the point of randomization has a negative impact on the size of the treatment

Table 1. BCVA ETDRS regression coefficients (Protocol S and CLARITY IPD).

Treatment arm	Parameter	Mean difference	SE	95% CI	
				Low	High
PRP	Intercept (1-yr)	−0.26712	0.65741	−1.55564	1.02140
	Base ETDRS score	−0.26729	0.06323	−0.39123	−0.14335
	Year (2-5)	0.26512	0.17274	−0.07344	0.60369
	Vitr. hem.	−0.01515	0.01690	−0.04827	0.01797
	Year × vitr. hem.	−0.26712	0.65741	−1.55564	1.02140
Anti-VEGF	Intercept (1-yr)	3.10601	1.12631	0.89845	5.31357
	Base ETDRS score	−0.26003	0.09347	−0.44324	−0.07682
	Year (2-5)	−1.12789	0.20189	−1.52360	−0.73218
	Vitr. hem.	0.00913	0.02175	−0.03349	0.05176
	Year × vitr. hem.	3.10601	1.12631	0.89845	5.31357

ETDRS indicates Early Treatment Diabetic Retinopathy Study; PRP, panretinal photocoagulation; SE, standard error; VEGF, vascular endothelial growth factor; vitr. hem., vitreous hemorrhage.

Table 2. Modeled resource use inputs.

Treatment administration frequency	Year	No. procedures (SD)		
		PDR (Protocol S)		DME (RESTORE)[23]
		Anti-VEGF	PRP	Anti-VEGF
	1	4.93 (2.56)	1.56 (0.70)	7.0 (0.26)
	2	2.88 (2.36)	0 (0)	3.9 (0.38)
	3	2.66 (2.82)	0 (0)	2.9 (0.32)
	4	2.35 (2.61)	0 (0)	2.9 (0.32)
	5+	1.75 (2.21)	0 (0)	2.9 (0.32)

Cost category	Parameter	Mean unit cost (SE)	Cost per treatment	Distribution	Source
Acquisition costs	Ranibizumab	£495.90	£215.61	N/A	BNF 2023[24] (Ximluci biosimilar)
	Aflibercept	£816.00		N/A	BNF 2023[24]
	Bevacizumab	£50		N/A	NICE TA824[25]
Administration costs	Intravitreal injection	£165.81 (£16.58)	£248.72	Gamma	NHS Reference Costs-BZ87A-minor-Total HRG (2021-2022)[26]
	Laser procedure	£165.81 (£16.58)	£331.62	Gamma	NHS Reference Costs-BZ87A-minor-Total HRG (2021-2022)[26]
	Intravitreal injection (nurse)	£66 (£6.60)		Gamma	PSSRU 2021 (1 hour of Band 7 nurse time)[27]
Monitoring costs	Routine monitoring visit	£143.93 (£14.39)		Gamma	NHS Reference Costs-WF01A-Code 130 Ophthalmology-Consultant led, non-admitted, face-to-face attendance, follow-up (2021-2022)[26]
	OCT	£158 (£15.80)		Gamma	NHS Reference Costs-BZ88A-Retinal tomography, 19 years and over (2021-2022)[26]
Adverse event management	Cataracts	£1267.89 (£126.79)		Gamma	NHS Reference Costs-BZ34C-Phacoemulsification cataract extraction and lens implant, with CC score 0-1 (2021-2022)[26]
	Raised IOP	£1152.66 (£115.26)		Gamma	50:50 weighted average surgery and medication. NICE TA824.[25] NHS Reference Costs (2021-2022)[26]
	Retinal detachment	£1579.00 (£157.90)		Gamma	80:20 weighted average intermediate and major procedure. NICE TA349. NHS Reference Costs (2021-2022)[26]
	Vitreous hemorrhage	£1352.12 (£135.21)		Gamma	NHS Reference Costs-Weighted average of BZ86B (2021-2022)[26]

			Frequency	% patients	
Blindness costs	Depression	£2513.92	Annual	39%	NICE TA824[25]
	Hip replacement	£5411.96	Annual	5%	NHS Reference Costs-HT14C-intermediate hip procedures for trauma (weighted) (2021-2022)[26]
	Community care	£12 617.35	Annual	6%	PSSRU 2014[28]
	Residential care	£38 531.26	Annual	30%	95:5 weighted average private and local authority. PSSRU 2021,[27] NICE TA824[26]

continued on next page

Table 2. Continued

			Frequency	% patients	
	Weighted average with 41% self-funding	£24 060.89	Annual	30%	NICE TA824[25]
	Annual cost per patient	£13 567.45 (£1356.75)			
	Blind registration	£161.76	One-off	95%	Colquitt 2008[29] (inflated to 2022 cost year)
	Low-vision aids	£211.00	One-off	33%	Colquitt 2008[29] (inflated to 2022 cost year)
	Low-vision rehabilitation	£364.32	One-off	11%	Colquitt 2008[29] (inflated to 2022 cost year)
	One-off cost per patient	£263.38 (£26.34)			

Adverse event rates	Adverse event	PRP (SD)	Anti-VEGF (SD)	
	Cataracts	50.00% (2.80%)	43.97% (2.83%)	AVID IPD
	Raised intraocular pressure	11.02% (1.64%)	9.77% (1.59%)	AVID IPD
	Retinal Detachment	9.09% (1.51%)	3.74% (1.02%)	AVID IPD

AVID IPD indicates source name for individual participant data; BNF, British National Formulary; DME, diabetic macular edema; HRG, healthcare resource group; IOP, intraocular pressure; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

effect in both treatment arms, ie, those with poorer vision at baseline experience a larger benefit of treatment. For each simulated patient, correlated coefficients were sampled from variance-covariance matrices using the Cholesky decomposition to capture the full range of possible effect estimates on each treatment.

