National Institute for Health and Care Excellence

Final

Diabetic retinopathy: management and monitoring

[E] Evidence reviews for the effectiveness and acceptability of anti-vascular endothelial growth factor agents and laser photocoagulation (alone or in combination) for the treatment of non-proliferative and proliferative diabetic retinopathy

NICE guideline NG242

Evidence reviews underpinning recommendations 1.5.1 to 1.5.6 and 1.5.15, and research recommendations 3, 5 and 9 in the NICE guideline

August 2024

Final

These evidence reviews were developed by NICE

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Contents

Effectiveness and acceptability of intravitreal steroids, laser photocoagulation and anti-vascular endothelial growth factor agents for non-proliferative and proliferative diabetic retinopathy

1.1 Review question

What is the effectiveness and acceptability of anti-vascular endothelial growth factor agents and laser photocoagulation (alone or in combination) for the treatment of non-proliferative and proliferative diabetic retinopathy without macular oedema?

1.1.1 Introduction

People with diabetic retinopathy are at risk of progression to more severe disease if they do not receive early treatment. There are several options for treatment of diabetic retinopathy including observation, panretinal photocoagulation and anti-VEGF treatments. Research has yet to compare all treatment options to establish which is the most effective for people with non-proliferative or proliferative diabetic retinopathy. This review therefore aims to compare each of the treatment options to identify the most effective strategy for people with non-proliferative or proliferative diabetic retinopathy, with the aim of stopping or slowing progression of the disease.

This evidence review informed recommendations in the NICE guideline on the management and treatment of diabetic retinopathy, which is a new NICE guideline in this area.

1.1.2 Summary of the protocol

Table 1: Summary PICO

Population	Inclusion: People with diabetic retinopathy (proliferative and non-proliferative) will be included. Exclusion: People with a principal indication for treatment of diabetic macular oedema will be excluded.
Interventions	Any anti-VEGF therapy: • Including aflibercept, bevacizumab, ranibizumab and their biosimilars • Anti-VEGF with, or subsequent to, laser photocoagulation • Laser photocoagulation (in any form, and any laser type)
Comparator	• Studies comparing the interventions described above will be included, included studies comparing different anti-VEGF agents. • Sham treatment, or other control interventions
Outcomes	Primary outcomes:

	• Visual acuity measurement
	• Functional impact on vision, e.g.
	  ○ driving vision (approx. 0.3logMAR)
	  ○ blind level vision (approx. 1.0logMAR)
	  ○ clinically important vision loss (0.3logMAR or worse)
	
	Secondary outcomes:
	• Number of treatments
	• Need for subsequent treatment (e.g. vitrectomy)
	• Complications and adverse effects E.g. Raised intraocular pressure, vitreous haemorrhage, retinal detachment, cataract formation, systemic AEs.
	• Progression of retinopathy (non-proliferative to proliferative)
	• Peripheral vision and visual field changes
	• Treatment withdrawal
	• Quality of life (NEI-VFQ-25, EQ-5D, SF-36)
	
	Additional outcomes to be extracted by NICE review team:
	• Macular ischaemia
	• Acceptability: Qualitative or quantitative data on acceptability collected alongside included randomised controlled trials will be included

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Information from this review was primarily from the systematic review produced by the University of York (Simmonds et al. 2023). Links to this review are provided throughout the document wherever data from this publication has been used. The studies included in the review by the University of York were screened for additional outcomes that were not included in that review, but were considered important by the committee (incidence of macular ischemia and qualitative or quantitative data on acceptability).

The review was judged to be high quality and directly applicable to the review (see Appendix D) and so information for this review was taken directly from Simmonds et al. (2023), rather than undertaking a new literature search or data analysis (see Table 2 in the methods document).

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

All studies in the review by Simmonds at el. (2023) were included in the NICE review. The search identified studies up until July 2022. 5928 records were identified at title and abstract level, with 318 articles screened at full-text. 15 studies met the inclusion criteria for the review. The search was re-run by NICE to identify any papers published after the date of the initial search. 129 additional papers were identified but none met the inclusion criteria. For more information on included studies, see Simmonds et al. (2023).

The review included people with non-proliferative diabetic retinopathy and people with proliferative diabetic retinopathy. Of the 15 included studies, 13 were for people with proliferative diabetic retinopathy and 2 were for those with non-proliferative diabetic retinopathy. Due to differences in the populations, people with non-proliferative diabetic retinopathy were not included in the NMA. Analyses for all outcomes for this group were instead based on pairwise meta-analysis.

See Appendix C for the study selection flow chart.

1.1.4.2 Excluded studies

303 studies were excluded at full-text screening. For more information on excluded studies from the main search, see Simmonds et al. (2023). No additional studies were examined at full-text screening from the NICE re-run search.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2. Summary of Simmonds et al. (2023) systematic review for treatments for diabetic retinopathy.

Study Country	Number of included studies	Population	Intervention	Comparator	Outcomes
Simmonds et al 2023 UK	15 studies	Inclusion criteria: • Randomised controlled trials comparing anti-VEGF to PRP in people with diabetic retinopathy (non-proliferative or proliferative diabetic retinopathy). Exclusion criteria • Studies which included patients with a principal indication for treatment of diabetic macular oedema or vitreous haemorrhage	Anti-VEGFs (aflibercept, bevacizumab or ranibizumab)	Panretinal photocoagulation	• Best corrected visual acuity (BCVA) measured on ETDRS or logMAR scales. • Functional impact on vision • Number of treatments • Need for subsequent treatment • Complications and adverse events • Progression • Peripheral vision changes • Treatment withdrawal • Quality of life

Table 3. Summary of primary studies included from the Simmonds et al. (2023) systematic review

All studies from the Simmonds et al. (2023) systematic review were included in the NICE review.

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Clarity 2017 UK	RCT 1 year	Inclusion criteria: • Type 1 or 2 diabetes, • Previously untreated. • Proliferative diabetic retinopathy or persistent retinal • Aged 18 years or older. Exclusion criteria • Eyes with clinical evidence of diabetic macular oedema • Moderate or dense vitreous haemorrhage • Tractional retinal detachment • Patients treated with intravitreal anti-vegf or steroid for diabetic macular oedema within 4 months or PRP within 8 weeks	Aflibercept	PRP	• BCVA • DR severity • Subsequent treatment complications
DRCRN 2021 **Protocol W** USA/Canada	2 years	Inclusion criteria: • Adults (age, ≥18 years) • Type 1 or 2 diabetes	Aflibercept	Sham injection	• Time to PDR or DME

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• Severe NPDR (some DMO) Exclusion criteria • Eyes with CI-DME			
PANORAMA 2021 International	1 & 2 years	Inclusion criteria: • Adult participants who had diabetes • severe treatment naive NPDR Exclusion criteria • DMO	Aflibercept (every 16 weeks vs. 8 weeks)	Sham injection	• DR severity • subsequent treatment, complications
RECOVERY 2019 USA	1 year	Inclusion criteria: • treatment-naive PDR Exclusion criteria: • DMO • vitreoretinal traction • vitreous haemorrhage • uveitis • uncontrolled glaucoma	Aflibercept (monthly)	Aflibercept (quarterly)	• BCVA, • DR severity • functional impact
Marashi 2017	1 year	Inclusion criteria:	Bevacizumab	PRP	• BCVA

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Jordan/Syria		• Age >= 18 years • Diagnosis of diabetes mellitus (type 1 or type 2) • PDR Exclusion criteria • Significant renal disease • Myocardial infarction • Tractional retinal detachment • Macular oedema			• DR severity
Ahmad 2012 Pakistan	3 months	Inclusion criteria: • All patients aged ≥18 year who presented with • first-time PDR with almost same changes in both eyes • with no prior retinal laser besides macular laser Exclusion criteria • history of prior PRP or vitrectomy.	Bevacizumab (+PRP)	PRP	• BCVA
Ali 2018	1 month	Inclusion criteria:	Bevacizumab (+PRP)	PRP	• BCVA

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Pakistan		• all patients of age 40-65 years • PDR with or without • clinically significant macular oedema (CSME) Exclusion criteria • non-proliferative diabetic retinopathy (NPDR) • advanced diabetic eye disease (tractional retinal detachment),			
Rebecca 2021 Pakistan	6 months	Inclusion criteria: • All patients with Type-1 andType-2 diabetes mellitus • 18 years to 65 years of age • PDR • without any previous treatment Exclusion criteria • patients with any media opacity like cataract	Bevacizumab (+PRP)	PRP	• BCVA

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Roohipour 2016 Iran	10 months	Inclusion criteria: • Bilateral PDR requiring treatment. Exclusion criteria • glaucoma • ocular hypertension, and/or significant corneal opacity • cataract, or vitreous opacity/haemorrhage • history of prior treatment for diabetic retinopathy • centre involved diabetic macular oedema	Bevacizumab (+PRP)	PRP	• BCVA
DRCRN Protocol S 2018 USA	2 & 5 years	Inclusion criteria: • PDR • 18 years old • had type 1or type 2 diabetes, • 1 eye with PDR • Eyes with or without DME Exclusion criteria	Ranibizumab	PRP	• DR severity • functional impact on vision • subsequent treatment, complications

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• no previous PRP			
Ferraz 2015 Brazil	6 months	Inclusion criteria: • All patients Type-2 diabetes mellitus • 18 years of age or older • Non-high-risk PDR • without any previous treatment Exclusion criteria • patients with any media opacity like cataract • macular ischemia • ocular hypertension	Ranibizumab (+PRP)	PRP	• BCVA
PRIDE 2019 Germany	1 year	Inclusion criteria: • PDR secondary to type 1 or type 2 diabetes. • age ≥18 years, Exclusion criteria • clinically significant DMO with centre involvement • proliferative vitreoretinopathy (PVR)	Ranibizumab (+PRP)	PRP	• BCVA, • DR severity • subsequent treatment

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• severe vitreous haemorrhage impairing imaging/treatment • previous treatment with PRP			
PROTEUS 2018	1 year	Inclusion criteria: • Type 2 diabetes • High risk PDR • Adults age 18 or over Exclusion criteria • Treatment with PRP or macular laser • Treatment with anti-VEGF	Ranibizumab (+PRP)	PRP	• BCVA • subsequent treatment, complications
Sao Paulo B 2011 Brazil	1 year	Inclusion criteria: • all adult patients with treatment-naive PDR • best-corrected visual acuity (BCVA) better than 20/800 Exclusion criteria • presence of advanced PDR (i.e., vitreous haemorrhage	Ranibizumab (+PRP)	PRP	• BCVA • pain

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• traction retinal detachment			
Sao Paulo A 2018 Brazil	1 year	Inclusion criteria: • all adult patients with high-risk PDR • presence of NVD associated with vitreous or pre-retinal haemorrhage, Exclusion criteria • history of prior laser or vitrectomy • myocardial infarction • uncontrolled hypertension	Ranibizumab (+PRP, ETRDS)	Ranibizumab (+PRP, PASCAL)	• BCVA

See appendix D for full evidence tables

1.1.6 Summary of the effectiveness evidence

Network meta-analysis

People with proliferative diabetic retinopathy

Table 4: Change in visual acuity (logMAR) relative to panretinal photocoagulation (up to 1 year)

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Aflibercept	-0.08 (-0.232, 0.042)	Low	Could not differentiate
Bevacizumab	-0.19 (-1.17, -0.78)		Favours Bevacizumab
Bevacizumab with panretinal photocoagulation	-0.17 (-0.28, -0.06)		Favours Bevacizumab with panretinal photocoagulation
Ranibizumab	-0.12 (-0.23, -0.01)		Favours Ranibizumab
Ranibizumab with panretinal photocoagulation	-0.08 (-0.16, 0.00)		Favours Ranibizumab with panretinal photocoagulation

Table 5: Change in visual acuity (logMAR) relative to panretinal photocoagulation (between 1 to 2 years)

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Aflibercept	-0.08 (-0.22, 0.03)	Low	Could not differentiate
Bevacizumab	-0.18 (-1.20, 0.80)		Could not differentiate
Ranibizumab	-0.07 (-0.16, 0.03)		Could not differentiate
Ranibizumab with panretinal photocoagulation	-0.06 (-0.14, 0.02)		Could not differentiate

Table 6: Change in visual acuity (logMAR) relative to panretinal photocoagulation (up to 2 years)

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Aflibercept	-0.09 (-0.24, 0.02)	Low	Could not differentiate
Bevacizumab	-0.18 (-1.18, 0.82)		Could not differentiate

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Bevacizumab with panretinal photocoagulation	-0.17 (-0.28, -0.05)		Favours Bevacizumab with panretinal photocoagulation
Ranibizumab	-0.08 (-0.17, 0.00)		Could not differentiate
Ranibizumab with panretinal photocoagulation	-0.06 (-0.15, 0.10)		Could not differentiate

For full GRADE assessment, and reasons quality of outcomes were downgraded, see Appendix F.

Pairwise Meta-analysis

People with proliferative diabetic retinopathy

Table 7: Anti-VEGF vs panretinal photocoagulation: Incidence of proliferative diabetic retinopathy

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs panretinal photocoagulation – proliferative diabetic retinopathy (1 year)					
1 (CLARITY)	Parallel RCT	232	RR: 3.08 (0.13, 74.84)	High	Could not differentiate
Aflibercept vs panretinal photocoagulation (2 years) – non-proliferative diabetic retinopathy					
1 (Protocol W)	Parallel RCT	328	RR: 0.38 (0.24, 0.60)	High	Favours aflibercept
Ranibizumab vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (PRIDE)	Parallel RCT	106	RR: 3.00 (0.65, 13.86)	Low	Could not differentiate
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (PRIDE)	Parallel RCT	106	RR: 2.43 (0.50, 11.71)	Low	Could not differentiate

Table 8: Anti-VEGF vs panretinal photocoagulation: Need for additional treatments (vitrectomy)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (CLARITY)	Parallel RCT	232	RR: 0.15 (0.02, 1.17)	High	Could not differentiate
Aflibercept vs panretinal photocoagulation (2 years) – non-proliferative diabetic retinopathy					
1 (Protocol W)	Parallel RCT	328	RR: 0.33 (0.01, 8.09)	High	Could not differentiate
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (PRIDE)	Parallel RCT	106	RR: 1.46 (0.26, 8.21)	Low	Could not differentiate
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (PROTEUS)	Parallel RCT	87	RR: 2.15 (0.20, 22.79)	Low	Could not differentiate
Ranibizumab vs panretinal photocoagulation (2 years) – proliferative diabetic retinopathy					
1 (PROTOCOL S)	Parallel RCT	305	RR 0.28 (0.13, 0.59)	High	Favours ranibizumab
Ranibizumab vs panretinal photocoagulation (5 years) – proliferative diabetic retinopathy					
1 (PROTOCOL S)	Parallel RCT	305	RR 0.57 (0.35, 0.94)	High	Favours ranibizumab

Table 9: Anti-VEGF vs panretinal photocoagulation: Complications and adverse events (vitreous haemorrhage)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (CLARITY)	Parallel RCT	232	RR: 0.49 (0.24, 0.99)	High	Could not differentiate
Aflibercept vs panretinal photocoagulation (2 years) – non-proliferative diabetic retinopathy					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 (Protocol W)	Parallel RCT	328	RR: 0.99 (0.25, 3.92)	High	Could not differentiate
Ranibizumab vs panretinal photocoagulation (6 months) – proliferative diabetic retinopathy					
1 (Ferraz)	Parallel RCT	60	RR 0.47 (0.16, 1.38)	Moderate	Could not differentiate
Ranibizumab vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (PRIDE)	Parallel RCT	106	RR 1.00 (0.07, 15.36)	Low	Could not differentiate
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (PRIDE)	Parallel RCT	106	RR: 0.97 (0.06, 14.94)	Low	Could not differentiate
1 (PROTEUS)	Parallel RCT	87	RR: 1.31 (0.61, 2.84)	Low	Could not differentiate
Ranibizumab vs panretinal photocoagulation (2 years) – proliferative diabetic retinopathy					
1 (PROTOCOL S)	Parallel RCT	305	RR 0.79 (0.59, 1.05)	High	Could not differentiate
Ranibizumab vs panretinal photocoagulation (5 years) – proliferative diabetic retinopathy					
1 (PROTOCOL S)	Parallel RCT	305	RR 1.04 (0.84, 1.28)	High	Could not differentiate
Bevacizumab vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (Marashi)	Parallel RCT	30	RR 3.00 (0.13, 68.09)	Low	Could not differentiate

Table 10: Anti-VEGF vs panretinal photocoagulation: Complications and adverse events (cataracts)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (CLARITY)	Parallel RCT	232	RR: 0.33 (0.01, 8.10)	High	Could not differentiate

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (PROTEUS)	Parallel RCT	87	RR: 5.36 (0.27, 108.42)	Low	Could not differentiate
Ranibizumab vs panretinal photocoagulation (2 years) – proliferative diabetic retinopathy					
1 (PROTOCOL S)	Parallel RCT	305	RR: 0.87 (0.56, 1.33)	High	Could not differentiate

Table 11: Anti-VEGF vs panretinal photocoagulation: Complications and adverse events (raised intraocular pressure)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (CLARITY)	Parallel RCT	232	RR: 3.00 (0.12, 72.89)	High	Could not differentiate
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (PROTEUS)	Parallel RCT	87	RR: 0.80 (0.19, 3.38)	Low	Could not differentiate
Ranibizumab vs panretinal photocoagulation (2 years) – proliferative diabetic retinopathy					
1 (PROTOCOL S)	Parallel RCT	305	RR: 0.89 (0.57, 1.38)	High	Could not differentiate

Table 12: Anti-VEGF vs panretinal photocoagulation: Complications and adverse events (retinal detachment)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
1 (PROTEUS)	Parallel RCT	232	RR: 0.21 (0.01, 4.34)	Low	Could not differentiate
Ranibizumab vs panretinal photocoagulation (2 years) – proliferative diabetic retinopathy					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 (PROTOCOL S)	Parallel RCT	305	RR: 0.43 (0.22, 0.81)	High	Favours ranibizumab
Aflibercept vs panretinal photocoagulation (2 years) – non-proliferative diabetic retinopathy					
1 (Protocol W)	Parallel RCT	328	RR: 0.99 (0.14, 6.94)	High	Could not differentiate

People with non-proliferative diabetic retinopathy

Table 13. Change in visual acuity (logMAR) relative to panretinal photocoagulation (up to 2 years)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy					
2 (PANORAMA, PROTOCOL W)	Parallel RCT	730	RR: -0.02 (-0.05, 0.01)	Moderate	Could not differentiate

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 672 studies. Based on title and abstract screening, 661 studies could confidently be excluded for this review question and a further 10 studies excluded following the full-text review (see Appendix G for study selection). One of the studies (Lin et al 2018) was excluded from this review because of serious limitations with the reporting of the economic modelling and because a more applicable analysis was being developed to answer this review question but was included in Evidence Review F as that was the only evidence available for that question. Thus, only one study was included in the review (see Appendix H).

1.1.7.2 Excluded studies

Ten studies were excluded at full text (see Appendix J).

1.1.8 Summary of included economic evidence

Table 14: Economic evidence profile

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
Hutton et al (2019) Five-year cost-effectiveness of intra vitreous ranibizumab therapy vs panretinal photocoagulation for treating proliferative diabetic retinopathy	Partially applicable – US study setting with 3% discount rate	Potentially serious limitations – the model structure and analysis were not clearly reported and the sources for estimates of the outcomes and intervention effects were not clear	Ranibizumab compared with panretinal photocoagulation (PRP), results separated by those with and without centre-involving diabetic macular oedema (DMO). Only the results for the population without centre involving DMO are presented here because the population of interest is proliferative diabetic retinopathy without macular oedema. Results were presented over 5 and 10 years.	10-year without centre-involving DMO $43,675 (£30,441*)	10-year without centre-involving DMO 0.059	10-year without centre-involving DMO $742,202 (£517,315*)	A sensitivity analysis including adverse event costs found that the ICERs increased slightly. The 1-way sensitivity analysis in those without baseline centre-involving DMO, ranibizumab was not likely to be cost-effective. The ICER decreased when numbers of ranibizumab injections were decreased to 1.5 annually after the 5th year. In probabilistic analysis there was only a 9% chance that ranibizumab injections would be cost effective vs PRP even at a very high threshold of $250,000/QALY.

DMO: Diabetic macular oedema; PRP: Panretinal photocoagulation
**Costs have been converted from dollars to pounds using EPPI-Centre Cost Converter https://eppi.ioe.ac.uk/costconversion/default.aspx*

1.1.9 Economic model

A de novo Markov economic model was developed from the perspective of UK NHS and personal social services (PSS) for this review question. The model was a lifetime cost-utility analysis comparing six first-line treatments for proliferative diabetic retinopathy: panretinal photocoagulation (PRP); aflibercept; ranibizumab (Lucentis); ranibizumab plus PRP; bevacizumab; and bevacizumab plus PRP. In addition, ranibizumab biosimilar (Ongavia) was considered as a scenario assuming the same efficacy, safety and resource use as ranibizumab (Lucentis). Based on the Protocol S study (Gross et al 2018), an important scenario analysis was explored around assuming stability of visual acuity following the application of the initial treatment effects (detailed in the economic model report). It should be noted that bevacizumab does not hold a marketing authorisation for intravitreal use and must be reconstituted from the 100mg vial into individual 1.25mg doses.

Clinical inputs in the model were based on the literature, while the results of a published network meta-analysis informed the mean difference in visual acuity (Simmonds et al 2023). Main outputs were costs, health outcomes (in quality-adjusted life-years; QALYs), incremental cost-effectiveness ratios (ICERs) and net monetary benefits (NMBs).

In the base-case probabilistic analysis using list prices for the anti-VEGF therapies, it was found that bevacizumab plus PRP had the lowest ICER of £8,947 compared with PRP alone. Bevacizumab plus PRP had the highest NMB (£221,374), Bevacizumab alone had the second highest NMB (£216,410) and PRP alone had the third highest NMB (£212,190) at a £20,000 per QALY gained threshold. The probabilistic base-case results are presented in Table 3 and Table 4. It should be noted that these results were not used by the committee when drafting recommendations for this review question, as they do not take into account the confidential Patient Access Scheme (PAS) discounts associated with each of the anti-VEGF treatments. Although bevacizumab with or without PRP had the highest NMB, this was based on the NMA outputs of mean difference in visual acuity that produced very large confidence intervals for bevacizumab; only one small study in Jordan/Syria compared bevacizumab alone with PRP alone and four small studies (three in Pakistan and one in Iran) compared bevacizumab plus PRP with PRP alone. These studies were also assessed to be at high risk of bias.

