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Journal Pre-proof



Anti-VEGF Drugs Compared with Panretinal Photocoagulation for the Treatment of Proliferative Diabetic Retinopathy: A Cost-Effectiveness Analysis

Matthew Walton, MSc, Laura Bojke, PhD, Mark Simmonds, PhD, Ruth Walker, MSc, Alexis Llewellyn, MSc, Helen Fulbright, PhD, Sofia Dias, PhD, Lesley A. Stewart, PhD, Tom Rush, David H. Steel, MD, John G. Lawrenson, PhD, Tunde Peto, PhD, Robert Hodgson, PhD

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Authors: Matthew Walton, MSc¹; Laura Bojke, PhD²; Mark Simmonds, PhD¹; Ruth Walker, MSc¹; Alexis Llewellyn, MSc¹; Helen Fulbright, PhD¹; Sofia Dias, PhD¹; Lesley A Stewart, PhD¹; Tom Rush³; David H Steel, MD⁴; John G Lawrenson, PhD⁵; Tunde Peto, PhD⁶; Robert Hodgson, PhD¹

1. Centre for Reviews and Dissemination, University of York, United Kingdom
2. Centre for Health Economics, University of York, United Kingdom
3. Patient representative
4. Biosciences Institute, Newcastle University, United Kingdom
5. Department of Optometry and Visual Sciences City, University of London, United Kingdom
6. Centre for Public Health, Queen's University Belfast, United Kingdom

Corresponding Author information:

Matthew Walton, MSc

Centre for Reviews and Dissemination, University of York

United Kingdom, York

Email: matthew.walton@york.ac.uk

Phone: (+44) 01904 321077

Précis

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Highlights

- Proliferative diabetic retinopathy (PDR), is a leading cause of visual impairment and blindness in the United Kingdom (UK) and worldwide. Anti-vascular endothelial growth factor (anti-VEGF) drugs aflibercept and ranibizumab are recommended by NICE for the treatment of various eye conditions, including diabetic macular oedema (DMO) 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 DES-based cost-effectiveness analysis in which we evaluate the cost-effectiveness of anti-VEGFs compared with panretinal photocoagulation (PRP) for the treatment of diabetic retinopathy in a UK setting. The analysis leveraged evidence from the AVID individual patient data meta-analysis which synthesised data from three randomised 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 PRP for treating early PDR in the UK. 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.

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Abstract

Objective: 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 UK.

Methods: A discrete event simulation model was developed, informed by individual patient data meta-analysis. The model captures treatment effects on best corrected visual acuity in both eyes, and the occurrence of diabetic macular oedema (DMO) and vitreous haemorrhage. 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 to PRP, generating 0.029 fewer QALYs at an additional cost of £3,688, 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 to PRP. Anti-VEGFs are generally associated with higher costs and similar health outcomes across various scenarios. Whilst anti-VEGFs were associated with lower DMO 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 non-adherence. Further research on long-term visual acuity, and rates of vision-threatening complications may be beneficial in resolving uncertainties.

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

1. Introduction

The rising prevalence of diabetes globally presents an increasing challenge to healthcare systems worldwide due to the burden of diabetic complications. The total costs to the United Kingdom (UK) 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 (UK) and worldwide.^{2,3}

The primary treatment for PDR is currently panretinal photocoagulation (PRP), an effective and long-lasting treatment which 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 NICE for the treatment of eye conditions including diabetic macular oedema (DMO) - 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 RCTs.^{6,7} However, they are not currently recommended for this use in the 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 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 DMO if it arises.

Previous economic analyses have considered the value of anti-VEGFs as a treatment for DR,^{5,10-15} which based on short-term trial evidence indicate possible superiority over PRP in terms of efficacy, but 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 DMO and vitreous haemorrhage (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 diabetic retinopathy, and is the first to use IPD to investigate the relationships between patient characteristics and effectiveness over time.