Time to event analysis

Treatment-specific times to DME and VH events were based on IPD from Protocol S and CLARITY, which were observed for up to 5 years in Protocol S. A range of parametric and spline models were fitted to Kaplan-Meier data for DME and VH independently for each treatment arm to account for observed nonproportionality of hazards. Model selection was based on visual and statistical fit (Akaike Information Criterion and Bayesian Information Criterion) to the observed data. The Gompertz curve had the best fit out of the parametric models for both the DME and VH outcomes. This function also best represented the expected plateau in ongoing DME risk (which is associated with administration of the interventions), and the continuing long-term risk of VH (more closely related to disease pathology). The flexsurv R package[22] was used to generate variance-covariance matrices to randomly sample event times using the Cholesky decomposition. Model fit statistics are presented in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.03.007.

Ocular adverse events

The economic analysis also considers other treatment related adverse events (AEs). These were informed by observed AE rates during the first year of follow-up in the AVID IPD. Event rates are reported in Table 2.[23-29] AEs were assumed to apply on a one-off basis when patients began a course of treatment, only affecting costs, assuming no independent effect upon health-related quality of life (HRQoL).

Treatment discontinuation and loss to follow-up

Because of the ad hoc nature of PDR treatment with anti-VEGFs, and the infrequency of extra PRP after full PRP, treatment "discontinuation" was judged to occur when patients were not receiving treatment at a given time but continued to attend monitoring appointments.

Genuine LTF is considered independently, with the implication that patients receive no further administrations of their current treatment nor do they incur the cost of monitoring visits. The base case assumes that LTF is independent of BCVA outcomes and the occurrence of DME and VH. However, scenarios are presented that explore the possibility of a frozen or declining BCVA (−1.30 EDTRS letters per year)[30] following LTF.

LTF was modeled using a 2-piece exponential function fitted to aggregate annual withdrawal rates from the AVID IPD. LTF was 8.8% and 14.4% on PRP and anti-VEGFs respectively in the first 12 months. An exponential function was used to estimate LTF using treatment-specific rates in the first year, with a separate exponential function applied from the end of the first year of treatment (based on Protocol S) for the remainder of the modeled time horizon. LTF over the full 5 years was similar between arms, with 59.70% patients remaining in the PRP arm, and 58.2% in the anti-VEGFs arm. Patients lost to follow-up could still develop DME and initiate treatment with anti-VEGFs.

Mortality

Mortality was modeled using the latest UK Office for National Statistics Life Table data (2018 to 2020).[31] Separate Gompertz models were fitted to mortality data for males and females, which were used to sample time to death on the basis of a simulated patient's age and sex. Excess mortality associated with diabetes and SVI, defined as BCVA of ≤25 ETDRS letters in both eyes, was separately accounted for by applying standardized mortality ratios (SMRs) of 1.95 (95% CI 1.64-2.33)[32] and 1.54 (95% CI 1.28-1.86),[33] respectively. This multiplicatively produces an SMR of 3.003, used to recalculate time of death in patients upon the development of SVI.

HRQoL

A 2-eye approach to estimating the impact of visual acuity on HRQoL was favored because HRQoL is thought to be a function of overall visual functioning, rather than best-eye-specific visual acuity.[34] There were no examples of appropriate utility weights identified in the review of cost-effectiveness studies in DR. We

therefore conducted literature searches for HRQoL studies in DR and other conditions.

We identified a patient-level analysis of 4 trials of intravitreal aflibercept for DME (n = 1320) reported in Brazier et al,[35] which was alone in directly eliciting utilities from a large sample of patients with DME. This study defined the relationship between visual acuity in both eyes (among other patient characteristics) and utility (EQ-5D and VFQ-UI) using ordinary least squares regression models. The EQ-5D regression model was used for consistency with NICE's decision-making preferences. The VFQ-UI regression is explored in scenario analysis, which, being specific to visual function assessment, places greater emphasis on the impact of visual decline on utility.

Utilities were independently adjusted as patients aged according to UK population norms, per Ara and Brazier.[36]

Administration Frequency and Ongoing Monitoring Requirements

Resource use frequency was based on Protocol S, recent NICE Technology Appraisals, and input from clinical experts. The number of procedures undertaken in each year for the primary treatment was based on AVID IPD (see Table 2). Patients with preexisting DME were excluded from these averages, as was any subsequent treatment following development of DME. Treatment frequency for DME itself is shown in Table 2, based on the RESTORE study.[23] Unit costs for procedures and clinician contact are based on the most recent NHS Reference Costs (2021/2022).[26] We used a 2022 to 2023 cost year throughout, costs are reported in Pounds Sterling (£).