The committee was also presented with the results of the probabilistic base-case and scenario analyses when the confidential PAS discounts were applied in the model and these results were used as the basis for their recommendations. These results cannot be presented here because they are commercially sensitive. When these discounts were applied, bevacizumab plus PRP still had the lowest ICER below NICE's £20,000 per QALY gained threshold. Additionally, when the confidential PAS discounts were applied and biosimilar costs were considered, ranibizumab biosimilar (Ongavia) compared with PRP alone had an ICER below £20,000 per QALY and produced the second highest NMB. Aflibercept and ranibizumab (Lucentis) both had ICERs below £25,000 per QALY. It should be noted that the threshold used for decision making in NICE Centre for Guidelines is £20,000 per QALY gained, but consideration can be given to therapies with an ICER between £20,000 and £30,000 in circumstances where there are additional benefits not captured by the economic analysis, for example reducing health inequalities or if there are few treatment options in a population.

Table 15: Economic model results (list price analysis) compared with PRP

Strategy	Absolute Costs	Absolute QALYs	Inc. costs	Inc. QALYs	ICER	NMB at £20K/QALY (95% CI)
PRP	£8,493	11.034	-	-	-	£212,190 (£196,602 to £225,597)
Bevacizumab	£12,615	11.451	£4,122	0.417	£9,883	£216,410 (£183,744 to £239,858)
Bevacizumab plus PRP	£15,926	11.865	£7,433	0.831	£8,947	£221,374 (£203,941 to £238,388)
Ranibizumab	£26,435	11.673	£17,942	0.639	£28,099	£207,018 (£188,241 to £224,329)
Ranibizumab plus PRP	£30,870	11.515	£22,377	0.481	£46,538	£199,430 (£180,774 to £215,929)
Aflibercept	£31,356	11.239	£23,112	0.511	£45,190	£193,416 (£172,171 to £212,348)

Table 16: Economic model incremental analysis results (list price)

Strategy	Absolute Costs	Absolute QALYs	Inc. costs	Inc. QALYs	ICER
PRP	£8,493	11.034	-	-	-
Bevacizumab	£12,615	11.451	£4,122	0.417	Extendedly dominated
Bevacizumab plus PRP	£15,926	11.865	£7,433	0.831	£8,947
Ranibizumab	£26,435	11.673	£10,509	-0.192	Dominated
Ranibizumab plus PRP	£30,870	11.515	£14,943	-0.350	Dominated
Aflibercept	£31,356	11.239	£15,430	-0.626	Dominated

Full details of the model are presented in the economic model report for review E.

1.1.10 Unit costs

The list prices of the drugs for this review question are presented in Table 16. It should be noted that aflibercept, ranibizumab and bevacizumab are recommended by NICE only if the manufacturer provides them with the agreed confidential patient access scheme discount.

Table 17: List prices for the treatments included in the recommendations

Resource	Unit costs	Source
Aflibercept 4.0mg/0.1ml	£816.00	BNF (accessed 13/02/2023)
Ranibizumab (Lucentis) 2.3mg/0.23ml	£551.00	BNF (accessed 13/02/2023)
Ranibizumab biosimilar (Ongavia) 2.3mg/0.23ml	£523.45	BNF (accessed 28/04/2023)
Bevacizumab 1.25mg*	£50.00	Poku et al (2012) cited in NICE TA824
Panretinal photocoagulation	£126.77	NHS national cost collection 2019/2020 BZ87A: Minor Vitreous Retinal Procedures. Total HRG. Assumption used in TA346

**Bevacizumab is only available in a 100mg per 4ml vial at a list price of £242.66, and for intravitreal use must be reconstituted into a 1.25mg dose in an aseptic pharmacy.*

1.1.11 Evidence statements

One published cost-utility analysis by Hutton et al (2019) was identified comparing intravitreal ranibizumab and PRP for the treatment of people with proliferative diabetic retinopathy without diabetic macular oedema. This study found that over a 10-year time horizon intravitreal ranibizumab was unlikely to be cost effective compared with PRP. However, this study was only partially applicable due to the US study setting, which is very different to the NHS and had serious limitations with how the analysis was conducted and reported.

A de-novo economic model was conducted for this guideline, comparing all first-line treatments that were considered relevant for decision making, from the perspective of NHS and PSS. The model was directly applicable to this review question, given it was developed specifically for this guideline. The model results indicated that under list prices and confidential PAS prices, bevacizumab and bevacizumab plus PRP had the lowest ICERs and were most likely to be considered cost-effective at an opportunity cost of £20,000 per QALY. The model also indicated that ranibizumab biosimilar (Ongavia) is likely to have an ICER below £20,000 per QALY.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The most commonly reported outcome was change in visual acuity. The committee highlighted that the risk of reduced vision is a major concern for people with diabetic retinopathy. However, this population generally have better vision than other populations, such as people with diabetic macular oedema. Therefore, change in visual acuity may not be as useful an outcome for people with proliferative diabetic retinopathy as other outcomes, such as changes in peripheral vision and visual field, or functional impact on vision. However, no data was available for these other

outcomes, and so the committee agreed that change in visual acuity was still a useful indicator of treatment effectiveness. The committee were also interested in incidence of macular ischemia, quality of life and the acceptability of different interventions, but no data was found for these outcomes.

There was no evidence for other non-vision related outcomes (number of treatments and treatment withdrawal). However, the committee thought these were less important for decision making than the vision-related outcomes.

1.1.12.2 The quality of the evidence

There was very limited evidence for people with non-proliferative diabetic retinopathy. Only two studies evaluated the effects of different treatments for this population. Each of these studies compared aflibercept to sham, and so there was no data available to compare between anti-VEGFs and panretinal photocoagulation. The only relevant outcome available for this group was change in visual acuity. This outcome was moderate quality and directly applicable to the review. Given the limited evidence base, the committee were unable to make recommendations for the most effective treatments options for this group of people. Instead, they made a research recommendation based on treatment strategies for people with severe non-proliferative diabetic retinopathy so that recommendations can be made for this group in future (see Appendix K). The focus of this research recommendation was people with severe non-proliferative diabetic retinopathy because people are typically observed, rather than treated, when they are at a less severe stage of the disease.

There was more evidence for people with proliferative diabetic retinopathy. NMA evidence was low quality, due to many studies being at high risk of bias, and pairwise meta-analysis outcomes ranged from low to high quality. All outcomes were directly applicable to the review. Evidence included comparisons between anti-VEGFs and panretinal photocoagulation, or between different dosing regimens for the same anti-VEGF. No studies compared between different types of anti-VEGF or considered the effects of combination treatments, such as anti-VEGFs combined with panretinal photocoagulation. Many of the studies had small sample sizes and while most of the anti-VEGFs (aflibercept and ranibizumab) were from trials conducted in Europe, North America or Brazil), bevacizumab was only included in trials conducted in the Middle East or South Asia. People of different ethnicities have different rates of diabetic retinopathy progression, such as people of South Asian descent who can progress more quickly. The different locations of the trials could therefore impact on the relative effectiveness of different anti-VEGFs. However, the committee thought the results were still relevant to help compare the effectiveness of anti-VEGFs to panretinal photocoagulation.

Based on their clinical knowledge and experience, the committee discussed how the effects of each treatment may differ depending on the severity of a person's diabetic retinopathy. They highlighted how panretinal photocoagulation is most effective for people with severe proliferative diabetic retinopathy. However, it was not possible to distinguish the effectiveness of different treatments based on severity of retinopathy in the analysis, as there was limited reporting in the studies about severity of retinopathy at baseline. Some of the studies used adjuvant treatments, which is a common approach in the treatment of diabetic retinopathy if there are signs that a person is continuing to progress despite first line treatment. For instance, laser photocoagulation can be used as an additional treatment if a person is having anti-VEGF treatment but still showing signs of progression. The committee thought that the use of adjuvant treatments was important but highlighted that they could make the treatment used in the study arms appear more effective. However, the use of adjuvant treatments was not clearly reported in some studies, making it difficult to be

sure whether the effect was purely a result of the treatment used in the intervention arm, or whether the results also represented the effect of any adjuvant treatments.

The committee discussed the lack of evidence for combination treatments for people with proliferative diabetic retinopathy, with most of the studies considering either panretinal photocoagulation or single anti-VEGFs. This limited the recommendations that the committee could make, as it is currently unclear whether combinations of different anti-VEGFs are more effective than single anti-VEGFs, or which anti-VEGFs are the most effective when combined with panretinal photocoagulation. They therefore made a research recommendation aimed at determining which is the most effective combination of treatments for people with proliferative diabetic retinopathy (see Appendix K).

1.1.12.3 Imprecision and clinical importance of effects.

For people with proliferative diabetic retinopathy, the analysis showed that after one year of treatment, bevacizumab and ranibizumab, when used on their own or when combined with panretinal photocoagulation, resulted in greater improvements in visual acuity than panretinal photocoagulation alone. However, the committee highlighted that these results were not clinically meaningful and did not meet the clinical decision threshold of 10 letters on the ETDRS chart (0.2 logMAR). These results therefore reflected little difference between the treatment options. Between one and two years, the evidence could not differentiate between the treatment options.

The evidence could not differentiate between the treatment options for most of the other outcomes, indicating that a similar number of people would need additional treatments or experience complications or adverse events with the use of anti-VEGFs or panretinal photocoagulation. As such, the committee thought the decisions about which treatment to recommend should be based on other factors, such as the number of appointments required for treatment, and certain indications, such as cataracts, that mean a particular treatment is more appropriate.

1.1.12.4 Benefits and harms

The committee discussed how, in their experience, panretinal photocoagulation is particularly effective for people with proliferative diabetic retinopathy who have high risk characteristics, such as those who have certain types of neovascularisations. They also highlighted how it can be beneficial for people when they first develop signs of proliferative retinopathy, given that the alternative option for this group is frequent monitoring. The committee were concerned that the risks associated with progression if people do not attend follow-up appointments are greater than the risk of adverse events from panretinal photocoagulation. There are also risks of non-attendance with the use of anti-VEGF treatments, as they require more frequent appointments than panretinal photocoagulation. People are therefore at risk of progressing if they are unable to attend these repeated appointments, In the committee's experience, there are some additional risks associated with anti-VEGFs, such as endophthalmitis, that are not associated with panretinal photocoagulation. For this reason, they recommended that people with proliferative diabetic retinopathy are offered panretinal photocoagulation when they are first diagnosed.

Timing of panretinal photocoagulation was considered, and the committee highlighted the importance of this being offered to people as soon after diagnosis as possible, to prevent progression to more advanced stages of retinopathy, which can result in loss of vision. Evidence from the review on thresholds for starting treatment (see evidence review B) supported this view. Two studies indicated that early

panretinal photocoagulation can result in fewer people experiencing severe visual loss and progression of retinopathy after 2 years in comparison to deferred panretinal photocoagulation. The committee thought that panretinal photocoagulation should ideally be offered on the same day as diagnosis, especially for those with high-risk characteristics, such as people who have neovascularisation. However, they were aware that this is not always possible, and therefore used their clinical experience to recommend that people other than those with high-risk characteristics should be given it within 4 to 6 weeks of it being offered. They highlighted that clinicians should aim to start treatment within 4 weeks but, because they were aware that resources may not always be sufficient for this, they specified that treatment should start no later than within 6 weeks of it being offered. Treatment within 4 to 6 weeks should reduce the risk of progression between the time of diagnosis and treatment. The committee noted that there are some people who find it difficult to attend appointments, such as people who have jobs with zero hours contracts, or those who have difficulty accessing or affording transport to the appointment. They thought that these people should always be offered photocoagulation on the same day as diagnosis. In instances where it is impossible to start treatment on the same day, PRP should be completed at the earliest opportunity.

Some people who are given panretinal photocoagulation will still have active proliferative diabetic retinopathy after treatment. It is therefore important that these people receive further treatment to reduce the risk of progression to more severe proliferative retinopathy or to diabetic macular oedema.

The committee was aware that, in some people, proliferative diabetic retinopathy will progress despite full panretinal photocoagulation. Anti-VEGF treatments were shown to be an effective method of improving visual acuity, and so it was recommended that these are considered for people whose proliferative diabetic retinopathy is still active after panretinal photocoagulation. The committee thought that anti-VEGFs would be an effective second-line treatment for people with proliferative diabetic retinopathy but highlighted the importance of those who also have tractional retinal detachment being monitored closely by the clinician and a vitreoretinal specialist.

While panretinal photocoagulation will benefit many people who have proliferative diabetic retinopathy, some people, such as those who have a cataract, are unable to have panretinal photocoagulation as the cataract can block the view of the back of the eye. However, delaying treatment until after cataract surgery, when the laser can be applied, increases the risk of progression and other consequences, such as loss in vision. It is therefore important that people who have a cataract receive treatment for their retinopathy as early as possible, rather than delaying until after surgery. The committee discussed how people who have a vitreous haemorrhage are also unable to have panretinal photocoagulation. For this reason, the committee recommended that people who have proliferative diabetic retinopathy and also have either vitreous haemorrhage which is preventing panretinal photocoagulation, or who need cataract surgery and the severity of the cataract is preventing panretinal photocoagulation, should be offered anti-VEGF treatment as a temporary solution. This will ensure that their proliferative diabetic retinopathy does not go untreated. The committee did not think this would result in a big rise in the use of anti-VEGF treatments, as they would only need to be given during the short time until surgery has taken place. This would typically result in 1 to 2 injections and would reduce the additional treatment associated with people who would otherwise have progressed if they had no treatment while waiting for cataract surgery. This recommendation means that these people will not miss out on treatment for their retinopathy that they would otherwise have if their cataract or vitreous haemorrhage was not preventing them from having panretinal photocoagulation.

The committee also highlighted the importance of making people aware of what proliferative diabetic retinopathy is, and whether they have high-risk characteristics. This will help them to understand why they are being offered treatment, and what this treatment aims to achieve. It is also important that each treatment option is discussed with patients. Although there was no evidence available for acceptability, the committee were aware that the thought of laser treatment or injections into the eye can cause anxiety. Discussing these treatments will give patients a chance to understand what will happen with each treatment, as well as giving them an opportunity to ask questions, which may help to reduce some of their concerns. Although the committee were confident that panretinal photocoagulation should be offered as first-line treatment, they still thought that all of the treatment options, and their associated risks and benefits, should be discussed before people are first offered treatment. This will help people to understand what treatments may be offered to them at various stages of the disease and make an informed decision about the treatment they are being offered.

1.1.12.5 Cost effectiveness and resource use

The committee considered the one cost-effectiveness study (Hutton et al 2019) found in the literature for the treatment of proliferative diabetic retinopathy. This study was only partially applicable because of the US study setting and had potentially serious limitations. No evidence was identified for non-proliferative diabetic retinopathy. Therefore, the de novo economic model was considered the key piece of economic evidence for making recommendations for this review question, allowing all treatment options to be considered within a single analysis from a UK NHS and PSS perspective.

The committee considered the de novo economic model results alongside the clinical evidence for proliferative diabetic retinopathy. In the probabilistic base-case of the economic model, bevacizumab plus PRP had the lowest ICER below £20,000 per QALY gained threshold compared with PRP alone. Although bevacizumab plus PRP had the highest net monetary benefit in the base-case results, indicating it to be the most cost-effective option, the committee discussed that for both bevacizumab alone and bevacizumab plus PRP, the NMA outcomes of mean difference were subject to great uncertainty with large confidence intervals. The committee also discussed the difficulties around recommending bevacizumab as an off-label treatment, the need for bevacizumab to be reconstituted in a specialist aseptic pharmacy environment, and the patient burden associated with needing to regularly attend clinic for injections. The scenario analysis based on the Protocol S study (Gross et al 2018) around assuming stability of visual acuity following the application of the initial treatment effects resulted in PRP alone having the highest net monetary benefit, followed by bevacizumab alone then bevacizumab plus PRP, in both the list price and PAS price analyses. The committee considered this scenario almost equally plausible to the base-case analysis, but the short-term trial outcomes thus far do not allow for confidence in the long-term stability of PDR treated with anti-VEGFs alone. Treatment effect may also sustain if patients receive treatment and assuming visual acuity to stabilise so early in the disease pathway may not be a fully reasonable approach. However, it was considered as an important scenario; further details are presented in the economic model report. This combination of factors is why the committee chose to recommend PRP alone to be offered first to patients with proliferative diabetic retinopathy.

PRP was found to remain in the top three treatments for net monetary benefit for the majority of scenarios explored which was why, in combination with the clinical evidence from the NMA and the committee's clinical expertise, PRP was

recommended to be offered first for the treatment of proliferative diabetic retinopathy. From the scenario analyses, the model results were most sensitive to changes in the choice of utility source and the assumptions around the frequency of monitoring and treatment visits. The committee felt that given visual acuity may not be the main consideration for treatment for proliferative diabetic retinopathy, it was important that population which the utility values are drawn from reflect the diabetic retinopathy population. For this reason, the committee felt the Brown et al (1999) utility values were most appropriate as the only utility mapping source from visual acuity which is based on a population of people with diabetic retinopathy.

Although PRP was considered the least cost effective based on net monetary benefit when patient costs were considered, it should be noted that this was only the patient costs associated with low vision that were outside an NHS perspective. The committee discussed that whilst data for transport costs associated with treatment and monitoring could not be included due to a lack of evidence, this is an important consideration for patients. Particularly for treatments such as anti-VEGFs which can require frequent visits over a long duration of time, this can be very burdensome for the patient in terms of both affordability and time. If these transport costs were able to be considered it is possible the results may be very different because typically PRP is delivered over fewer sessions and requires less frequent follow up. When the confidential cost of the biosimilar for ranibizumab (Ongavia) was considered as a scenario, it was considered a cost-effective treatment compared with PRP alone.

The committee discussed that timeliness of treatment is important for those with active proliferative diabetic disease, which is why the recommendation suggests a preference for treatment to be offered on the same day. The committee discussed the resource implications of this recommendation, and considered there may be capacity constraints faced in clinical practice. The committee expressed the importance of PRP being offered promptly whilst allowing for some flexibility up to two weeks to allow for capacity challenges some clinics may face. The committee discussed that often the people who have the most difficulty attending appointments should be offered PRP treatment on the same day because these people are often the most at risk of sight loss because they may find it difficult to return to the clinic for timely treatment. The committee felt this was an important recommendation for reducing health inequalities as it is commonly those people in the most disadvantaged groups which have the most difficulty in attending appointments.

The committee wanted to ensure those people whose proliferative diabetic retinopathy remains active after completing PRP had a treatment option to prevent sight loss which is why the committee made the recommendation to offer anti-VEGF treatments. When the confidential price of ranibizumab biosimilar (Ongavia) was considered, it had an ICER below £20,000 which is the opportunity cost used for decision making in NICE Centre for Guidelines, and the committee considered this likely to be a cost-effective use of resources. Similarly, bevacizumab had an ICER below £20,000 and was considered cost-effective by the committee. In addition, this population is expected to be small because for most people PRP is effective in managing proliferative diabetic retinopathy.

The committee discussed that anti-VEGFs should be considered for those whom PRP is not suitable due to either vitreous haemorrhage or because they need cataract surgery. Whilst there was very limited evidence for this recommendation, the committee did not expect there to be a large resource impact because anti-VEGFs would only be expected for short term treatment such as 1 to 2 injections to prevent progression whilst waiting for cataract treatment or treatment of vitreous haemorrhage. The committee felt that the resources saved by reduced progression

whilst waiting for these other treatments would offset the increase in short term costs associated with anti-VEGF treatments.

Overall, the committee considered PRP to be a cost-effective treatment option for people with active proliferative diabetic retinopathy. The committee does not anticipate a resource impact because of these recommendations as PRP is currently considered as a standard practice within clinics.

1.1.12.6 Other factors the committee took into account

When discussing panretinal photocoagulation, the committee highlighted their concerns that this treatment is not always delivered using the most effective methods. In some cases, they were aware of people being given panretinal photocoagulation at a lower intensity, which reduces the need for anaesthesia but also means that a greater number of treatments are required, and treatment can be less effective. None of the studies in the review compared different intensities of panretinal photocoagulation and so the committee thought it was important to include a research recommendation to help determine which is the most effective and acceptable method (see Appendix K).

1.1.13 Recommendations supported by this evidence review

This evidence review supports Recommendations 1.5.1 to 1.5.6 and the research recommendations on effectiveness of different treatment strategies for non-proliferative diabetic retinopathy, effectiveness of combination treatments for proliferative diabetic retinopathy, and effectiveness of different methods of delivering panretinal photocoagulation for proliferative diabetic retinopathy.

1.1.14 References – included studies

1.1.14.1 Effectiveness

Included studies from the Simmonds (2023) paper were part of a wider review. The studies included here are those that were used for the comparisons in the NMA and meta-analyses.

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1.1.14.2 Economic

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1.1.14.3 Other

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Appendices

Appendix A – Review protocols

Review protocol for anti-vascular endothelial growth factor agents and laser photocoagulation for diabetic retinopathy.

