National Institute for Health and Care Excellence

Final

Diabetic retinopathy

[H] Evidence reviews for clinical features or factors that suggest treatment should be switched or stopped for people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema

NICE guideline NG242

Evidence reviews underpinning recommendation 1.6.7 to 1.6.9 and research recommendation 1 in the NICE guideline

August 2024

Final

These evidence reviews were developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-6435-2

Contents

1 Clinical features or factors that suggest treatment should be switched or stopped for people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema.

1.1 Review question

What are the clinical features or factors that suggest treatment should be switched or stopped for people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema?

1.1.1 Introduction

The decision to switch or stop treatment for individuals diagnosed with proliferative diabetic retinopathy or diabetic macular oedema should be based on various clinical features and factors. The knowledge of which clinical features or factors are the best indicators that treatment should be switched or stopped is therefore important as it ensures that people can get the most effective treatment at the most appropriate time. This can help to stop, or reduce, progression of diabetic retinopathy and macular oedema and improve patient outcomes. The aim of this review is therefore to assess the evidence on which are the most effective criteria for switching or stopping treatment for a person who has diabetic retinopathy or diabetic macular oedema.

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: Clinical features or factors that suggest treatment should be switched or stopped for people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema.

Population	People diagnosed with proliferative diabetic retinopathy. People diagnosed with diabetic macular oedema
Intervention	Switching/stopping treatments according to clinical features or criteria specified in trial protocol (for example, response to treatment) Limited to the following interventions being considered under other review questions in the guideline for this population: • Vitrectomy • Laser photocoagulation • Anti-VEGF agents

	• Intravitreal steroids • Combinations of the treatments listed above
Comparator	Not switching/stopping treatments.
Outcomes	**Primary:** Best corrected visual acuity • Best correct visual acuity will be presented per eye when this data is available in the study. • Per patient data will only be extracted when this data is not presented in a study. Progression of proliferative diabetic retinopathy or macular oedema **Secondary:** Quality of life (measured using validated tool) Driving vision (dichotomous outcome, number of participants with vision sufficient to allow driving).

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.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

2324 records were identified in the search for title and abstract screening. Following the title and abstract screening, 8 records were selected for full-text screening. Of these, only 2 studies were found to meet the inclusion criteria and were therefore included in the review. The re-run searches identified 164 additional studies, but none met the inclusion criteria for the review.

Of the two included studies, one was a randomised controlled trial (RCT), and the other was a comparative observational study. Both included people with diabetic macular oedema and considered criteria for switching, rather than stopping, treatment. The 2 studies considered the following criteria for switching treatment:

- RCT: Persistent centre-involving diabetic macular oedema - recent treatment of the eye which resulted in no improvement in eye condition and/or suboptimal vision

(Intervention: Bevacizumab with switch to aflibercept at week 12 vs aflibercept monotherapy)

- Observational study: Suboptimal response to the anti-VEGF loading phase (Intervention: Switch to steroids vs Anti-VEGF only).

1.1.4.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence.

Table 2: Table of included studies

Study	Longest Follow-up time	Population	Intervention	Comparator	Outcomes	Criteria for switching
RCT						
Jhaveri 2022	2 years	Diabetic macular oedema Aflibercept group – Median age (IQR): 60 (55-66), Female 48% Bevacizumab-First Group – Median age (IQR): 61 (54-67, Female 48%	Bevacizumab-First, (1.25 mg) with switch to aflibercept (2.0 mg) from 12 weeks (n=154 eyes)	Aflibercept-Monotherapy 2.0 mg (n=158 eyes)	Visual acuity letter score	Persistent centre-involved diabetic macular oedema Recent treatment of eye No recent improvement in eye condition, Suboptimal vision[1]
Observational – retrospective cohort study[2]						
Busch 2019	2 years	Treatment Naïve diabetic macular oedema, Anti-VEGF only – mean age (SD): 60 (10.2) Anti-VEGF with switch to steroids 2nd year – mean age (SD): 62.1 (13.1)	Anti-VEGF throughout 1st year +switch to steroids in 2nd year (n=14 eyes) Early switch to DEX implant (n=29 eyes)	Only anti-VEGF during study period (65.9% Ranibizumab, 15.9% Aflibercept, 18.2% Bevacizumab) (n=44 eyes)	Visual acuity, letter score / logMAR	Not provided: *'There was no predefined treatment protocol, and treatment decisions could have differed between centres.* *Reasons for switching therapies*

Study	Longest Follow-up time	Population	Intervention	Comparator	Outcomes	Criteria for switching
		Early switch to DEX implant – mean age (SD): 64 (12.7)				*were not assessed'.* But all participants had a suboptimal response to anti-VEGF loading phase

1. See Appendix D, Jhaveri 2022 evidence table for how criteria were defined.
2. Non-randomised study. Authors adjusted for age, gender, stage of diabetic retinopathy, EZ disruption at baseline, lens status at baseline

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

A mean difference less than 0 favours the intervention (anti-VEGF treatment) and a mean difference greater than 0 favours the control arm (placebo). If the confidence interval crosses the line of no effect (0) this would be interpreted as unable to differentiate between switching criteria.

