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Research Article

A systematic review of the cost-effectiveness of anti-VEGF drugs for the treatment of diabetic retinopathy

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Abstract

Background: Non-proliferative and proliferative diabetic retinopathy are common complications of diabetes and a major cause of sight loss. Anti-vascular endothelial growth factor drugs represent a treatment option for people with diabetic retinopathy and are routinely used to treat various other eye conditions. However, anti-vascular endothelial growth factor drugs are expensive relative to current care options, and it is unclear whether this additional cost is justified when the immediate risk of vision loss is lower compared to patients with more aggressive ophthalmological conditions.

Objective: To systematically review the evidence supporting the cost-effectiveness of alternative treatments for diabetic retinopathy.

Methods: A systematic review of all comparative cost-effectiveness studies evaluating any treatment for diabetic retinopathy was conducted. Bibliographic searches were carried out to identify studies reporting on the cost-effectiveness of treatments for diabetic retinopathy; the latest searches were conducted on 28 April 2023. Included studies were synthesised narratively and evaluated with reference to UK decision-making. Studies were grouped by population into non-proliferative diabetic retinopathy and proliferative diabetic retinopathy.

Results: The review identified five studies in the proliferative diabetic retinopathy population, all of which examined the cost-effectiveness of anti-vascular endothelial growth factor treatments compared to pan-retinal photocoagulation. Results of these studies suggest that anti-vascular endothelial growth factor treatments offer some additional benefits in terms of preserved visual acuity but also incur substantial additional costs relative to pan-retinal photocoagulation. Most authors agreed that the additional costs outweigh the limited benefits, especially in certain patient subgroups without pre-existing oedema. As most of the identified evidence considered a US perspective, it is unclear how these results would translate to a UK setting.

Two studies were identified in the non-proliferative diabetic retinopathy population. There was limited evidence to support the early use of anti-vascular endothelial growth factor treatment. However, one UK study suggested that early treatment of non-proliferative diabetic retinopathy with pan-retinal photocoagulation is cost-effective compared to delayed pan-retinal photocoagulation.

Conclusions: Overall, there is a dearth of cost-effectiveness evidence considering the UK context. The identified studies raised doubts about the cost-effectiveness of anti-vascular endothelial growth factor treatments for proliferative diabetic retinopathy. No conclusions can be made regarding the cost-effectiveness of anti-vascular endothelial growth factor treatments for non-proliferative diabetic retinopathy. Future research should focus on developing rigorous model-based cost-effectiveness analyses integrating all available evidence.

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Introduction

Diabetic retinopathy (DR) is a common complication of diabetes, which occurs when high levels of blood sugar damage the blood vessels in the retina which, over time, can lead to vision loss, particularly when left untreated. Globally, 22% of people (103 million) living with diabetes have DR with 6% (29 million) having vision-threatening DR. It represents a leading cause of visual impairment in working-age adults. In the UK, the cost of treating sight-threatening DR in 2010–1 was estimated to be £57 million and is predicted to reach £97 million (inflation-adjusted) by 2035–6.[1]

Treatment of DR depends on the stage of the disease. In the early non-proliferative stages of DR, treatment aims to control metabolic dysfunction and includes careful monitoring of blood sugar levels, blood pressure and cholesterol. In the more advanced proliferative form of DR, proliferative diabetic retinopathy (PDR), the current standard of care is laser photocoagulation. Treatment with laser photocoagulation [pan-retinal photocoagulation (PRP)] aims to prevent disease progression and effect regression of existing proliferative disease, to preserve visual function.[2]

Anti-vascular endothelial growth factor (VEGF) medications have been proposed as an alternative treatment for DR, principally in PDR, and are already used to treat a variety of ophthalmological conditions including diabetic macular oedema (DMO) and neovascular age-related macular degeneration (nAMD), where they have been shown to be cost-effective.[3–5] Treatment with anti-VEGFs has been shown to be similarly effective to PRP in PDR.[6] However, using anti-VEGF drugs to treat DR would potentially also significantly increase treatment expenses, and it is unclear whether they would be a cost-effective treatment for DR, where immediate risks of sight loss are low compared to those for patients with DMO and nAMD.

Given uncertainties about the relative clinical benefits of anti-VEGF treatments for DR and the potential for additional costs, the UK National Institute for Health and Care Research (NIHR) funded the Anti-VEGF in Diabetic Retinopathy (AVID) project. The project aims to evaluate whether anti-VEGF drugs are clinically effective and cost-effective for the treatment of DR and its complications, either as a replacement for or in addition to laser photocoagulation, within the UK NHS. The project included several components: (1) a systematic review and individual participant data (IPD) meta-analysis of existing evidence on the clinical effectiveness of anti-VEGF drugs for the management of DR, (2) a systematic review of existing evidence on the cost-effectiveness of anti-VEGF drugs for the management of DR and (3) the development of a de novo model evaluating the cost-effectiveness of anti-VEGF drugs for the management of DR in a UK setting.

This manuscript focuses on the second component and aims to systematically review and synthesise cost-effectiveness evidence evaluating treatments for both non-proliferative diabetic retinopathy (NPDR) and PDR. The review was conducted to provide a summary of the existing cost-effectiveness evidence and to ascertain its suitability to inform decision-making in the UK. The findings from the review were also used to help inform the development of a new decision-analytic model conducted in part three of the AVID project.

Methods

The AVID study followed a protocol registered on PROSPERO (CRD42021272642). Findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[7,8]

Inclusion criteria

The review considered a broad range of economic studies including trial-based economic evaluations, modelling studies and analyses of administrative databases. Studies were eligible for inclusion if they:

- Included patients with DR (proliferative and non-proliferative). Studies modelling patients with a principal indication of DMO were excluded, as were patients with vitreous haemorrhage.
- Patients received any treatment including, but not limited to, the following anti-VEGF therapies: aflibercept, bevacizumab, ranibizumab or their biosimilars – either alone or in combination with PRP.
- Reported full economic evaluations comparing two or more alternative interventions in terms of both costs and consequences, that is, cost-minimisation, cost-effectiveness, cost–utility or cost–benefit analyses.

No restrictions were placed on outcomes reported. Outcomes of relevant study designs were, however, expected to include one of the following: functional impact on vision, progression of retinopathy (non-proliferative to proliferative), health-related quality of life (National Eye Institute Visual Functioning Questionnaire-25, EuroQol-5 Dimensions, Short Form questionnaire-36 items), quality-adjusted life-years (QALYs), costs, resource use, incremental costs and QALYs or incremental cost-effectiveness ratios (ICERs). Non-comparative costing studies were excluded. There were no restrictions on language or date of publication.

Study identification and selection process

Bibliographic searches were carried out to identify studies reporting on the cost-effectiveness of treatments for DR. An Information Specialist (HF) designed a preliminary search strategy in Ovid MEDLINE in consultation with the research team. The final MEDLINE strategy was then adapted for use in all resources searched. The initial searches were performed on 8 November 2021 and were updated on 28 April 2023. The following databases were searched: Ovid MEDLINE(R) ALL, EMBASE (Ovid), EconLit (Ovid), Cochrane Database of Systematic Reviews (Wiley), Science Citation Index Expanded (Web of Science), Social Sciences Citation Index (Web of Science), International Health Technology Assessment (HTA) database, NHS Economic Evaluation Database (EED) [Centre for Reviews and Dissemination (CRD)] and HTA (CRD). Search results were imported into EndNote 20 (Clarivate Analytics, Philadelphia, PA, USA) and deduplicated. All search strategies are presented in full in *Appendix 1*.

The protocol for the selection of relevant studies defined two selection stages: (1) assessment and screening for possible inclusion of titles and abstracts identified by the search strategy and (2) acquisition and screening for inclusion of the full texts of potentially relevant studies. Two researchers (RH and MW) independently screened the titles and abstracts of all reports identified by the bibliographic searches. Full texts of potentially relevant studies were screened in duplicate against the eligibility criteria. Discrepancies were resolved by discussion.

Data extraction and quality assessment strategy

Details of eligible studies including setting, population, technologies assessed, study type and where applicable modelling approach were extracted and entered into a data extraction template developed in Microsoft Excel™ (Microsoft Corporation, Redmond, WA, USA). Data were extracted by one reviewer (RH) and then subsequently checked by a second reviewer (MW). Extraction templates and data extracted are available on request. Discrepancies between reviewers were resolved through discussion. Quality assessment of the included studies was also conducted using the Consolidated Health Economic Evaluation Reporting Standards checklist developed by Drummond *et al.*[9] In line with the data extraction process, this was completed by one review (RH) and checked by a second (MW).

Data analysis

No formal synthesis of identified studies was attempted. Instead, studies were synthesised narratively. A descriptive summary of each identified study was generated, and key features were tabulated. Studies were grouped by population (NPDR and PDR).