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

2. 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 diabetic retinopathy, 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 to 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 three randomised controlled trials:

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

Methods and results from the AVID IPD meta-analysis are reported in Simmonds *et al.*^{6,7}

2.1 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 modelling of best corrected visual acuity (BCVA) in both eyes, utilising known information about individual patients' disease characteristics. DES accommodates essentially unlimited permutations of health state combinations without the need for large numbers of discretely modelled health states, as in a state transition model. The model was coded in Microsoft Excel using Visual Basic for Applications (VBA). It was built in alignment with the general principles of patient

level simulation modelling 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 modelled the cost-effectiveness of anti-VEGFs as a therapeutic class, followed by further anti-VEGF treatment for DMO as required. The comparator arm comprises PRP followed by anti-VEGF treatment for DMO as required. Figure 1 presents a schematic depicting the model structure.

Figure 1 AVID Model Schematic

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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 (i.e. DMO, 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 re-present if DMO 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 DMO, previous vitreous haemorrhage (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. Whilst most patients with unilateral PDR will develop proliferative disease in the fellow eye, there may be a multi-year 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 (i.e., lifetime). Costs and benefits are discounted at 3.5% per annum. The analysis adopts a UK National Health Service (NHS) and

Personal Social Services (PSS) perspective. A severity-based QALY weight multiplier would not be applicable in this indication under current NICE methods.¹⁹

2.2 AVID IPD Analysis

2.2.1 Baseline characteristics

The population considered in the economic model included all patients for whom IPD was obtained (see supplementary materials). Baseline characteristics were drawn from a normal distribution for each patient to allow heterogeneity to be propagated in model outcomes.

Modelled patient characteristics were broadly comparable to published UK epidemiological sources. The mean age of the modelled population was 50.65 (SD 12.46) years – lower than the 58.9 (SD 14.6) years reported by Scanlon and colleagues.²⁰ However, this might be expected given the early-stage PDR without baseline macular oedema considered in the present study.

2.2.2 BCVA regression analysis

Longitudinal data on ETDRS score in Protocol S and CLARITY were analysed using linear mixed-effects regression (lmer) models to characterise the relationship between BCVA and key predictor variables. PROTEUS was excluded from this analysis as combination therapy may affect long-term outcomes, and DMO was managed primarily using further laser in the PRP arm, which differed to the other trials. DMO and VH were excluded as covariates as 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 one year, allowing one-year and long-term treatment response to be modelled separately. Regression coefficients are summarised in Table 1 and are depicted graphically in the supplementary material. This analysis showed that anti-VEGFs improve vision compared to PRP at one year, but there was evidence that BCVA

improves on PRP with increasing duration of follow-up, while on anti-VEGFs it declines by comparison, suggesting that any BCVA benefit relative to PRP is lost within three years on average. Greater visual acuity at the point of randomisation has a negative impact on the size of the treatment effect in both treatment arms, i.e. 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.

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

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2.2.3 *Time to event analysis*

Treatment-specific times to DMO 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 DMO and VH independently for each treatment arm to account for observed non-proportionality 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 DMO and VH outcomes. This function also best represented the expected plateau in ongoing DMO 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 package²² was used to generate variance-covariance matrices to randomly sample event times using the Cholesky decomposition. Model fit statistics are presented in the supplementary materials.

2.2.4 *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. AEs were assumed to apply on a one-off basis when patients began a course of treatment, only impacting costs, assuming no independent effect upon HRQoL.

2.2.5 *Treatment discontinuation and loss to follow-up*

Due to the ad hoc nature of PDR treatment with anti-VEGFs, and the infrequency of extra PRP following 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 loss to follow-up (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 DMO and VH. However, scenarios are presented which explore the possibility of a frozen or declining BCVA (-1.30 EDTRS letters per year)²³ following LTF.

LTF was modelled using a two-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 modelled time horizon. LTF over the full five 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 DMO and initiate treatment with anti-VEGFs.