Table 3: Persistent centre-involving diabetic macular oedema - recent treatment of the eye which resulted in no improvement in eye condition and/or suboptimal vision (Bevacizumab first with switch to aflibercept at week 12 vs aflibercept monotherapy) (n= number of eyes)

Outcomes	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Mean change in visual acuity over 2-year study period[1]	1 (Jhaveri 2022, RCT)	260	MD -0.80 (-2.50, 0.90)	Moderate	Unable to differentiate
Visual acuity (letter score) at 2 years	1 (Jhaveri 2022, RCT)	260	MD 1.00 (-2.41. 4.41)	Moderate	Unable to differentiate
Visual acuity – number of eyes 20/20 or better	1 (Jhaveri 2022, RCT)	260	RR 1.00 (0.88,1.14)	Moderate	Unable to differentiate
Visual acuity – number of eyes 20/40 or better	1 (Jhaveri 2022, RCT)	260	RR 1.02 (0.88,1.18)	Moderate	Unable to differentiate
Visual acuity – number of eyes 20/200 or worse	1 (Jhaveri	260	RR 0.34 (0.07,1.67)	Moderate	Unable to differentiate

Outcomes	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
	2022, RCT)				
Visual acuity - Mean change from baseline in letter score at 2 years	1 (Jhaveri 2022, RCT)	260	MD 1.80 (-1.30, 4.90)	Moderate	Unable to differentiate
Visual acuity - Improvement by ≥ 15 letters	1 (Jhaveri 2022, RCT)	260	RR 1.09 (0.88, 1.36)	Moderate	Unable to differentiate
Visual acuity - Improvement by ≥ 10 letters	1 (Jhaveri 2022, RCT)	260	RR 1.00 (0.87, 1.14)	Moderate	Unable to differentiate
Visual acuity - Worsening by ≥ 10 letters	1 (Jhaveri 2022, RCT)	260	RR 0.57 (0.20, 1.66)	Moderate	Unable to differentiate
Visual acuity - Worsening by ≥ 15 letters	1 (Jhaveri 2022, RCT)	260	RR 0.52 (0.16, 1.67)	Moderate	Unable to differentiate

1) The primary outcome was the time-averaged change in the visual-acuity letter score over a period of 104 weeks. The score was derived by calculating the area under the curve (AUC) over the 104-week period for the change in visual acuity from baseline and dividing by the length of follow-up.

Table 4: Suboptimal response to the anti-VEGF loading phase (Anti-VEGF only vs switch to steroids) (n= number of eyes)

Outcomes	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Anti-VEGF only vs Switch to steroids in 2nd year (n= number of eyes)					
Visual acuity logMAR – 24 months	1 (Busch 2019, observational)	58	MD 0.05 (-0.09, 0.19)	Low	Unable to differentiate
Visual acuity – mean change in letters month 3-24	1 (Busch 2019, observational)	58	MD 4.40 (-1.38, 10.18)	Low	Unable to differentiate
Visual acuity gain ≥ 5 letters at month 24 (from month 3)	1 (Busch 2019, observational)	58	RR 1.32 (0.75, 2.33)	Low	Unable to differentiate
Visual acuity gain ≥ 10 letters at month 24 (from month 3)	1 (Busch 2019, observational)	58	RR 2.00 (0.96, 4.16)	Low	Unable to differentiate
VA loss ≥ 5 letters at month 24 (from month 3)	1 (Busch 2019, observational)	58	RR 0.24 (0.03, 1.69)	Low	Unable to differentiate
Anti-VEGF only vs early switch (3 months) to DEX implant (n=number of eyes)					

Outcomes	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual acuity – mean logMAR at 24 months	1 (Busch 2019, observational)	73	MD -0.02 (-0.13, 0.09)	Low	Unable to differentiate
Visual acuity - change in letters from month 3-24	1 (Busch 2019, observational)	73	MD 6.10 (-0.03, 12.23)	Low	Unable to differentiate
Visual acuity gain ≥ 5 letters at month 24 (from month 3)	1 (Busch 2019, observational)	73	RR 1.60 (1.05, 2.43)	Low	Favours early switch to DEX implant
Visual acuity gain ≥ 10 letters at month 24 (from month 3)	1 (Busch 2019, observational)	73	RR 2.34 (1.29, 4.26)	Low	Favours early switch to DEX implant
Visual acuity loss ≥ 5 letters at month 24 (from month 3)	1 (Busch 2019, observational)	73	RR 0.58 (0.23, 1.46)	Low	Unable to differentiate

See Appendix F for full GRADE and tables and Appendix E for forest plots.

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, 671 of the studies could confidently be excluded for this review question. One study was excluded following the full-text review. No relevant health economic studies were included.

1.1.7.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

See the health economic study selection flow chart presented in Appendix G.

1.1.8 Summary of included economic evidence

No relevant health economic studies were identified to be included.

1.1.9 Economic model

Original health economic modelling was not conducted for this review question.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

The committee considered deterioration of visual acuity as a primary outcome for assessing the need to switch or stop treatment. Visual acuity is a crucial factor in evaluating the effectiveness of interventions for diabetic retinopathy and making treatment decisions.

Progression of retinopathy is also important, as this can lead to serious consequences, such as loss of vision. Quality of life is an important aspect to consider as it assesses the impact of the disease and its treatments on a person's overall well-being and daily functioning. Similarly, driving vision, which includes factors such as peripheral vision and visual field, is crucial for safe and independent mobility. However, there was no evidence available for either quality of life or driving vision.

1.1.10.2 The quality of the evidence

The review included two studies, one of which was a moderate quality RCT, and the other was a low-quality retrospective observational study. Both studies considered switching criteria for people who have diabetic macular oedema. There was no evidence for people who have proliferative diabetic retinopathy. Evidence considered the criteria for switching treatments, but there was no evidence for when to stop treatment.