Results

The systematic searches yielded a total of 8357 articles (*Figure 1*). After the removal of 2274 duplicates, the remaining 6083 titles and abstracts were screened against the inclusion criteria. A total of 33 studies were considered potentially relevant and were taken forward for full-text examination. Overall, we identified seven studies that reported on economic evaluations for treatments for DR (*Table 1*). Only two of the identified studies considered a UK setting,[10,11] with all remaining studies considering a US setting. Five studies evaluated treatments for PDR,[11–15] all of which evaluated one or more anti-VEGF compared with PRP. The study by Lin and colleagues[15] also additionally considered pars plana vitrectomy (PPV) as a comparator. The two remaining studies evaluated whether early treatment of patients with NPDR was cost-effective. The first, Patel *et al.*,[16] considered the use of aflibercept compared with best supportive care. The second, Royle *et al.*,[10] evaluated treatment with PRP at the onset of NPDR versus treatment with PRP at the onset of PDR.

Results of the quality assessment identified several limitations in the included studies (see *Appendix 2* for details).

Two studies by Hutton *et al.* were largely methodologically sound, with key concerns relating to the perspective of the analysis (which was not stated) and the justification of discount rates which appear not to have been applied. Related studies reported by Lin *et al.*[14] and Lin *et al.*,[15] both of which presented modelled-based analysis, were poorly reported. This meant that it was not possible to fully establish the model structure and assumptions made in the model. There were substantive issues with how cost-effectiveness was assessed which do not conform with

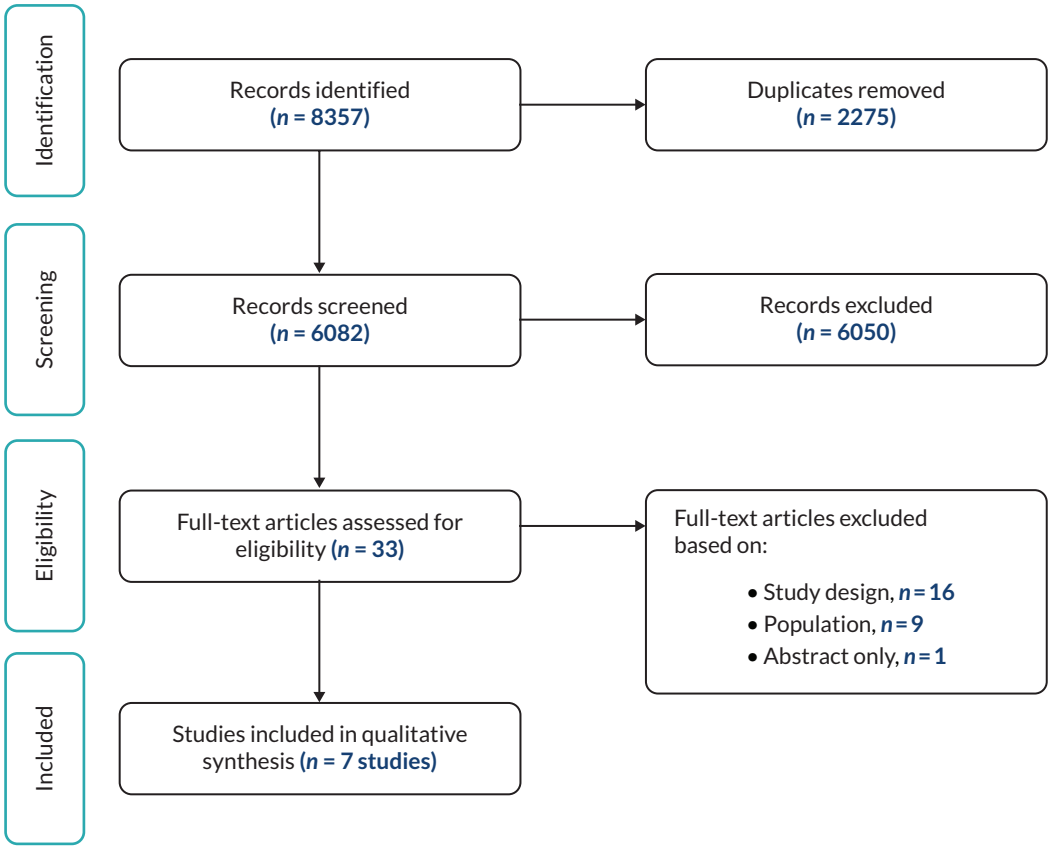

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing study selection.

TABLE 1 Summary of study characteristics

Study (country)	Interventions under consideration	Population (base case where clearly stated)	Type of economic evaluation	Perspective, discounting and time horizon	Results
Hutton, 2017[12] (US)	1. Intravitreal ranibizumab (0.5 mg) 2. PRP	PDR	Trial-based, cost–utility analysis	Perspective: not stated Discounting benefits: 0% Discounting costs: 0% Time horizon: 2 years	Patients with baseline DMO: $55,568/QALY. Patients without baseline DMO $662,978/QALY.
Hutton, 2019[13] (US)	1. Intravitreal ranibizumab (0.5 mg) 2. PRP	PDR	Trial-based, cost–utility analysis	Perspective: not stated Discounting benefits: 3% Discounting costs: 3% Time horizon: 5 years	Base-case (5-year) results: Patients with baseline DMO: $65,576/QALY. Patients without baseline DMO $582,268/QALY. Scenario analysis (10-year) results: patients with baseline DME: $63,390/QALY. Patients without baseline DMO $742,202/QALY.
Lin, 2016[14] (US)	1. Intravitreal ranibizumab (0.5 mg) 2. PRP	PDR	Model-based, cost–utility analysis using Markov modelling approach	Perspective: not stated Discounting benefits: not stated Discounting costs: not stated Time horizon: 2 years (lifetime explored in scenario analysis)	Results were presented as cost per QALY for each intervention, no incremental results were presented. Cost per QALY for PRP in the facility setting was $7988, in the non-facility setting cost per QALY was $6297. Cost per QALY for ranibizumab in the facility setting was $19,150, in the non-facility setting the cost per QALY was $16,238.

TABLE 1 Summary of study characteristics (*continued*)

Study (country)	Interventions under consideration	Population (base case where clearly stated)	Type of economic evaluation	Perspective, discounting and time horizon	Results
Lin, 2018[15] (US)	1. Intravitreal ranibizumab (0.3 mg) 2. PRP 3. PPV	PDR	Model-based, cost–utility analysisusing a Markov modelling approach	Perspective: not stated Discounting benefits: 0% Discounting costs: 3% Time horizon: 2 years (lifetime explored in scenario analysis)	Results were presented as cost per QALY for each intervention, no incremental results were presented. Cost per QALY for PRP in the facility setting was $163,988, in the non-facility setting cost per QALY was $102,559. Cost per QALY for ranibizumab *n* the facility setting was $436,992, in the non-facility setting the cost per QALY was $326,424. Cost per QALY for PPV in the facility setting was $181,144, in the non-facility setting cost per QALY was $107,965.
Sivaprasad, 2018[11] (UK)	1. Intravitreal aflibercept 2. PRP	PDR	Trial-based, cost-effective-ness and cost–utility analysis	Perspective: payer Discounting benefits: not applied Discounting costs: not applied Time horizon: 1 year	Cost-effectiveness analysis: Incremental costs per BCVA letter were £1393 for aflibercept as compared with PRP laser treatment. Sensitivity analysis showed that at the threshold of WTP threshold of £1400 per BCVA letter there was a 57% probability of aflibercept being cost-effective. Cost–utility analysis results found aflibercept to be less effective and more costly compared with PRP. Results were presented as a negative ICER: −£252,827 per QALY.
Patel, 2022[16] (US)	1. Intravitreal aflibercept (0.5 mg) 2. Standard of care	Moderate to severe NPDR	Trial-based, cost- effec-tiveness analysis	Perspective: not stated Discounting benefits: not state Discounting costs: not stated Time horizon: 2 years	Cost per point change in DRSS was $2700 (hospital-based) and $2400 (non-hospital-based). Using Protocol W data, cost per PDR case prevented was $83,700 (hospital-based) and $72,400 (non-hospital-based). Using PANORAMA data, cost per PDR case prevented was $89,400 (hospital-based) and $75,000 (non-hospital-based). Using Protocol W data, cost to prevent one case of DMO was $154,000 (hospital-based) and $133,000 (non-hospital-based). Using PANORAMA data, cost to prevent one case of DM was $70,900 (hospital-based) and $59,500 (non-hospital-based).
Royle, 2015[10] (UK)	1. PRP initiated at the onset of severe NPDR 2. Watchful waiting, PRP initiated at the onset of PDR	NPDR	Model-based, cost–utility analysis	Perspective: payer Discounting benefits: 3.5% Discounting costs: 3.5% Time horizon: 30 years	Results showed early intervention with PRP was less costly (−£1112) and more effective (01292 QALYs). Results from probabilistic sensitivity analysis suggested there was a 60% probability of cost-effectiveness assuming a £20,000 WTP threshold.