There was no fixed limit to the duration of treatment in the base-case analysis—treatment frequency observed in year 5 was applied to each subsequent year. We assumed no further PRP sessions in the PRP arm beyond the first year (per Protocol S).

Monitoring costs comprised routine monitoring visits, in which optical coherence tomography (OCT) scans were undertaken to detect DME. No additional monitoring cost was incurred for patients actively undergoing treatment, with the cost of OCT applied twice per year. Patients who developed DME underwent 4 monitoring visits per year. Patients who developed SVI had reduced monitoring requirements (0.5 per year).[5] Patients who were lost to follow-up incurred no ongoing monitoring costs unless a symptomatic pathology (DME and VH) developed.

Treatment Acquisition and Administration Costs

The unit cost of anti-VEGFs was based on the cheapest option at list price per the British National Formulary.[24] Units per administration were based on the European Medicines Agency (EMA) summary of product characteristics for each treatment. It is important to note that confidential discounts on drug unit costs are available to the NHS. In the base-case analysis we used the list price of ranibizumab biosimilar, with scenario analysis exploring the impact of discounts on cost-effectiveness.

We assumed each administration of anti-VEGFs required an average of 1.5 visits for the treatment of 2 eyes, conducted in an outpatient setting. Full PRP was assumed to be performed over an average of 2.5 sessions.

Costs associated with AE management included resolution of cataracts, raised intraocular pressure (IOP), retinal detachment, and VH.

Value of Information

The expected value of perfect information (EVPI) was estimated to consider the value of resolving all uncertainty in the evidence base through collection of further evidence. This analysis followed the methods described in Fenwick et al,[37] estimating EVPI by determining the consequences of an incorrect implementation decision, given decision uncertainty. Net monetary benefit at a willingness-to-pay threshold of £20 000 per QALY gained is used to quantify losses to the health system when patients would hypothetically gain more benefit from the intervention which appears less cost-effective on average across the whole population. A discount rate of 3.5% was applied, we assumed anti-VEGFs would have a useful life of 10 years before a significant change in treatment will occur.

We used Scanlon et al[20] (n = 35 873) to estimate size of the incident population, in which there were 0.302 annual PDR diagnoses per 100 people with diabetes. Based on a diagnosed diabetic population of 4.3 million individuals in the United Kingdom in 2023,[38] 12 986 people would be diagnosed with PDR in the United Kingdom annually. Population EVPI was calculated by multiplying the mean EVPI by the incident population size, which was assumed to remain stable.

Generation of Results and Scenario Analysis

All analyses assume that ranibizumab and aflibercept have equivalent clinical effectiveness and a comparable AE profile. Because the real cost of each drug to the NHS is unknown, all analyses assume that clinicians would choose the cheapest option, which at list price is ranibizumab. A base-case analysis was assembled on the basis of clinical validity and a pragmatic interpretation of the IPD data set.

The base-case analysis considered the following key assumptions:

- Population has bilateral PDR at treatment initiation.
- Fifty-year (lifetime) time horizon.
- Utilities based on EQ-5D model.
- BCVA model applied for 5 years.

All analyses were run using 3000 probabilistic iterations, across a cohort of 250 patients (750 000 total simulations). This was sufficient to achieve first- and second-order convergence and allowed a large number of different permutations of parameter samples to be represented across a wide range of patient characteristics. Incremental cost-effectiveness ratios (ICERs) and net health benefit (NHB) at a willingness-to-pay (WTP) threshold of £20 000 was used to represent the cost-effectiveness of anti-VEGFs versus PRP.

To explore the sensitivity of the model results to a range of key assumptions, the following scenario analyses were explored. These may not represent plausible alternatives in themselves but illustrate the impact of structural and parameter assumptions:

Model structure:

1. Five-year stopping rule for DME treatment.
2. VH excluded from model.
3. DME excluded from model.
4. LTF not modeled.

HRQoL:

5. Utilities based on Brazier VFQ-UI model.

Treatment effect:

6. BCVA regression coefficients extended over 10 years.
7. 1-year BCVA outcomes maintained indefinitely.
8. BCVA at LTF maintained indefinitely.

Table 3. Base-case and scenario analysis results (WTP threshold £20 000).