2.3 Mortality

Mortality was modelled using the latest UK Office for National Statistics (ONS) Life Table data (2018 to 2020).²⁴ 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 standardised mortality ratios (SMR) of 1.95 (95% CI 1.64 – 2.33)²⁵ and 1.54 (95% CI 1.28 – 1.86)²⁶ respectively. This multiplicatively produces an SMR of 3.003, used to recalculate time of death in patients upon the development of SVI.

2.4 Health-related quality of life

A two-eye approach to estimating the impact of visual acuity on health-related quality of life (HRQoL) was favoured, as HRQoL is thought to be a function of overall visual functioning, rather than best-eye-specific visual acuity.²⁷ 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 four trials of intravitreal aflibercept for DMO (n=1320) reported in Brazier *et al.* (2017)²⁸, which was alone in directly eliciting utilities from a large sample of patients with DMO. This study defined the relationship between visual acuity in both eyes (amongst other patient characteristics) and utility (EQ-5D and VFQ-UI) using ordinary least squares (OLS) 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.²⁹

2.5 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 pre-existing DMO were excluded from these averages, as was any subsequent treatment following development of DMO. Treatment frequency for DMO itself is shown in Table 2, based on the RESTORE study.³⁰ Unit costs for procedures and clinician contact are based on the most recent NHS

Reference Costs (2021/22).³¹ We used a 2022-23 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 five 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 DMO. No additional monitoring cost was incurred for patients actively undergoing treatment, with the cost of OCT applied twice per year. Patients who developed DMO underwent four 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 (DMO, VH) developed.

2.6 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.³² Units per administration were based on the EMA summary of product characteristics (SmPC) 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 two 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 intra-ocular pressure (IOP), retinal detachment, and VH.

Table 2 Modelled resource use inputs

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2.7 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.*,³³ estimating EVPI by determining the consequences of an incorrect implementation decision, given decision uncertainty. Net monetary benefit (NMB) 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.* (n = 35,873) to estimate size of the incident population,²⁰ 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 UK in 2023,³⁴ 12,986 people would be diagnosed with PDR in the UK annually. Population EVPI was calculated by multiplying the mean EVPI by the incident population size, which was assumed to remain stable.

2.8 Generation of results and scenario analysis

All analyses assume that ranibizumab and aflibercept have equivalent clinical effectiveness and a comparable AE profile. As 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 dataset.

The base-case analysis considered the following key assumptions:

- Population have bilateral PDR at treatment initiation;
- 50-year (lifetime) time horizon;

- Utilities based on EQ-5D model;
- BCVA model applied for 5 years.

All analyses were run using 3,000 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. 5-year stopping rule for DMO treatment;
2. Vitreous haemorrhage excluded from model;
3. DMO excluded from model;
4. LTF not modelled;

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;

9. LTF results in BCVA decline (1.3 ETDRS letters/year)²³ on a) anti-VEGFs and b) both treatments;

Resource use:

10. Anti-VEGF injections administered by Band 7 nurse;³⁵
 11. 80% discount on ranibizumab biosimilar (Ximluci) (£99.18 vial cost);³²
 12. Bevacizumab used off-label (£50 per vial);³⁶

Scenario combinations:

13. Favourable anti-VEGF analysis (Scenarios 7, 9b, 10, and 11);
 14. Unfavourable 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 modelling expert (RH). 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 three UK clinical experts (DHS, JGL, TP).

3. Results

3.1 Base case

The base-case economic analysis considered the lifetime cost-effectiveness of anti-VEGFs compared to PRP for treating PDR. We assume that the trends in visual acuity observed in Protocol S do not continue beyond five-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, the distribution of probabilistic results is illustrated in Figure 2. Anti-VEGFs were more costly than PRP and generated 0.029 fewer QALYs with an associated incremental cost of £3,688. Anti-VEGFs generated a NHB

of -0.214 and were the more cost-effective treatment option in only 0.60% of probabilistic iterations.

3.2 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 (i.e. one-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 DMO 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 favourable 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 favourable 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.