BCVA, best corrected visual acuity; DRSS, diabetic retinopathy severity scale; WTP, willingness-to-pay threshold.

standard practice of estimating ICERs. No methodological concerns were identified regarding Sivaprasad *et al.*[11]

The key limitations of Patel *et al.*[16] related to the perspective and discount rate applied which were not stated. The study used a cost–consequence approach, the motivation for which was explained in the manuscript but not fully justified. It was not clear how the outcomes selected were informative decision-makers. Limitations with the Royle study centred on key assumptions made regarding the durability of the treatment effect; these were, however, largely a consequence of underlying limitations in the available data, rather than the analysis conducted.

Studies evaluating treatments for proliferative diabetic retinopathy

Hutton *et al.*[12] and Hutton *et al.*[13] were primarily trial-based analyses of Protocol S,[17,18] which included a within-study prospective cost-effectiveness analysis at 2- and 5-year follow-up. The analysis utilised outcome data on

visual acuity, safety and resource use. Visual acuity scores from the best-seeing eye were mapped to health state utilities using the Brown *et al.*[19] algorithm and were used to estimate total QALYs, while resource data from the trial were supplemented by unit cost data from the Medicare fee schedule and used to estimate total costs. Safety data were only used in scenario analysis to estimate costs associated with managing adverse events.

In both studies, results were stratified based on baseline DMO, which significantly influenced both clinical benefits and cost-effectiveness. Findings from both subgroups indicated that while ranibizumab improved visual acuity outcomes at 2 and 5 years, the incremental QALY benefits were modest. Moreover, ranibizumab incurred substantial incremental costs compared to PRP primarily due to high drug acquisition expenses. Consequently, estimated ICERs were consistently high across all analyses (see *Table 1*). These, however, varied substantively across analyses and were notably lower in the subgroup with baseline DMO. These differences were primarily driven by larger incremental QALY benefits in the baseline DMO subgroup. Hutton *et al.*[13] also reported analysis using a 10-year time horizon which extrapolated the 5-year data from Protocol S,[17,18] assuming visual acuity is maintained at the level reported at the end of 5-year follow-up. Results from this analysis were largely similar to those considering a 5-year time horizon.

Lin *et al.*[14] and Lin *et al.*[15] were both model-based analyses. Both studies used the same underlying model but addressed different populations. The modelled population in Lin *et al.*[14] reflected the whole population recruited to Protocol S[17,18] which included patients both with and without DMO at baseline, while Lin *et al.*[15] addressed a subgroup of patients without DMO at baseline. Reporting on the model structure adopted was limited in both study reports, making it difficult to establish the approach taken. The authors described the model as a Markov-style decision tree, and it appears that health states were defined with respect to the treatment received but few other details were provided. The benefits of treatment were evaluated using the diabetic retinopathy severity scale (DRSS) as a surrogate for severe vision loss, assuming nine lines would be saved on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart. This was then converted to QALYs based on a published algorithm,[20] suggesting a conversion factor of 0.03 QALYs per line of vision saved. In scenarios using a lifetime time horizon, it was assumed that any QALY benefits were retained throughout the time horizon. Costs were modelled using Medicare fee schedule data with resource use data informed by values reported in Protocol S[17,18] and appear to have primarily focused on procedure and drug administration and acquisition costs. Poor reporting hampered a thorough quality assessment; in particular, it was difficult to establish the structural assumptions made in the model and consequently the key mechanisms of benefit.

Results from Lin *et al.*[14] and Lin *et al.*[15] were not expressed in comparative terms; instead, costs per QALY were estimated individually for each arm and compared. The lack of incremental analysis prevents meaningful interpretation of the results. The authors noted that PRP is less costly than ranibizumab per QALY gained, but also noted that cost–utility ratios for both comparators fall well below the accepted cost per QALY upper limit of $100,000 per QALY. There was no discussion as to why this threshold was adopted. In Lin *et al.*,[15] which also evaluated PPV as an alternative, the authors concluded that PPV demonstrates similar cost–utility ratios to PRP and favourable cost–utility ratios compared with ranibizumab (see *Table 1*).

Sivaprasad *et al.*[11] carried out a cost-effectiveness and cost–utility analysis. Both were trial-based analyses that were conducted alongside the CLARITY[21] clinical trial which compared aflibercept (2 mg) with PRP in patients with PDR. Analysis of CLARITY[21] showed that aflibercept was associated with additional costs but also resulted in improved visual acuity. For the cost-effectiveness analysis, the incremental cost of an additional best corrected visual acuity letter was £1393. For the cost–utility analysis, QALY benefits were derived directly from EuroQol-5 Dimensions, three-level version data collected in the CLARITY[21] trial. This analysis found aflibercept to be less effective and more costly compared with PRP. Based on the cost-effectiveness analysis, the authors concluded that aflibercept was more costly and more effective. The authors did not consider the results of the cost–utility analysis robust and noted that the measures of quality of life were not sensitive enough to capture the clinical difference between treatments.

Studies evaluating treatments for non-proliferative diabetic retinopathy

Patel *et al.*[16] conducted a trial-based analysis that leveraged data from two randomised trials: Protocol W and PANORAMA.[22] Both studies evaluated aflibercept compared with sham injection in patients with moderate to severe NPDR without DMO, although each used different aflibercept dosages. The outcomes of both studies indicated modest benefits in terms of visual acuity. Consequently, the authors deemed a cost–utility analysis impractical and instead structured their analysis as a cost-effectiveness analysis estimating the cost per case of PDR and DMO avoided. The analysis also considered the

costs per case of a change in DRSS scores using data from Protocol W only.

Outcome data (PDR, DMO and DRSS scores) were estimated using published data from Protocol W and PANORAMA[22] using values reported at 2 years. Resource use considered only injection frequency and was also informed by published trial data from Protocol W and PANORAMA.[22] This was combined with unit cost data from the Medicare fee schedule to estimate total costs. In the base-case analysis, only aflibercept was considered as an alternative to usual care; however, scenario analysis also considered the costs of bevacizumab assuming equal efficacy with aflibercept.

Key results from Patel *et al.*[16] are summarised in *Table 1*. The authors concluded that treatment with anti-VEGF was associated with substantial costs per case of PDR and DMO avoided, and DRSS improvement.

Royle *et al.*[10] developed a Markov model to determine whether offering PRP treatment to patients with severe NPDR is cost-effective compared with delaying treatment until the onset of PDR. The model structure was based on 18 health states which were defined with respect to the severity of DR and whether patients had DMO. Each health state in the model was associated with one of four levels of visual acuity defined on the ETDRS visual acuity chart with more severe health states associated with lower visual acuity. The onset of DMO was also associated with an additional utility decrement. Delaying progression of the disease and onset of DMO, therefore, represented the main mechanism through which benefits were generated in the model.

Transition probabilities were estimated using data from a range of published sources. Primary sources included Klein *et al.*,[23] Klein *et al.*,[24] ETDRS report #9 and ETDRS report #12. Where data were unavailable, it was assumed that early PRP resulted in a 20% reduction in the risk of progression to a subsequent health state. Utility values were sourced from three studies: Brown *et al.*,[25] Fong *et al.*[26] and Smith *et al.*[27] Resource use information was based on RCOphth guidelines[28] and expert clinical opinion. Costs modelled included: PRP procedure costs, clinic visits, vitrectomy surgery and annual blindness costs. Cost information was based on national reference costs and values published in the literature. Transition probabilities were estimated using data from a range of published sources. Primary sources included Klein *et al.*,[23] Klein *et al.*,[24] ETDRS report #9[29] and ETDRS report #12.[30] Where data were unavailable, it was assumed that early PRP resulted in a 20% reduction in the risk of progression to a subsequent health state. Utility values were sourced from three studies: Brown *et al.*,[25] Fong *et al.*[26] and Smith *et al.*[27] Resource use information was based on RCOphth guidelines and expert clinical opinion. Costs modelled included: PRP procedure costs, clinic visits, vitrectomy surgery and annual blindness costs. Cost information was based on national reference costs and values published in the literature.

Results from the Royle *et al.*[10] analysis showed early PRP treatment was more effective and less costly than treatment upon the onset of PDR (see *Table 1*). The benefits of early treatment were driven by slowed disease progression and retention of visual acuity. Slowed disease progression also resulted in cost savings due to more severe health states being associated with increased management and subsequent treatment costs. Uncertainties around the cost-effectiveness of PRP at NPDR or early PDR stage were explored in a range of scenario analyses and found to be robust with early PRP either dominating delayed PRP or generating low ICERs below accepted WTP norms.