Intervention	Total		Incremental		ICER	NHB	CE prob.
	Costs	QALYs	Costs	QALYs			
Base-case analysis							
PRP	£9935	12.330					
Anti-VEGFs	£13 624	12.301	£3688	−0.029	Dominated	−0.214	0.60%
1. 5-year stopping rule for DME treatment							
PRP	£7468	12.330					
Anti-VEGFs	£11 621	12.301	£4153	−0.029	Dominated	−0.237	0.27%
2. Vitreous hemorrhage excluded from model							
PRP	£9446	12.330					
Anti-VEGFs	£12 792	12.301	£3346	−0.029	Dominated	−0.197	4.90%
3. DME excluded from model							
PRP	£3425	12.330					
Anti-VEGFs	£11 550	12.301	£8125	−0.029	Dominated	−0.436	0.00%
4. Loss to follow-up not included							
PRP	£17 369	12.330					
Anti-VEGF	£24 218	12.301	£6850	−0.029	Dominated	−0.372	14.93%
5. Utilities based on Brazier VFQ-UI model							
PRP	£9935	12.011					
Anti-VEGF	£13 624	11.952	£3688	−0.059	Dominated	−0.243	1.07%
6. BCVA regression coefficients extended over 10 years							
PRP	£9935	12.348					
Anti-VEGF	£13 624	12.208	£3688	−0.140	Dominated	−0.325	0.00%
7. 1-year BCVA on both treatments maintained indefinitely							
PRP	£9935	12.313					
Anti-VEGF	£13 624	12.375	£3688	0.061	£60 154	−0.123	35.27%
8. BCVA at loss to follow-up maintained indefinitely							
PRP	£9935	12.327					
Anti-VEGF	£13 624	12.311	£3688	−0.016	Dominated	−0.200	2.33%
9a. BCVA declines (1.3 letters per year) upon loss to follow-up on anti-VEGFs							
PRP	£9935	12.327					
Anti-VEGF	£17 373	12.109	£7438	−0.218	Dominated	−0.589	0.00%
9b. BCVA declines (1.3 letters per year) upon loss to follow-up on both treatments							
PRP	£14 002	12.110					
Anti-VEGF	£17 373	12.109	£3371	0.001	Dominated	−0.170	20.63%
10. Anti-VEGF injections administered by Band 7 nurse							
PRP	£8198	12.330					
Anti-VEGFs	£10 493	12.301	£2295	−0.029	Dominated	−0.144	1.90%
11. Discount analysis: 80% discount on ranibizumab biosimilar (Ximluci)							
PRP	£7940	12.330					
Anti-VEGFs	£10 028	12.301	£2088	−0.029	Dominated	−0.134	2.13%
12. Bevacizumab price used to represent anti-VEGFs (assumed £50 per vial)							
PRP	£8020	12.330					
Anti-VEGFs	£10 171	12.301	£2152	−0.029	Dominated	−0.137	2.07%
13. Favorable anti-VEGF analysis: Scenarios 7, 9b, 10, and 11							
PRP	£6203	12.313					

continued on next page

Table 3. Continued

Intervention	Total		Incremental		ICER	NHB	CE prob.
	Costs	QALYs	Costs	QALYs			
Anti-VEGF	£6897	12.375	£694	0.061	£11 322	0.027	75.57%
14. Unfavorable anti-VEGF analysis: Scenarios 1, 6, and 9a.							
PRP	£7468	12.337					
Anti-VEGF	£17 025	12.048	£9557	−0.288	Dominated	−0.766	0.00%

BCVA indicates best corrected visual acuity; CE prob., cost-effectiveness probability; CI, confidence interval; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year.

9. LTF results in BCVA decline (1.3 ETDRS letters/year)[30] on (a) anti-VEGFs and (b) both treatments.

Resource use:

10. Anti-VEGF injections administered by band 7 nurse.[39]
11. Eighty percent discount on ranibizumab biosimilar (Ximluci) (£99.18 vial cost).[24]
12. Bevacizumab used off-label (£50 per vial).[25]

Scenario combinations:

13. Favorable anti-VEGF analysis (Scenarios 7, 9b, 10, and 11);
14. Unfavorable anti-VEGF analysis (Scenarios 1, 6, and 9a).

The model was validated using detailed patient- and iteration-level outputs of event timing and prevalence to ensure alignment with the input data. The model was independently validated by a second economic modeling expert (R.H.). The face validity of the clinical and resource input data, the passage of patients through the model structure, and the model outcomes was confirmed by 3 UK clinical experts (D.H.S., J.G.L., and T.P.).

Results

Base Case

The base-case economic analysis considered the lifetime cost-effectiveness of anti-VEGFs compared with PRP for treating PDR. We assume that the trends in visual acuity observed in Protocol S do not continue beyond 5-year observed period. This analysis used the EQ-5D model to convert visual acuity to utility.

Results of the base-case analysis are presented in Table 3, and the distribution of probabilistic results is illustrated in Fig. 2. Anti-VEGFs were more costly than PRP and generated 0.029 fewer QALYs with an associated incremental cost of £3688. Anti-VEGFs generated a NHB of −0.214 and were the more cost-effective treatment option in only 0.60% of probabilistic iterations.

Scenario Analyses

The scenario analysis results suggest that only under very select conditions may anti-VEGFs offer significant potential for cost-effective use in early treatment of PDR. Across almost all scenarios, anti-VEGFs were more costly and of similar effectiveness to PRP. Scenario analysis results are presented in Table 3.