Based on the systematic review by Simmonds et al. 2023, with additional information included by NICE

ID	Field	Content
0.	PROSPERO registration number	This protocol will be not be registered on PROSPERO as it describes an adaptation of systematic review that being undertaken outside of NICE. This review is already registered on PROSPERO: CRD42021272642
1.	Review title	Anti-vascular endothelial growth factor agents and laser photocoagulation for diabetic retinopathy
2.	Review question	What is the effectiveness and acceptability of anti-vascular endothelial growth factor agents and laser photocoagulation (alone or in combination) for the treatment of non-proliferative and proliferative diabetic retinopathy without macular oedema?
3.	Objective	To determine the clinical, cost effectiveness and acceptability of laser photocoagulation and anti-vascular endothelial growth factor agents for treating diabetic retinopathy.
4.	Searches	No systematic search will initially be conducted at NICE, as this review will be conducted externally by the University of York. A search will be run 6 weeks before final submission of the review to cover the time period following University of York search, and further studies retrieved for inclusion: The following databases will be searched for the clinical review: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • HTA (legacy records) • INAHTA • MEDLINE • Medline in Process • Medline EPub Ahead of Print

		For the economics review the following databases will be searched on population only: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA Searches will be restricted by: • Studies reported in English • Study design RCT filters will be applied and the Cochrane RCT classifier will be used. • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • Date limit: searches will be restricted to the date of the search carried out by the University of York. • None identified
5.	Condition or domain being studied	Diabetic retinopathy
6.	Population	Inclusion: People with diabetic retinopathy (proliferative and non-proliferative) will be included. Exclusion: Patients with a principal indication for treatment of diabetic macular oedema will be excluded.
7.	Intervention/Exposure/Test	Any anti-VEGF therapy: • Including aflibercept, bevacizumab, ranibizumab and their biosimilars • Anti-VEGF with, or subsequent to, laser photocoagulation Laser photocoagulation (in any form, and any laser type)
8.	Comparator/Reference standard/Confounding factors	• Studies comparing the interventions described above will be included, included studies comparing different anti-VEGF agents. • Sham treatment, or other control interventions
9.	Types of study to be included	• Randomised controlled trials • Qualitative studies running alongside included randomised trials (sibling studies)

		reporting qualitative data on acceptability will also be included.
10.	Other exclusion criteria	• No language limits will be applied for the review carried out by the University of York. Studies identified in the search 6 weeks before submission will be limited to English language only.
11.	Context	Diabetic retinopathy is a leading cause of sight loss in the UK. This review will inform a new NICE guideline on diabetic retinopathy.

12.	Primary outcomes (critical outcomes)	• Visual acuity measurement
		• Functional impact on vision, e.g.
		  • driving vision (approx. 0.3logMAR)
		  • blind level vision (approx. 1.0logMAR)
		  • clinically important vision loss (0.3logMAR or worse)

13.	Secondary outcomes (important outcomes)	• Number of treatments • Need for subsequent treatment (e.g. vitrectomy) • Complications and adverse effects E.g. Raised intraocular pressure, vitreous haemorrhage, retinal detachment, cataract formation, systemic AEs. • Progression of retinopathy (non-proliferative to proliferative) • Peripheral vision and visual field changes • Treatment withdrawal • Quality of life (NEI-VFQ-25, EQ-5D, SF-36) Additional outcomes to be extracted by NICE review team: • Macular ischaemia • Acceptability: Qualitative or quantitative data on acceptability collected alongside included randomised controlled trials will be included
14.	Data extraction (selection and coding)	Two researchers will independently screen all titles and abstracts retrieved from electronic database and other searches. Full text publications will be retrieved for potentially relevant trials. Full text articles will be screened by two reviewers for final inclusion. Where no full paper exists and/or trial eligibility is uncertain, study authors will be contacted and asked to provide further information. Two researchers will independently assess the relevance of each trial using the fullest available information. Any discrepancies in screening decisions will be resolved by consensus and discussion with a senior team member or advisory group members, as required.

		'Near miss' studies that do not meet all of the inclusion criteria and have therefore been excluded will be tabulated and their bibliographic details listed with reasons for exclusion in the final project report and PRISMA diagram. A data extraction form will be developed in advance and piloted by two reviewers using a selection of included studies. Data on interventions used, patient characteristics outcomes reported, and all outcome data will be extracted for all included studies from included publications by one reviewer and checked by a second. Where studies are reported in multiple publications data will be extracted from the most recent, complete publication; data will be extracted from other publications if they report additional outcome data.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Randomised controlled trials will be assessed using the Cochrane risk of bias 2.0 checklist.
16.	Strategy for data synthesis	A network meta-analysis will be carried out for all outcomes where the network is connected, assumptions for network meta-analysis are met and the results of the network meta-analysis are considered useful for decision making. Network meta-analysis will be carried out using winbugs. In cases where the assumptions for network meta-analysis are not met, pairwise meta-analysis will be conducted. Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as $I2 \geq 50\%$, when random effects models will be used instead.

		To be carried out by NICE review team: A modified version of GRADE will be used to assess the quality of the outcomes. Imprecision will not be assessed in the GRADE profile but will be summarised narratively in the committee discussion section of the evidence review. Outcomes using evidence from RCTs will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered. If multiple qualitative studies are identified, information from the studies will be combined using a thematic synthesis. The thematic synthesis will based partly on a priori categories describing phenomena the committee was interested in (for this review: • Factors that increase acceptability of interventions • Factors that reduce acceptability of interventions) and partly on themes that emerge from the coding of the included studies. Papers will be uploaded to NVivo 11 software where the relevant data from the papers will be coded. The resulting sets of codes will be aggregated into themes and sub-themes. The aggregated themes will be used to develop interpretive 'review findings'. CERQual will be used to assess the confidence we have in the summary findings of each of the identified themes. Incorporation of additional studies identified 6 weeks before submission for consultation: If additional studies are identified for inclusion by the NICE review team during searches conducted 6 weeks before submission for consultation, data from these studies will be included in the evidence review and presented to the guideline committee. If additional studies are broadly consistent with the rest of the evidence base, and in the view of the guideline committee are unlikely to change the conclusions of the network meta-analysis, these studies will not be incorporated. If there is a possibility that additional studies may have an impact on the conclusions of the network meta-analysis, the network meta-analysis will be rerun with the new studies incorporated.
17.	Analysis of sub-groups	The following potential effect modifiers have been identified for investigation: • Type of retinopathy (proliferative, non-proliferative retinopathy grade, presence of maculopathy) • Low and high-risk PDR

<table>
<tr><td></td><td></td><td colspan="3">• Vitreous haemorrhage or tractional retinal detachment
• Type 1 vs Type 2 diabetes
• Age, gender, ethnicity
Where feasible, subgroup analysis and meta-regression will be used to identify the possible impact of these effect modifiers.</td></tr>
<tr><td>18.</td><td>Type and method of review</td><td colspan="3">☒ Intervention
☐ Diagnostic
☐ Prognostic
☐ Qualitative
☐ Epidemiologic
☐ Service Delivery
☐ Other (please specify)</td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">August 2022</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">April 2023</td></tr>
<tr><td>23.</td><td>Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td></td><td></td><td>Preliminary searches</td><td>☑</td><td>☐</td></tr>
<tr><td></td><td></td><td>Piloting of the study selection process</td><td>☑</td><td>☐</td></tr>
<tr><td></td><td></td><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td></td><td></td><td>Data extraction</td><td>☑</td><td>☐</td></tr>
<tr><td></td><td></td><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td></td><td></td><td>Data analysis</td><td>☐</td><td>☐</td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">5a. Named contact
Guideline development team

5b Named contact e-mail
Diabeticretinopathy@nice.org.uk

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE) and NICE guideline development team</td></tr>
<tr><td>25.</td><td>Review team members</td><td colspan="3">From the University of York:
• Mark Simmonds</td></tr>
</table>

		• Sofia Dias From the Guideline development team: • Kathryn Hopkins • Ahmed Yosef • Syed MohiuddinHannah Lomax • Kirsty Hounsell • Jenny Craven • Jenny Kendrick
26.	Funding sources/sponsor	This systematic review is being completed by the University of York, which has received funding for this project from the NIHR and the Guideline development team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10160
30.	Reference/URL for published protocol	https://njl-admin.nihr.ac.uk/document/download/2037853
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

32.	Keywords	Diabetic retinopathy, anti-VEGF, laser
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Search design and peer review

No searches were required for RQ5 at development stage as the team used the York network meta-analysis. NICE information specialists were required to update the searches. The Medline strategy taken form the original York network meta-analysis and adapted.

NICE information specialists ran update searches in March 2023. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources used in the York network meta-analysis and listed in the protocol, taking into account their size, search functionality and subject coverage.

Review Management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude, conference abstract or conference paper or "conference review" were applied in adherence to standard NICE practice and the review protocol. The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ, 309(6964), 1286.

Search filters

The following search filters were applied to the clinical searches in MEDLINE and Embase to identify:

RCTs

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version. The standard NICE modifications were used: randomized.mp changed to randomi?ed.mp.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

Observational studies

The terms used for observational studies are standard NICE practice that have been developed in house.

Clinical search strategies

Database	Date searched	Database Platform	Database segment or version
Cochrane Central Register of Controlled Trials (CENTRAL)	28-Feb-2023	Wiley	Issue 2 of 12, February 2023
Cochrane Database of Systematic Reviews (CDSR)	28-Feb-2023	Wiley	Issue 2 of 12, February 2023
Embase	28-Feb-2023	Ovid	Embase <1974 to 2023 February 27>
Epistemonikos	n/a	Epistemonikos	
MEDLINE	28-Feb-2023	Ovid	Ovid MEDLINE(R) <1946 to February 27, 2023>
MEDLINE-in-Process	28-Feb-2023	Ovid	Ovid MEDLINE(R) In-Process & In-Data-Review Citations <1946 to February 27, 2023>
MEDLINE ePub Ahead-of-Print	28-Feb-2023	Ovid	Ovid MEDLINE(R) Epub Ahead of Print <February 27, 2023>

Cost effectiveness searches

A broad search covering the diabetic retinopathy population was used to identify studies on cost effectiveness. The searches were run in February 2022. Update searches were run in February 2023.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude, comment or letter or editorial or historical articles or conference abstract or conference paper or "conference review" or letter or case report were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ, 309(6964), 1286.

Search filters

Cost utility

The NICE cost utility filter was applied to the search strategies in MEDLINE and Embase to identify cost-utility studies.

Hubbard W, et al. Development of a validated search filer to identify cost utility studies for NICE economic evidence reviews. NICE Information Services.

Cohort studies

For the modelling, cohort/registry terms were used from the NICE observational filter that was developed in-house.

The NICE Organisation for Economic Co-operation and Development (OECD) filter was also applied to search strategies in MEDLINE and Embase.

Ayiku, L., Hudson, T., et al (2021)The NICE OECD countries geographic search filters: Part 2 – Validation of the MEDLINE and Embase (Ovid) filters. Journal of the Medical Library Association)

Cost effectiveness search strategies

Database	Date searched	Database Platform	Database segment or version
EconLit	16/02/2022	OVID	<1886 to February 13, 2022>
Embase (filters applied: specific cost utility filter, cohort terms plus OECD filter)	16/02/2022	Ovid	<1974 to 2022 February 16>
HTA	16/02/2022	CRD	16-Feb-2022
INAHTA	16/02/2022	INAHTA	16-Feb-2022
MEDLINE (filters applied: specific cost utility filter, cohort terms plus OECD filter)	16/02/2022	Ovid	<1946 to February 16, 2022>
MEDLINE-in-Process (filters applied: specific cost utility filter, cohort terms)	16/02/2022	Ovid	<1946 to February 16, 2022>

MEDLINE Epub Ahead-of-Print (filters applied: specific cost utility filter, cohort terms)	16/02/2022	Ovid	<February 16, 2022>
NHS EED	16/02/2022	CRD	N/A

Database: EconLit

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 14

4 1 or 2 or 3 14

Database: Embase

Cost utility search:

1 diabetic retinopathy/ 45217
2 macular edema/ 5687
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47443
4 1 or 2 or 3 65931
5 cost utility analysis/ 10912
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 26154
7 ((incremental* adj2 cost*) or ICER).tw. 26757
8 (cost adj2 utilit*).tw. 9655
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 2715
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 31906
11 (cost and (effect* or utilit*)).ti. 51363
12 or/5-11 81030
13 4 and 12 417
14 nonhuman/ not human/ 4929899
15 13 not 14 415
16 (conference abstract or conference paper or conference proceeding or "conference review").pt. 5091583
17 15 not 16 302

Cohort studies:

1 diabetic Retinopathy/ 45440
2 macular Edema/ 5828
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47762
4 or/1-3 66388
5 cohort analysis/ 811098
6 Retrospective study/ 1206857

7 Prospective study/ 748103
8 (Cohort adj (study or studies)).tw. 380594
9 (cohort adj (analy* or regist*)).tw. 16437
10 (follow up adj (study or studies)).tw. 68508
11 longitudinal.tw. 384899
12 prospective.tw. 981024
13 retrospective.tw. 1068301
14 or/5-13 3358085
15 4 and 14 13743
16 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ 1511773
17 exp "organisation for economic co-operation and development"/ 1933
18 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ 3545238

19 european union/ 29144
20 developed country/ 34415
21 or/17-20 3576072
22 16 not 21 1373176
23 15 not 22 12938
24 limit 23 to english language 12133
25 nonhuman/ not human/ 4938000
26 24 not 25 12067
27 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 7072757
28 26 not 27 8733

29 limit 28 to dc=20120101-20220228 6467

Database: HTA

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118
2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82
3 ((diabet* adj4 (retin* or eye* or macular*))) 216
4 #1 OR #2 OR #3 245
5 * IN HTA FROM 2012 TO 2022 5598

6 #4 AND #5 26

Database: : International Network of Agencies for Health Technology Assessment (INAHTA)

6 #5 AND #4 47
5 * FROM 2012 TO 2022 7610
4 #3 OR #2 OR #1 92
3 ((diabet* AND (retin* or eye* or macular*))) 84
2 "Macular Edema"[mh] 27
1 "Diabetic Retinopathy"[mh] 39

Database: Ovid Medline (R)

Cost utility search:

1 Diabetic Retinopathy/ 27250
2 Macular Edema/ 8126
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 29608
4 1 or 2 or 3 40314

5 Cost-Benefit Analysis/ 88398
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 13197
7 ((incremental* adj2 cost*) or ICER).tw. 13599
8 (cost adj2 utilit*).tw. 5176
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 1698
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 17986
11 (cost and (effect* or utilit*)).ti. 30223
12 or/5-11 100083
13 4 and 12 287
14 animals/ not humans/ 4924997
15 13 not 14 287

Cohort studies:

1 Diabetic Retinopathy/ 27317
2 Macular Edema/ 8133
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 29694
4 or/1-3 40407
5 exp Cohort Studies/ 2302163
6 (cohort adj (study or studies)).tw. 225137
7 (cohort adj (analy* or regist*)).tw. 8773
8 (follow up adj (study or studies)).tw. 48799
9 longitudinal.tw. 243228
10 prospective.tw. 570236
11 retrospective.tw. 546033
12 or/5-11 2652900
13 4 and 12 10289
14 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or

"saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ 1201994
15 "organisation for economic co-operation and development"/ 417
16 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ 3386234
17 european union/ 17116
18 developed countries/ 21089
19 or/15-18 3401513
20 14 not 19 1115138
21 13 not 20 9710
22 limit 21 to english language 8875
23 Animals/ not Humans/ 4930479
24 22 not 23 8825
25 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 2225022
26 24 not 25 8658
27 limit 26 to ed=20120101-20220228 4813

Database: Ovid MEDLINE(R) In-Process & In-Data-Review Citations

Cost utility search:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 335
4 1 or 2 or 3 335
5 Cost-Benefit Analysis/ 0
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 196
7 ((incremental* adj2 cost*) or ICER).tw. 177
8 (cost adj2 utilit*).tw. 74
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 29
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 242
11 (cost and (effect* or utilit*)).ti. 286

12 or/5-11 450
13 4 and 12 2
14 animals/ not humans/ 0
15 13 not 14 2

Cohort studies:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 336
4 or/1-3 336
5 exp Cohort Studies/ 0
6 (cohort adj (study or studies)).tw. 4157
7 (cohort adj (analy* or regist*)).tw. 155
8 (follow up adj (study or studies)).tw. 263
9 longitudinal.tw. 3119
10 prospective.tw. 5190
11 retrospective.tw. 6965
12 or/5-11 15689
13 4 and 12 71
14 limit 13 to english language 71
15 limit 14 to dt=20120101-20220228 70

Database: Ovid MEDLINE(R) Epub Ahead of Print

Cost utility search:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 585
4 1 or 2 or 3 585
5 Cost-Benefit Analysis/ 0
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 459
7 ((incremental* adj2 cost*) or ICER).tw. 395
8 (cost adj2 utilit*).tw. 195
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 59
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 625
11 (cost and (effect* or utilit*)).ti. 615
12 or/5-11 1199
13 4 and 12 9
14 animals/ not humans/ 0
15 13 not 14 9

Cohort studies:

1 Diabetic Retinopathy/ 0

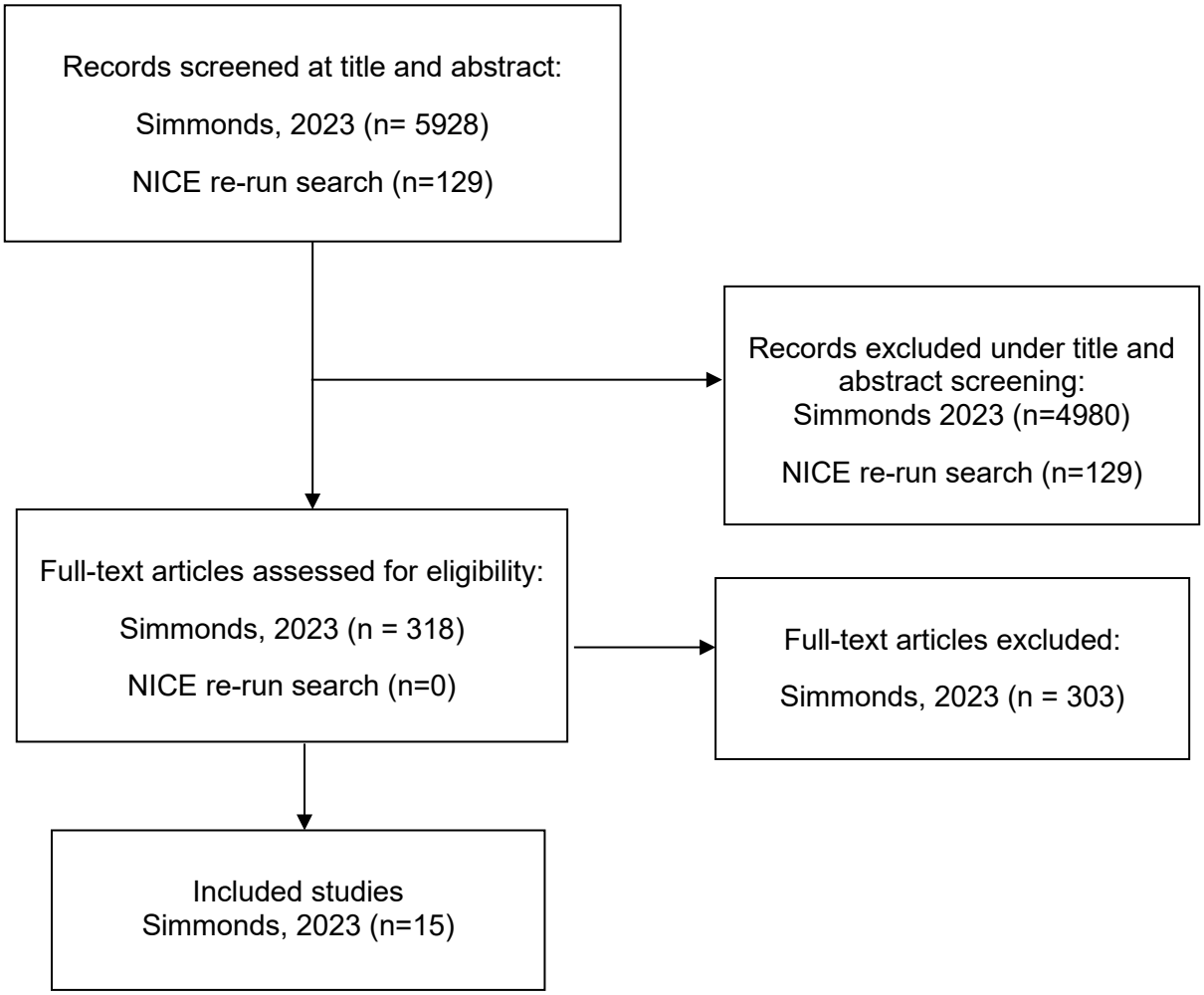
2	Macular Edema/	0
3	(diabet* adj4 (retin* or eye* or macular*)).tw.	563
4	or/1-3	563
5	exp Cohort Studies/	0
6	(cohort adj (study or studies)).tw.	9207
7	(cohort adj (analy* or regist*)).tw.	349
8	(follow up adj (study or studies)).tw.	607
9	longitudinal.tw.	6722
10	prospective.tw.	12241
11	retrospective.tw.	18324
12	or/5-11	37987
13	4 and 12	147
14	limit 13 to english language	147

Database: NHS Economic Evaluation Database

1	MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES	118
2	MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES	82
3	((diabet* adj4 (retin* or eye* or macular*)))	216
4	#1 OR #2 OR #3	245
5	* IN NHSEED FROM 2012 TO 2022	4897
6	#4 AND #5	19

Appendix C – Effectiveness evidence study selection

PRISMA diagram is taken from the systematic review (Simmonds et al., 2023), with the addition of information about the NICE re-run search. For more information about reasons for study exclusion, see Simmonds et al. (2023).



Appendix D – Effectiveness evidence

D.1.1 Primary studies included in the Simmonds et al. (2023) systematic review

For risk of bias assessments, see Table 2 in the Simmonds et al. 2023 systematic review.