Discussion

Our systematic review aimed to identify existing studies assessing the cost-effectiveness of treatments for DR focusing on a UK decision-making perspective. We identified several relevant analyses considering both proliferative and non-proliferative forms of DR.

Proliferative diabetic retinopathy

The review identified five studies in the PDR population, all of which examined the cost-effectiveness of anti-VEGF treatments compared to PRP. While individual studies used different sources of data and made a variety of different assumptions, several common themes emerged.

All the studies concluded that anti-VEGF treatments incurred additional costs compared to PRP. These increased costs were primarily driven by drug acquisition and administration costs. Several studies[14,15] also explored the use of bevacizumab as a lower-cost alternative to ranibizumab and aflibercept, resulting in substantial reductions in incremental costs associated with anti-VEGF treatment. Additionally, these studies found that differences in visual acuity outcomes between anti-VEGF and PRP groups were small, leading to modest QALY benefits. These findings align with our systematic review and IPD meta-analysis, which showed consistent short-term, modest visual acuity gains in patients receiving anti-VEGFs.[6,31]

Authors generally expressed scepticism about the value of anti-VEGF treatments, as they believed that the limited benefits of these treatments did not justify the often-substantial additional costs. This was particularly evident in subgroups of patients without DMO at baseline, where the benefits of anti-VEGF treatment were smaller. One notable exception was Sivaprasad *et al.*,[11] the only UK study identified in the PDR population. The authors of this study were more optimistic about the value of anti-VEGF treatment, although their cost–utility analysis indicated that aflibercept was (more costly and less effective) by PRP.

Overall, the reviewed studies raised doubts about the cost-effectiveness of anti-VEGF treatments for PDR, with most authors expressing reservations about the additional costs outweighing the limited benefits, especially in certain patient subgroups without pre-existing DMO. It is important to interpret these conclusions cautiously, especially in the UK context, as most studies were conducted from a US payer perspective. Significant differences between healthcare settings may impact estimates of cost-effectiveness, limiting the reliability and relevance of these studies to UK decision-making. On this point, it is important to note that anti-VEGF treatments in the UK are all subject to confidential commercial discounts and that the included studies were conducted prior to the availability of biosimilars. Consequently, the acquisition costs associated with anti-VEGF treatments are likely very different from those currently relevant to the UK NHS. Concerns raised regarding high incremental costs may therefore not be relevant to the current UK setting.

This may be addressed by forthcoming National Institute for Health and Care Excellence (NICE) Guidelines on DR, which, it is understood, will include an economic model conducted from an NHS perspective. However, currently no existing cost-effectiveness analyses fully account for the therapeutic value of anti-VEGFs. Most evaluations considered relatively short time horizons based on the maximum follow-up of the trial data used to underpin the analysis. This represents a significant limitation in the context of evaluating cost-effectiveness in PDR. The therapeutic aims of treating DR reflect a desire not only to prevent retinopathy-related vision loss but also to prevent the escalation of disease to DMO as well as the avoidance of complications such as vitreous haemorrhage and tractional retinal detachment. The limited time horizons used in the identified studies mean that these downstream consequences, which may negatively impact visual acuity and management costs, cannot be adequately accounted for and therefore potentially do not fully reflect the costs and benefits of treatment.

More sophisticated model-based approaches considering a lifetime time horizon may more fully address these limitations, allowing for better integration of other forms of evidence to inform long-term patient outcomes. Moreover, a model-based analysis may more appropriately integrate a synthesis of all randomised controlled trial (RCT) evidence, addressing a weakness of the current literature, which is all based on individual RCTs, and therefore does not reflect the totality of the available clinical effectiveness evidence appropriately synthesised.

Non-proliferative diabetic retinopathy

Just two studies were identified in the NPDR population, each considering different interventions and comparators. Results from Patel *et al.*[16] suggested substantial incremental costs associated with anti-VEGF treatments compared to standard of care. However, due to the nature of their cost-effectiveness analysis, it is challenging to determine whether these incremental costs are justified. Patel and colleagues extensively discussed the need for metrics to evaluate value for money in such contexts. Nevertheless, in the UK, where an established value assessment framework exists, we would argue against this approach and recommend instead that future research focus on developing rigorous cost-effectiveness analyses using model-based approaches that link intermediate outcomes to long-term QALY gains.

Results from Royle *et al.*[10] provide more informative insights, as they employed a model-based analysis considering a lifetime horizon and a UK payer perspective. Their findings strongly support the early use of PRP in NPDR and were robust across a range of alternative scenarios and assumptions. However, their analysis has limitations. Firstly, it relies on non-randomised studies and makes extensive assumptions about the ability of PRP to preserve visual acuity in the NPDR population, which is not fully supported by clinical evidence. Secondly, as acknowledged by the study authors, the deferred PRP arms in the studies may not reflect routine care, where delays in treatment may result in patients having vitreous bleeds or other complications. Finally, a significant limitation in the context of the AVID NIHR HTA project is that the Royle study did not evaluate anti-VEGF treatments for NPDR and therefore offers no insights into the cost-effectiveness of these treatments within the NPDR population.

Patient and public involvement

Patient and clinical representatives participated in every phase of this project as members of our advisory group. Patient representatives highlighted key areas of concern, emphasising that most cost-effectiveness studies

adopted a one-eye model and did not account for the impact of binocular vision on the quality of life. They also expressed worries about the lack of long-term evidence, noting significant uncertainties regarding the prolonged management of PDR. Additionally, patients noted that anti-VEGF treatments often require multiple repeated injections over time, leading to a greater burden due to frequent clinic visits, compared to the typically fewer sessions needed for PRP treatment.

Equality, diversity and inclusion

As this was a systematic review of existing studies, we could not account for equality issues in this population beyond what was reported in included publications or data. None of the studies included in the review highlighted any equality issues.

Diabetes and its associated complications are more prevalent among individuals of South Asian ethnicity and those from socioeconomically deprived backgrounds. However, providing anti-VEGF or other treatments for DR will not address these underlying disparities.

Conclusions

We carried out a systematic review of studies evaluating the cost-effectiveness of anti-VEGF or laser photocoagulation therapies for the treatment of DR, with a specific focus on UK-relevant studies. We identified several studies considering both (PDR) and NPDR. However, the majority of evidence pertained to patients with PDR. Results from these studies suggest that anti-VEGF treatments offer some additional benefits in terms of preserved visual acuity but also incur substantial additional costs compared to PRP. It is unclear whether these additional costs are justified. Study authors generally considered the magnitude of these costs unjustified in patients without DMO at baseline. Most studies identified in the PDR population considered a US perspective, raising uncertainty about their applicability to the UK setting and limiting their relevance to UK decision-makers.

In the NDPR population, there was limited evidence supporting the early use of anti-VEGF treatment. However, one UK study suggested that early treatment of NPDR with PRP is cost-effective compared to delayed PRP. Limitations in the data underpinning this analysis and questions regarding specific modelling assumptions limit the strength of conclusions that can be drawn. Overall, there is a dearth of cost-effectiveness evidence considering the UK context.

Additional information

CRediT contribution statement

Robert Hodgson (https://orcid.org/0000-0001-6962-2893): Conceptualisation (lead), Data curation (lead), Formal analysis (lead), Funding acquisition, Investigation (co-lead), Methodology (lead), Project administration, Writing – original draft (lead), Writing – reviewing and editing (lead).

Matthew Walton (https://orcid.org/0000-0003-1932-3689): Conceptualisation, Data curation, Formal analysis, Investigation (co-lead), Methodology, Project administration, Writing – original draft, Writing – reviewing and editing.

Helen Fulbright (https://orcid.org/0000-0002-1073-1099): Investigation, Methodology.

Laura Bojke (https://orcid.org/0000-0001-7921-9109): Conceptualisation, Funding acquisition, Writing – reviewing and editing.

Ruth Walker (https://orcid.org/0000-0003-2765-7363): Conceptualisation, Writing – reviewing and editing.

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Sofia Dias (https://orcid.org/0000-0002-2172-0221): Conceptualisation, Funding acquisition, Writing – reviewing and editing.

Lesley Stewart (https://orcid.org/0000-0003-0287-4724): Conceptualisation, Funding acquisition, Writing – reviewing and editing.

David Steel (https://orcid.org/0000-0001-8734-3089): Conceptualisation, Funding acquisition, Writing – reviewing and editing.

John Lawrenson (https://orcid.org/0000-0002-2031-6390): Conceptualisation, Funding acquisition, Writing – reviewing and editing.

Tunde Peto (https://orcid.org/0000-0001-6265-0381): Conceptualisation, Funding acquisition, Writing – reviewing and editing.

Mark Simmonds (https://orcid.org/0000-0002-1999-8515): Conceptualisation, Funding acquisition (lead), Project administration, Writing – reviewing and editing.