If observed BCVA trends are extended over longer periods, PRP becomes increasingly dominant over anti-VEGFs beyond year 5. Notably, even if longer-term evidence from Protocol S is disregarded (ie, 1-year outcomes are maintained indefinitely), anti-VEGFs still generated negligible incremental QALYs (Scenario 7). If LTF leads to BCVA decline on anti-VEGFs but patients with full PRP continue to remain stable, NHB for anti-VEGFs drops to −0.589 (Scenario 9a).

The primary driver of costs in the PRP arm was subsequent treatment of DME with anti-VEGFs, demonstrated in Scenario 3. Hence discounts on the acquisition cost of anti-VEGFs also reduce the total costs associated with PRP and did not notably improve the cost-effectiveness of anti-VEGFs (Scenarios 10, 11, and 12).

An additional analysis (Scenario 13) explored a combination of scenarios most favorable to anti-VEGFs (Scenarios 7, 9b, 10, and 11). Anti-VEGFs had the highest probability of cost-effectiveness (75.57%) in this analysis, generating a nominally positive NHB of 0.027, owing to a reduction in treatment costs and a small QALY benefit. Note that this scenario is unlikely to be clinically plausible, representing the maximum cost-effectiveness of anti-VEGFs in the present model structure given the most optimistic combination of assumptions.

Scenario 14 presents a less favorable interpretation of the available data, combining Scenarios 1,6, and 9a. This sees significant divergence in long-term BCVA outcomes. There were no probabilistic iterations in which anti-VEGFs were the more cost-effective option, which generated a mean NHB of −0.766 A cost-effectiveness plane depicting the distribution of probabilistic simulation results in the base-case compared with scenarios 13 and 14 is presented in Figure 2.

Value of Information Analysis

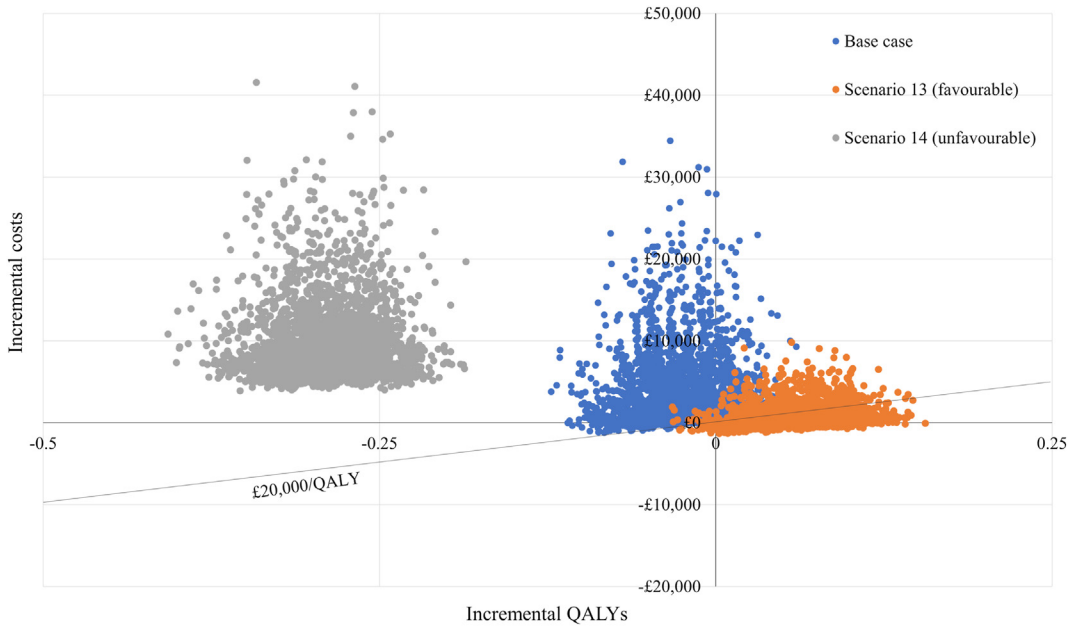
At a £20 000 WTP threshold, typically adopted by decision makers in the United Kingdom, the expected value of resolving all decision uncertainty over 10 years is £143 524 in the base-case analysis, which is likely to be insufficient to justify further research. Population EVPI remains at or near 0 in many of the scenarios analyzed, reflecting the low decision uncertainty across most clinically plausible interpretations of the available evidence. However, when long-term data from Protocol S is omitted (Scenario 7), EVPI increases to £31 095 671 and to £16 415 952 when we assume LTF is associated with long-term BCVA decline on both treatments (Scenario 9b). This indicates that there may be sufficient economic value in resolving these uncertainties to justify funding further research.

Table 4 presents a summary of population EVPI estimates across a selection of scenarios.

Discussion

This study presents the results of a DES-based cost-effectiveness analysis comparing anti-VEGF therapies with PRP for treating early PDR in the UK NHS. The model integrates detailed data on long-term BCVA trajectories, patient characteristics, and event timings derived from analysis of the AVID IPD dataset to represent the effects of patient heterogeneity on treatment outcomes.

Figure 2. Cost-effectiveness plane: base case, Scenario 13, and Scenario 14.