CLARITY, 2017

Bibliographic Reference	Sandra Halim, MBBS; Manjula Nugawela, PhD; Usha Chakravarthy, PhD; Tunde Peto, PhD;Savita Madhusudhan, MBBS; Pauline Lenfestey, MBBS; Barbara Hamill, BSc; Yalin Zheng, PhD;David Parry, BSc; Luke Nicholson, MD(Res); John Greenwood, PhD; Sobha Sivaprasad, DM

Study details

Study type	Randomised controlled trial (RCT)
Study location	UK
Sources of funding	not detailed
Inclusion criteria	• Type 1 or 2 diabetes, • Previously untreated. • Proliferative diabetic retinopathy or persistent retinal • Aged 18 years or older.
Exclusion criteria	• Eyes with clinical evidence of diabetic macular oedema • Moderate or dense vitreous haemorrhage • Tractional retinal detachment • Patients treated with intravitreal anti-VEGF or steroid for diabetic macular oedema within 4 months or PRP within 8 weeks
Intervention(s)	patients were randomized to receive intravitreal aflibercept. (2 mg/0.05 mL at baseline, 4 weeks, and 8 weeks, and as needed from 12 weeks onward)
Comparator	PRP (completed in initial fractionated sessions and then on an as-needed basis when reviewed every 8 weeks).
Outcome measures	• BCVA • DR severity • Subsequent treatment complications
Number of participants	120
Duration of follow-up	1 Year
Loss to follow-up	0 lost to follow up in both arms
Baseline characteristics	The duration of diabetes: Mean Age: 54.8 [14.6] years

DRCRN 2021

Bibliographic Reference	Maturi RK, Glassman AR, Josic K, Antoszyk AN, Blodi BA, Jampol LM, Marcus DM, Martin DF, Melia M, Salehi-Had H, Stockdale CR, Punjabi OS, Sun JK; DRCR Retina Network. Effect of Intravitreous Anti-Vascular Endothelial Growth Factor vs Sham Treatment for Prevention of Vision-Threatening Complications of Diabetic Retinopathy: The Protocol W Randomized Clinical Trial. JAMA Ophthalmol. 2021 Jul 1;139(7):701-712. doi: 10.1001/jamaophthalmol.2021.0606. PMID: 33784735; PMCID: PMC8010644.

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA / Canada
Study setting	64 US and Canadian sites
Sources of funding	not detailed
Inclusion criteria	• Adults (age, ≥18 years) • Type 1 or 2 diabetes • Severe NPDR (some DMO)
Exclusion criteria	• Eyes with CI-DME
Intervention(s)	Aflibercept
Comparator	Sham injection
Outcome measures	• Time to PDR or DME
Number of participants	328 adults (399 eyes)
Duration of follow-up	2 year
Loss to follow-up	19 lost to follow up
Baseline characteristics	Mean Age: [SD] 56 [11] years), Male to female ratio: (57.6% men [230 of 399 eyes];

PANORAMA 2021

Bibliographic Reference	David M. Brown, MD; Charles C. Wykoff, MD, PhD; David Boyer, MD; Jeffrey S. Heier, MD; W. Lloyd Clark, MD; Andres Emanuelli, MD;Patrick M. Higgins, MD; Michael Singer, MD; David M. Weinreich, MD; George D. Yancopoulos, MD, PhD;

Alyson J. Berliner, MD, PhD; Karen Chu, MS; Kimberly Reed, OD; Yenchieh Cheng, PhD; Robert Vitti, MD

Study details

Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	US, Japan, Germany, Hungary, and the United Kingdom.
Sources of funding	This study was funded by Regeneron Pharmaceuticals.
Inclusion criteria	• Adult participants who had diabetes • severe treatment naive NPDR
Exclusion criteria	• DMO
Intervention(s)	Intravitreal injections of aflibercept, 2 mg, every 16 weeks after 3 initial monthly doses and one 8-week interval (aflibercept 2q16 group); intravitreal injections of aflibercept, 2 mg, every 8 weeks after 5 initial monthly doses, with pro re nata (PRN) dosing beginning at week 56 (aflibercept 2q8/PRN group)
Comparator	Sham injection
Outcome measures	• DR severity • subsequent treatment, complications
Number of participants	402
Duration of follow-up	2 years
Loss to follow-up	37 lost to follow up
Baseline characteristics	The duration of diabetes: Mean Age (SD): 55.7 (10.5) Male to female ratio: 225 (56.0%) males,

RECOVERY 2019

Bibliographic Reference	Ahmed Roshdy Alagorie, MD; Muneeswar Gupta Nittala, MPhil; Swetha Velaga, MPhil; Brenda Zhou, MD; Alexander M. Rusakevich, MD; Charles C. Wykoff, MD, PhD; SriniVas R. Sadda, MD

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Sources of funding	not detailed
Inclusion criteria	• treatment-naive PDR
Exclusion criteria	• DMO • vitreoretinal traction • vitreous haemorrhage • uveitis • uncontrolled glaucoma
Intervention(s)	Aflibercept (monthly)
Comparator	Aflibercept (quarterly)
Outcome measures	• BCVA, • DR severity • functional impact
Number of participants	40
Duration of follow-up	1 Year
Loss to follow-up	Three patients were lost to follow-up at month 12, and 5 patients were excluded from. Analysis because of poor OCTA image quality,
Baseline characteristics	Mean Age: Male to female ratio:

Marashi 2017

Bibliographic Reference	Marashi A, Abukhalaf I, Alfaraji R, et al. Panretinal photocoagulation versus intravitreal bevacizumab for proliferative diabetic retinopathy treatment Ophthalmol Vis Syst. 2017;7(1):268–272. DOI: 10.15406/aovs.2017.07.00211

Study details

Study type	Randomised controlled trial (RCT)
Study location	Jordan/Syria

Sources of funding	not detailed
Inclusion criteria	• Age >= 18 years • Diagnosis of diabetes mellitus (type 1 or type 2) • PDR
Exclusion criteria	• Significant renal disease • Myocardial infarction • Tractional retinal detachment • Macular oedema
Intervention(s)	Bevacizumab
Comparator	PRP
Outcome measures	• BCVA • DR severity
Number of participants	30 eyes of 30 patients
Duration of follow-up	1 year
Loss to follow-up	Not reported
Baseline characteristics	Mean Age: the median age was 52 (46-59), Male to female ratio: 20% of them were men.

Ahmad 2012

Bibliographic Reference	Mushtaq Ahmad, Sanaullah Jan Department of Vitreoretinal Ophthalmology, Khyber Institute of Ophthalmic Medical Sciences, Hayatabad Medical Complex, Peshawar

Study details

Study type	Randomised controlled trial (RCT)
Study location	Pakistan
Study setting	Department of Vitreoretinal Surgery, Khyber Institute of

	Ophthalmic Medical Sciences, Hayatabad Medical Complex, Peshawar
Sources of funding	not detailed
Inclusion criteria	• All patients aged ≥18 year who presented with • first-time PDR with almost same changes in both eyes • with no prior retinal laser besides macular laser
Exclusion criteria	• history of prior PRP or vitrectomy.
Intervention(s)	Bevacizumab (+PRP)
Comparator	PRP
Outcome measures	BCVA
Number of participants	54
Duration of follow-up	3 months
Loss to follow-up	Not reported
Baseline characteristics	PRP group (Mean ±SD) Age: 50.8±6.8. Male to female ratio: Male (%) 59.25 PRP-Plus group Mean ±SD) Age: 51.0±6.0. Male to female ratio Male (%) 62.96

Rebecca 2021

Bibliographic Reference	Rebecca, Shaikh FF, Jatoi SM. Comparison of efficacy of combination therapy of an Intravitreal injection of bevacizumab and photocoagulation versus Pan Retinal Photocoagulation alone in High risk Proliferative Diabetic Retinopathy. Pak J Med Sci.2021;37(1):157-161. doi:https://doi.org/10.12669/pjms.37.1.3141

Study details

Study type	Randomised controlled trial (RCT)
Study location	Pakistan
Study setting	at ISRA University Hospital, Hyderabad

Sources of funding	not detailed
Inclusion criteria	• All patients with Type-1 andType-2 diabetes mellitus • 18 years to 65 years of age • PDR • without any previous treatment
Exclusion criteria	• Patients with any media opacity like cataract
Intervention(s)	Bevacizumab (+PRP)
Comparator	PRP
Outcome measures	BCVA
Number of participants	76
Duration of follow-up	6 months
Loss to follow-up	Not reported
Baseline characteristics	Mean Age: Age (year) in Group A was 50.7±6.9, Mean Age: Age (year) n Group B was 51.1±5.9. Male to female ratio in Group-A: male 58.25 (%) female 41.75 (%) Male to female ratio in Group-B: male 62.96 (%) female 37.04 (%)

Roohipour 2016

Bibliographic Reference	Roohipour R, Sharifian E, Moghimi S,Aghsaei Fard M, Ghassemi F, Zarei M, et al. The effect of panretinal photocoagulation (PRP) versus intravitreal bevacizumab (IVB) plus PRP on peripapillary retinal nerve fiber layer (RNFL) thickness analysed by optical coherence tomography in patients with proliferative diabetic retinopathy. J Ophthalmic Vis Res 2019;14:157-63.

Study details

Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Farabi Eye Hospital

Sources of funding	not detailed
Inclusion criteria	• Bilateral PDR requiring treatment.
Exclusion criteria	• glaucoma • ocular hypertension, and/or significant corneal opacity • cataract, or vitreous opacity/haemorrhage • history of prior treatment for diabetic retinopathy • centre involved diabetic macular oedema
Intervention(s)	Bevacizumab (+PRP)
Comparator	PRP
Outcome measures	BCVA
Number of participants	64 eyes (32 Adults)
Duration of follow-up	10 months
Loss to follow-up	13 losses to follow up
Baseline characteristics	The duration of diabetes: 12.5 ± 5.2 years (range, 5-22 years), Mean Age: 53.6 ± 6.6 years (range, 40-65 years) Male to female ratio: 26 female subjects. Mean HbA1c: 8.4 ± 1.7% (range, 6.2-12.9%)

DRCRN Protocol S 2018

Bibliographic Reference	Susan B. Bressler, MD1, Wesley T. Beaulieu, PhD2, Adam R. Glassman, MS2, Jeffrey G.Gross, MD3, Michele Melia, ScM2, Eric Chen, MD4, Michael R. Pavlica, MD5, Lee M. Jampol,MD6, and Diabetic Retinopathy Clinical Research Network

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Multicenter (55 US sites).
Sources of funding	This study was supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, U. S.

	Department of Health and Human Services (grants EY14231, EY14229, EY18817). Genentech (South San Francisco, CA, USA) provided ranibizumab for the study and funds to the DRCR.net to defray the study's clinical site costs.
Inclusion criteria	• PDR • 18 years old • had type 1or type 2 diabetes, • 1 eye with PDR • Eyes with or without DME
Exclusion criteria	• No previous PRP
Intervention(s)	Ranibizumab
Comparator	PRP
Outcome measures	• DR severity • functional impact on vision • subsequent treatment, complications
Number of participants	394 eyes from 305 participants
Duration of follow-up	2 and 4 years
Loss to follow-up	17% of participants with one study eye were lost to follow-up by the 2-year visit,
Baseline characteristics	The duration of diabetes: The median age was 54 Male to female ratio: 95 (44%) were women,

Ferraz 2015

Bibliographic Reference	Ferraz, Daniel A. MD*,†; Vasquez, Lisa M. MD*; Preti, Rony C. MD, PhD*; Motta, Augusto MD*; Sophie, Raafay MD‡; Bittencourt, Millena G. MD‡; Sepah, Yasir J. MBBS†; Monteiro, MÁrio L. R. MD, PhD*; Nguyen, Quan dong MD, MSc†; Takahashi, Walter yukihiko MD, PhD*.

Study details

Study type	Randomised controlled trial (RCT)
Study location	Brazil
Study setting	Sao Paulo
Sources of funding	Sponsored by Genentech

Inclusion criteria	• All patients Type-2 diabetes mellitus • 18 years of age or older • Non-high-risk PDR • without any previous treatment
Exclusion criteria	• patients with any media opacity like cataract • macular ischemia • ocular hypertension
Intervention(s)	Ranibizumab (+PRP)
Comparator	PRP
Outcome measures	BCVA
Number of participants	30
Duration of follow-up	6 months
Loss to follow-up	1 lost to follow up
Baseline characteristics	The duration of diabetes:14 (6.4) Mean Age: 52.6.(7.9) Male to female ratio:15 (53)

PRIDE, 2019

Bibliographic Reference	Lang GE, Stahl A, Voegeler J, Quiering C, Lorenz K, Spital G, Liakopoulos S. Efficacy and safety of ranibizumab with or without panretinal laser photocoagulation versus laser photocoagulation alone in proliferative diabetic retinopathy - the PRIDE study. Acta Ophthalmol. 2020 Aug;98(5):e530-e539. doi: 10.1111/aos.14312. Epub 2019 Dec 6. PMID: 31808278.

Study details

Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	Not reported
Sources of funding	not detailed
Inclusion criteria	• PDR secondary to type 1 or type 2 diabetes.

	• age ≥18 years,
Exclusion criteria	• clinically significant DMO with centre involvement • proliferative vitreoretinopathy (PVR) • severe vitreous haemorrhage impairing imaging/treatment • previous treatment with PRP
Intervention(s)	Ranibizumab (+PRP)
Comparator	PRP
Outcome measures	• BCVA • DR severity subsequent treatment
Number of participants	106
Duration of follow-up	1 year
Loss to follow-up	Not reported
Baseline characteristics	The duration of diabetes: Mean Age: The mean (SD) 53.5 (12.1) years Male to female ratio: 68.9% male and 31.1% female.

PROTEUS 2018

Bibliographic Reference	Filho JA, Messias A, Almeida FP, Ribeiro JA, Costa RA, Scott IU, Jorge R. Panretinal photocoagulation (PRP) versus PRP plus intravitreal ranibizumab for high-risk proliferative diabetic retinopathy. Acta Ophthalmol. 2011 Nov;89(7):e567-72. doi: 10.1111/j.1755-3768.2011.02184.x. Epub 2011 Jul 5. PMID: 21726427.

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	
Sources of funding	not detailed
Inclusion criteria	• Type 1 or 2 diabetes • age 18 years • high-risk proliferative diabetic retinopathy (HR-PDR)
Exclusion criteria	• Any intraocular surgery within 6 months before trial enrolment,

	• including prior PRP or focal/grid photocoagulation • previous yttrium aluminium garnet (YAG) laser • laser retinopexy for retinal tears • fibrovascular proliferation with retinal traction • other cause of retinal NV (retinal vein occlusion, radiation retinopathy, or others); • atrophy/scarring/fibrosis/hard exudates involving the center of the • macula. • DME with central involvement
Intervention(s)	ranibizumab (RBZ) 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP)
Comparator	PRP alone
Outcome measures	best-corrected visual acuity (BCVA) changes from baseline to month 12,
Number of participants	87
Duration of follow-up	12 months
Loss to follow-up	2 lost to follow up
Baseline characteristics	The duration of diabetes: Mean Age: The mean ages of participants in the RBZ+PRP groups were: 59 years (SD, 13) The mean ages of participants in the PRP monotherapy groups were: 52 years (SD, 12) Male to female ratio: RBZ+PRP groups:32% were women. PRP monotherapy groups: 41% were women

Sao Paulo B 2011

Bibliographic Reference	Lucena CR, Ramos Filho JA, Messias AM, Silva JA, Almeida FP, Scott IU, Ribeiro JA, Jorge R. Panretinal photocoagulation versus intravitreal injection retreatment pain in high-risk proliferative diabetic retinopathy. Arq Bras Oftalmol. 2013 Jan-Feb;76(1):18-20. doi: 10.1590/s0004-27492013000100006. PMID: 23812521.

Study details

Study type	Randomised controlled trial (RCT)
Study location	Brazil

Study setting	School of Medicine of Ribeirão Preto,
Sources of funding	Supported by CNPq: Grant number: 306692/2008-2.
Inclusion criteria	• all adult patients with treatment-naive PDR • best-corrected visual acuity (BCVA) better than 20/800
Exclusion criteria	• presence of advanced PDR (i.e., vitreous haemorrhage • traction retinal detachment
Intervention(s)	Ranibizumab (+PRP)
Comparator	PRP
Outcome measures	• BCVA • pain
Number of participants	33
Duration of follow-up	1 year
Loss to follow-up	3 lost to follow up
Baseline characteristics	PRP group Mean ± SD age (years) 63.5 ± 8.9. HbA1c (%): 9.3 ± 1.1 disease duration (years)12.9 ± 8.8 PRP plus group mean ± SD age (years) 51.1 ± 11.3. HbA1c (%): 9.1 ± 0.8 disease duration (years) 14.7 ± 6.9)

Sao Paulo A 2018

Bibliographic Reference	Barroso RMP, Messias K, Garcia DM, Cardillo JA, Scott IU, Messias A, Jorge R. ETDRS panretinal photocoagulation combined with intravitreal ranibizumab versus PASCAL panretinal photocoagulation with intravitreal ranibizumab versus intravitreal ranibizumab alone for the treatment of proliferative diabetic retinopathy. Arq Bras Oftalmol. 2020 Nov-Dec;83(6):526-534. doi: 10.5935/0004-2749.20200096. PMID: 33470281.

Study details

Study type	Randomised controlled trial (RCT)
Study location	Brazil

Study setting	Faculty of Medicine of Ribeirão Preto, University of São Paulo
Sources of funding	not detailed
Inclusion criteria	• all adult patients with high-risk PDR • presence of NVD associated with vitreous or pre-retinal haemorrhage,
Exclusion criteria	• history of prior laser or vitrectomy • myocardial infarction • uncontrolled hypertension
Intervention(s)	Ranibizumab (+PRP, ETRDS)
Comparator	Ranibizumab (+PRP, PASCAL)
Outcome measures	• BCVA
Number of participants	50
Duration of follow-up	1 year
Loss to follow-up	20
Baseline characteristics	The duration of diabetes: 11.3 ± 2.6 Mean Age: 58.5 ± 3.1 Male to female ratio:

D.1.2 Systematic Review

Bibliographic Reference

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

Study Characteristics

Study design	Systematic review

Study details	Dates searched up to July 2022
Inclusion criteria	Randomised controlled trials comparing anti-VEGF to PRP in people with diabetic retinopathy (non-proliferative or proliferative diabetic retinopathy).
Exclusion criteria	Studies which included patients with a principal indication for treatment of diabetic macular oedema or vitreous haemorrhage.
Intervention(s)	Anti-VEGFs (aflibercept, bevacizumab or ranibizumab) Panretinal photocoagulation
Outcome(s)	• Best corrected visual acuity (BCVA) measured on ETDRS or logMAR scales. • Functional impact on vision, number of treatments, need for subsequent treatment, complications and adverse events, progression, peripheral vision changes, treatment withdrawal, quality of life
Number of studies included in the systematic review	16 studies
Studies from the systematic review that are relevant for use in the current review	• CLARITY • DRCRN • Protocol W • PANORAMA • RECOVERY • Marashi • Ahmad • Ali • Rebecca • Roohipour • DRCRN Protocol S • Ferraz • PRIDE • PROTEUS • Sao Paulo B • Sao Paulo A
Studies from the systematic review that are not relevant for use in the current review	None
Additional comments	Summary details of included RCTs available in summary and full evidence tables and risk of bias assessments can be found in Simmonds et al. (2023)

Critical appraisal - GDT Crit App - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low *(No concerns with study eligibility criteria, search strategy, data collection or data synthesis)*
Overall study ratings	Applicability as a source of data	Directly applicable

Appendix E – Forest plots

Forest plots are presented in the Simmonds et al. (2023) review. See the supplementary file for all published data analyses for BCVA and the supplementary file for all published data analyses for outcomes other than BCVA.