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Data-sharing statement
All data used in this analysis are provided in the main body of the text. Requests should be submitted to the corresponding Author.

Ethics statement
As this was a systematic review of existing published data, no ethics approval was required.

Information governance statement
All data used in this paper were taken from published sources: no personal data were included.

Disclosure of interests
Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/NHYK3694.

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This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

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About this article
The contractual start date for this research was in August 2021. This article began editorial review in October 2023 and was accepted for publication in August 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

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List of abbreviations

AVID	Anti-VEGF in Diabetic Retinopathy
CRD	Centre for Reviews and Dissemination
DMO	diabetic macular oedema
DR	diabetic retinopathy
DRSS	diabetic retinopathy severity scale
EED	Economic Evaluation Database
ETDRS	Early Treatment Diabetic Retinopathy Study
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IPD	individual participant data
NAMD	neovascular age-related macular degeneration
NIHR	National Institute for Health and Care Research
NPDR	non-proliferative diabetic retinopathy

PDR	proliferative diabetic retinopathy
PPV	pars plana vitrectomy
PRP	pan-retinal photocoagulation
QALY	quality-adjusted life-year
RCT	randomised controlled trial
VEGF	vascular endothelial growth factor

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**:855–62.
2. The Royal College of Ophthalmologists. *Diabetic Retinopathy Guidelines*. RCO; 2013. URL: www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-301-FINAL-DR-GUIDELINES-DEC-2012-updated-July-2013.pdf (accessed 4 September 2020).
3. National Institute for Health and Care Excellence. *Ranibizumab for Treating Diabetic Macular Oedema*. NICE; 2013. URL: www.nice.org.uk/guidance/ta274/resources/ranibizumab-for-treating-diabetic-macular-oedema-pdf-82600612458181 (accessed 5 July 2023).
4. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal 2013*. NICE; 2013. URL: www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 (accessed 11 September 2020).
5. National Institute for Health and Care Excellence. *Aflibercept for Treating Diabetic Macular Oedema*. NICE; 2015. URL: www.nice.org.uk/guidance/ta346/resources/aflibercept-for-treating-diabetic-macular-oedema-pdf-82602611201221 (accessed 5 July 2023).
6. Simmonds MC, Llewellyn A, Walker RAE, Fulbright HA, Walton MJ, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of diabetic retinopathy: a systematic review and meta-analysis. *NIHR J Lib* 2023. URL: https://eprints.whiterose.ac.uk/201744/
7. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9, W64.
8. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF; PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD statement. *JAMA* 2015;**313**:1657–65.
9. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press; 2015.
10. Royle P, Mistry H, Auguste P, Shyangdan D, Freeman K, Lois N, Waugh N. Pan-retinal photocoagulation and other forms of laser treatment and drug therapies for non-proliferative diabetic retinopathy: systematic review and economic evaluation. *Health Technol Assessment* 2015;**19**:v–xxviii, 1.
11. Sivaprasad S, Hykin P, Prevost AT, Vasconcelos J, Riddell A, Ramu J, *et al*. Intravitreal aflibercept compared with panretinal photocoagulation for proliferative diabetic retinopathy: the CLARITY non-inferiority RCT. *Efficacy Mech Eval* 2018;**5**:1–112.
12. Hutton DW, Stein JD, Bressler NM, Jampol LM, Browning D, Glassman AR; Diabetic Retinopathy Clinical Research Network. 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**:576–84.
13. Hutton DW, Stein JD, Glassman AR, Bressler NM, Jampol LM, Sun JK; for the DRCR Retina Network. 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**:1424–9.
14. Lin J, Chang JS, Smiddy WE. Cost evaluation of panretinal photocoagulation versus intravitreal ranibizumab for proliferative diabetic retinopathy. *Ophthalmology* 2016;**123**:1912–8.
15. 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**:1393–400.
16. 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**:213–8.
17. Gross JG, Glassman AR, Liu D, Sun JK, Antoszyk AN, Baker CW, *et al*.; Diabetic Retinopathy Clinical Research Network. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol* 2018;**136**:1138–48.

18. Gross JG, Glassman AR, Jampol LM; Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2016;**314**:2137–2146. [Erratum published in *JAMA* 2016;315:944.]

19. Brown MM, Brown GC, Sharma S, Landy J. Health care economic analyses and value-based medicine. *Surv Ophthalmol* 2003;**48**:204–23.

20. Brown MM, Brown GC, Lieske HB, Lieske PA. Preference-based comparative effectiveness and cost–effectiveness: a review and relevance of value-based medicine for vitreoretinal interventions. *Curr Opin Ophthalmol* 2012;**23**:163–74.

21. Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J, *et al.*; CLARITY Study Group. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (clarity): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet* 2017;**389**:2193–203.

22. Brown DM, Wykoff CC, Boyer D, Heier JS, Clark WL, Emanuelli A, *et al*. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: results from the panorama randomized clinical trial. *JAMA Ophthalmol* 2021;**139**:946.

23. Klein R, Klein BEK, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* 1998;**105**:1801–15.

24. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BEK. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology* 2008;**115**:1859–68.

25. Brown MM, Brown GC, Sharma S, Shah G. Utility values and diabetic retinopathy. *Am J Ophthalmol* 1999;**128**:324–30.

26. Fong DS, Sharza M, Chen W, Paschal JF, Ariyasu RG, Lee PP. Vision loss among diabetics in a group model Health Maintenance Organization (HMO). *Am J Ophthalmol* 2002;**133**:236–41.

27. Smith DH, Johnson ES, Russell A, Hazlehurst B, Muraki C, Nichols GA, *et al*. Lower visual acuity predicts worse utility values among patients with type 2 diabetes. *Qual Life Res* 2008;**17**:1277–84.

28. The Royal College of Ophthalmologists. *Guidelines for Diabetic Retinopathy*. 2012. URL: www.rcophth.ac.uk/page.asp?section=451&sectionTitle=Clinical+Guidelines (accessed 24 September 2023).

29. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology* 1991;**98**:766–85.

30. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology* 1991;**98**:823–33.

31. Simmonds MC, Llewellyn A, Walker RAE, Fulbright HA, Walton MJ, Hodgson R, *et al*. Anti-VEGF drugs compared with laser photocoagulation for the treatment of proliferative diabetic retinopathy: a systematic review and IPD meta-analysis. *NIHR J Lib* 2024. URL: https://eprints.whiterose.ac.uk/208232/

Appendix 1 Search strategies – cost-effectiveness

Ovid MEDLINE(R) ALL <1946 to 5 November 2021>

via Ovid http://ovidsp.ovid.com/
Date range searched: 1946 to 5 November 2021
Date searched: 8 November 2021
Records retrieved: 952
Lines 29–41 below are based on a study filter developed by CADTH to identify studies about costs/economics on Ovid Medline. Available at: https://searchfilters.cda-amc.ca/

1 exp Vascular Endothelial Growth Factors/ai (9078)
2 exp Receptors, Vascular Endothelial Growth Factor/ai (3263)
3 (anti adj2 VEGF*).ti,ab,kw. (7931)
4 (anti-VEGF* or antiVEGF*).ti,ab,kw. (8061)
5 ((anti vascular or anti-vascular or antivascular) adj2 endothelial growth factor*).ti,ab,kw. (4799)
6 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).ti,ab,kw. (10084)
7 (vascular proliferation adj4 inhibit*).ti,ab,kw. (33)
8 or/1-7 (25417)
9 Angiogenesis Inhibitors/ (26841)
10 exp Angiogenesis Inducing Agents/ai (118)
11 (angiogen* adj2 (antagonist* or inhibit*)).ti,ab,kw. (13820)
12 ((antiangiogen* or anti angiogen* or anti-angiogen*) adj2 (agent* or drug* or effect*)).ti,ab,kw. (10073)
13 (angiostatic adj2 (agent* or drug*)).ti,ab,kw. (102)
14 ((neovasculari?ation or vasculari?ation) adj2 inhibit*).ti,ab,kw. (1159)
15 or/9-14 (41679)
16 Aflibercept*.ti,ab,kw,rn. (2752)

17 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).ti,ab,kw. (281)
18 Bevacizumab/ (12748)
19 Bevacizumab*.ti,ab,kw,rn. (20120)
20 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).ti,ab,kw. (1596)
21 (IVB adj2 inject*).ti,ab,kw. (296)
22 Ranibizumab/ (4033)
23 Ranibizumab*.ti,ab,kw,rn. (5536)
24 (Lucentis or "rhuFab V2").ti,ab,kw. (428)
25 (IVR adj2 inject*).ti,ab,kw. (126)
26 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).ti,ab,kw. (137)
27 or/16-26 (24968)
28 8 or 15 or 27 (66319)
29 economics/ (27381)
30 exp "costs and cost analysis"/ (251331)
31 economics, dental/ (1920)
32 exp "economics, hospital"/ (25380)
33 economics, medical/ (9169)
34 economics, nursing/ (4009)
35 economics, pharmaceutical/ (3033)
36 exp "Fees and Charges"/ (30949)
37 exp Budgets/ (13917)
38 budget*.ti,ab,kf. (32430)
39 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. (251144)
40 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq=2 (328499)
41 or/29-40 (618705)
42 28 and 41 (967)
43 exp animals/ not humans.sh. (4911284)
44 42 not 43 (956)
45 limit 44 to yr="2000-Current" (954)
46 remove duplicates from 45 (952)

Key:
/ or.sh. = indexing term (Medical Subject Heading: MeSH)
exp = exploded indexing term (MeSH)
/ai = MeSH subheading for antagonists and inhibitors
* or $ = truncation
ti,ab,kw = terms in either title, abstract or keyword fields
rn = registry number/name of substance
adj3 = terms within three words of each other (any order).