QALY indicates quality-adjusted life-year.

Our findings indicate that using anti-VEGFs as an early treatment for PDR is unlikely to be cost-effective compared with PRP, typically being associated with higher costs and similar health outcomes over a lifetime time horizon across a range of scenarios. Although anti-VEGFs were associated with lower rates of DME, the number of cases avoided is insufficient to offset the additional treatment costs on anti-VEGFs.

Table 4. Population EVPI (£20 000 WTP threshold) in selected scenarios.

Model scenario	EVPI/patient	Population EVPI (T = 10 years)
Base case	£1.33	£143 524
1. 5-year stopping rule for DME treatment	£0.58	£62 652
6. BCVA regression applied for 10 years	£0	£0
7. 1-year BCVA outcomes maintained indefinitely	£288	£31 095 671
9a. BCVA declines (1.3 letters per year) upon LTF on anti-VEGFs	£0	£0
9b. BCVA declines (1.3 letters per year) upon LTF on both treatments	£152	£16 415 952
13. Favorable anti-VEGF analysis	£866	£93 531 171
14. Unfavorable anti-VEGF analysis	£0	£0

BCVA indicates best corrected visual acuity; DME, diabetic macular edema; EVPI, expected value of perfect information; LTF, lost to follow-up; VEGF, vascular endothelial growth factor; WTP, willingness-to-pay.

Small 1-year BCVA benefits compared with PRP appeared to be short-lived based on Protocol S, which, over 5 years, suggested slow decline on ranibizumab and stability on PRP. Extrapolating these trends over longer time horizons consistently showed PRP to be less costly and increasingly effective compared with anti-VEGFs, which may be a plausible expectation in clinical practice. Scenario analyses confirm the robustness of the primary model results and indicated that BCVA changes on each treatment are unlikely to be clinically valuable at the magnitude observed in current trial evidence. Because utility defined by the EQ-5D instrument is relatively insensitive to moderate changes in visual acuity, treatments that avoid incurring costs are more likely to be cost-effective. Anti-VEGFs were predicted to have a positive net health benefit relative to PRP only when assuming that very substantial discounts on ranibizumab are available to the NHS and that 1-year BCVA outcomes are maintained indefinitely.

If regular administration of anti-VEGFs is required to maintain equivalence with a full PRP, estimates of the clinical effectiveness of anti-VEGFs may not be generalizable to an NHS population, with its higher burden of comorbidities and poorer treatment adherence. In scenarios assuming poorer outcomes in patients who stop attending treatment visits on anti-VEGFs, the model predicted significant divergence in health outcomes compared with PRP, illustrating the potential risks of displacement of PRP with anti-VEGFs for treating PDR.

There are structural barriers limiting the scope for anti-VEGFs or other new technologies to demonstrate cost-effectiveness in early PDR in which PRP is readily available. First, the costs associated with PRP are largely driven by the subsequent use of anti-VEGFs to treat DME (the upfront costs of machine acquisition were not considered). It is therefore unlikely that drug discounts or off-label use of bevacizumab could meaningfully improve the cost-effectiveness of anti-VEGFs as a primary treatment. Second, early PDR inherently represents an early phase of visual loss, meaning that there is

limited scope to restore vision in the short term. New technologies are therefore unlikely to yield clinically significant short-term improvements in BCVA; therefore, QALY gains will be insufficient to justify the additional costs. Any scope for cost-effectiveness depends on avoidance of complications precipitating substantial drops in BCVA, or accrual of additional costs (eg, DME treatment).

Although Protocol S represents the largest single randomized comparison of an anti-VEGFs with PRP, it remains a single data source, and as such, this economic analysis relies on the external validity and generalizability of Protocol S to NHS practice. Patients recruited to PDR trials may be poorly representative of the NHS case mix and management practices, and the randomized studies struggle to demonstrate the frequency and consequences of LTF. Furthermore, vitrectomy rates, complications, and overall outcomes vary according to grade of retinopathy at presentation.[40,41] This means that performance of anti-VEGFs in optimized trial populations may not appropriately represent clinical reality.

The value of information (VoI) analysis indicated that in particular circumstances there may remain some potential economic value associated with resolving remaining uncertainty around particular components of the modeled treatment effect. Long-term BCVA outcomes and complication rates are the most important drivers of cost-effectiveness; however, these parameters are informed solely by the Protocol S study. Should there be doubts regarding the external validity of these longer-term outcomes from Protocol S, decision uncertainty increases substantially. Despite the existence of a number of high-quality trials in this area reducing uncertainties in comparative long-term visual acuity outcomes and disease exacerbations on PRP and anti-VEGFs may be of sufficient value to the NHS to justify the collection of further long-term evidence to corroborate the findings of Protocol S.

Future trials in early PDR should prioritize demonstrating equivalence or superiority to PRP in long-term preservation of visual acuity and the avoidance of vision-threatening complications. Observational studies considering the impact of comorbidities and grade of retinopathy on treatment adherence and vision loss may also help interpretation of trial evidence in the context of real-world clinical practice.