Appendix F – GRADE tables

F.1 Network meta-analyses

People with proliferative diabetic retinopathy

Table 18. Change in visual acuity (logMAR) relative to panretinal photocoagulation

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Quality
Change in visual acuity (logMAR) relative to panretinal photocoagulation (up to 1 year)							
11	RCT	827	See section 1.1.6 and Simmonds (2023)	High[1]	No serious	N/A	Low
Change in visual acuity (logMAR) relative to panretinal photocoagulation (between 1 to 2 years)							
6	RCT	651	See section 1.1.6 and Simmonds (2023)	High[1]	No serious	N/A	Low
Change in visual acuity (logMAR) relative to panretinal photocoagulation (up to 2 years)							
12	RCT	1155	See section 1.1.6 and Simmonds (2023)	High[1]	No serious	N/A	Low

1. Greater than 33.3% of studies in the NMA at high risk of bias

F.2 Pairwise meta-analysis

People with proliferative diabetic retinopathy

Table 19: Anti-VEGF vs panretinal photocoagulation: Incidence of proliferative diabetic retinopathy

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Aflibercept vs panretinal photocoagulation – proliferative diabetic retinopathy (1 year)									
1 (CLARITY)	Parallel RCT	232	RR: 3.08 (0.13, 74.84)	0 per 1000[2]	0 per 1000 (0 more to 0 more)	No serious	n/a	No serious	High
Aflibercept vs panretinal photocoagulation (2 years) – non-proliferative diabetic retinopathy									
1 (Protocol W)	Parallel RCT	328	RR: 0.38 (0.24, 0.60)	286 per 1000	177 fewer per 1000 (217 fewer to 114 fewer)	No serious	n/a	No serious	High
Ranibizumab vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (PRIDE)	Parallel RCT	106	RR: 3.00 (0.65, 13.86)	57 per 1000	114 more per 1000 (20 fewer to 733 more)	Very serious [1]	n/a	No serious	Low
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (PRIDE)	Parallel RCT	106	RR: 2.43 (0.50, 11.71)	57 per 1000	82 more per 1000 (28 fewer to 610 more)	Very serious [1]	n/a	No serious	Low

1. Study downgraded by two increments for high risk of bias due to missing data and measurement of outcome
2. Zero events in control arm reported

Table 20: Anti-VEGF vs panretinal photocoagulation: Need for additional treatments (vitrectomy)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Aflibercept vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (CLARITY)	Parallel RCT	232	RR: 0.15 (0.02, 1.17)	63 per 1000	54 fewer per 1000 (62 fewer to 11 more)	No serious	n/a	No serious	High
Aflibercept vs panretinal photocoagulation (2 years) – non-proliferative diabetic retinopathy									
1 (Protocol W)	Parallel RCT	328	RR: 0.33 (0.01, 8.09)	5 per 1000	3 fewer per 1000 (5 fewer to 35 more)	No serious	n/a	No serious	High
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (PRIDE)	Parallel RCT	106	RR: 1.46 (0.26, 8.21)	57 per 1000	26 more per 1000 (42 fewer to 411 more)	Very serious[1]	n/a	No serious	Low
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (PROTEUS)	Parallel RCT	87	RR: 2.15 (0.20, 22.79)	23 per 1000	26 more per 1000 (18 fewer to 501 more)	Very serious[1]	n/a	No serious	Low
Ranibizumab vs panretinal photocoagulation (2 years) – proliferative diabetic retinopathy									
1 (PROTOCOL S)	Parallel RCT	305	RR: 0.28 (0.13, 0.59)	179 per 1000	129 fewer per 1000 (156 fewer to 73 fewer)	No serious	n/a	No serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Ranibizumab vs panretinal photocoagulation (5 years) – proliferative diabetic retinopathy									
1 (PROTOCOL S)	Parallel RCT	305	RR 0.57 (0.35, 0.94)	192 per 1000	83 fewer per 1000 (125 fewer to 12 fewer)	No serious	n/a	No serious	High

1. Study downgraded by two increments for high risk of bias due to missing data and measurement of outcome

Table 21: Anti-VEGF vs panretinal photocoagulation: Complications and adverse events (vitreous haemorrhage)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Aflibercept vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (CLARITY)	Parallel RCT	232	RR: 0.49 (0.24, 0.99)	118 per 1000	96 fewer (per 1000 143 fewer to 2 fewer)	No serious	n/a	No serious	High
Aflibercept vs panretinal photocoagulation (2 years) – non-proliferative diabetic retinopathy									
1 (Protocol W)	Parallel RCT	328	RR: 0.99 (0.25, 3.92)	20 per 1000	0 more per 1000 (15 fewer to 58 more)	No serious	n/a	No serious	High
Ranibizumab vs panretinal photocoagulation (6 months) – proliferative diabetic retinopathy									
1 (Ferraz)	Parallel RCT	60	RR 0.47 (0.16, 1.38)	286 per 1000	152 fewer per 1000 (240 fewer to 109 more)	Serious[2]	n/a	No serious	Moderate
Ranibizumab vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (PRIDE)	Parallel RCT	106	RR 1.00 (0.07, 15.36)	29 per 1000	0 more per 1000 (27 fewer to 416 more)	Very serious[1]	n/a	No serious	Low
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (PRIDE)	Parallel RCT	106	RR: 0.97 (0.06, 14.94)	29 per 1000	1 fewer per 1000 (27 fewer to 404 more)	Very serious[1]	n/a	No serious	Low
1 (PROTEUS)	Parallel RCT	87	RR: 1.31 (0.61, 2.84)	205 per 1000	64 more per 1000 (80 fewer to 377 more)	Very serious[1]	n/a	No serious	Low
Ranibizumab vs panretinal photocoagulation (2 years) – proliferative diabetic retinopathy									
1 (PROTOCOL S)	Parallel RCT	305	RR 0.79 (0.59, 1.05)	411 per 1000	86 fewer per 1000 (169 fewer to 21 more)	No serious	n/a	No serious	High
Ranibizumab vs panretinal photocoagulation (5 years) – proliferative diabetic retinopathy									
1 (PROTOCOL S)	Parallel RCT	305	RR 1.04 (0.84, 1.28)	458 per 1000	18 more per 1000 (73 fewer to 128 more)	No serious	n/a	No serious	High
Bevacizumab vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (Marashi)	Parallel RCT	30	RR 3.00 (0.13, 68.09)	0 per 1000	0 per 1000(0 more to 0 more)	Very serious[1]	n/a	No serious	Low

1. Study downgraded by two increments for high risk of bias due to missing data and measurement of outcome.

2. Study downgraded by one increment for high risk of bias due to randomization and selective reporting.

Table 22: Anti-VEGF vs panretinal photocoagulation: Complications and adverse events (cataracts)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Aflibercept vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (CLARITY)	Parallel RCT	232	RR: 0.33 (0.01, 8.10)	9 per 1000	6 fewer per 1000 (9 fewer to 64 more)	No serious	n/a	No serious	High
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (PROTEUS)	Parallel RCT	87	RR: 5.36 (0.27, 108.42)	0 per 1000	0 per 1000 (0 more to 0 more)	Very serious[1]	n/a	No serious	Low
Ranibizumab vs panretinal photocoagulation (2 years) – proliferative diabetic retinopathy									
1 (PROTOCOL S)	Parallel RCT	305	RR: 0.87 (0.56, 1.33)	187 per 1000	24 fewer per 1000 (82 fewer to 62 more)	No serious	n/a	No serious	High

1. Study downgraded by two increments for high risk of bias due to missing data and measurement of outcome.

Table 23: Anti-VEGF vs panretinal photocoagulation: Complications and adverse events (raised intraocular pressure)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Aflibercept vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (CLARITY)	Parallel RCT	232	RR: 3.00 (0.12, 72.89)	0 per 1000	0 per 1000	No serious	n/a	No serious	High
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (PROTEUS)	Parallel RCT	87	RR: 0.80 (0.19, 3.38)	91 per 1000	18 fewer per 1000 (74 fewer to 217 more)	No serious	n/a	No serious	High
Ranibizumab vs panretinal photocoagulation (2 years) – proliferative diabetic retinopathy									
1 (PROTOCOL S)	Parallel RCT	305	RR: 0.89 (0.57, 1.38)	177 per 1000	19 fewer per 1000 (76 fewer to 67 more)	No serious	n/a	No serious	High

Table 24: Anti-VEGF vs panretinal photocoagulation: Complications and adverse events (retinal detachment)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Ranibizumab with panretinal photocoagulation vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
1 (PROTEUS)	Parallel RCT	232	RR: 0.21 (0.01, 4.34)	45 per 1000	36 fewer per 1000 (45 fewer to 150 more)	No serious	n/a	No serious	High
Ranibizumab vs panretinal photocoagulation (2 years) – proliferative diabetic retinopathy									
1 (PROTOCOL S)	Parallel RCT	305	RR: 0.43 (0.22, 0.81)	148 per 1000	84 fewer per 1000	No serious	n/a	No serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
					(115 fewer to 28 fewer)				
Aflibercept vs panretinal photocoagulation (2 years) – non-proliferative diabetic retinopathy									
1 (Protocol W)	Parallel RCT	328	RR: 0.99 (0.14, 6.94)	16 per 1000	0 more per 1000 (14 fewer to 95 more)	No serious	n/a	No serious	High

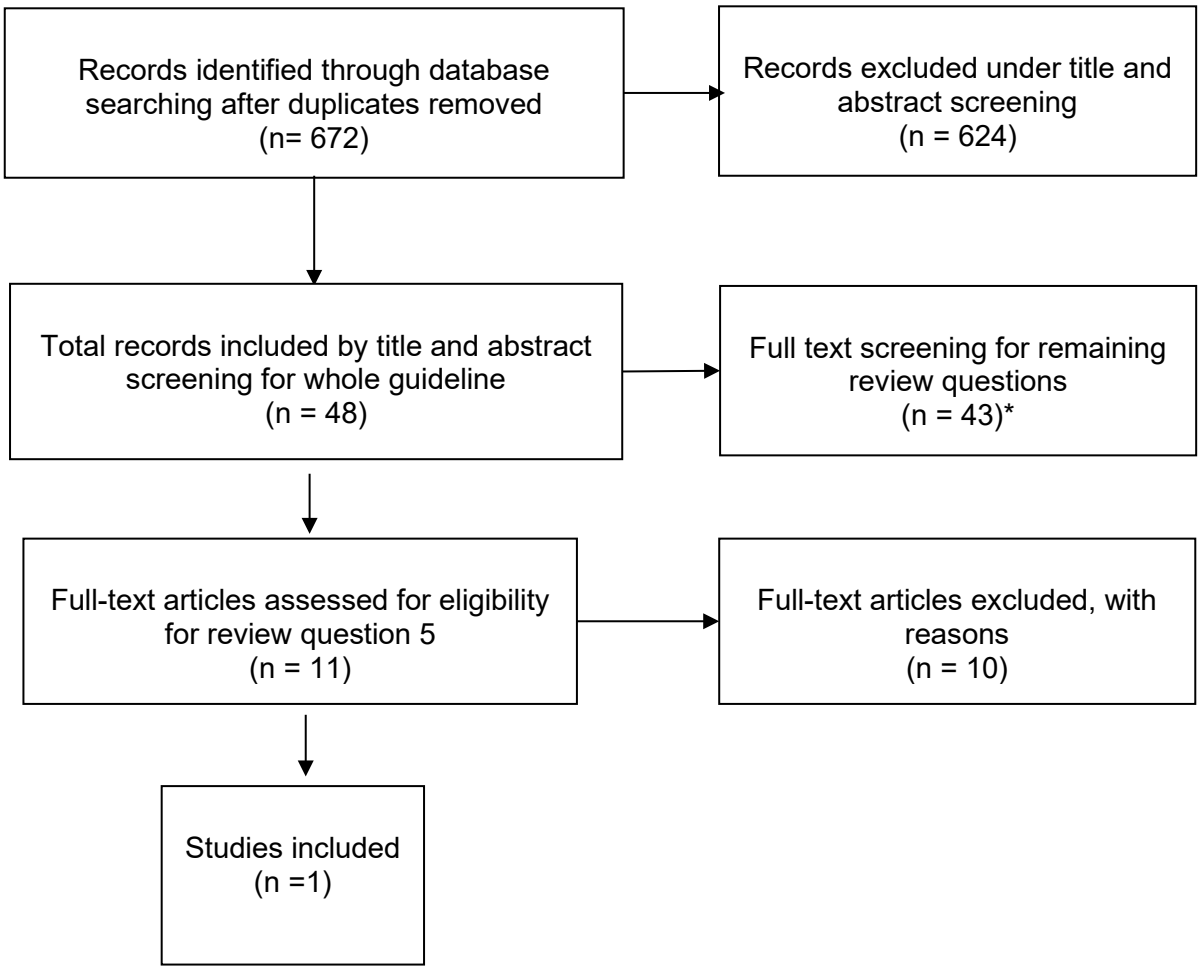
People with non-proliferative diabetic retinopathy

Table 25. Change in visual acuity (logMAR) relative to panretinal photocoagulation (up to 2 years)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Aflibercept vs panretinal photocoagulation (1 year) – proliferative diabetic retinopathy									
2 (PANORAMA, PROTOCOL W)	Parallel RCT	730	MD: -0.02 (-0.05, 0.01)	-	-	Serious[1]	No serious	No serious	Moderate

1.Study downgraded by one increment for high risk of bias due to missing outcome data and measurement of outcome.

Appendix G – Economic evidence study selection



* Note this number is higher than (total – includes) as some papers were included in multiple review questions

Appendix H – Economic evidence tables

Table 26: Economic evidence table

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
Hutton et al (2019)	Cost-utility analysis over a 10-year time horizon The model methods were not clearly explained, but beyond the 5-year study period outcomes were simulated up to 10 years and were informed by assumptions only	US study Health system perspective	Ranibizumab (as frequently as every 4 weeks based on structured re-treatment protocol) Pan-retinal photocoagulation (PRP) at baseline	Adults diagnosed with proliferative diabetic retinopathy, with or without centre-involving diabetic macular oedema (DMO) at baseline. Only the results for the population without centre-involving DMO are presented here because the population of interest is proliferative diabetic retinopathy without macular oedema. Baseline characteristics: Mean age 53 years; Female 43%; White 73%.	Outcomes in the first 5 years were taken from the protocol S study. Data on resource use was taken from the trial and costs were applied to those resources from the 2018 Medicare fee schedule of allowable charges. Utility data was based on visual acuity in the best-seeing eye. Utility was attached to visual acuity in the model although it was not clear how visual acuity was modelled over time. Adverse events were also modelled. 10-year time horizon; Costs and QALYs were discounted at 3% per year.	Absolute costs: PRP: $9,509 (£6,628*) Ranibizumab: $53,183 (£37,069*) Absolute QALYs: PRP: 0.040 Ranibizumab: 0.098 ICER: $742,202 (£517,315*) per QALY gained	A sensitivity analysis including adverse event costs found that the ICERs increased slightly. The 1-way sensitivity analysis in those without baseline centre-involving DMO, ranibizumab was not likely to be cost-effective. The ICER decreased when numbers of ranibizumab injections were decreased to 1.5 annually after the 5th year. In probabilistic analysis there was only a 9% chance that ranibizumab injections would be cost effective vs PRP even at a very high threshold of $250,000/QALY.	This study was supported by grants EY23207 and EY18817 through a cooperative agreement from the NEI and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH), US Department of Health and Human Services. There was no mention of health inequalities in the study. Limitations included a large proportion of trial participants lost to follow-up, use of visual acuity as a surrogate outcome for quality of life, utility being anchored at perfect vision vs perfect health.

**Costs have been converted from dollars to pounds using EPPI-Centre Cost Converter https://eppi.ioe.ac.uk/costconversion/default.aspx*
CI-DMO, centre involving diabetic macular oedema; NEI, National eye institute; PRP, panretinal photocoagulation.;

Table 27: Economic evaluation checklist

Study identification **Hutton et al. (2019) Five-Year Cost-effectiveness of Intravitreous Ranibizumab Therapy vs Panretinal Photocoagulation for Treating Proliferative Diabetic Retinopathy**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	People diagnosed with proliferative diabetic retinopathy.
1.2 Are the interventions appropriate for the review question?	Yes	Intravitreous ranibizumab (0.5mg) vs. Pan-retinal photocoagulation (PRP)
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US study
1.4 Is the perspective for costs appropriate for the review question?	Yes	Health care system perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	Health care system perspective
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Costs and QALYs were discounted at 3% annually.
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	QALYs derived using utility values from a TTO approach directly related to visual acuity.
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Unclear	It was unclear how the model was structured. The study implies the first 5 years are taken directly from the trial observed data, and the 5- to 10-year period was simulated but it was unclear how this was done.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	The cost-effectiveness analysis is over 10 years, with patients entering the model at an average of 53 years old.
2.3 Are all important and relevant outcomes included?	Yes	ICER, BCVA, resource utilisation.

Study identification Hutton et al. (2019) Five-Year Cost-effectiveness of Intravitreous Ranibizumab Therapy vs Panretinal Photocoagulation for Treating Proliferative Diabetic Retinopathy		
Category	**Rating**	**Comments**
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	From the trial and then extrapolated using assumptions.
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	From the trial.
2.6 Are all important and relevant costs included?	Yes	Physician and facility fees, drug costs, clinic visits, diagnostic procedures, adverse events.
2.7 Are the estimates of resource use from the best available source?	Yes	From the trial data for the first 5 years and further outcomes simulated based on assumptions.
2.8 Are the unit costs of resources from the best available source?	Yes	Based on the 2018 Medicare fee schedule of allowable charges, and literature.
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	One-way and two-way sensitivity analyses were conducted for some key parameters, and probabilistic analysis was also conducted.
2.11 Has no potential financial conflict of interest been declared?	Yes	Drs Hutton and Sun reported receiving grants from the JAEB Center for Health Research. Drs Stein, Glassman, and Jampol reported receiving grants from the National Eye Institute (NEI). Dr Glassman also reported receiving grants from Genentech and Regeneron and nonfinancial support from Regeneron. Dr Bressler reported receiving grants from Bayer, Genentech/Roche, Novartis, and Samsung Bioepis. Dr Sun also reported receiving grants from Boehringer Ingelheim, Genentech/Roche, and JDRF; equipment loaned for research from Adaptive Sensory Technologies, Boston Micromachines, and Optovue; nonfinancial support from Boerhinger Ingelheim, Genentech/Roche, Merck, Novartis, and Novo Nordisk; and personal fees from Current Diabetes Reports (as the diabetic retinopathy section editor, 2008-2017), JAMA Ophthalmology (as CME editor), Merck, and Novartis.
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	**IT IS UNCLEAR WHAT THE MODEL STRUCTURE WAS AND THEREFORE LIMITED ON THE QUALITY OF THE ANALYSIS.**

Appendix I – Health economic model

A de novo economic analysis was conducted for this review question and is detailed in the economic model report for review E.

Appendix J – Excluded studies

Effectiveness evidence

Reasons for study exclusion from Simmonds et al. (2023)

Excluded studies	Reasons for exclusion
Bayer A G. An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg aflibercept administered by intr.	- RCT of diabetic macular oedema
Braimah I Z, Kenu E and Amissah-Arthur K N; Akafo S ; Kwarteng K O; Amoaku W M;. (2019). Safety of intravitreal ziv-aflibercept in choroido-retinal vascular diseases: A randomised double-blind intervention study. *PLoS ONE [Electronic Resource]*, 14(10), pp.e0223944.	- RCT of diabetic macular oedema
Bressler S B, Qin H, Beck R W; Chalam K V; Kim J E; Melia M ; Wells J A; 3rd ; Diabetic Retinopathy Clinical Research and Network;. (2012). Factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab. *Archives of Ophthalmology*, 130(9), pp.1153-61.	- RCT of diabetic macular oedema
Bressler S B, Qin H, Melia M ; Bressler N M; Beck R W; Chan C K; Grover S ; Miller D G; Diabetic Retinopathy Clinical Research and Network;. (2013). Exploratory analysis of the effect of intravitreal ranibizumab or triamcinolone on worsening of diabetic retinopathy in a randomized clinical trial. *JAMA Ophthalmology*, 131(8), pp.1033-40.	- RCT of diabetic macular oedema
Bressler S B, Liu D, Glassman A R; Blodi B A; Castellarin A A; Jampol L M; Kaufman P L; Melia M ; Singh H ; Wells J A; Diabetic Retinopathy Clinical Research and Network;. (2017). Change in Diabetic Retinopathy Through 2 Years: Secondary Analysis of a Randomized Clinical Trial Comparing Aflibercept, Bevacizumab, and Ranibizumab. *JAMA Ophthalmology*, 135(6), pp.558-568.	- RCT of diabetic macular oedema
Dep of Ophthalmology and Medical University of Vienna. *A randomized, double-masked study with intraocular Bevacizumab (Avastin®) compared with intravitreal Ranibizumab (Lucentis®) in patients with persistent diabetic macular edema or persistent active*. [online] . Available at: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-001469-28.	- RCT of diabetic macular oedema
Dhoot D, Hill L and Tarnowski K ; Stoilov I ;. (2018). Baseline factors associated with >= 2-step diabetic retinopathy (DR) severity improvement with ranibizumab (RBZ). *Investigative Ophthalmology and Visual Science. Conference*, 59(9).	- RCT of diabetic macular oedema
Dhoot D S, Hill L F; Ghanekar A and Tarnowski K W; Ali F S;. (2021). Baseline Factors Associated with Diabetic Retinopathy Improvement in RIDE/RISE. *Ophthalmology Retina*, 5(1), pp.101-103.	- RCT of diabetic macular oedema

Excluded studies	Reasons for exclusion
Dhoot D S, Moini H and Reed K ; Du W ; Vitti R ; Berliner A J; Singh R P;. (2022). Functional outcomes of sustained improvement on Diabetic Retinopathy Severity Scale with intravitreal aflibercept in the VISTA and VIVID trials. *Eye*, 19, pp.19.	- RCT of diabetic macular oedema
Dimitriou E, Theodossiadis P and Chatzirallis A ; Kazantzis D ; Theodossiadis G ; Chatziralli E ;. (2020). Intravitreal ranibizumab alone or in combination with panretinal photocoagulation for the treatment of proliferative diabetic retinopathy with coexistent macular edema: Long-term outcomes in real-life data. *Investigative Ophthalmology and Visual Science. Conference*, 61.	- RCT of diabetic macular oedema
Ekinci M, Ceylan E and Cakici O ; Tanyildiz B ; Olcaysu O ; Cagatay H H;. (2014). Treatment of macular edema in diabetic retinopathy: Comparison of the efficacy of intravitreal bevacizumab and ranibizumab injections. *Expert Review of Ophthalmology*, 9(2), pp.139-143.	- RCT of diabetic macular oedema
Euctr-009909-25-De . (2009). Evaluation of the efficacy and safety of a Macugen monotherapy versus Combined Therapies in the Treatment of Diabetic Retinopathy – a single centre, randomized, prospective Phase II trial. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-009909-25-DE*	- RCT of diabetic macular oedema
Glassman A R, Stockdale C R; Beck R W; Baker C, Bressler N M; Diabetic Retinopathy Clinical Research and Network;. (2012). Evaluation of masking study participants to intravitreal injections in a randomized clinical trial. *Archives of Ophthalmology*, 130(2), pp.190-4.	- RCT of diabetic macular oedema
Gonzalez V H. (2006). Pegaptanib in Diabetic Retinopathy: improvements in Diabetic Macular Edema, Retinal Neovascularization, and Diabetic Retinopathy Severit. *American academy of ophthalmology*, pp.192.	- RCT of diabetic macular oedema
Gonzalez V H and Wang P W; Ruiz C Q;. (2019). Panretinal Photocoagulation for Diabetic Retinopathy in the RIDE and RISE Trials: Not "1 and Done". *Ophthalmology*, 21, pp.21.	- RCT of diabetic macular oedema
Gonzalez V H and Wang P W; Ruiz C Q;. (2021). Panretinal Photocoagulation for Diabetic Retinopathy in the RIDE and RISE Trials: Not "1 and Done". *Ophthalmology*, 128, pp.1448-1457.	- RCT of diabetic macular oedema
Hassan M, Sadiq M A and Halim M S; Afridi R ; Nguyen N V; Sepah Y J;. (2018). Short-Term Effects of Ranibizumab on Diabetic Retinopathy Severity and Progression. *Ophthalmology Retina*, 2(7), pp.749-751.	- RCT of diabetic macular oedema
Hassan M, Sadiq M A and Halim M S; Afridi R ; Nguyen N V; Sepah Y J;. (2018). Short-term effects of ranibizumab on diabetic retinopathy severity and progression in the ranibizumab for edema of the macula in diabetes - Protocol 3 with high dose (READ-3) study. *Investigative Ophthalmology and Visual Science. Conference*, 59(9).	- RCT of diabetic macular oedema