The quality of the RCT was downgraded due to concerns related to the lack of information about blinding and missing data. The observational study included a small number of participants and was downgraded because it was non-randomised, and there were concerns about how the interventions were classified. The committee also considered the limitations in the study design, where in the second year of the study, some participants who switched treatments were divided into two groups: those who switched to a dexamethasone implant and those who switched to a fluocinolone acetonide implant. Additionally, within the group that switched to the dexamethasone implant, some participants later switched to the fluocinolone acetonide implant, while others received additional anti-VEGF injections. The variation in treatments within this arm of the study made it challenging to assess the specific effects of switching to dexamethasone implants. The committee were concerned that the different interventions and subsequent switches introduced confounding factors that could impact the interpretation of the results.

The committee decided that the presence of various treatment options and switching patterns introduced complexity to the evidence and limited their ability to draw clear conclusions regarding the effects of specific switching criteria. The trial also had a small sample size and a relatively short follow-up period.

Given the limited data available, the committee could not determine which clinical features best indicate the need to switch or stop treatments. Each study used different treatments and had different criteria for switching treatments, with one study assessing specific clinical features and the other focusing on lack of response to treatment. Furthermore, the results of each study were only applicable to the specific switching criteria defined by that particular study. It was noted that neither study included an exhaustive list of features to assess treatment response and so it was not possible to determine which criteria would be the most effective. As a result, the committee decided they could not make recommendations about the best criteria or clinical features to indicate that treatments should be switched or stopped for people who have diabetic macular oedema. Instead, they made a research recommendation designed to provide further information on these criteria in future (see Appendix K).

1.1.10.3 Benefits and harms.

The evidence for switching from bevacizumab to aflibercept at 12 weeks based on a lack of improvement in vision, suboptimal vision, or recent treatment of the eye did not demonstrate any evidence of benefit compared to aflibercept monotherapy. Given the limited evidence and the limitations of the study mentioned in the quality of the evidence section, the committee did not think they could recommend this specific switching criteria. They emphasised the

importance of considering the longer-term effects of switching treatments and the need for more robust evidence in this area.

The committee were concerned that switching treatments in diabetic macular oedema requires careful consideration, taking into account factors such as treatment response, individual patient characteristics, and potential long-term effects. The committee acknowledged the need for additional research to provide a more comprehensive understanding of the effects of switching treatments and to establish appropriate criteria for guiding treatment decisions in the long term (see Appendix K).

The evidence for switching treatment based on a suboptimal response to an anti-VEGF loading phase showed minimal differences between people who remained on anti-VEGFs and those who met the switching criteria and changed to a dexamethasone implant. Both treatment approaches led to some improvements in visual acuity over the 2-year follow-up period. However, the evidence could not differentiate between changes in visual acuity between those who were given the switch in treatment at 2 years and those who remained on anti-VEGF monotherapy. When people switched treatment at 3 months, more people had a visual acuity gain of over 10 letters at 2 years, but no other outcomes could differentiate between those who did, or did not, follow the switching criteria. The low-quality evidence, limited definition of the switching criteria and concerns about the methods used when switching meant that the committee did not think they could recommend this as a way of deciding when to switch treatments.

The committee highlighted the importance of assessing response to treatment after the loading phase. They highlighted an additional concern about the treatment regimen used in the studies, which involved participants receiving a monthly loading dose of anti-VEGF therapy for 3 months before being assessed for treatment response. The committee expressed concerns that a 3-month loading phase may not be sufficient to accurately assess responsiveness to treatment, as it does not account for delayed responders. It is well-known that some individuals with diabetes may require longer loading phases to achieve a therapeutic response. Considering this, the committee made a recommendation to highlight the need to assess response to treatments after 12 months and then consider switching treatments if that response is suboptimal.

The committee thought that ideally there should be a list of clinical, anatomical, and biochemical features that can be used to define responsiveness to anti-VEGF therapy to help determine whether to continue, switch or stop treatment. It was discussed how the criteria for switching treatments currently varies among centres. However, there was insufficient evidence to develop this kind of recommendation and so the committee decided to make a research recommendation (see Appendix K). This should improve knowledge on the most important switching and stopping criteria and help make more specific recommendations in future guideline updates.

1.1.10.4 Cost effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost effectiveness of the clinical features or factors that suggest treatment should be switched or stopped for people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema. The committee discussed the importance of having a long enough loading phase of treatment to allow for a response to occur and noted that no response at all is unusual. The committee noted that continuing treatment in people who do not have a response to treatment could have resource implications such as cost of unnecessary treatment and avoidable treatment-related adverse events, so assessing response after the loading phase could minimise these costs and

negative outcomes. It is expected that these assessments would happen during existing monitoring visits so would not require additional resources.

Overall, the committee were not concerned about any resource impact as a result of the recommendations as the assessments and loading phase are part of current practice.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.7 to 1.6.9 and the research recommendation on effectiveness of clinical features or factors that suggest treatment should be switched or stopped.

1.1.12 References – included studies.

1.1.12.1 Effectiveness

Busch, Catharina, Fraser-Bell, Samantha, Iglicki, Matias et al. (2019) Real-world outcomes of non-responding diabetic macular edema treated with continued anti-VEGF therapy versus early switch to dexamethasone implant: 2-year results. Acta diabetologica 56(12): 1341-1350

Jhaveri, Chirag D, Glassman, Adam R, Ferris, Frederick L 3rd et al. (2022) Aflibercept Monotherapy or Bevacizumab First for Diabetic Macular Edema. The New England journal of medicine 387(8): 692-703

1.1.12.2 Economic

No economic studies were included.

Appendices

Appendix A – Review protocols

What are the clinical features or factors that suggest treatment should be switched or stopped for people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema?