EMBASE <1974 to 5 November 2021>
via Ovid http://ovidsp.ovid.com/
Date range searched: 1974 to 5 November 2021
Date searched: 8 November 2021
Records retrieved: 3724
From lines 30–68, the CRD's NHS EED filter for Ovid EMBASE was used as a study filter for economics papers. Available at: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase

1 vasculotropin inhibitor/ (6509)
2 (anti adj2 VEGF*).ti,ab,kw. (13359)
3 (anti-VEGF* or antiVEGF*).ti,ab,kw. (13751)
4 ((anti vascular or anti-vascular or antivascular) adj2 endothelial growth factor*).ti,ab,kw. (5918)
5 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).ti,ab,kw. (15663)
6 (vascular proliferation adj4 inhibit*).ti,ab,kw. (43)
7 or/1-6 (33736)
8 angiogenesis inhibitor/ (18946)
9 (angiogen* adj2 (antagonist* or inhibit*)).ti,ab,kw. (18824)
10 ((antiangiogen* or anti angiogen* or anti-angiogen*) adj2 (agent* or drug* or effect*)).ti,ab,kw. (14318)
11 (angiostatic adj2 (agent* or drug*)).ti,ab,kw. (120)
12 ((neovasculari?ation or vasculari?ation) adj2 inhibit*).ti,ab,kw. (1584)
13 or/8-12 (41476)
14 aflibercept/ (7200)
15 Aflibercept*.ti,ab,kw,dy,tn. (7391)
16 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).ti,ab,dy,tn. (1470)
17 bevacizumab/ (64164)
18 Bevacizumab*.ti,ab,kw,dy,tn. (66047)
19 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).ti,ab,kw,dy,tn. (10552)
20 (IVB adj2 inject*).ti,ab,kw. (364)
21 ranibizumab/ (10841)
22 Ranibizumab*.ti,ab,kw,dy,tn. (11176)
23 (Lucentis or "rhuFab V2").ti,ab,kw,dy,tn. (2965)
24 (IVR adj2 inject*).ti,ab,kw. (182)
25 pegaptanib.dy,tn. (2341)
26 Pegaptanib*.ti,ab,kw,dy,tn. (2412)
27 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).ti,ab,kw,dy,tn. (1221)
28 or/14-27 (74887)
29 7 or 13 or 28 (124899)
30 Health Economics/ (33785)
31 exp Economic Evaluation/ (325524)

32 exp Health Care Cost/ (309887)
33 pharmacoeconomics/ (8693)
34 30 or 31 or 32 or 33 (572228)
35 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (1198661)
36 (expenditure$ not energy).ti,ab. (44620)
37 (value adj2 money).ti,ab. (2659)
38 budget$.ti,ab. (42129)
39 35 or 36 or 37 or 38 (1238398)
40 34 or 39 (1471682)
41 letter.pt. (1196484)
42 editorial.pt. (707059)
43 note.pt. (870983)
44 41 or 42 or 43 (2774526)
45 40 not 44 (1362695)
46 (metabolic adj cost).ti,ab. (1657)
47 ((energy or oxygen) adj cost).ti,ab. (4645)
48 ((energy or oxygen) adj expenditure).ti,ab. (34002)
49 46 or 47 or 48 (39157)
50 45 not 49 (1354688)
51 animal/ (1536312)
52 exp animal experiment/ (2760652)
53 nonhuman/ (6707562)
54 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (6020944)
55 51 or 52 or 53 or 54 (9503388)
56 exp human/ (22905864)
57 human experiment/ (558235)
58 56 or 57 (22907818)
59 55 not (55 and 58) (6821499)
60 50 not 59 (1225472)
61 0959-8146.is. (63484)
62 (1469-493X or 1366-5278).is. (23408)
63 1756-1833.en. (36978)
64 61 or 62 or 63 (110528)
65 60 not 64 (1218098)
66 conference abstract.pt. (4243056)
67 65 not 66 (989632)
68 29 and 67 (3736)
69 limit 68 to yr="2000-Current" (3724)

Key:
/ or.sh. = indexing term (Emtree Subject Heading)
exp = exploded indexing term (Emtree)
/ai = MeSH subheading for antagonists and inhibitors
* or $ = truncation
ti,ab,kw = terms in either title, abstract or keyword fields
dy = drugs index terms word
tn = drug trade name
adj3 = terms within three words of each other (any order).
pt = publication type
is = ISSN
en = Electronic ISSN

EconLit <1886 to 28 October 2021>
via Ovid http://ovidsp.ovid.com/
Date range searched: 1974 to 28 October 2021
Date searched: 8 November 2021
Records retrieved: 10

1 (anti adj2 VEGF*).ti,ab,kw. (1)
2 (anti-VEGF* or antiVEGF*).ti,ab,kw. (1)
3 ((anti vascular or anti-vascular or antivascular) adj2 endothelial growth factor*).ti,ab,kw. (1)
4 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj4 (trap* or inhibit* or antagonist*)).ti,ab,kw. (0)
5 (vascular proliferation adj4 inhibit*).ti,ab,kw. (0)
6 or/1-5 (1)
7 (angiogen* adj2 (antagonist* or inhibit*)).ti,ab,kw. (1)
8 ((antiangiogen* or anti angiogen* or anti-angiogen*) adj2 (agent* or drug* or effect*)).ti,ab,kw. (0)
9 (angiostatic adj2 (agent* or drug*)).ti,ab,kw. (0)
10 ((neovasculari?ation or vasculari?ation) adj2 inhibit*).ti,ab,kw. (0)
11 or/7-10 (1)
12 Aflibercept*.ti,ab,kw. (1)
13 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).ti,ab,kw. (0)
14 Bevacizumab*.ti,ab,kw. (5)
15 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).ti,ab,kw. (6)
16 (IVB adj2 inject*).tw,kw. (0)
17 Ranibizumab*.ti,ab,kw. (1)
18 (Lucentis or "rhuFab V2").ti,ab,kw. (4)
19 (IVR adj2 inject*).ti,ab,kw. (0)
20 Pegaptanib*.ti,ab,kw. (0)
21 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).ti,ab,kw. (0)
22 or/12-21 (10)
23 6 or 11 or 22 (10)
24 limit 23 to yr="2000-Current" (10)

Key:
* or $ = truncation
ti,ab,kw = terms in either title, abstract or keyword fields
adj3 = terms within three words of each other (any order).

Cochrane Database of Systematic Reviews (CDSR)
via Wiley http://onlinelibrary.wiley.com/
Date range: Issue 11 of 12, November 2021
Date searched: 8 November 2021
Records retrieved: 47

#1 [mh "Vascular Endothelial Growth Factors"/ai]643

#2 [mh "Receptors, Vascular Endothelial Growth Factor"/ai]112
#3 (anti NEAR/2 VEGF*):ti,ab,kw 1408
#4 (antiVEGF*):ti,ab,kw 1337
#5 ((anti NEXT vascular or antivascular) NEAR/2 "endothelial growth" NEXT factor*):ti,ab,kw 606
#6 ((("vascular endothelial" NEAR/2 growth NEXT factor*) or vasculotropin or VEGF* or "vascular permeability" NEXT factor* or VPF) NEAR/2 (trap* or inhibit* or antagonist*)):ti,ab,kw 1830
#7 ("vascular proliferation" NEAR/4 inhibit*):ti,ab,kw1
#8 {OR #1-#7}3259
#9 [mh ^"Angiogenesis Inhibitors"]1275
#10 [mh "Angiogenesis Inducing Agents"/ai]0
#11 (angiogen* NEAR/2 (antagonist* or inhibit*)):ti,ab,kw 1714
#12 ((antiangiogen* or anti NEXT angiogen*) NEAR/2 (agent* or drug* or effect*)):ti,ab,kw 654
#13 (angiostatic NEAR/2 (agent* or drug*)):ti,ab,kw7
#14 ((neovasculari?ation or vasculari?ation) NEAR/2 inhibit*):ti,ab,kw 33
#15 {OR #9-#14}2249
#16 Aflibercept*:ti,ab,kw958
#17 (Eylea or Zaltrap or Ziv NEXT Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005):ti,ab,kw 233
#18 [mh ^Bevacizumab]2077
#19 Bevacizumab*:ti,ab,kw 6677
#20 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb NEXT VEGF or "NSC 704865" or NSC704865):ti,ab,kw 904
#21 (IVB NEAR/2 inject*):ti,ab,kw 80
#22 [mh ^Ranibizumab]910
#23 Ranibizumab*:ti,ab,kw 2120
#24 (Lucentis or "rhuFab V2"):ti,ab,kw 423
#25 (IVR NEAR/2 inject*):ti,ab,kw 29
#26 Pegaptanib*:ti,ab,kw 167
#27 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838):ti,ab,kw 81
#28 {OR #16-#27}9155
#29 (#8 or #15 or #28) with Cochrane Library publication date Between Jan 2000 and Nov 2021, in Cochrane Reviews47