Excluded studies	Reasons for exclusion
Irct201205029617N . (2012). Efficacy of Macular laser Photocoagulation with or without Intravitreal Injection of Bevacizumab (Avastin) or Triamcinolone Acetonide for Diffuse Diabetic Macular Edema. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201205029617N1*	- RCT of diabetic macular oedema
Mehta H, Lim L L and Nguyen V ; Qatarneh D ; Wickremasinghe S S; Hodgson L A. B; Quin G J; McAllister I L; Gillies M C; Fraser-Bell S ;. (2019). Development of New Proliferative Diabetic Retinopathy in the BEVORDEX Trial. *Ophthalmology Retina*, 3(3), pp.286-287.	- RCT of diabetic macular oedema
Mitchell P, McAllister I and Larsen M ; Staurenghi G ; Korobelnik J F; Boyer D S; Do D V; Brown D M; Katz T A; Berliner A ; Vitti R ; Zeitz O ; Metzig C ; Lu C ; Holz F G;. (2018). Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies. *Ophthalmology Retina*, 2(10), pp.988-996.	- RCT of diabetic macular oedema
Nct (2007). Laser-Ranibizumab-Triamcinolone for Proliferative Diabetic Retinopathy. *https://clinicaltrials.gov/show/NCT00445003*	- RCT of diabetic macular oedema
Nct. (2009). Anterior and Posterior Segment Vascular Changes Following Laser and Anti-Vascular Endothelial Growth Factor (VEGF) Treatment of Diabetic Retinopathy.	- RCT of diabetic macular oedema
Nct (2015). Laser Therapy Combined With Intravitreal Aflibercept vs Intravitreal Aflibercept Monotherapy (LADAMO). *https://clinicaltrials.gov/show/NCT02432547*	- RCT of diabetic macular oedema
Novartis Pharma and A G . A 12-Month, 2-Arm, Randomized, Double-Masked, Multicenter Phase III Study Assessing the Efficacy and Safety of Brolucizumab every 4 weeks versus Aflibercept every 4 weeks in Adult Patients with Vis.	- RCT of diabetic macular oedema
Novartis Pharma Gmb and H . A randomized, single-blinded, multicenter, phase IV study to compare systemic VEGF protein dynamics following monthly intravitreal injections of 0.5 mg ranibizumab versus 2 mg aflibercept until stu.	- RCT of diabetic macular oedema
Novartis Pharma and A G . A Two-Year, Three-Arm, Randomized, Double Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to D.	- RCT of diabetic macular oedema
Novartis Pharma and A G . A Two-Year, Two-Arm, Randomized, Double Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Dia.	- RCT of diabetic macular oedema
Oxurion N V. A Phase 2, randomised, single-masked, active-controlled, multicentre study to evaluate the efficacy and safety of intravitreal THR-317 administered in combination with ranibizumab, for the treatmen.	- RCT of diabetic macular oedema

Excluded studies	Reasons for exclusion
Quark Pharmaceuticals and Inc . An Open-Label Dose Escalation Study of PF-04523655 (Stratum I) Combined With A Prospective, Randomized, Double-Masked, Multi-Center, Controlled Study (Stratum II) Evaluating The Efficacy and Safety.	- RCT of diabetic macular oedema
Sadiq M A, Hassan M and Soliman M K; Afridi R ; Do D V; Nguyen Q D; Sepah Y J;. (2017). Effects of Two Different Doses of Ranibizumab on Diabetic Retinopathy Severity. *Ophthalmology Retina*, 1(6), pp.566-567.	- RCT of diabetic macular oedema
Sameen M, Khan M S and Mukhtar A ; Yaqub M A; Ishaq M ;. (2017). Efficacy of intravitreal bevacizumab combined with pan retinal photocoagulation versus panretinal photocoagulation alone in treatment of proliferative diabetic retinopathy. *Pakistan Journal of Medical Sciences*, 33(1), pp.142-145.	- RCT of diabetic macular oedema
Sasongko M B, Rogers S and Constantinou M ; Sandhu S S; Wickremasinghe S S; Al-Qureshi S ; Lim L L;. (2020). Diabetic retinopathy progression 6 months post-cataract surgery with intravitreous bevacizumab vs triamcinolone: A secondary analysis of the DiMECAT trial. *Clinical & Experimental Ophthalmology*, 48(6), pp.793-801.	- RCT of diabetic macular oedema
Shahraki T, Arabi A and Nourinia R ; Beheshtizadeh N F; Entezari M ; Nikkhah H ; Karimi S ; Ramezani A ;. (2022). Panretinal photocoaguliation versus intravitreal bevacizumab versus a proposed modified combination therapy for treatment of proliferative diabetic retinopathy: A Randomized Three-Arm Clinical Trial (CTPDR Study). *Retina*, 42, pp.1065-1076.	- RCT of diabetic macular oedema
Yan P, Qian C and Wang W ; Dong Y ; Wan G ; Chen Y ;. (2016). Clinical effects and safety of treating diabetic macular edema with intravitreal injection of ranibizumab combined with retinal photocoagulation. *Therapeutics & Clinical Risk Management*, 12, pp.527-33.	- RCT of diabetic macular oedema
Ahmadieh H, Shoeibi N and Entezari S M;. (2008). Intravitreal Bevacizumab for Early Post-vitrectomy Hemorrhage in Diabetics: a Randomized, DoubleMasked Clinical Trial. *American academy of ophthalmology*, pp.181.	- RCT of vitreous haemorrhage or vitrectomy
Ahmadieh H, Shoeibi N and Entezari M ; Monshizadeh R ;. (2009). Intravitreal bevacizumab for prevention of early postvitrectomy hemorrhage in diabetic patients: a randomized clinical trial. *Ophthalmology*, 116(10), pp.1943-8.	- RCT of vitreous haemorrhage or vitrectomy
Ahn J, Woo S J and Chung H ; Park K H;. (2011). The effect of adjunctive intravitreal bevacizumab for preventing postvitrectomy hemorrhage in proliferative diabetic retinopathy. *Ophthalmology*, 118(11), pp.2218-26.	- RCT of vitreous haemorrhage or vitrectomy
Albuquerque T L and Pierozzi G S; Araujo A C. C; Neto N H; Carregal T B; Martins M C; Souza J C; Carlos G A; Bordon A F;. (2014). Comparative, randomized, double blinded study of the use of Anti-VEGF in patients with vitreous hemorrhage or tractional retinal detachment secondary to diabetic retinopathy. *Investigative Ophthalmology and Visual Science*, 55 (13), pp.4391.	- RCT of vitreous haemorrhage or vitrectomy

Excluded studies	Reasons for exclusion
Aleman I, Castillo Velazquez and J ; Rush S W; Rush R B;. (2019). Ziv-aflibercept versus bevacizumab administration prior to diabetic vitrectomy: a randomised and controlled trial. *British Journal of Ophthalmology*, 103(12), pp.1740-1746.	- RCT of vitreous haemorrhage or vitrectomy
Arevalo J F, Lasave A F; Kozak I and Al Rashaed S ; Al Kahtani E ; Maia M ; Farah M E; Cutolo C ; Brito M ; Osorio C ; Navarro P ; Wu L ; Berrocal M H; Morales-Canton V ; Serrano M A; Graue-Wiechers F ; Sabrosa N A; Alezzandrini A A; Gallego-Pinazo R ; Pan-American Collaborative Retina Study; Group ;. (2019). Preoperative Bevacizumab for Tractional Retinal Detachment in Proliferative Diabetic Retinopathy: A Prospective Randomized Clinical Trial. *American Journal of Ophthalmology*, 207, pp.279-287.	- RCT of vitreous haemorrhage or vitrectomy
Bhavsar A. (2013). A Randomized trial evaluating intravitreal ranibizumab or intravitreal saline for vitreous hemorrhage from proliferative diabetic retinopathy. *Investigative Ophthalmology and Visual Science. Conference*, 54(15).	- RCT of vitreous haemorrhage or vitrectomy
Bhavsar A R, Torres K and Beck R W; Friedman S M; Glassman A R; Maturi R K; Melia M ; Singer M A; Stockdale C R; Diabet Retinopathy Clin Res; Networ ;. (2013). Randomized Clinical Trial Evaluating Intravitreal Ranibizumab or Saline for Vitreous Hemorrhage From Proliferative Diabetic Retinopathy Diabetic Retinopathy Clinical Research Network. *Jama Ophthalmology*, 131(3), pp.283-293.	- RCT of vitreous haemorrhage or vitrectomy
Castillo J, Aleman I and Rush S W; Rush R B;. (2017). Preoperative Bevacizumab Administration in Proliferative Diabetic Retinopathy Patients Undergoing Vitrectomy: A Randomized and Controlled Trial Comparing Interval Variation. *American Journal of Ophthalmology*, 183, pp.1-10.	- RCT of vitreous haemorrhage or vitrectomy
Castillo Velazquez, J and Aleman I ; Rush S W; Rush R B;. (2018). Bevacizumab before Diabetic Vitrectomy: A Clinical Trial Assessing 3 Dosing Amounts. *Ophthalmology Retina*, 2(10), pp.1010-1020.	- RCT of vitreous haemorrhage or vitrectomy
Chelala E, Nehme J and El Rami H ; Aoun R ; Dirani A ; Fadlallah A ; Jalkh A ;. (2018). Efficacy of Intravitreal Ranibizumab Injections in the Treatment of Vitreous Hemorrhage Related to Proliferative Diabetic Retinopathy. *Retina*, 38(6), pp.1127-1133.	- RCT of vitreous haemorrhage or vitrectomy
ChiCtr . (2018). Feasibility study of anti-VEGF instead of intraoperative PRP in proliferative diabetic retinopathy. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1800017448*	- RCT of vitreous haemorrhage or vitrectomy
ChiCtr . (2020). A prospective and randomized controlled clinical study for pre- and after-operative intravitreal injection of anti-VEGF combined with pars plana vitrectomy. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000029884*	- RCT of vitreous haemorrhage or vitrectomy
ChiCtr . (2021). A prospective randomized controlled study of long-acting dexamethasone implant to improve the prognosis of PDR patients after vitrectomy. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2100043399*	- RCT of vitreous haemorrhage or vitrectomy

Excluded studies	Reasons for exclusion
ChiCTR1800019455 . (2018). *Effects of intraocular injection of different anti-VEGF drugs on inflammatory factors in aqueous humor of patients with diabetic retinopathy*.	- RCT of vitreous haemorrhage or vitrectomy
ChiCTR2000035032 . (2020). *Efficacy of different doses of anti-VEGF with vitrectomy in the treatment of proliferative diabetic retinopathy*.	- RCT of vitreous haemorrhage or vitrectomy
Comyn O and Bainbridge J W. B. (2014). A pilot randomized controlled trial of ranibizumab pre-treatment for diabetic vitrectomy (The RaDiVit study). *Investigative Ophthalmology and Visual Science*, 55 (13), pp.2302.	- RCT of vitreous haemorrhage or vitrectomy
Comyn O, Wickham L and Charteris D G; Sullivan P M; Ezra E ; Gregor Z ; Aylward G W; da Cruz L ; Fabinyi D ; Peto T ; Restori M ; Xing W ; Bunce C ; Hykin P G; Bainbridge J W;. (2017). Ranibizumab pretreatment in diabetic vitrectomy: a pilot randomised controlled trial (the RaDiVit study). *Eye*, 31(9), pp.1253-1258.	- RCT of vitreous haemorrhage or vitrectomy
Comyn O, Lange C and Bainbridge J W. B;. (2019). Vitreous and plasma cytokine levels in subjects with advanced proliferative diabetic retinopathy in the Ranibizumab in Diabetic Vitrectomy (RaDiVit) Study. *Investigative Ophthalmology and Visual Science. Conference*, 60(9).	- RCT of vitreous haemorrhage or vitrectomy
Cui J, Chen H and Lu H ; Dong F ; Wei D ; Jiao Y ; Charles S ; Gu W ; Wang L ;. (2018). Efficacy and Safety of Intravitreal Conbercept, Ranibizumab, and Triamcinolone on 23-Gauge Vitrectomy for Patients with Proliferative Diabetic Retinopathy. *Journal of ophthalmology*, 2018, pp.4927259.	- RCT of vitreous haemorrhage or vitrectomy
da R Lucena D and Ribeiro J A; Costa R A; Barbosa J C; Scott I U; de Figueiredo-Pontes L L; Jorge R. (2009). Intraoperative bleeding during vitrectomy for diabetic tractional retinal detachment with versus without preoperative intravitreal bevacizumab (IBeTra study). *British Journal of Ophthalmology*, 93(5), pp.688-91.	- RCT of vitreous haemorrhage or vitrectomy
di Lauro R, De Ruggiero P and di Lauro R ; di Lauro M T; Romano M R;. (2010). Intravitreal bevacizumab for surgical treatment of severe proliferative diabetic retinopathy. *Graefes Archive for Clinical & Experimental Ophthalmology*, 248(6), pp.785-91.	- RCT of vitreous haemorrhage or vitrectomy
Diabetic Retinopathy Clinical Research and Network. (2013). Randomized clinical trial evaluating intravitreal ranibizumab or saline for vitreous hemorrhage from proliferative diabetic retinopathy. *JAMA Ophthalmology*, 131(3), pp.283-93.	- RCT of vitreous haemorrhage or vitrectomy
Dong F, Yu C and Ding H ; Shen L ; Lou D ;. (2016). Evaluation of Intravitreal Ranibizumab on the Surgical Outcome for Diabetic Retinopathy With Tractional Retinal Detachment. *Medicine*, 95(8), pp.e2731.	- RCT of vitreous haemorrhage or vitrectomy
Dong X. (2019). Effect of ranibizumab on the efficacy of vitrectomy in patients with PDR. [Chinese] Pdr. *International Eye Science*, 19(5), pp.809-812.	- RCT of vitreous haemorrhage or vitrectomy

Excluded studies	Reasons for exclusion
Luo. (2019). Effect of ranibizumab combined with vitrectomy on the serum VEGF-A and SDF-1 expression in patients with proliferative diabetic retinopathy. *International eye science*, 19(3), pp.438-441.	- RCT of vitreous haemorrhage or vitrectomy
Euctr-000780-21-Gb . (2007). A randomised, single-masked, Phase IV pilot study of the efficacy and safety of adjunctive intravitreal Avastin® (bevacizumab) in the prevention of early postoperative vitreous haemorrhage following diabetic vitrectomy - Intravitreal Avastin® in diabetic vitrectomy. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2007-000780-21-GB*	- RCT of vitreous haemorrhage or vitrectomy
Euctr-015559-25-Gb . (2010). Preoperative intravitreal ranibizumab for persistent diabetic vitreous haemorrhage: a randomized, double-masked, controlled study - Vitreous Haemorrhage Study. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-015559-25-GB*	- RCT of vitreous haemorrhage or vitrectomy
Euctr-024062-22-Gb . (2011). A prospective, randomised controlled trial of Ranibizumab pre-treatment in Diabetic Vitrectomy – a pilot study. - A pilot RCT of ranibizumab in diabetic vitrectomy - The RaDiVit Study. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2010-024062-22-GB*	- RCT of vitreous haemorrhage or vitrectomy
Farahvash M S, Majidi A R; Roohipoor R and Ghassemi F ;. (2011). Preoperative injection of intravitreal bevacizumab in dense diabetic vitreous hemorrhage. *Retina*, 31(7), pp.1254-60.	- RCT of vitreous haemorrhage or vitrectomy
Ferraz D A, Morita C and Preti R C; Nascimento V P; Maia O O; de Barros A C; SayuriTakahashi B ; Takahashi W Y;. (2013). Use of intravitreal bevacizumab or triamcinolone acetonide as a preoperative adjunct to vitrectomy for vitreous haemorrhage in diabetics. *Revista Brasileira De Oftalmologia*, 72(1), pp.12-16.	- RCT of vitreous haemorrhage or vitrectomy
Gao S, Lin Z and Chen Y ; Xu J ; Zhang Q ; Chen J ; Shen X ;. (2020). Intravitreal Conbercept Injection as an Adjuvant in Vitrectomy with Silicone Oil Infusion for Severe Proliferative Diabetic Retinopathy. *Journal of Ocular Pharmacology & Therapeutics*, 36(5), pp.304-310.	- RCT of vitreous haemorrhage or vitrectomy
Genovesi-Ebert F, Rizzo S and Di Bartolo E; Miniaci S ; Vento A ; Palla M ; Cresti F ;. (2007). Injection of Intravitreal Avastin Before Vitrectomy Surgery in the Treatment of Severe Proliferative Diabetic Retinopathy. *Iovs*, 48, pp.ARVO E-Abstract 5044.	- RCT of vitreous haemorrhage or vitrectomy
Glassman A R, Beaulieu W T; Maguire M G; Antoszyk A N; Chow C C; Elman M J; Jampol L M; Salehi-Had H and Sun J K; Network Drcr Retina;. (2021). Visual Acuity, Vitreous Hemorrhage, and Other Ocular Outcomes After Vitrectomy vs Aflibercept for Vitreous Hemorrhage Due to Diabetic Retinopathy: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Ophthalmology*, 139(7), pp.725-733.	- RCT of vitreous haemorrhage or vitrectomy
Han X X, Guo C M; Li Y and Hui Y N;. (2012). Effects of bevacizumab on the neovascular membrane of proliferative diabetic retinopathy: reduction of endothelial cells and	- RCT of vitreous haemorrhage or vitrectomy

Excluded studies	Reasons for exclusion
expressions of VEGF and HIF-1alpha. *Molecular Vision*, 18, pp.1-9.	
Hernandez-Da Mota S. E and Nunez-Solorio S M;. (2010). Experience with intravitreal bevacizumab as a preoperative adjunct in 23-G vitrectomy for advanced proliferative diabetic retinopathy. *European Journal of Ophthalmology*, 20(6), pp.1047-52.	- RCT of vitreous haemorrhage or vitrectomy
Hu B J, Zeng Q and Liu X L; Li X R; Song W J;. (2013). Influence of intravitreal avastin on the expression of cell factors in retinal proliferative membrane in proliferative diabetic retinopathy eye. [Chinese]. *Zhonghua Shiyan Yanke Zazhi/Chinese Journal of Experimental Ophthalmology*, 31(1), pp.55-59.	- RCT of vitreous haemorrhage or vitrectomy
Hu Z, Cao X and Chen L ; Su Y ; Ji J ; Yuan S ; Fransisca S ; Mugisha A ; Zou W ; Xie P ; Liu Q ;. (2021). Monitoring intraocular proangiogenic and profibrotic cytokines within 7 days after adjunctive anti-vascular endothelial growth factor therapy for proliferative diabetic retinopathy. *Acta Opthalmologica*, 14, pp.14.	- RCT of vitreous haemorrhage or vitrectomy
Jeon S and Lee W K. (2012). Intravitreal bevacizumab increases intraocular interleukin-6 levels at 1 day after injection in patients with proliferative diabetic retinopathy. *Cytokine*, 60(2), pp.535-9.	- RCT of vitreous haemorrhage or vitrectomy
Jiang T T and Gu J X; Zhang P J; Chen W W; Chang Q. (2020). The effect of adjunctive intravitreal conbercept at the end of diabetic vitrectomy for the prevention of post-vitrectomy hemorrhage in patients with severe proliferative diabetic retinopathy: a prospective, randomized pilot study. *Bmc Ophthalmology*, 20(1), pp.9.	- RCT of vitreous haemorrhage or vitrectomy
Jiao C, Spee C and He S ; Mullins R ; Eliott D ; Hinton D R; Sohn E H;. (2014). Angiofibrotic response to bevacizumab on fibrovascular membranes in proliferative Diabetic retinopathy. *Investigative Ophthalmology and Visual Science*, 55 (13), pp.5821.	- RCT of vitreous haemorrhage or vitrectomy
Jorge D M, Tavares Neto and Jeds ; Poli-Neto O B; Scott I U; Jorge R ;. (2021). Intravitreal bevacizumab (IVB) versus IVB in combination with pars plana vitrectomy for vitreous hemorrhage secondary to proliferative diabetic retinopathy: a randomized clinical trial. *International Journal of Retina and Vitreous*, 7(1), pp.35.	- RCT of vitreous haemorrhage or vitrectomy
Jprn-Umin . (2012). Low dose of intravitreal bevacizumab (Avastin) used as preoperative adjunct therapy for proliferative diabetic retinopathy. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000007482*	- RCT of vitreous haemorrhage or vitrectomy
Kanclerz P and Raczynska K . (2016). Preoperative bevacimab as an adjunct for vitrectomy in proliferative diabetic retinopathy patients. *Ophthalmologica. Journal international d'ophtalmologie [International journal of ophthalmology]*, 236, pp.58-.	- RCT of vitreous haemorrhage or vitrectomy

Excluded studies	Reasons for exclusion
Li Q, Wang J H and Zhang M M; Wang Y ;. (2016). Effect of Ranibizumab intravitreal injection before 23G-vitrectomy surgery in the treatment of patients with proliferative diabetic retinopathy. [Chinese]. *International Eye Science*, 16(10), pp.1959-1961.	- RCT of vitreous haemorrhage or vitrectomy
Li B, Li M D and Ye J J; Chen Z ; Guo Z J; Di Y ;. (2020). Vascular endothelial growth factor concentration in vitreous humor of patients with severe proliferative diabetic retinopathy after intravitreal injection of conbercept as an adjunctive therapy for vitrectomy. *Chinese Medical Journal*, 133(6), pp.664-669.	- RCT of vitreous haemorrhage or vitrectomy
Manabe A, Shimada H and Hattori T ; Nakashizuka H ; Yuzawa M ;. (2015). Randomized Controlled Study of Intravitreal Bevacizumab 0.16 Mg Injected One Day before Surgery for Proliferative Diabetic Retinopathy. *Retina*, 35(9), pp.1800-7.	- RCT of vitreous haemorrhage or vitrectomy
Meng N and Ren B C. (2016). Effect of intravitreal injection of Bevacizumab for vitreous hemorrhage in patients with proliferative diabetic retinopathy. [Chinese]. *International Eye Science*, 16(5), pp.972-974.	- RCT of vitreous haemorrhage or vitrectomy
Modarres M, Nazari H and Falavarjani K G; Naseripour M ; Hashemi M ; Parvaresh M M;. (2009). Intravitreal injection of bevacizumab before vitrectomy for proliferative diabetic retinopathy. *European Journal of Ophthalmology*, 19(5), pp.848-52.	- RCT of vitreous haemorrhage or vitrectomy
Nct (2007). Intravitreal Bevacizumab for Proliferative Diabetic Retinopathy. *https://clinicaltrials.gov/show/NCT00423059*	- RCT of vitreous haemorrhage or vitrectomy
Nct (2007). Evaluation of Ranibizumab in Proliferative Diabetic Retinopathy (PDR) Requiring Vitrectomy. *https://clinicaltrials.gov/show/NCT00516464*	- RCT of vitreous haemorrhage or vitrectomy
Nct (2008). Preoperative Bevacizumab for Vitreous Hemorrhage. *https://clinicaltrials.gov/show/NCT00596297*	- RCT of vitreous haemorrhage or vitrectomy
Nct (2009). Safety and Efficacy of Intravitreal Ranibizumab as a Preoperative Adjunct Treatment Before Vitrectomy Surgery in Proliferative Diabetic Retinopathy (PDR) Compared to Vitrectomy Alone. *https://clinicaltrials.gov/show/NCT00931125*	- RCT of vitreous haemorrhage or vitrectomy
Nct (2011). Acute Changes in Intraocular Cytokines After Intravitreal Bevacizumab. *https://clinicaltrials.gov/show/NCT01439178*	- RCT of vitreous haemorrhage or vitrectomy
Nct. (2011) Ranibizumab in Diabetic Vitrectomy. A Prospective, Randomised Controlled Trial of Ranibizumab Pre-treatment in Diabetic Vitrectomy - a Pilot Study. *https://ClinicalTrials.gov/show/NCT01306981*	- RCT of vitreous haemorrhage or vitrectomy