ID	Field	Content
0.	PROSPERO registration number	CRD42022354268
1.	Review title	What are the clinical features or factors that suggest treatment should be switched or stopped for people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema?
2.	Review question	Q8: What are the clinical features or factors that suggest treatment should be switched or stopped for people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema?
3.	Objective	To determine what clinical features or factors that suggest treatment should be switched or stopped for people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema? The aim is to inform recommendations for people diagnosed with proliferative diabetic retinopathy and/or macular oedema.
4.	Searches	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 and observational filters will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results

		• No date limit will be set unless specified by the protocol • Cost Utility (specific) and Cohort Studies for the economic search Other searches: • None identified The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for all databases will be published in the final review.
5.	Condition or domain being studied	Diabetic retinopathy, diabetic macular oedema
6.	Population	Inclusion: People diagnosed with proliferative diabetic retinopathy People diagnosed with diabetic macular oedema
7.	Intervention	Switching/stopping treatments according to clinical features or criteria specified in trial protocol (for example, response to treatment) Limited to the following interventions being considered under other review questions in the guideline for this population: • Vitrectomy • Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids

		• Combinations of the treatments listed above
8.	Comparators	Not switching/stopping treatments.
9.	Types of study to be included	Randomised controlled trials Comparative observational studies with a concurrent control group and adjustment for confounding factors to ensure comparable intervention and comparator groups. Examples of possible confounding confounders include: • age • proportion of participants with complications of diabetic retinopathy such as vitreous haemorrhage or tractional retinal detachment • visual acuity • measures of disease severity (e.g. high risk vs low risk proliferative retinopathy, centre involvement vs non-centre involving macular oedema)
10.	Other exclusion criteria	Trials that were not reported in English
11.	Context	Diabetic retinopathy is an important cause of sight loss in adults in the United Kingdom.
12.	Primary outcomes (critical outcomes)	• Best corrected visual acuity

		○ Best correct visual acuity will be presented per eye when this data is available in the study. ○ Per patient data will only be extracted when this data is not presented in a study. • Progression of proliferative diabetic retinopathy or macular oedema
13.	Secondary outcomes (important outcomes)	• Quality of life (measured using validated tool) • Driving vision (dichotomous outcome, number of participants with vision sufficient to allow driving). Outcomes will be reported at the latest time point reported by the study. Reporting at earlier timepoints will be considered to facilitate meta-analysis or where dropout means that earlier timepoints are associated with substantially more precision.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. This review will use of the priority screening functionality within the EPPI-reviewer software. 50% of the database will be screened. Following this point, if 5% of the database is screened without finding an include based on title and abstract screening, screening will be stopped, and the remaining records excluded. These stopping criteria are considered appropriate based on the experience of the team, given this topic is a well defined clinical area with clear inclusion and exclusion criteria. As additional measure, the full database will be searched if there are a very small number of included studies (<30). 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Extracted information for the quantitative review will include: study type; study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; inclusion and exclusion criteria; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using appropriate checklists as described in Developing NICE guidelines: the manual. Risk of bias in RCTs will be assessed using the Cochrane risk of bias version 2 tool. Risk of bias in comparative observational studies will be assessed using the ROBINS-I checklist.
16.	Strategy for data synthesis	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≥50%, when random effects models will be used instead.

		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 and comparative observational studies assessed with ROBINS-I will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered.
17.	Analysis of sub-groups	Data will be presented separately for the following groups: • Pregnant women • Proliferative diabetic retinopathy vs diabetic macular oedema If data is available a subgroup analysis will be conducted by: • Ethnicity • People with a learning disability • Socioeconomic status • Severity of proliferative retinopathy (low vs high risk), Severity of diabetic macular oedema (centre involving vs non-centre involving) • Age: (People under the age of 18, people aged 18 to 80, people aged greater than 80) (if a study has been adjusted for these factors, we will not conduct subgroup analyses on these factors for evidence from that study).
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic

		☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	April 2022		
22.	Anticipated completion date	April 2024		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑

		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** NICE 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		

25.	Review team members	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 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
29.	Other registration details	None

30.	Reference/URL for published protocol	None
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, diabetic macular oedema, switching and stopping treatments
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued

35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Search design and peer review

NICE information specialists conducted the literature searches for the evidence review. The searches were run in September 2022. 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 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, 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

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)	21/09/2022	Wiley	Issue 8 of 12, August 2022
Cochrane Database of Systematic Reviews (CDSR)	21/09/2022	Wiley	Issue 9 of 12, September 2022
Embase	21/09/2022	Ovid	1974 to 2022 September 20
Epistemonikos	21/09/2022	Epistemonikos	Search run on 21 September 2022
HTA	21/09/2022	CRD	Search run on 21 September 2022
INAHTA	21/09/2022	N/A	Search run on 21 September 2022
MEDLINE	21/09/2022	Ovid	1946 to September 20, 2022
MEDLINE-in-Process	21/09/2022	Ovid	1946 to September 20, 2022
MEDLINE ePub Ahead-of-Print	21/09/2022	Ovid	September 20, 2022

Database: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)
#1 MeSH descriptor: [Diabetic Retinopathy] this term only 1577 #2 MeSH descriptor: [Macular Edema] this term only 1277 #3 (diabet* near/6 (retin* or eye* or macular* or maculopath*)):ti,ab,kw 5633 #4 {or #1-#3} 6075 #5 MeSH descriptor: [Retreatment] this term only 861 #6 Retreat*:ti,ab,kw 4498 #7 MeSH descriptor: [Treatment Failure] this term only 3424 #8 MeSH descriptor: [Treatment Switching] this term only 3 #9 MeSH descriptor: [Drug Substitution] this term only 416 #10 MeSH descriptor: [Drug Administration Schedule] this term only 24301