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

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

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3.3 *Value of information analysis*

At a £20,000 WTP threshold, typically adopted by decision makers in the UK, 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 zero in many of the scenarios analysed, 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 loss to follow-up is associated with long-term BCVA decline on both treatments (Scenario 9b). This indicates 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.

Table 4 Population EVPI (£20,000 willingness to pay threshold) in selected scenarios

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4. 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.

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. Whilst anti-VEGFs were associated with lower rates of DMO, the number of cases avoided is insufficient to offset the additional treatment costs on anti-VEGFs.

Small one-year BCVA benefits compared to PRP appeared to be short-lived based on Protocol S, which over five 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 to 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. As utility defined by the EQ-5D instrument is relatively insensitive to moderate changes in visual acuity, treatments which avoid incurring costs are more likely to be cost-effective. Only by assuming very substantial discounts on ranibizumab are available to the NHS, and that one-year BCVA outcomes are maintained indefinitely, were anti-VEGFs predicted to have a positive net health benefit relative to PRP.

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 generalisable to an NHS population, with its higher burden of co-morbidities 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 where PRP is readily available. Firstly, the costs associated with PRP are largely driven by the subsequent use of anti-VEGFs to treat DMO (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. Secondly, early PDR inherently represents an early phase of visual loss, meaning 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, so 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 (e.g. DMO treatment).

Whilst Protocol S represents the largest single randomised 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 generalisability 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 randomised 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.^{37,38} This means that performance of anti-VEGFs in optimised trial populations may not appropriately represent clinical reality.

The VoI analysis indicated that in particular circumstances there may remain some potential economic value associated with resolving remaining uncertainty around particular components of the modelled 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 prioritise 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.

5. 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, two-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 UK. 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. Whilst there are 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 non-adherence on vision outcomes may be beneficial to reducing these uncertainties.

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

Treatment arm	Parameter	Mean difference	SE	95% Confidence Interval	
				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. haem.	-0.01515	0.01690	-0.04827	0.01797
	Year * vitr. haem.	-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. haem.	0.00913	0.02175	-0.03349	0.05176
	Year * vitr. haem.	3.10601	1.12631	0.89845	5.31357

Table 2 Modelled resource use inputs

Treatment administration frequency	Year	No. procedures (SD)			
		PDR (Protocol S)		DMO (RESTORE) ³⁰	
		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 ³² (Ximluci biosimilar)
	Aflibercept	£816.00		N/A	BNF 2023 ³²
	Bevacizumab	£50		N/A	NICE TA824 ³⁶
Administration costs	Intravitreal injection	£165.81 (£16.58)	£248.72	Gamma	NHS Reference Costs - BZ87A - minor - Total HRG (2021-22) ³¹
	Laser procedure	£165.81 (£16.58)	£331.62	Gamma	NHS Reference Costs - BZ87A - minor - Total HRG (2021-22) ³¹
	Intravitreal injection (nurse)	£66 (£6.60)		Gamma	PSSRU 2021 (1 hr of Band 7 nurse time) ³⁹
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 (2021-22) ³¹	
	OCT	£158 (£15.80)	Gamma	NHS Reference Costs - BZ88A - Retinal tomography, 19 years and over (2021-22) ³¹	
Adverse event management	Cataracts	£1267.89 (£126.79)	Gamma	NHS Reference Costs - BZ34C - Phacoemulsification cataract extraction and lens implant, with CC score 0-1 (2021-22) ³¹	
	Raised IOP	£1152.66 (£115.26)	Gamma	50:50 weighted average surgery and medication. NICE TA824. ³⁶ NHS Reference Costs (2021- 22) ³¹	
	Retinal detachment	£1,579.00 (£157.90)	Gamma	80:20 weighted average intermediate and major procedure. NICE TA349. NHS Reference Costs (2021-22) ³¹	
	Vitreous haemorrhage	£1,352.12 (£135.21)	Gamma	NHS Reference Costs - Weighted average of BZ86B (2021-22) ³¹	
			Frequency	% patients	
Blindness costs	Depression	£2,513.92	Annual	39%	NICE TA824 ³⁶
	Hip replacement	£5,411.96	Annual	5%	NHS Reference Costs - HT14C - intermediate