Excluded studies	Reasons for exclusion
Nct (2013). Prospective Randomized Controlled Study of Intravitreal Injection of Bevacizumab for Proliferative Diabetic Retinopathy. *https://clinicaltrials.gov/show/NCT01854593*	- RCT of vitreous haemorrhage or vitrectomy
Nct (2013). Aflibercept Injection for Proliferative Diabetic Retinopathy. *https://clinicaltrials.gov/show/NCT01805297*	- RCT of vitreous haemorrhage or vitrectomy
Nct (2013). Pre-Operative Intravitreal Bevacizumab for Tractional Retinal Detachment Secondary to Proliferative Diabetic Retinopathy. *https://clinicaltrials.gov/show/NCT01976923*	- RCT of vitreous haemorrhage or vitrectomy
Nct (2015). Comparison of Interval Variation and Dosage in Preoperative Bevacizumab and Ziv-Aflibercept Administration in Proliferative Diabetic Retinopathy Undergoing Vitrectomy. *https://clinicaltrials.gov/show/NCT02590094*	- RCT of vitreous haemorrhage or vitrectomy
Nct (2015). 25-G Vitrectomy With Ranibizumab or Triamcinolone Acetonide on PDR in China-Randomized Clinical Trial. *https://clinicaltrials.gov/show/NCT02447185*	- RCT of vitreous haemorrhage or vitrectomy
Nct (2016). Intravitreal Injection of Ranibizumab Versus Sham Before Vitrectomy in Patients With Proliferative Diabetic Retinopathy. *https://clinicaltrials.gov/show/NCT02857491*	- RCT of vitreous haemorrhage or vitrectomy
Nct (2020). Pre-vitrectomy Intravitreal Ranibizumab for Patients With Proliferative Diabetic Retinopathy Combined With Diabetic Macular Edema. *https://clinicaltrials.gov/show/NCT04464694*	- RCT of vitreous haemorrhage or vitrectomy
Pakzad-Vaezi K, Albiani D A and Kirker A W; Merkur A B; Kertes P J; Eng K T; Fallah N ; Forooghian F ;. (2014). A randomized study comparing the efficacy of bevacizumab and ranibizumab as pre-treatment for pars plana vitrectomy in proliferative diabetic retinopathy. *Ophthalmic Surgery and Lasers & Imaging Retina*, 45(6), pp.521-4.	- RCT of vitreous haemorrhage or vitrectomy
Petrarca R, Soare C and Wong R ; Desai R ; Neffendorf J ; Simpson A ; Jackson T L;. (2020). Intravitreal ranibizumab for persistent diabetic vitreous haemorrhage: a randomised, double-masked, placebo-controlled feasibility study. *Acta Ophthalmologica*, 98(8), pp.E960-E967.	- RCT of vitreous haemorrhage or vitrectomy
Qi Q F and Shi Y W; Guo T. (2014). Clinical observation on preoperative application of Bevacizumab in proliferative diabetic retinopathy. [Chinese]. *International Eye Science*, 14(9), pp.1646-1648.	- RCT of vitreous haemorrhage or vitrectomy
Ren X J, Bu S C; Zhang X M; Jiang Y F; Tan L Z; Zhang H and Li X R;. (2019). Safety and efficacy of intravitreal conbercept injection after vitrectomy for the treatment of proliferative diabetic retinopathy. *Eye*, 33(7), pp.1177-1183.	- RCT of vitreous haemorrhage or vitrectomy

Excluded studies	Reasons for exclusion
Reza N M, Hosein A M; Hesamsadat H and Amir E M; Narges H ; Amin N ;. (2019). Intravitreal tissue plasminogen activator in diabetic vitreous hemorrhage. *International Journal of Pharmaceutical Research*, 11(Supplementry 1), pp.823-827.	- RCT of vitreous haemorrhage or vitrectomy
Sohn E H, He S and Kim L A; Salehi-Had H ; Javaheri M ; Spee C ; Dustin L ; Hinton D R; Eliott D ;. (2012). Angiofibrotic response to vascular endothelial growth factor inhibition in diabetic retinal detachment: report no. 1. *Archives of Ophthalmology*, 130(9), pp.1127-34.	- RCT of vitreous haemorrhage or vitrectomy
Starnes D C, Lalane R and Walia H ; Farooq A ; Frazier H ; Marcus W ; Singh H ; Marcus D M;. (2019). Endolaserless vitrectomy with intravitreal aflibercept injection (IAI) for proliferative diabetic retinopathy (PDR)-related vitreous hemorrhage: LASER LESS TRIAL 1-year results. *Investigative Ophthalmology and Visual Science. Conference*, 60(9).	- RCT of vitreous haemorrhage or vitrectomy
Su L, Ren X and Wei H ; Zhao L ; Zhang X ; Liu J ; Su C ; Tan L ; Li X ;. (2016). Intravitreal Conbercept (Kh902) for Surgical Treatment of Severe Proliferative Diabetic Retinopathy. *Retina*, 36(5), pp.938-43.	- RCT of vitreous haemorrhage or vitrectomy
Sun M and Li M X. (2015). Study of anti-vascular endothelial growth factor medicine for proliferative diabetic retinopathy at perioperative period. [Chinese]. *International Eye Science*, 15(10), pp.1772-1774.	- RCT of vitreous haemorrhage or vitrectomy
Sun L and Tao Y . (2017). Effects of Bevacizumab on CTGF and PEDF in proliferative membrane in patients with PDR. [Chinese]. *International Eye Science*, 17(6), pp.1051-1054.	- RCT of vitreous haemorrhage or vitrectomy
Tegins E, Javaheri M and Eliott D ; Kim L ; Salehi-Had H ; Hinton D ; Sohn E ;. (2013). One year clinical outcomes of A randomized clinical trial investigating pre-operative adjunctive bevacizumab for tractional retinal detachment (TRD) due to proliferative diabetic retinopathy (PDR). *Investigative Ophthalmology and Visual Science. Conference*, 54(15).	- RCT of vitreous haemorrhage or vitrectomy
Victor A A, Gondhowiardjo T D; Waspadji S and Wanandi S I; Bachtiar A ; Suyatna F D; Muhiddin H ;. (2014). Effect of laser photocoagulation and bevacizumab intravitreal in proliferative diabetic retinopathy: Review on biomarkers of oxidative stress. *Medical Journal of Indonesia*, 23(2), pp.79-86.	- RCT of vitreous haemorrhage or vitrectomy
Wang Y P and Chen M Z; Chen G C; Chen Y J;. (2014). Clinical effect of vitrectomy with intravitreal ranibizumab for diabetic retinopathy. [Chinese]. *International Eye Science*, 14(7), pp.1257-1259.	- RCT of vitreous haemorrhage or vitrectomy
Wildan A, Winarto and Kristina T N;. (2019). Aflibercept and bevacizumab injection effects on visual acuity of post vitrectomy diabetic retinopathy. *Pakistan Journal of Medical and Health Sciences*, 13(4), pp.1214-1218.	- RCT of vitreous haemorrhage or vitrectomy
Yamaji H, Shiraga F and Shiragami C ; Nomoto H ; Fujita T ; Fukuda K ;. (2011). Reduction in dose of intravitreous bevacizumab before vitrectomy for proliferative diabetic retinopathy. *Archives of Ophthalmology*, 129(1), pp.106-7.	- RCT of vitreous haemorrhage or vitrectomy

Excluded studies	Reasons for exclusion
Yang X C, Xu J B; Wang R L; Mei Y and Lei H ; Liu J ; Zhang T ; Zhao H Y;. (2016). A Randomized Controlled Trial of Conbercept Pretreatment before Vitrectomy in Proliferative Diabetic Retinopathy. *Journal of Ophthalmology*, 2016, pp.8.	- RCT of vitreous haemorrhage or vitrectomy
Yao T T, Yang Y and Jin X L; Wang Y X; Zhou Y L; Xu A J; He F L; Wang Z Y;. (2020). Intraocular pharmacokinetics of anti-vascular endothelial growth factor agents by intraoperative subretinal versus intravitreal injection in silicone oil-filled eyes of proliferative diabetic retinopathy: a randomized controlled pilot study. *Acta Opthalmologica*, 98(7), pp.e795-e800.	- RCT of vitreous haemorrhage or vitrectomy
Yin N, Zhao S and Zhu H N;. (2017). Efficacy comparison of Conbercept and Ranibizumab as pre-treatment for pars plana vitrectomy in proliferative diabetic retinopathy. [Chinese]. *International Eye Science*, 17(7), pp.1300-1302.	- RCT of vitreous haemorrhage or vitrectomy
Yu X Q and Cao G P; Tang M X;. (2015). Effect of vitrectomy combined medication hyperplastic on patients with diabetic retinopathy. [Chinese]. *International Eye Science*, 15(8), pp.1402-1404.	- RCT of vitreous haemorrhage or vitrectomy
Zahaf A, Zghal I and Fekih O ; Zayani M ; Mahjoub A ; Bouguila H ;. (2015). Preoperative intravitreal bevacizumab effects on the course of Pars Plana vitrectomy in diabetic vitreous hemorrhage. *Acta Ophthalmologica. Conference*, 93(Supplement 255).	- RCT of vitreous haemorrhage or vitrectomy
Zaman Y, Rehman A U and Memon A F;. (2013). Intravitreal Avastin as an adjunct in patients with proliferative diabetic retinopathy undergoing pars plana vitrectomy. *Pakistan Journal of Medical Sciences*, 29(2), pp.590-2.	- RCT of vitreous haemorrhage or vitrectomy
Zhao X L, Yang G and Yang J ; Zhang J J;. (2017). Effect of intravitreal conbercept vs triamcinolone acetonide at the end of surgery on macular structure and function in patients with severe proliferative diabetic retinopathy. *International Journal of Clinical and Experimental Medicine*, 10(10), pp.14511-14518.	- RCT of vitreous haemorrhage or vitrectomy
Zhou A Y, Zhou C J; Yao J and Quan Y L; Ren B C; Wang J M;. (2016). Panretinal photocoagulation versus panretinal photocoagulation plus intravitreal bevacizumab for high-risk proliferative diabetic retinopathy. *International Journal of Ophthalmology*, 9(12), pp.1772-1778.	- RCT of vitreous haemorrhage or vitrectomy
Zhou J, Liu Z and Chen M ; Luo Z H; Li Y Q; Qi G Y; Liu T ;. (2018). Concentrations of VEGF and PlGF Decrease in Eyes After Intravitreal Conbercept Injection. *Diabetes Therapy Research and Treatment and Education of Diabetes and Related Disorders*, 9(6), pp.2393-2398.	- RCT of vitreous haemorrhage or vitrectomy
Altaweel M M. 2006. "Changes in Severity of Diabetic Retinopathy Following Pegaptanib (Macugen®) Therapy". *Iovs* 47:ARVO E-abstract 5441.	- Other (no further reason provided in review)
Chae J B and Joe S G; Yang S J; Lee J Y; Sung K R; Kim J Y; Kim J G; Yoon Y H;. 2014. "Effect of combined cataract surgery and ranibizumab injection in postoperative macular edema in nonproliferative diabetic retinopathy". *Retina* 34(1):149-56.	- Other (no further reason provided in review)

Excluded studies	Reasons for exclusion
Cheema R A and Al-Mubarak M M; Amin Y M; Cheema M A;. 2009. "Role of combined cataract surgery and intravitreal bevacizumab injection in preventing progression of diabetic retinopathy: prospective randomized study". *Journal of Cataract & Refractive Surgery* 35(1):18-25.	- Other (no further reason provided in review)
Euctr-004648-12-Es . 2017. "this is a phase 3, multicenter, randomized, masked, controlled, parallel group study of 12 months duration in treatment naïve subjects with RVO". *http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-004648-12-ES*	- Other (no further reason provided in review)
Dept of Ophthalmology and Medical University of Vienna. "European Intravitreal Avastin® Trial 1". https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-003132-21	- Other (no further reason provided in review)
JPRN-jRCTs031180307 (2019). "The effect of an anti-VEGF drug on proliferative retinopathy." https://jrct.niph.go.jp/latest-detail/jRCTs031180307	- Other (no further reason provided in review)
Kodiak Sciences and Inc . . "A Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 Compared with Intravitreal A".	- Other (no further reason provided in review)
Nct. (2017) "Analysis of Aqueous and Vitreous Humor". https://ClinicalTrials.gov/show/NCT02067013	- Other (no further reason provided in review)
Novartis Farmacéutica and S A . . "A 12-month, phase IIIb, randomized, visual acuity, assessor-masked, multicenter study assessing the efficacy and safety of ranibizumab 0.5mg in treat and extend regimen compared to monthly regimen".	- Other (no further reason provided in review)
Novartis Pharma Services and A G. . "A 24-month randomized, double-masked, multicenter, phase II study assessing safety and efficacy of verteporfin (Visudyne®) photodynamic therapy administered in conjunction with Lucentis™ versus Luc".	- Other (no further reason provided in review)
Novartis Pharma Services and A G. . "A 24-month, phase IIIb, open-label, randomized, activecontrolled, 3-arm, multicenter study assessing the efficacy and safety of an individualized, stabilization-criteria-driven PRN dosing regimen w".	- Other (no further reason provided in review)
Novartis Pharma Services and A G. . "A 24-month, phase IIIb, open-label, single arm, multicenter study assessing the efficacy and safety of an individualized, stabilization criteria-driven PRN dosing regimen with 0.5-mg ranibizumab in".	- Other (no further reason provided in review)
Novartis Pharma Services and A G. . "A 24-month, phase IIIb, randomized, double-masked, multicenter study assessing the efficacy and safety of two treatment regimens of 0.5 mg ranibizumab intravitreal injections guided by functional a".	- Other (no further reason provided in review)

Excluded studies	Reasons for exclusion
Novartis Pharma and A G . . "A 64-week, two-arm, randomized, double-masked, multi-center, phase IIIb study assessing the efficacy and safety of brolucizumab 6 mg compared to aflibercept 2 mg in a treat-to-control regimen in pa".	- Other (no further reason provided in review)
Nct (2016). "Effects of Intravitreal Ranibizumab for Macular Edema With Nonproliferative Diabetic Retinopathy". https://ClinicalTrials.gov/show/NCT02834663	- Other (no further reason provided in review)
Opthea Limited. . "A Phase 3, Multicentre, Double-masked, Randomised Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Ranibizumab, Compared with Ranibizumab Alone, in Participants".	- Other (no further reason provided in review)
Yu B and Liu Z . 2019. "The clinical efficacy of vitreous injection of ranibizumab in patients with ocular fundus disease and its effect on hemorheology". *International Journal of Clinical and Experimental Medicine* 12(9):11249-11256.	- Other (no further reason provided in review)
Abadia B, Calvo P and Ferreras A ; Bartol F ; Verdes G ; Pablo L ;. (2016). Clinical Applications of Dexamethasone for Aged Eyes. *Drugs & Aging*, 33(9), pp.639-646.	- Irrelevant intervention
Altun A, Kanar H S and Aki S F; Arsan A ; Hacisalihoglu A ;. (2021). Effectiveness and Safety of Coadministration of Intravitreal Dexamethasone Implant and Silicone Oil Endotamponade for Proliferative Diabetic Retinopathy with Tractional Diabetic Macular Edema. *Journal of Ocular Pharmacology & Therapeutics*, 37(2), pp.131-137.	- Irrelevant intervention
Ctri . (2020). A Clinical Study to Assess and Compare the Efficacy and Safety of Hydroxychloroquine and Teneligliptin in Type 2 Diabetes Patients with Non-proliferative Diabetic Retinopathy. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2020/04/024637*	- Irrelevant intervention
Antoszyk A N, Glassman A R; Beaulieu W T; Jampol L M; Jhaveri C D; Punjabi O S; Salehi-Had H and Wells J A; 3rd ; Maguire M G; Stockdale C R; Martin D F; Sun J K; Network Drcr Retina;. (2020). Effect of Intravitreous Aflibercept vs Vitrectomy With Panretinal Photocoagulation on Visual Acuity in Patients With Vitreous Hemorrhage From Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. *JAMA*, 324(23), pp.2383-2395.	- Irrelevant comparator
Khodabandeh A, Fadaifard S and Abdollahi A ; Karkhaneh R ; Roohipoor R ; Abdi F ; Ghasemi H ; Habibollahi S ; Mazloumi M ;. (2018). Role of combined phacoemulsification and intravitreal injection of bevacizumab in prevention of postoperative macular edema in non-proliferative diabetic retinopathy. *Journal of Current Ophthalmology*, 30(3), pp.245-249.	- Irrelevant comparator
Shi R, Ma Y and Wang F ; Wang J P;. (2015). Effects of intravitreous injection on the expression of vascular endothelial growth inhibitor in vitreous of proliferative diabetic retinopathy. [Chinese]. *International Eye Science*, 15(6), pp.985-988.	- Irrelevant comparator

Excluded studies	Reasons for exclusion
Yan P, Zhang X H and Zhang L ; Li J ;. (2019). Effect of Intravitreal Injection of Ranibizumab Combined with Voritine on Hemorrhagic Proliferative Diabetic Retinopathy and Its Effect on Visual Acuity and Endothelial Growth Factor. [Chinese]. *Chinese Journal of Pharmaceutical Biotechnology*, 26(2), pp.127-130.	- Irrelevant comparator
Khalaf H, Rostamizadeh M and Gonzalez V H;. (2018). Foveal Avascular Zone in high risk proliferative diabetic retinopathy treated with intravitreal aflibercept injection (ELYSIAN). *Investigative Ophthalmology and Visual Science. Conference*, 59(9).	- No relevant outcomes
Ababneh O H, Yousef Y A; Gharaibeh A M; Abu Ameerh and M A ; Abu-Yaghi N E; Al Bdour M D;. (2013). Intravitreal bevacizumab in the treatment of diabetic ocular neovascularization. *Retina*, 33(4), pp.748-55.	- Inappropriate trial design
Abdallah W and Fawzi A A. (2009). Anti-VEGF therapy in proliferative diabetic retinopathy. *International Ophthalmology Clinics*, 49(2), pp.95-107.	- Inappropriate trial design
Al-Khersan H, Hariprasad S M and Salehi-Had H ;. (2019). Dexamethasone and Anti-VEGF Combination Therapy for the Treatment of Diabetic Macular Edema. *Ophthalmic Surgery and Lasers & Imaging Retina*, 50(1), pp.4-7.	- Inappropriate trial design
Bakri S J and Donaldson M J; Link T P;. (2006). Rapid regression of disc neovascularization in a patient with proliferative diabetic retinopathy following adjunctive intravitreal bevacizumab. *Eye*, 20(12), pp.1474-5.	- Inappropriate trial design
Beaulieu W T and Bressler N M; Gross J G; Diabet Retinopathy Clinical; Res . (2017). Panretinal Photocoagulation Versus Ranibizumab for Proliferative Diabetic Retinopathy: Patient-Centered Outcomes From a Randomized Clinical Trial Reply. *American Journal of Ophthalmology*, 177, pp.233-233.	- Inappropriate trial design
Bi S S, Jiang T and Chen Y ; Ma X F;. (2020). Effects of laser photocoagulation combined with anti-VEGF drugs at different time in the treatment of diabetic retinopathy. *International eye science*, 20, pp.613-618.	- Inappropriate trial design
Brown D M and Wykoff C C;. (2017). Intravitreal aflibercept for proliferative diabetic retinopathy. *Lancet*, 390(10108), pp.2141-2141.	- Inappropriate trial design
Browning D J, Lee C and Stewart M W; Landers M B; 3rd ;. (2016). Vitrectomy for center-involved diabetic macular edema. *Clinical Ophthalmology*, 10, pp.735-42.	- Inappropriate trial design
Chen E and Park C H. (2006). Use of intravitreal bevacizumab as a preoperative adjunct for tractional retinal detachment repair in severe proliferative diabetic retinopathy. *Retina*, 26(6), pp.699-700.	- Inappropriate trial design