#11 ((Treat* or therap* or techni* or medic* or prescript* or drug* or generic* or agent*) near/4 (switch* or chang* or choic* or choos* or mov* or transfer* or sequenc* or sequent* or order* or opt* or success* or unsuccess* or futil* or fail* or remission* or substitut* or replac* or exchang* or swap* or contraindicat* or ending or ended or end? or stop? or stopping or stopped or terminat* or discontinue* or desist* or cease? or ceasing or halt* or finish* or suspen* or schedule* or plan* or calendar* or itinerary* or program* or timetabl* or alternative* or subsequent* or extend*)):ti,ab,kw 303804
#12 {or #5-#11} 306404
#13 #4 and #12 1245
#14 MeSH descriptor: [Ophthalmologic Surgical Procedures] this term only 404
#15 ((ophthalm* or ocular* or eye*) near/4 (surg* or operat* or proced* or resect* or re-sect* or remov*)):ti,ab,kw 6417
#16 MeSH descriptor: [Vitrectomy] this term only 568
#17 MeSH descriptor: [Vitreoretinal Surgery] this term only 36
#18 vitrectom*:ti,ab,kw 1869
#19 (vitreous* near/4 (surg* or operat* or proced* or resect* or re-sect* or remov*)):ti,ab,kw 374
#20 ((vitreoretinal* or vitreo-retinal*) near/4 (surg* or operat* or proced* or resect* or re-sect* or remov*)):ti,ab,kw 349
#21 {or #14-#20} 8062
#22 MeSH descriptor: [Light Coagulation] explode all trees 767
#23 (photocoagulat* or thermocoagulat* or argon or diode or micropulse):ti,ab,kw 4995
#24 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) near/4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)):ti,ab,kw 20882
#25 ((focal or grid) near/3 laser*):ti,ab,kw 346
#26 PRP:ti,ab,kw 2889
#27 {or #22-#26} 25149
#28 MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees 1482
#29 MeSH descriptor: [Receptors, Vascular Endothelial Growth Factor] explode all trees 448
#30 (anti near/2 VEGF*):ti,ab,kw 1510
#31 (anti-VEGF* or antiVEGF*):ti,ab,kw 1488
#32 ((anti-vascular or antivascular) near/2 endothelial growth factor*):ti,ab,kw 648
#33 (((vascular endothelial near/2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) near/2 (trap* or inhibit* or antagonist*)):ti,ab,kw 6588
#34 (vascular proliferation near/4 inhibit*):ti,ab,kw 93
#35 (endothelial near/2 growth near/2 factor*):ti,ab,kw 4577
#36 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees 1372
#37 MeSH descriptor: [Angiogenesis Inducing Agents] this term only 51

#38 Aflibercept*:ti,ab,kw 1017
#39 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005):ti,ab,kw 246
#40 MeSH descriptor: [Bevacizumab] this term only 2242
#41 Bevacizumab*:ti,ab,kw 6984
#42 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865):ti,ab,kw 927
#43 (IVB near/2 inject*):ti,ab,kw 84
#44 MeSH descriptor: [Ranibizumab] this term only 965
#45 Ranibizumab*:ti,ab,kw 2179
#46 (Lucentis or rhuFab):ti,ab,kw 446
#47 (IVR near/2 inject*):ti,ab,kw 30
#48 (Faricimab or Vabysmo):ti,ab,kw 36
#49 (Pegaptanib* or macugen*):ti,ab,kw 183
#50 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838):ti,ab,kw 82
#51 MeSH descriptor: [Sunitinib] this term only 353
#52 (Sunitinib or Sutent):ti,ab,kw 1321
#53 MeSH descriptor: [Sorafenib] this term only 537
#54 (Sorafenib or Nexavar):ti,ab,kw 2013
#55 MeSH descriptor: [Axitinib] this term only 110
#56 (Axitinib or Inlyta):ti,ab,kw 368
#57 (Pazopanib or Votrient):ti,ab,kw 608
#58 {or #28-#57} 20926
#59 MeSH descriptor: [Intravitreal Injections] this term only 979
#60 (Intravitreal* near/2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)):ti,ab,kw 3164
#61 MeSH descriptor: [Dexamethasone] this term only 5068
#62 MeSH descriptor: [Fluocinolone Acetonide] this term only 351
#63 MeSH descriptor: [Triamcinolone Acetonide] this term only 1196
#64 (Dexamethasone* or kenalog or kenacort or retisert*):ti,ab,kw 14050
#65 ((fluocinolone* or triamcinolone*) near/2 acetonide*):ti,ab,kw 2890
#66 Iluvien*:ti,ab,kw 15
#67 (Adcortyl* or Kenalog*):ti,ab,kw 112
#68 {or #59-#67} 19336
#69 #21 or #27 or #58 or #68 67249
#70 #13 and #69 872

Database: Embase

1 diabetic retinopathy/47174
2 macular edema/ 6300
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 52164