Conclusions

In this study we report the results of the first DES-based cost-effectiveness analysis undertaken in PDR, using the results of the AVID IPD meta-analysis to explore complex time-varying, 2-eye relationships between patient characteristics and the effect of treatment. We found that anti-VEGFs are unlikely to be a cost-effective treatment option compared with PRP for treating early PDR in the United Kingdom. This holds across a variety of scenarios, with anti-VEGFs generally associated with higher costs and similar health outcomes over a lifetime time horizon.

Despite these results, important uncertainties remain. Although there a number of high-quality trials in this area, data on the long-term comparative effectiveness of anti-VEGFs and PRP and their impact on complication rates remains limited to a single study. Further research, focusing on long-term visual acuity trends on anti-VEGFs and PRP, the respective rates of vision-threatening complications, and the impact of nonadherence on vision outcomes may be beneficial to reducing these uncertainties.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2024.03.007.

Article and Author Information

Accepted for Publication: March 14, 2024

Published Online: April 22, 2024

doi: https://doi.org/10.1016/j.jval.2024.03.007

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Obtaining funding: All authors
Administrative, technical, or logistic support: Fulbright
Methodological advice: Bojke, Dias, Stewart, Simmonds
Clinical expert Advice: Steel, Lawrenson, Peto
PPI expert advice: Rush

Funding/Support: This article is based on work completed as part of the NIHR commissioned health technology assessment: Anti-VEGF drugs compared with laser photocoagulation for the treatment of diabetic retinopathy: A systematic review and economic analysis, project number NIHR132948.

Role of the Funders/Sponsors: This article presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Acknowledgment: The authors thank the authors of the CLARITY, PROTEUS, and PROTOCOL S trials for the provision of data.

REFERENCES

1. Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of type 1 and type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med*. 2012;29(7):855–862.
2. Rahman F, Zekite A, Bunce C, Jayaram H, Flanagan D. Recent trends in vision impairment certifications in England and Wales. *Eye (Lond)*. 2020;34(7):1271–1278.
3. Teo ZL, Tham YC, Yu M, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. *Ophthalmology*. 2021;128(11):1580–1591.
4. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991;98(5):766–785.
5. Royle P, Mistry H, Auguste P, et al. Pan-retinal photocoagulation and other forms of laser treatment and drug therapies for non-proliferative diabetic retinopathy: systematic review and economic evaluation. *Health Technol Assess*. 2015;19(51). v-247.
6. Simmonds MC, Llewellyn A, Walker RAE, et al. *Anti-VEGF Drugs Compared With Laser Photocoagulation for the Treatment of Diabetic Retinopathy: A Systematic Review and Meta -Analysis*. NIHR Journals Library; 2023. https://eprints.whiterose.ac.uk/201744/. Accessed April 12, 2024.
7. Simmonds MC, Llewellyn A, Walker RAE, et al. *Anti-VEGF Drugs Compared With Laser Photocoagulation for the Treatment of Proliferative Diabetic Retinopathy: A Systematic Review and IPD Meta-analysis*. NIHR Journals Library; 2024. https://eprints.whiterose.ac.uk/208232/. Accessed April 12, 2024.