Key:
mh = unexploded indexing term (MeSH)
mh ^ = exploded indexing term (MeSH)
/ai = MeSH subheading for antagonists and inhibitors
* = truncation
ti,ab,kw = terms in either title or abstract or keyword fields
near/3 = terms within three words of each other (any order)
next = terms are next to each other.

Science Citation Index Expanded
Date range searched: 1900 to 8 November 2021
Social Sciences Citation Index
Date range searched: 1956 to 8 November 2021
via Web of Science, Clarivate Analytics https://clarivate.com/
Date searched: 8 November 2021
Records retrieved: 2122
This was a multi-database search of SCIE and SSCI concurrently.

33 #30 NOT #31 [Timespan: 2000-01-01 to 2021-11-08 (Publication Date)]2,122
32 #30 NOT #312,127
31 TI=(animal or animals or rat or rats or rodent* or mouse or mice or "mus musculus" or "mus domesticus" or murine or murinae or porcine or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or sheep or ovine or "ovis aries" or lamb or lambs or ewe or ewes or rabbit or rabbits or leporide or leporidae or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or bovine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*)3,169,950
30 #20 AND #292,167
29 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #283,057,333
28 TS=(decision* NEAR/2 (tree* or analy* or model*))79,643
27 TS=("monte carlo")250,699
26 TS=(markov)105,416
25 TS=("economic model*")12,073
24 TS=(value NEAR/2 (money or monetary))6,184
23 TS=(cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))364,716
22 TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)2,616,928
21 TS=(budget*)117,788
20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #1975,023
19 TS=("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838)139
18 TS=(Pegaptanib*)691
17 TS=(IVR NEAR/2 inject*)155
16 TS=(Lucentis or "rhuFab V2")541
15 TS=(Ranibizumab*)8,305
14 TS=(IVB NEAR/2 inject*)293

13 TS=(Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabe v or rhuMAb-VEGF or rhuMAb-VEGF or "rhuMAb VEGF" or "NSC 704865" or NSC704865)3,246
12 TS=(Bevacizumab*)32,289
11 TS=(Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005)299
10 TS=(Aflibercept*)3,458
9 TS=((neovascularisation or neovascularization or vascularisation or vascularization) NEAR/2 inhibit*)1,737
8 TS=(angiostatic NEAR/2 (agent* or drug*))104
7 TS=((antiangiogen* or "anti angiogen*" or anti-angiogen*) NEAR/2 (agent* or drug* or effect*))10,868
6 TS=(angiogen* NEAR/2 (antagonist* or inhibit*))18,489
5 TS=("vascular proliferation" NEAR/4 inhibit*)40
4 TS=((("vascular endothelial" NEAR/2 "growth factor*") or vasculotropin or VEGF* or "vasc ular permeability factor*" or VPF) NEAR/2 (trap* or inhibit* or antagonist*))13,339
3 TS=(("anti vascular" or anti-vascular or antivascular) NEAR/2 "endothelial growth factor*")4,209
2 TS=(anti-VEGF* or antiVEGF*)8,803
1 TS=(anti NEAR/2 VEGF*)9,201

Key:
TS= terms in either title, abstract, author keywords, and keywords plus fields
TI= search in title field
NEAR/3 = terms within three words of each other (any order).
* = truncation

International HTA **database**
via https://database.inahta.org/
Date range: Inception to 8 November 2021
Date searched: 8 November 2021
Records retrieved: 583
(* FROM 2000 TO 2021) AND ((((anti VEGF* OR anti-VEGF* OR antiVEGF*))[Title] OR ((anti VEGF* OR anti-VEGF* OR antiVEGF*))[abs] OR ((anti VEGF* OR anti-VEGF* OR antiVEGF*))[Keywords] OR (((anti vascular OR anti-vascular OR antivascular) AND endothelial growth factor*))[Title] OR (((anti vascular OR anti-vascular OR antivascular) AND endothelial growth factor*))[abs] OR (((anti vascular OR anti-vascular OR antivascular) AND endothelial growth factor*))[Keywords] OR ((((vascular endothelial growth factor*) OR vasculotropin OR VEGF* OR vascular permeability factor* OR VPF) AND (trap* OR inhibit* OR antagonist*)))[Title] OR ((((vascular endothelial growth factor*) OR vasculotropin OR VEGF* OR vascular permeability factor* OR VPF) AND (trap* OR inhibit* OR antagonist*)))[abs] OR ((((vascular endothelial growth factor*) OR vasculotropin OR VEGF* OR vascular permeability factor* OR VPF) AND (trap* OR inhibit* OR antagonist*)))[Keywords] OR ((vascular proliferation AND inhibit*))[Title] OR ((vascular proliferation AND inhibit*))[abs] OR ((vascular proliferation AND inhibit*))[Keywords] OR ((angiogen* AND (antagonist* OR inhibit*)))[Title] OR ((angiogen* AND (antagonist* OR inhibit*)))[abs] OR ((angiogen* AND (antagonist* OR inhibit*)))[Keywords] OR (((antiangiogen* OR anti angiogen* OR anti-angiogen*) AND (agent* OR drug* OR effect*)))[Title] OR (((anti-angiogen* OR anti angiogen* OR anti-angiogen*) AND (agent* OR drug* OR effect*)))[abs] OR (((antiangiogen* OR anti angiogen* OR anti-angiogen*) AND (agent* OR drug* OR effect*)))[Keywords] OR ((angiostatic AND (agent* OR drug*)))[Title] OR ((angiostatic AND (agent* OR drug*)))[abs] OR ((angiostatic AND (agent* OR drug*)))[Keywords] OR (((neovascularisation OR vascularisation OR neovascularization OR vascularization) AND inhibit*))[Title] OR (((neovascularisation OR vascularisation OR neovascularization OR vascularization) AND inhibit*))[abs] OR (((neovascularisation OR vascularisation OR neovascularization OR vascularization) AND inhibit*))[Keywords] OR ((Aflibercept* OR Eylea OR Zaltrap OR Ziv-Aflibercept OR AVE 0005 OR AVE0005 OR AVE 00 OR AVE005))[Title] OR ((Aflibercept* OR Eylea OR Zaltrap OR Ziv-Aflibercept OR AVE 0005 OR AVE0005 OR AVE 00 OR AVE005))[abs] OR ((Aflibercept* OR Eylea OR Zaltrap OR Ziv-Aflibercept OR AVE 0005 OR AVE0005 OR AVE 00 OR AVE005))[Keywords] OR ((Bevacizumab* OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAb-VEGF OR rhuMAb-VEGF OR rhuMAb VEGF OR NSC 704865 OR NSC704865))[Title] OR ((Bevacizumab* OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAbVEGF OR rhuMAb-VEGF OR rhuMAb VEGF OR NSC 704865 OR NSC704865))[abs] OR ((Bevacizumab* OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAbVEGF OR rhuMAb-VEGF OR rhuMAb VEGF OR NSC 704865 OR NSC704865))[Keywords] OR ((IVB AND inject*))[Title] OR ((IVB AND inject*))[abs] OR ((IVB AND inject*))[Keywords] OR ((Ranibizumab* OR Lucentis OR rhuFab V2))[Title] OR ((Ranibizumab* OR Lucentis OR rhuFab V2))[abs] OR ((Ranibizumab* OR Lucentis OR rhuFab V2))[Keywords] OR ((IVR AND inject*))[Title] OR ((IVR AND inject*))[abs] OR ((IVR AND inject*))[Keywords] OR ((EYE 001 OR EYE001 OR Macugen OR NX 1838 OR NX1838))[Title] OR ((EYE 001 OR EYE001 OR Macugen OR NX 1838 OR NX1838))[abs] OR ((EYE 001 OR EYE001 OR Macugen OR NX 1838 OR NX1838))[Keywords]) OR ("Ranibizumab"[mh]) OR ("Bevacizumab"[mh]) OR ("Angiogenesis Inhibitors"[mh]))583