4 or/1-3 70902
5 retreatment/ 14267
6 Retreat*.tw. 20635
7 treatment failure/ or treatment switching/ 152467
8 drug substitution/ 49775
9 drug administration/ 53540
10 ((Treat* or therap* or techni* or medic* or prescript* or drug* or generic* or agent*) adj4 (switch* or chang* or choic* or choos* or mov* or transfer* or sequenc* or sequent* or order* or opt* or success* or unsuccess* or futil* or fail* or remission* or substitut* or replac* or exchang* or swap* or contraindicat* or ending or ended or end? or stop? or stopping or stopped or terminat* or discontinue* or desist* or cease? or ceasing or halt* or finish* or suspen* or schedule* or plan* or calendar* or itinerary* or program* or timetabl* or alternative* or subsequent* or extend*)).tw. 2517722
11 or/5-10 2699085
12 4 and 11 6832
13 eye surgery/ 20324
14 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 43006
15 vitrectomy/ or vitreoretinal surgery/ 26239
16 vitrectom*.tw. 22018
17 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 3393
18 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 3215
19 or/13-18 84328
20 exp laser coagulation/ 23278
21 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 59853
22 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 140345
23 ((focal or grid) adj3 laser*).tw. 1448
24 PRP.tw. 24529
25 or/20-24 218090
26 exp vasculotropin/ 152773
27 exp vasculotropin receptor/ 12661
28 (anti adj2 VEGF*).tw. 14403
29 (anti-VEGF* or antiVEGF*).tw. 14031
30 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 6580
31 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 16456
32 (vascular proliferation adj4 inhibit*).tw. 44
33 (endothelial adj2 growth adj2 factor*).tw. 87718

34 angiogenesis/ or angiogenesis inhibitor/ or angiogenic factor/ or endothelial cell growth factor/ 162876
35 aflibercept/ 8006
36 Aflibercept*.tw. 4404
37 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 1607
38 bevacizumab/ 68468
39 Bevacizumab*.tw. 34014
40 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).tw. 10653
41 (IVB adj2 inject*).tw. 382
42 ranibizumab/ 11646
43 Ranibizumab*.tw. 6918
44 (Lucentis or rhuFab).tw. 3054
45 (IVR adj2 inject*).tw. 189
46 faricimab/ 153
47 (Faricimab or Vabysmo).tw. 77
48 pegaptanib/ 2401
49 (Pegaptanib* or macugen*).tw. 1569
50 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 1242
51 sunitinib/ 25911
52 (Sunitinib or Sutent).tw. 13909
53 sorafenib/ 34806
54 (Sorafenib or Nexavar).tw. 20385
55 axitinib/ 6381
56 (Axitinib or Inlyta).tw. 2631
57 pazopanib/ 9783
58 (Pazopanib or Votrient).tw. 4439
59 or/26-58 379015
60 intravitreal drug administration/ 6218
61 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 18577
62 dexamethasone/ or fluocinolone acetonide/ or triamcinolone acetonide/ 190328
63 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 91044
64 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 6959
65 Iluvien*.tw. 379
66 (Adcortyl* or Kenalog*).tw. 1802
67 or/60-66 220731
68 19 or 25 or 59 or 67 858062
69 12 and 68 3789
70 random:.tw. 1835567
71 placebo:.mp. 501609
72 double-blind:.tw. 233829
73 or/70-72 2105598

74 Clinical study/ 160374
75 Case control study/ 192923
76 Family study/ 25689
77 Longitudinal study/ 178369
78 Retrospective study/ 1308963
79 comparative study/ 968911
80 Prospective study/ 795513
81 Randomized controlled trials/ 234699
82 80 not 81 786127
83 Cohort analysis/ 896498
84 cohort analy$.tw. 17346
85 (Cohort adj (study or studies)).tw. 412338
86 (Case control$ adj (study or studies)).tw. 161374
87 (follow up adj (study or studies)).tw. 70364
88 (observational adj (study or studies)).tw. 226477
89 (epidemiologic$ adj (study or studies)).tw. 117471
90 (cross sectional adj (study or studies)).tw. 302140
91 prospective.tw. 1025267
92 retrospective.tw. 1138517
93 or/74-79,82-92 4917932
94 73 or 93 6511573
95 69 and 94 1926
96 Nonhuman/ not Human/ 5056555
97 95 not 96 1911
98 limit 97 to english language 1824
99 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5316113
100 98 not 99 1250

Database: Epistemonikos

(title:((Diabetic retinopath* OR macular edema OR macular oedema OR diabetic maculopath*)) OR abstract:((Diabetic retinopath* OR macular edema OR macular oedema OR diabetic maculopath*)))

AND

(title:(Treat* OR therap* OR techni* OR medic* OR prescript* OR drug* OR generic* OR agent*) OR abstract:(Treat* OR therap* OR techni* OR medic* OR prescript* OR drug* OR generic* OR agent*))

AND

(title:(switch* OR chang* OR choic* OR choos* OR mov* OR transfer* OR sequenc* OR sequent* OR order* OR opt* OR success* OR unsuccess* OR futil*

OR fail* OR remission* OR substitut* OR replac* OR exchang* OR swap* OR contraindicat* OR ending OR ended OR end? OR stop? OR stopping OR stopped OR terminat* OR discontinue* OR desist* OR cease? OR ceasing OR halt* OR finish* OR suspen* OR schedule* OR plan* OR calendar* OR itinerary* OR program* OR timetabl* OR alternative* OR subsequent* OR extend*) OR abstract:(switch* OR chang* OR choic* OR choos* OR mov* OR transfer* OR sequenc* OR sequent* OR order* OR opt* OR success* OR unsuccess* OR futil* OR fail* OR remission* OR substitut* OR replac* OR exchang* OR swap* OR contraindicat* OR ending OR ended OR end? OR stop? OR stopping OR stopped OR terminat* OR discontinue* OR desist* OR cease? OR ceasing OR halt* OR finish* OR suspen* OR schedule* OR plan* OR calendar* OR itinerary* OR program* OR timetabl* OR alternative* OR subsequent* OR extend*))

Database: Health Technology Assessment (HTA)