8. Obeid A, Su D, Patel SN, et al. Outcomes of eyes lost to follow-up with proliferative diabetic retinopathy that received panretinal photocoagulation versus intravitreal anti-vascular endothelial growth factor. *Ophthalmology*. 2019;126(3):407–413.
9. Wubben TJ, Johnson MW, Anti-VEGF Treatment Interruption Study Group. Anti VTISG. Anti-vascular endothelial growth factor therapy for diabetic retinopathy: consequences of inadvertent treatment interruptions. *Am J Ophthalmol*. 2019;204:13–18.
10. Hutton DW, Stein JD, Bressler NM, et al. Cost-effectiveness of intravitreous ranibizumab compared with panretinal photocoagulation for proliferative diabetic retinopathy: secondary analysis from a diabetic retinopathy clinical research network randomized clinical trial. *JAMA Ophthalmol*. 2017;135(6):576–584.
11. Hutton DW, Stein JD, Glassman AR, et al. Five-year cost-effectiveness of intravitreous ranibizumab therapy vs panretinal photocoagulation for treating proliferative diabetic retinopathy: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2019;137(12):1–9.
12. Lin J, Chang JS, Smiddy WE. Cost Evaluation of Panretinal Photocoagulation Versus Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy. *Ophthalmology*. 2016;123(9):1912–1918.
13. Lin J, Chang JS, Yannuzzi NA, Smiddy WE. Cost evaluation of early vitrectomy versus panretinal photocoagulation and intravitreal ranibizumab for proliferative diabetic retinopathy. *Ophthalmology*. 2018;125(9):1393–1400.
14. Patel NA, Yannuzzi NA, Lin J, Smiddy WE. A cost-effectiveness analysis of intravitreal aflibercept for the prevention of progressive diabetic retinopathy. *Ophthalmol Retina*. 2022;6(3):213–218.
15. Sivaprasad S, Hykin P, Prevost AT, et al. *Intravitreal aflibercept compared with panretinal photocoagulation for proliferative diabetic retinopathy: the clarity non-inferiority RCT*. Southampton, UK: NIHR Journals Library; 2018.
16. Hodgson R, Walton MJ, Fulbright HA, et al. A systematic review of the cost-effectiveness of anti-VEGF drugs for the treatment of diabetic retinopathy. NIHR Journals Library. Published 2023. https://pure.york.ac.uk/portal/en/publications/a-systematic-review-of-the-cost-effectiveness-of-anti-vegf-drugs. Accessed April 12, 2024.
17. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-4. *Value Health*. 2012;15(6):821–827.
18. Davis S, Stevenson M, Tappenden P, Wailoo A. *NICE DSU Technical Support Document 15: Cost-Effectiveness Modelling Using Patient-Level Simulation*. London: National Institute for Health and Care Excellence (NICE); 2014.
19. National Institute for Health & Care Excellence. NICE health technology evaluations: the manual. Published 2022. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. Accessed June 6, 2023.
20. Scanlon PH, Nevill CR, Stratton IM, et al. Prevalence and incidence of diabetic retinopathy (DR) in the UK population of Gloucestershire. *Acta Ophthalmol*. 2022;100(2):e560–e570.
21. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*. 2015;67(1):1–48.
22. Jackson CH. flexsurv: a Platform for Parametric Survival Modeling in R. *J Stat Softw*. 2016;70(8):i08.
23. Régnier SA, Malcolm W, Haig J, Xue W. Cost-effectiveness of ranibizumab versus aflibercept in the treatment of visual impairment due to diabetic macular edema: a UK healthcare perspective. *Clinicoecon Outcomes Res*. 2015;7:235–247.
24. Joint Formulary Committee. British National Formulary. https://bnf.nice.org.uk/. Accessed September 1, 2023.
25. National Institute for Health and Care Excellence. Dexamethasone intravitreal implant for treating diabetic macular oedema. NICE. https://www.nice.org.uk/guidance/ta824/. Accessed January 1, 2024.
26. NHS. 2021/22 National costs collection data publication. https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/. Accessed July 10, 2023.
27. Jones KC, Burns A. Unit Costs of Health and Social Care 2021. University of Kent, Kent Academic Repository. https://kar.kent.ac.uk/92342/. Accessed June 6, 2023.
28. Curtis L. Unit Costs of Health and Social Care 2014. University of Kent, Kent Academic Repository. https://kar.kent.ac.uk/id/eprint/46138. Accessed June 6, 2023.
29. Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess*. 2008;12(16):iii–iv. ix-201.
30. Maturi RK, Glassman AR, Josic K, et al. Effect of intravitreous anti–vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: The protocol w randomized clinical trial. *JAMA Ophthalmol*. 2021;139(7):701–712.
31. Office for National Statistics. Data from: National life tables-life expectancy in the UK: 2018 to 2020. Published 2021. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2018to2020. Accessed February 13, 2023.
32. Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the framingham heart study, 1950 to 2005. *Circulation*. 2009;119(13):1728–1735.
33. Christ SL, Lee DJ, Lam BL, Zheng DD, Arheart KL. Assessment of the effect of visual impairment on mortality through multiple health pathways: structural equation modeling. *Invest Ophthalmol Vis Sci*. 2008;49(8):3318–3323.
34. Hodgson R, Reason T, Trueman D, et al. Challenges associated with estimating utility in wet age-related macular degeneration: a novel regression analysis to capture the bilateral nature of the disease. *Adv Ther*. 2017;34(10):2360–2370.
35. Brazier J, Muston D, Konwea H, et al. Evaluating the relationship between visual acuity and utilities in patients with diabetic macular edema enrolled in intravitreal aflibercept studies. *Invest Ophthalmol Vis Sci*. 2017;58(11):4818–4825.
36. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health*. 2011;14(4):539–545.
37. Fenwick E, Claxton K, Sculpher M. The value of implementation and the value of information: combined and uneven development. *Med Decis Making*. 2008;28(1):21–32.
38. Wise J. Diabetes cases in UK reach all time high, charity warns. *BMJ*. 2023;381:848.
39. Curtis L, Burns A. Unit Costs of Health and Social Care 2020. University of Kent, Kent Academic Repository. https://kar.kent.ac.uk/84818/13/Unit_Costs_of_Health_and_Social_Care_2020%20%281%29.pdf. Accessed June 6, 2023.
40. Parikh R, Shah RJ, VanHouten JP, Cherney EF. Ocular findings at initial pan retinal photocoagulation for proliferative diabetic retinopathy predict the need for future pars plana vitrectomy. *Retina*. Oct 2014;34(10):1997–2002.
41. Jackson TL, Johnston RL, Donachie PH, Williamson TH, Sparrow JM, Steel DH. The Royal College of Ophthalmologists' National Ophthalmology Database Study of Vitreoretinal Surgery: Report 6, Diabetic Vitrectomy. *JAMA Ophthalmol*. 2016;134(1):79–120.