				hip procedures for trauma (weighted) (2021-22) ³¹
	Community care	£12,617.35	Annual	6% PSSRU 2014 ⁴⁰
	Residential care	£38,531.26	Annual	30% 95:5 weighted average private and local authority. PSSRU 2021 ³⁹ , NICE TA824 ³¹
	Weighted average with 41% self-funding	£24,060.89	Annual	30% NICE TA824 ³⁶
	Annual cost per patient	£13,567.45 (£1,356.75)		
	Blind registration	£161.76	One-off	95% Colquitt 2008 ⁴¹ (inflated to 2022 cost year)
	Low-vision aids	£211.00	One-off	33% Colquitt 2008 ⁴¹ (inflated to 2022 cost year)
	Low-vision rehabilitation	£364.32	One-off	11% Colquitt 2008 ⁴¹ (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
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Table 3 Base case and scenario analysis results (WTP threshold £20,000)

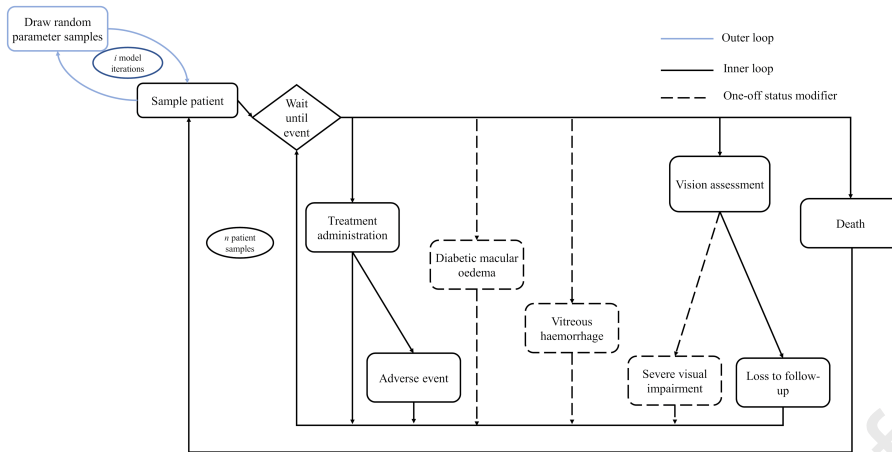
Intervention	Total		Incremental		ICER	NHB	CE prob.
	Costs	QALYs	Costs	QALYs			
Base-case analysis							
PRP	£9,935	12.330					
Anti-VEGFs	£13,624	12.301	£3,688	-0.029	Dominated	-0.214	0.60%
1. 5-year stopping rule for DMO treatment							
PRP	£7,468	12.330					
Anti-VEGFs	£11,621	12.301	£4,153	-0.029	Dominated	-0.237	0.27%
2. Vitreous haemorrhage excluded from model							
PRP	£9,446	12.330					
Anti-VEGFs	£12,792	12.301	£3,346	-0.029	Dominated	-0.197	4.90%
3. DMO excluded from model							
PRP	£3,425	12.330					
Anti-VEGFs	£11,550	12.301	£8,125	-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	£6,850	-0.029	Dominated	-0.372	14.93%
5. Utilities based on Brazier VFQ-UI model							
PRP	£9,935	12.011					
Anti-VEGF	£13,624	11.952	£3,688	-0.059	Dominated	-0.243	1.07%
6. BCVA regression coefficients extended over 10 years							
PRP	£9,935	12.348					
Anti-VEGF	£13,624	12.208	£3,688	-0.140	Dominated	-0.325	0.00%
7. 1-year BCVA on both treatments maintained indefinitely							
PRP	£9,935	12.313					
Anti-VEGF	£13,624	12.375	£3,688	0.061	£60,154	-0.123	35.27%
8. BCVA at loss to follow-up maintained indefinitely							
PRP	£9,935	12.327					