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118
2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82
3 ((diabet* near (retin* or eye* or macular* or maculopath*))) 225
4 #1 OR #2 OR #3 254
5 MeSH DESCRIPTOR Retreatment EXPLODE ALL TREES 55
6 (Retreat*) 133
7 MeSH DESCRIPTOR Treatment Failure EXPLODE ALL TREES 290
8 MeSH DESCRIPTOR Treatment Switching EXPLODE ALL TREES 0
9 MeSH DESCRIPTOR Drug Substitution EXPLODE ALL TREES 32
10 MeSH DESCRIPTOR Drug Administration Schedule EXPLODE ALL TREES 821
11 ((((Treat* or therap* or techni* or medic* or prescript* or drug* or generic* or agent*) near (switch* or chang* or choic* or choos* or mov* or transfer* or sequenc* or sequent* or order* or opt* or success* or unsuccess* or futil* or fail* or remission* or substitut* or replac* or exchang* or swap* or contraindicat* or ending or ended or end? or stop? or stopping or stopped or terminat* or discontinue* or desist* or cease? or ceasing or halt* or finish* or suspen* or schedule* or plan* or calendar* or itinerary* or program* or timetabl* or alternative* or subsequent* or extend*)))) 11229
12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 11295
13 #4 AND #12 53
14 * IN HTA 17351
15 #13 AND #14 10

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

13 #12 AND #4 6

12 #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 6275
11 (((Treat* or therap* or techni* or medic* or prescript* or drug* or generic* or agent*) AND (switch* or chang* or choic* or choos* or mov* or transfer* or sequenc* or sequent* or order* or opt* or success* or unsuccess* or futil* or fail* or remission* or substitut* or replac* or exchang* or swap* or contraindicat* or ending or ended or end? or stop? or stopping or stopped or terminat* or discontinue* or desist* or cease? or ceasing or halt* or finish* or suspen* or schedule* or plan* or calendar* or itinerary* or program* or timetabl* or alternative* or subsequent* or extend*))) 6264
10 "Drug Administration Schedule"[mh] 18
9 "Drug Substitution"[mh] 1
8 "Treatment Switching"[mh] 0
7 "Treatment Failure"[mh] 9
6 Retreat* 20
5 "Retreatment"[mh] 1
4 #3 AND #2 AND #1 12
3 (diabet* AND (retin* or eye* or macular* or maculopath*)) 87
2 "Macular Edema"[mh] 28
1 "Diabetic Retinopathy"[mh] 40

Database: Ovid MEDLINE(R)

1 Diabetic Retinopathy/ 28410
2 Macular Edema/ 8536
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 32853
4 or/1-3 43110
5 Retreatment/ 9889
6 Retreat*.tw. 11808
7 Treatment Failure/ or Treatment Switching/ 37075
8 Drug Substitution/ 4450
9 Drug Administration Schedule/ 103274
10 ((Treat* or therap* or techni* or medic* or prescript* or drug* or generic* or agent*) adj4 (switch* or chang* or choic* or choos* or mov* or transfer* or sequenc* or sequent* or order* or opt* or success* or unsuccess* or futil* or fail* or remission* or substitut* or replac* or exchang* or swap* or contraindicat* or ending or ended or end? or stop? or stopping or stopped or terminat* or discontinue* or desist* or cease? or ceasing or halt* or finish* or suspen* or schedule* or plan* or calendar* or itinerary* or program* or timetabl* or alternative* or subsequent* or extend*)).tw. 1470035
11 or/5-10 1587810
12 4 and 11 3589
13 Ophthalmologic Surgical Procedures/ 13042

14 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 30354
15 Vitrectomy/ or Vitreoretinal Surgery/ 15854
16 vitrectom*.tw. 15076
17 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 2238
18 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 2282
19 or/13-18 57894
20 exp Light Coagulation/ 13110
21 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 36333
22 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 96156
23 ((focal or grid) adj3 laser*).tw. 860
24 PRP.tw. 15492
25 or/20-24 142163
26 exp Vascular Endothelial Growth Factors/ 62068
27 exp Receptors, Vascular Endothelial Growth Factor/ 17807
28 (anti adj2 VEGF*).tw. 7057
29 (anti-VEGF* or antiVEGF*).tw. 6818
30 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 4241
31 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 9382
32 (vascular proliferation adj4 inhibit*).tw. 29
33 (endothelial adj2 growth adj2 factor*).tw. 61460
34 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 113158
35 Aflibercept*.tw. 2051
36 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 232
37 Bevacizumab/ 13599
38 Bevacizumab*.tw. 15339
39 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).tw. 1371
40 (IVB adj2 inject*).tw. 234
41 Ranibizumab/ 4491
42 Ranibizumab*.tw. 3757
43 (Lucentis or rhuFab).tw. 362
44 (IVR adj2 inject*).tw. 105
45 (Faricimab or Vabysmo).tw. 35
46 (Pegaptanib* or macugen*).tw. 457
47 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 118