Key:
[mh] = indexing term: Medical Subject Heading (MeSH)
[Keywords] = search of keywords field
[abs] = search of abstract field
[Title] = search of title field
* = truncation
NHS EED
via www.crd.york.ac.uk/CRDWeb/
Date range searched: Inception to 2015
Date searched: 8 November 2021
Records retrieved: 88

1 MeSH DESCRIPTOR Vascular Endothelial Growth Factors EXPLODE ALL TREES WITH QUALIFIER AI IN NHSEED 11
2 MeSH DESCRIPTOR Receptors, Vascular Endothelial Growth Factor EXPLODE ALL TREES WITH QUALIFIER AI IN NHSEED0
3 (anti NEAR2 VEGF*) IN NHSEED1
4 (anti-VEGF* or antiVEGF*) IN NHSEED1
5 ((anti vascular or anti-vascular or antivascular) NEAR2 endothelial growth factor*) IN NHSEED4
6 (((vascular endothelial NEAR2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) NEAR2 (trap* or inhibit* or antagonist*)) IN NHSEED12
7 (vascular proliferation NEAR4 inhibit*) IN NHSEED0
8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #717
9 MeSH DESCRIPTOR Angiogenesis Inhibitors IN NHSEED 41
10 MeSH DESCRIPTOR Angiogenesis Inducing Agents EXPLODE ALL TREES WITH QUALIFIER AI IN NHSEED0
11 (angiogen* NEAR2 (antagonist* or inhibit*)) IN NHSEED42
12 ((antiangiogen* or anti angiogen* or anti-angiogen*) NEAR2 (agent* or drug* or effect*)) IN NHSEED0
13 (angiostatic NEAR2 (agent* or drug*)) IN NHSEED0
14 ((neovascularisation* or neovascularization* or vascularisation* or vascularization*) NEAR2 inhibit*) IN NHSEED0
15 #9 OR #10 OR #11 OR #12 OR #13 OR #1442
16 (Aflibercept*) IN NHSEED2
17 (Eylea or Zaltrap or Ziv-Aflibercept or AVE 0005 or AVE0005 or AVE 005 or AVE005) IN NHSEED0
18 MeSH DESCRIPTOR Bevacizumab IN NHSEED 42
19 (Bevacizumab*) IN NHSEED54
20 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb-VEGF or rhuMAb VEGF or NSC 704865 or NSC704865) IN NHSEED1
21 (IVB NEAR2 inject*) IN NHSEED0
22 MeSH DESCRIPTOR Ranibizumab IN NHSEED 22
23 (Ranibizumab*) IN NHSEED27
24 (Lucentis or rhuFab V2) IN NHSEED2
25 (IVR NEAR2 inject*) IN NHSEED0
26 (Pegaptanib*) IN NHSEED12
27 (EYE 001 or EYE001 or Macugen or NX 1838 or NX1838) IN NHSEED1
28 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #2776
29 #8 OR #15 OR #2889
30 * IN NHSEED FROM 2000 TO 2015 14762
31 #29 AND #30 88

Key:
MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)
EXPLODE ALL TREES = exploded indexing term (MeSH)
* = truncation
NEAR3 = terms within three words of each other (only in the order specified).
HTA
via www.crd.york.ac.uk/CRDWeb/
Date range searched: Inception to March 2018
Date searched: 8 November 2021
Records retrieved: 137

1 MeSH DESCRIPTOR Vascular Endothelial Growth Factors EXPLODE ALL TREES WITH QUALIFIER AI IN HTA3
2 MeSH DESCRIPTOR Receptors, Vascular Endothelial Growth Factor EXPLODE ALL TREES WITH QUALIFIER AI IN HTA0
3 (anti NEAR2 VEGF*) IN HTA9
4 (anti-VEGF* or antiVEGF*) IN HTA9
5 ((anti vascular or anti-vascular or antivascular) NEAR2 endothelial growth factor*) IN HTA6
6 (((vascular endothelial NEAR2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) NEAR2 (trap* or inhibit* or antagonist*)) IN HTA16
7 (vascular proliferation NEAR4 inhibit*) IN HTA0
8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #725
9 MeSH DESCRIPTOR Angiogenesis Inhibitors IN HTA 58
10 MeSH DESCRIPTOR Angiogenesis Inducing Agents EXPLODE ALL TREES WITH QUALIFIER AI IN HTA0
11 (angiogen* NEAR2 (antagonist* or inhibit*)) IN HTA66
12 ((antiangiogen* or anti angiogen* or anti-angiogen*) NEAR2 (agent* or drug* or effect*)) IN HTA1
13 (angiostatic NEAR2 (agent* or drug*)) IN HTA1
14 ((neovascularisation* or neovascularization* or vascularisation* or vascularization*) NEAR2 inhibit*) IN HTA0

15 #9 OR #10 OR #11 OR #12 OR #13 OR #1467
16 (Aflibercept*) IN HTA22
17 (Eylea or Zaltrap or Ziv-Aflibercept or AVE 0005 or AVE0005 or AVE 005 or AVE005) IN HTA10
18 MeSH DESCRIPTOR Bevacizumab IN HTA 11
19 (Bevacizumab*) IN HTA79
20 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAb-VEGF or rhuMAb-VEGF or rhuMAb VEGF or NSC 704865 or NSC704865) IN HTA41
21 (IVB NEAR2 inject*) IN HTA0
22 MeSH DESCRIPTOR Ranibizumab IN HTA1
23 (Ranibizumab*) IN HTA29
24 (Lucentis or rhuFab V2) IN HTA7
25 (IVR NEAR2 inject*) IN HTA0
26 (Pegaptanib*) IN HTA11
27 (EYE 001 or EYE001 or Macugen or NX 1838 or NX1838) IN HTA4
28 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27120
29 #8 OR #15 OR #28151
30 * IN HTA FROM 2000 TO 2018 14815
31 #29 AND #30 137

Key:
MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)
EXPLODE ALL TREES = exploded indexing term (MeSH)
* = truncation
NEAR3 = terms within three words of each other (only in the order specified)

Appendix 2 Quality assessment – Drummond checklist

Item	Hutton (2017)	Hutton (2019)	Lin (2016)	Lin (2018)	Sivaprasad (2018)	Patel (2022)	Royle (2015)
Study design/structure							
1. Is there a clear statement of the decision problem?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Is the perspective and scope of the model stated clearly?	No	No	No	No	Yes	No	Yes
3. Are the model inputs consistent with the stated perspective?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Yes	Yes	Yes	Yes	Yes	Partially	Yes
5. Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	NA	NA	Unclear	Unclear	NA	NA	Unclear
6. Is there a clear definition and justification for the alternative options under evaluation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	NA	NA	Unclear	Unclear	NA	NA	Yes
8. Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and appropriately justified?	NA	Yes	Yes	Yes	NA	NA	Partially
9. Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	NA	NA	Unclear	Unclear	NA	NA	Yes
10. Is the cycle length defined and justified in terms of the natural history of disease?	NA	NA	Unclear	Unclear	NA	NA	Yes

Item	Hutton (2017)	Hutton (2019)	Lin (2016)	Lin (2018)	Sivaprasad (2018)	Patel (2022)	Royle (2015)
Data collection							
11. Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Has the quality of the data been assessed appropriately?	NA	NA	No	No	NA	No	No
13. Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Is the choice of baseline data described and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
15. Are transition probabilities calculated appropriately?	NA	NA	Unclear	Unclear	NA	NA	Yes
16. Has a half-cycle correction been applied to both costs and outcomes?	NA	NA	Unclear	Unclear	NA	NA	No
17. If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Yes	Yes	Yes	Yes	Yes	Yes	NA
18. Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	NA	NA	NA	NA	NA	NA	NA
19. Have alternative assumptions been explored through sensitivity analysis?	Yes	Yes	No	Yes	Yes	Yes	Yes
20. Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	NA	Partially	Partially	Partially	NA	NA	No
Costs and discounting							
21. Are the costs incorporated into the model described and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22. Has the source for all costs been described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23. Have discount rates been described and justified given the target decision-maker?	No	No	No	No	Yes	No	Yes
24. Were currency, price date and price adjustments/currency conversion information stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Health-related quality of life							
25. Are the utilities incorporated into the model appropriate?	Yes	Yes	Yes	Yes	Yes	NA	Yes
26. Is the source for the utility weights referenced?	Yes	Yes	No	No	Yes	NA	Yes
Validation							
27. Has heterogeneity been dealt with by running the model separately for different subgroups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
28. Have the results of the model been compared with those of previous models and any differences in results explained?	No	Yes	No	No	No	No	No