Anti-VEGF	£13,624	12.311	£3,688	-0.016	Dominated	-0.200	2.33%
9a. BCVA declines (1.3 letters per year) upon loss to follow-up on anti-VEGFs							
PRP	£9,935	12.327					
Anti-VEGF	£17,373	12.109	£7,438	-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	£3,371	0.001	Dominated	-0.170	20.63%
10. Anti-VEGF injections administered by Band 7 nurse							
PRP	£8,198	12.330					
Anti-VEGFs	£10,493	12.301	£2,295	-0.029	Dominated	-0.144	1.90%
11. Discount analysis: 80% discount on ranibizumab biosimilar (Ximluci)							
PRP	£7,940	12.330					
Anti-VEGFs	£10,028	12.301	£2,088	-0.029	Dominated	-0.134	2.13%
12. Bevacizumab price used to represent anti-VEGFs (assumed £50 per vial)							
PRP	£8,020	12.330					
Anti-VEGFs	£10,171	12.301	£2,152	-0.029	Dominated	-0.137	2.07%
13. Favourable anti-VEGF analysis: Scenarios 7, 9b, 10, and 11							
PRP	£6,203	12.313					
Anti-VEGF	£6,897	12.375	£694	0.061	£11,322	0.027	75.57%
14. Unfavourable anti-VEGF analysis: Scenarios 1, 6, and 9a.							
PRP	£7,468	12.337					
Anti-VEGF	£17,025	12.048	£9,557	-0.288	Dominated	-0.766	0.00%

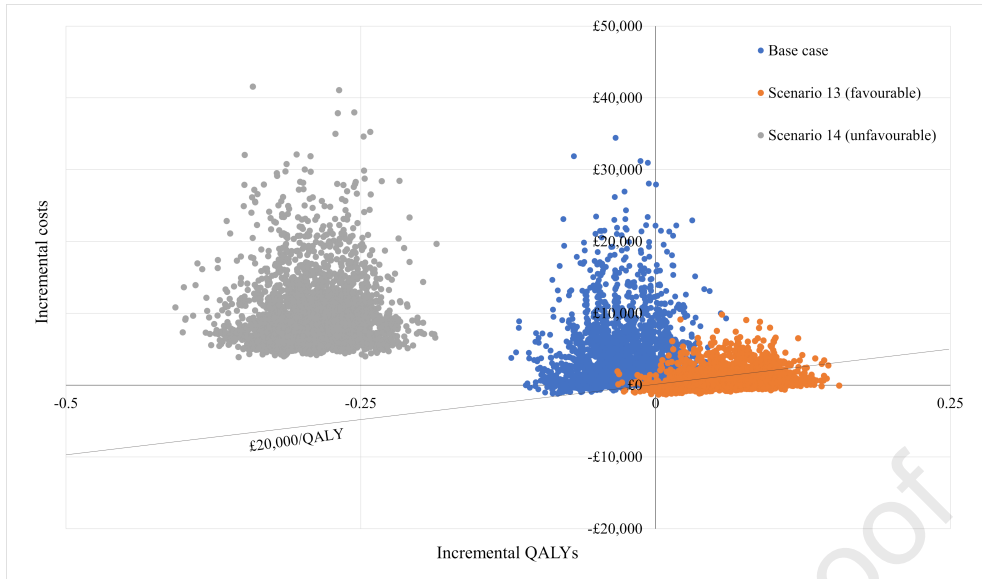
BCVA, best-corrected visual acuity; CE prob., cost-effectiveness probability; CI, confidence interval; NHB, net health benefit; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 4 Population EVPI (£20,000 willingness to pay 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 DMO 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		
9b. BCVA declines (1.3 letters per year) upon LTF on both treatments	£152	£16,415,952
13. Favourable anti-VEGF analysis	£866	£93,531,171
14. Unfavourable anti-VEGF analysis	£0	£0



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