Excluded studies	Reasons for exclusion
Chen Po-Yu, Wang Te-Wei and Wang Wei-Chen ; Liao Jou-Chien ; Yang Shuang-An ; Hsu Yu-Tien ;. (2020). Clinical outcome of Diabetic retinopathy with the treatment of photocoagulation versus Anti-VEGF.	- Inappropriate trial design
Desapriya E, Khoshpouri P and Al-Isa A ;. (2017). Panretinal Photocoagulation Versus Ranibizumab for Proliferative Diabetic Retinopathy: Patient-Centered Outcomes From a Randomized Clinical Trial. *American Journal of Ophthalmology*, 177, pp.232-233.	- Inappropriate trial design
Ergur O, Bayhan H A and Kurkcuoglu P ; Takmaz T ; Gurdal C ; Can I ;. (2009). Comparison of panretinal photocoagulation (PRP) with PRP plus intravitreal bevacizumab in the treatment of proliferative diabetic retinopathy. [Turkish] Proliferatif diyabetik retinopati tedavisinde tek basina panretinal fotokoagulasyon (PRF) ile PRF ve intravitreal bevacizumab kombinasyonunun karsilastirilmasi. *Retina-Vitreus*, 17(4), pp.273-277.	- Inappropriate trial design
Gibson J M and McGinnigle S. (2016). Diabetes: Intravitreous ranibizumab for proliferative diabetic retinopathy. *Nature Reviews Endocrinology*, 12(3), pp.130-1.	- Inappropriate trial design
Glassman A R. (2017). Results of a Randomized Clinical Trial of Aflibercept vs Panretinal Photocoagulation for Proliferative Diabetic Retinopathy: Is It Time to Retire Your Laser?. *JAMA Ophthalmology*, 135(7), pp.685-686.	- Inappropriate trial design
Gross J G and Glassman A R;. (2016). A Novel Treatment for Proliferative Diabetic Retinopathy: Anti-Vascular Endothelial Growth Factor Therapy. *JAMA Ophthalmology*, 134(1), pp.13-4.	- Inappropriate trial design
Gupta M P, Kiss S and Chan R V. P;. (2018). Reversal of Retinal Vascular Leakage and Arrest of Progressive Retinal Nonperfusion With Monthly Anti-Vascular Endothelial Growth Factor Therapy for Proliferative Diabetic Retinopathy. *Retina*, 38(9), pp.e74-e75.	- Inappropriate trial design
Hershberger V, Hill L F and Tuomi L L; Ghanekar A ;. (2018). Ranibizumab-induced diabetic retinopathy improvement-results from patients at high risk for vision loss in ride/rise and protocol s. *Diabetes*, 67 (Supplement 1), pp.A158.	- Inappropriate trial design
Krishnan R, Goverdhan S and Lochhead J ;. (2009). Intravitreal pegaptanib in severe proliferative diabetic retinopathy leading to the progression of tractional retinal detachment. *Eye*, 23(5), pp.1238-9.	- Inappropriate trial design
Krzystolik M G, Filippopoulos T and Ducharme J F; Loewenstein J I;. (2006). Pegaptanib as an adjunctive treatment for complicated neovascular diabetic retinopathy. *Archives of Ophthalmology*, 124(6), pp.920-1.	- Inappropriate trial design
Li J and Liu F . (2007). Clinical evidence on the treatment of non-proliferative diabetic retinopathy. *Chinese Journal of Evidence-Based Medicine*, 7(12), pp.894-898.	- Inappropriate trial design

Excluded studies	Reasons for exclusion
Melia M, Edwards A and Kollman C ;. (2012). Interim analysis with sample size re-estimation for binary outcome in a trial of intravitreal ranibizumab versus saline injection for prevention of vitrectomy in eyes with proliferative diabetic retinopathy and vitreous hemorrhage. *Clinical Trials*, 9 (4), pp.523-524.	- Inappropriate trial design
Olsen T W. (2015). Anti-VEGF Pharmacotherapy as an Alternative to Panretinal Laser Photocoagulation for Proliferative Diabetic Retinopathy. *JAMA*, 314(20), pp.2135-6.	- Inappropriate trial design
Ospedale Sacro Cuore-Don and Calabria. *Evaluation of safety and efficacy on visual acuity outcome of intravitreal somministration of Bevacizumab in patients with diabetic retinopathy*. [online] . Available at: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-005315-10.	- Inappropriate trial design
Parikakis E. (2018). Laser or Anti-VEGF for proliferative diabetic retinopathy. *Acta Ophthalmologica*, 96 (Supplement 261), pp.94.	- Inappropriate trial design
Tan T E, Sivaprasad S and Wong T Y;. (2023). Anti-Vascular Endothelial Growth Factor Therapy for Complications of Diabetic Retinopathy-From Treatment to Prevention?. *JAMA Ophthalmology*, 141, pp.223-225.	- Inappropriate trial design
Wise J. (2015). Lucentis offers treatment alternative for diabetic retinopathy, trial finds. *BMJ*, 351, pp.h6145.	- Inappropriate trial design
Zucchiatti I and Bandello F . (2017). Intravitreal Ranibizumab in Diabetic Macular Edema: Long-Term Outcomes. *Developments in Ophthalmology*, 60, pp.63-70.	- Inappropriate trial design
ChiCtr-Oon . (2017). Effect of anti VEGF on the expression of vitreous Ang2 in patients with PDR. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-OON-17012170*	- Not an RCT
Chung E J and Kang S J; Koo J S; Choi Y J; Grossniklaus H E; Koh H J;. (2011). Effect of intravitreal bevacizumab on vascular endothelial growth factor expression in patients with proliferative diabetic retinopathy. *Yonsei Medical Journal*, 52(1), pp.151-7.	- Not an RCT
Department of Ophthalmology and M U W;. Disease-modification under treatment with aflibercept in advanced diabetic retinopathy - A pilot study.	- Not an RCT
EUCTR2006-005315-10-IT . (2006). *Evaluation of safety and efficacy on visual acuity outcome of intravitreal somministration of Bevacizumab in patients with diabetic retinopathy - ND*.	- Not an RCT

Excluded studies	Reasons for exclusion
He F and Yu W . (2020). Longitudinal neovascular changes on optical coherence tomography angiography in proliferative diabetic retinopathy treated with panretinal photocoagulation alone versus with intravitreal conbercept plus panretinal photocoagulation: a pilot study. *Eye*, 34(8), pp.1413-1418.	- Not an RCT
IRCT138903314232N1 . (2010). *Intravitreal Bevacizumab (Avastin) therapy for Proliferative Diabetic Retinopathy*.	- Not an RCT
Jprn-Umin . (2016). Evaluate the effect of intravitreal Bevacizumab injection for ocular proliferative diseases. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000020467*	- Not an RCT
Kernt M, Cserhati S and Seidensticker F ; Liegl R ; Kampik A ; Neubauer A ; Ulbig M W; Reznicek L ;. (2013). Improvement of diabetic retinopathy with intravitreal Ranibizumab. *Diabetes Research & Clinical Practice*, 100(1), pp.e11-3.	- Not an RCT
Lopez-Lopez F, Gomez-Ulla F and Rodriguez-Cid M J; Arias L ;. (2012). Triamcinolone and bevacizumab as adjunctive therapies to panretinal photocoagulation for proliferative diabetic retinopathy. *Isrn Ophthalmology Print*, 2012, pp.267643.	- Not an RCT
Nct (2006). Intravitreal Bevacizumab for Management of Active Progressive Proliferative Diabetic Retinopathy (PDR). https://ClinicalTrials.gov/show/NCT00370721	- Not an RCT
Nct (2012). Analysis of Angiogenic Factor Levels in Eyes With Diabetic Retinopathy. https://ClinicalTrials.gov/show/NCT02026843	- Not an RCT
Nct (2012). Combined Triple Therapy in Diabetic Retinopathy (DRP). https://clinicaltrials.gov/study/NCT00806169	- Not an RCT
Nct (2012). Effect of Macugen(Pegaptanib)on Surgical Outcomes and VEGF Levels in Diabetic Patients With PDR (Diabetic Retinopathy or CSDME (Macular Edema). https://ClinicalTrials.gov/show/NCT00446381	- Not an RCT
Nct (2015). Ziv-aflibercept in Ocular Disease Requiring Anti-VEGF Injection. https://ClinicalTrials.gov/show/NCT02486484	- Not an RCT
Park Y J, Ahn J and Kim T W; Park S J; Joo K ; Park K H; Shin J Y;. Efficacy of bevacizumab for vitreous haemorrhage in proliferative diabetic retinopathy with prior complete panretinal photocoagulation. *Eye*, pp.8.	- Not an RCT

Excluded studies	Reasons for exclusion
Park J M and Lee S J;. (2015). The effect of panretinal photocoagulation and additive Intravitreal bevacizumab injections on central retinal vessel diameters in diabetic retinopathy. *Acta Ophthalmologica. Conference*, 93(Supplement 255).	- Not an RCT
Vidinova C N, Gouguchkova P T; Dimitrov T and Vidinov K N; Nocheva H ;. (2020). [Comparative Clinical and Ultrastructural Analysis of the Results from Ranibizumab and Aflibercept in Patients with PDR]. *Klinische Monatsblatter fur Augenheilkunde*, 237(1), pp.79-84.	- Not an RCT
Frimley Park Hospital and N H S. Foundation Trust;. A randomised controlled trial of efficacy of Pegaptanib sodium in the prevention of proliferative diabetic retinopathy.	- Protocols of excluded and ongoing studies
Fakultní nemocnice Královské and Vinohrady . A randomized, 12 months, active controlled study of the efficacy of repeated doses of intravitreal aflibercept in subjects with prolipherative diabetic retinopathy.	- Protocols of excluded and ongoing studies
Euctr-000658-30-Ie . (2007). Randomised controlled trial of Intravitreal Bevacizumab vs. conventional treatment for proliferative diabetic retinopathy. - Randomised controlled trial of Intravitreal Bevacizumab vs. conventional treatment for proliferative. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2007-000658-30-IE	- Protocols of excluded and ongoing studies
Euctr-001856-36-Fr . (2016). Efficacy and safety of Aflibercept (Eylea®) in proliferative diabetic retinopathy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-001856-36-FR	- Protocols of excluded and ongoing studies
Euctr-004203-39-Cz . (2014). Study of efect of intravitreal aflibercept in subjects with prolipherative diabetic retinopathy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-004203-39-CZ	- Protocols of excluded and ongoing studies
Euctr-006795-10-Gb . (2008). A randomised controlled trial of efficacy of Pegaptanib sodium in the prevention of proliferative diabetic retinopathy - EPPPDR. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2007-006795-10-GB	- Protocols of excluded and ongoing studies
Isrctn . (2010). A prospective randomised controlled trial assessing the efficacy of Pegatanib sodium (Macugen®) in the prevention of proliferative diabetic retinopathy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN27864936	- Protocols of excluded and ongoing studies
Nct (2008). Ranibizumab for Treatment of Persistent Diabetic Neovascularization Assessed by Wide-Field Imaging. https://clinicaltrials.gov/show/NCT00606138	- Protocols of excluded and ongoing studies
Nct (2011). Prospective, Randomized, Open Label, Phase II Study to Assess Efficacy and Safety of Macugen® (Pegaptanib 0.3 mg Intravitreal Injections) Plus Panretinal Photocoagulation and PRP (Monotherapy) in the Treatment With High Risk PDR. https://clinicaltrials.gov/show/NCT01281098	- Protocols of excluded and ongoing studies

Excluded studies	Reasons for exclusion
Nct (2013). Prevention of Macular Edema In Patients With Diabetic Retinopathy Undergoing Cataract Surgery. https://clinicaltrials.gov/show/NCT01988246	- Protocols of excluded and ongoing studies
Nct (2013). Treatment With Intravitreal Aflibercept Injection For Proliferative Diabetic Retinopathy, The A.C.T Study. https://clinicaltrials.gov/show/NCT01813773	- Protocols of excluded and ongoing studies
Nct. (2015). Safety and Efficacy of Aflibercept in Proliferative Diabetic Retinopathy. https://ClinicalTrials.gov/show/NCT02151695	- Protocols of excluded and ongoing studies
Nct (2016). Conbercept vs Panretinal Photocoagulation for the Management of Proliferative Diabetic Retinopathy. https://clinicaltrials.gov/show/NCT02911311	- Protocols of excluded and ongoing studies
Nct (2018). Intravitreal Aflibercept as Indicated by Real-Time Objective Imaging to Achieve Diabetic Retinopathy Improvement. https://clinicaltrials.gov/show/NCT03531294	- Protocols of excluded and ongoing studies
Nct (2018). Multicenter Clinical Study of Anti-VEGF Treatment on High Risk Diabetic Retinopathy (DR). https://clinicaltrials.gov/show/NCT03452657	- Protocols of excluded and ongoing studies
Nct (2020). A Multicenter, Randomized Study in Participants With Diabetic Retinopathy Without Center-involved Diabetic Macular Edema To Evaluate the Efficacy, Safety, and Pharmacokinetics of Ranibizumab Delivered Via the Port Delivery System Relative to the Comparator Arm. https://clinicaltrials.gov/show/NCT04503551	- Protocols of excluded and ongoing studies
Nct (2020). Intravitreal Bevacizumab for Nonproliferative Diabetic retinopathy.	- Protocols of excluded and ongoing studies
Nct (2020). Study of Efficacy and Safety of Brolucizumab Versus Panretinal Photocoagulation Laser in Patients With Proliferative Diabetic Retinopathy. https://ClinicalTrials.gov/show/NCT04278417	- Protocols of excluded and ongoing studies
Nct (2021). Intravitreal Bevacizumab vs Laser vs Combination of Bevacizumab and Modified Laser in PDR. https://clinicaltrials.gov/show/NCT04800679	- Protocols of excluded and ongoing studies
Tctr . (2021). Change of OCT findings after Intravitreal Anti-VEGF injection in patients with diabetic tractional retinal detachment : a Randomized Controlled Trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=TCTR20210524001	- Protocols of excluded and ongoing studies

Excluded studies	Reasons for exclusion
Neri Alvarez-Villalobos Humberto de León-Gutiérrez Fernando Ruiz-Hernandez. Safety and clinical effectiveness behavior of bevacizumab biosimilars in the intravitreal application.	- Irretrievable

Economic evidence

Table 28: Excluded studies - economics

Study	Reason for exclusion
Crijns, H; Casparie, A F; Hendrikse, F (1999) Continuous computer simulation analysis of the cost-effectiveness of screening and treating diabetic retinopathy. International journal of technology assessment in health care 15(1): 198-206	- Population (diabetes NOT diabetic retinopathy)
Hutton, David W, Stein, Joshua D, Bressler, Neil M et al. (2017) 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 ophthalmology 135(6): 576-584	- Serious limitations (minimal information on modelling; very short time horizon for a disease with long-term effects)
Javitt J C, Aiello L P (1996) Cost-effectiveness of detecting and treating diabetic retinopathy. Annals of Internal Medicine 124(1 Part 2): 164-169	- Not applicable (US study, pre-1990 analysis different from current UK setting) - Population (diabetes NOT diabetic retinopathy) - Not applicable (inappropriate comparison of interventions)
Javitt, J C; Canner, J K; Sommer, A (1989) Cost effectiveness of current approaches to the control of retinopathy in type I diabetics. Ophthalmology 96(2): 255-64	- Not applicable (US study, pre-1990 analysis different from current UK setting) - Population (diabetes NOT diabetic retinopathy)
Lin, James; Chang, Jonathan S; Smiddy, William E (2016) Cost Evaluation of Panretinal Photocoagulation versus Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy. Ophthalmology 123(9): 1912-8	- Serious limitations (minimal information on modelling; issues with sensitivity analysis)
Lin, James, Chang, Jonathan S, Yannuzzi, Nicolas A et al. (2018) Cost Evaluation of Early Vitrectomy versus Panretinal Photocoagulation and Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy. Ophthalmology 125(9): 1393-1400	- Serious limitations (minimal information on modelling; issues with sensitivity analysis)
Patel, N.A., Yannuzzi, N.A., Lin, J. et al. (2021) A Cost-Effectiveness Analysis of Intravitreal Aflibercept for the Prevention of Progressive Diabetic Retinopathy. Ophthalmology Retina	- Not applicable (non-QALY outcomes; discounting not applied)

Study	Reason for exclusion
Royle, Pamela, Mistry, Hema, Auguste, Peter et al. (2015) Pan-retinal photocoagulation and other forms of laser treatment and drug therapies for non-proliferative diabetic retinopathy: systematic review and economic evaluation. Health technology assessment (Winchester, England) 19(51): v-247	- Not applicable (comparison between timing of treatment, not between treatments)
Vondeling, H (1993) Evaluation of argon laser treatment of diabetic retinopathy and its diffusion in The Netherlands. Health policy (Amsterdam, Netherlands) 23(12): 97-111	- Not applicable (US study, pre-1990 analysis different from current UK setting)
Yannuzzi, Nicolas A, Sridhar, Jayanth, Chang, Jonathan S et al. (2018) Cost Evaluation of Laser versus Intravitreal Aflibercept for Proliferative Diabetic Retinopathy. Ophthalmology 125(7): 1121-1122	- Author manuscript only, no results

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

What is the effectiveness and acceptability of observation, anti-vascular endothelial growth factor agents and laser photocoagulation (alone or in combination) for the treatment of severe non-proliferative diabetic retinopathy?

K.1.1.1 Why this is important

Very limited evidence is currently available for the effectiveness of observation or different treatments for managing severe non-proliferative diabetic retinopathy. Therefore it is currently unclear which treatment options are the best methods of preventing people progressing to more severe disease. Further evidence is therefore needed so that recommendations can be made on treatments for severe non-proliferative diabetic retinopathy in the future, reducing the number of people who experience the more severe effects associated with progression.

K.1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	There is limited evidence on the best treatments for people with severe non-proliferative diabetic retinopathy. By understanding which treatments are the most effective at preventing progression, fewer people will experience the more severe effects associated with progression of retinopathy.
Relevance to NICE guidance	There is currently very limited evidence for the best treatments for people with non-proliferative diabetic retinopathy.
Relevance to the NHS	An understanding of the most effective treatments will reduce the number of people who progress to more severe disease. This will reduce the time needed to treat people with more severe disease as well as reducing the costs associated with treatment.
National priorities	Moderate
Current evidence base	Minimal short- or long-term data
Equality considerations	None known

K.1.1.3 Modified PICO table

Population	People with non-proliferative diabetic retinopathy
Intervention	Any anti-VEGF therapy: • Including aflibercept, bevacizumab, ranibizumab and their biosimilars • Anti-VEGF with, or subsequent to, laser photocoagulation

	Laser photocoagulation (in any form, and any laser type) Observation
Comparator	• Other interventions described above (including comparisons of different anti-VEGF agents)
Outcome	• Change in visual acuity • Functional impact on vision • Number of treatments • Need for subsequent treatments • Adverse events • Progression of retinopathy (non-proliferative to proliferative) • Peripheral vision and visual field changes • Quality of life • Acceptability (qualitative or quantitative data on acceptability collected alongside randomised controlled trials)
Study design	RCTs Qualitative or quantitative data on acceptability (stand-alone qualitative studies were not searched for in the NICE review)
Timeframe	Long term
Additional information	None

K.1.2 Research recommendation

What is the effectiveness and acceptability of combination treatments for proliferative diabetic retinopathy?

K.1.2.1 Why this is important

While there is evidence on the effectiveness of different treatments for proliferative diabetic retinopathy, studies have yet to consider the effectiveness of different combinations of treatments. Therefore, it is currently unclear whether combining different treatments could improve patient outcomes in comparison to using anti-VEGFs or panretinal photocoagulation alone. Further evidence is therefore needed to identify whether combinations of treatment could reduce the number of people who progress to more severe disease.

K.1.2.2 Rationale for research recommendation

Importance to 'patients' or the population	There is no evidence on combined treatments for people with severe non-proliferative diabetic retinopathy. If evidence shows that combined treatments are more effective at preventing progression, it will be possible to reduce the number of people who progress to more severe disease.

Relevance to NICE guidance	There is currently no evidence on combined treatments for people with proliferative diabetic retinopathy.
Relevance to the NHS	A better understanding of the most effective treatments will reduce the number of people who progress to more severe disease. This will reduce the time needed to treat people with more severe disease as well as reducing the costs associated with treatment.
National priorities	Moderate
Current evidence base	No short- or long-term data
Equality considerations	None known

K.1.2.3 Modified PICO table

Population	People with proliferative diabetic retinopathy
Intervention	Any combinations of: • Laser photocoagulation (in any form, and any laser type) • anti-VEGF therapy (Including aflibercept, bevacizumab, ranibizumab and their biosimilars) Including different combinations of anti-VEGF treatments
Comparator	• Other combinations of interventions described above
Outcome	• Change in visual acuity • Functional impact on vision • Number of treatments • Need for subsequent treatments • Adverse events • Progression of retinopathy (non-proliferative to proliferative) • Peripheral vision and visual field changes • Quality of life • Acceptability (qualitative or quantitative data on acceptability collected alongside randomised controlled trials)
Study design	RCTs Qualitative or quantitative data on acceptability (stand-alone qualitative studies were not searched for in the NICE review)
Timeframe	Long term
Additional information	None

K.1.3 Research recommendation

What is the most effective and acceptable method of delivering panretinal photocoagulation for people with proliferative diabetic retinopathy?

K.1.3.1 Why this is important

While there is evidence that panretinal photocoagulation is effective at treating proliferative diabetic retinopathy, there is limited evidence comparing the effectiveness of different types of panretinal photocoagulation. Therefore, it is currently unclear which type of photocoagulation is the most effective. Further evidence is therefore needed to identify whether there is a particular type of photocoagulation that is best at stopping or slowing progression of disease.

K.1.3.2 Rationale for research recommendation

Importance to 'patients' or the population	There is no evidence on the most effective type of panretinal photocoagulation. If evidence shows that a particular type of photocoagulation is the most effective at preventing progression, it will be possible to reduce the number of people who progress to more severe disease.
Relevance to NICE guidance	There is currently no evidence comparing different types of panretinal photocoagulation for people with proliferative diabetic retinopathy.
Relevance to the NHS	A better understanding of the most effective treatments will reduce the number of people who progress to more severe disease. This will reduce the time needed to treat people with more severe disease as well as reducing the costs associated with treatment.
National priorities	Moderate
Current evidence base	No short- or long-term data
Equality considerations	None known

K.1.3.3 Modified PICO table

Population	People with proliferative diabetic retinopathy
Intervention	• Any type of panretinal photocoagulation
Comparator	• Other types of panretinal photocoagulation •
Outcome	• Change in visual acuity • Functional impact on vision • Number of treatments • Need for subsequent treatments • Adverse events • Progression of retinopathy (non-proliferative to proliferative)

	• Peripheral vision and visual field changes • Quality of life • Acceptability (qualitative or quantitative data on acceptability collected alongside randomised controlled trials)
Study design	RCTs Qualitative or quantitative data on acceptability (stand-alone qualitative studies were not searched for in the NICE review)
Timeframe	Long term
Additional information	None