48 Sunitinib/ 4036
49 (Sunitinib or Sutent).tw. 5374
50 Sorafenib/ 5946
51 (Sorafenib or Nexavar).tw. 7964
52 Axitinib/ 675
53 (Axitinib or Inlyta).tw. 962
54 (Pazopanib or Votrient).tw. 1593
55 or/26-54 150226
56 Intravitreal Injections/ 9334
57 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 11394
58 Dexamethasone/ or Fluocinolone Acetonide/ or Triamcinolone Acetonide/ 61562
59 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 57221
60 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 4936
61 Iluvien*.tw. 54
62 (Adcortyl* or Kenalog*).tw. 216
63 or/56-62 94045
64 19 or 25 or 55 or 63 419549
65 12 and 64 2176
66 randomized controlled trial.pt. 577297
67 randomi?ed.mp. 932749
68 placebo.mp. 219490
69 or/66-68 989062
70 Observational Studies as Topic/ 8149
71 Observational Study/ 132536
72 Epidemiologic Studies/ 9185
73 exp Case-Control Studies/ 1355584
74 exp Cohort Studies/ 2397615
75 Cross-Sectional Studies/ 440839
76 Comparative Study.pt. 1911562
77 case control$.tw. 133020
78 (cohort adj (study or studies)).tw. 247026
79 cohort analy$.tw. 9389
80 (follow up adj (study or studies)).tw. 50102
81 (observational adj (study or studies)).tw. 121907
82 longitudinal.tw. 257971
83 prospective.tw. 596744
84 retrospective.tw. 584210
85 cross sectional.tw. 386442
86 or/70-85 4947297
87 69 or 86 5543766
88 65 and 87 1334
89 Animals/ not Humans/ 5015560
90 88 not 89 1329
91 limit 90 to english language 1240

92 limit 91 to (letter or historical article or comment or editorial or news or case reports) 61
93 91 not 92 1179

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

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 1
4 or/1-3 1
5 Retreatment/ 0
6 Retreat*.tw. 1
7 Treatment Failure/ or Treatment Switching/ 0
8 Drug Substitution/ 0
9 Drug Administration Schedule/ 0
10 ((Treat* or therap* or techni* or medic* or prescript* or drug* or generic* or agent*) adj4 (switch* or chang* or choic* or choos* or mov* or transfer* or sequenc* or sequent* or order* or opt* or success* or unsuccess* or futil* or fail* or remission* or substitut* or replac* or exchang* or swap* or contraindicat* or ending or ended or end? or stop? or stopping or stopped or terminat* or discontinue* or desist* or cease? or ceasing or halt* or finish* or suspen* or schedule* or plan* or calendar* or itinerary* or program* or timetabl* or alternative* or subsequent* or extend*)).tw. 232
11 or/5-10 233
12 4 and 11 0
13 Ophthalmologic Surgical Procedures/ 0
14 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 1
15 Vitrectomy/ or Vitreoretinal Surgery/ 0
16 vitrectom*.tw. 0
17 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 0
18 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 0
19 or/13-18 1
20 exp Light Coagulation/ 0
21 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 3
22 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 14
23 ((focal or grid) adj3 laser*).tw. 0
24 PRP.tw. 1
25 or/20-24 17
26 exp Vascular Endothelial Growth Factors/ 0
27 exp Receptors, Vascular Endothelial Growth Factor/ 0

28 (anti adj2 VEGF*).tw. 2
29 (anti-VEGF* or antiVEGF*).tw. 2
30 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 1
31 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 1
32 (vascular proliferation adj4 inhibit*).tw. 0
33 (endothelial adj2 growth adj2 factor*).tw. 7
34 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 0
35 Aflibercept*.tw. 1
36 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 0
37 Bevacizumab/ 0
38 Bevacizumab*.tw. 6
39 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).tw. 0
40 (IVB adj2 inject*).tw. 0
41 Ranibizumab/ 0
42 Ranibizumab*.tw. 0
43 (Lucentis or rhuFab).tw. 0
44 (IVR adj2 inject*).tw. 0
45 (Faricimab or Vabysmo).tw. 0
46 (Pegaptanib* or macugen*).tw. 0
47 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 0
48 Sunitinib/ 0
49 (Sunitinib or Sutent).tw. 0
50 Sorafenib/ 0
51 (Sorafenib or Nexavar).tw. 1
52 Axitinib/ 0
53 (Axitinib or Inlyta).tw. 0
54 (Pazopanib or Votrient).tw. 0
55 or/26-54 15
56 Intravitreal Injections/ 0
57 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 1
58 Dexamethasone/ or Fluocinolone Acetonide/ or Triamcinolone Acetonide/ 0
59 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 8
60 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 0
61 Iluvien*.tw. 0
62 (Adcortyl* or Kenalog*).tw. 0
63 or/56-62 9
64 19 or 25 or 55 or 63 41
65 12 and 64 0
66 randomized controlled trial.pt. 0
67 randomi?ed.mp. 188

68 placebo.mp. 27
69 or/66-68 191
70 Observational Studies as Topic/ 0
71 Observational Study/ 0
72 Epidemiologic Studies/ 0
73 exp Case-Control Studies/ 0
74 exp Cohort Studies/ 0
75 Cross-Sectional Studies/ 0
76 Comparative Study.pt. 0
77 case control$.tw. 27
78 (cohort adj (study or studies)).tw. 112
79 cohort analy$.tw. 1
80 (follow up adj (study or studies)).tw. 2
81 (observational adj (study or studies)).tw. 60
82 longitudinal.tw. 61
83 prospective.tw. 129
84 retrospective.tw. 227
85 cross sectional.tw. 132
86 or/70-85 581
87 69 or 86 727
88 65 and 87 0
89 Animals/ not Humans/ 0
90 88 not 89 0
91 limit 90 to english language 0
92 limit 91 to (letter or historical article or comment or editorial or news or case reports) 0
93 91 not 92 0

Database: Ovid MEDLINE(R) Epub Ahead of Print

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 499
4 or/1-3 499
5 Retreatment/ 0
6 Retreat*.tw. 236
7 Treatment Failure/ or Treatment Switching/ 0
8 Drug Substitution/ 0
9 Drug Administration Schedule/ 0
10 ((Treat* or therap* or techni* or medic* or prescript* or drug* or generic* or agent*) adj4 (switch* or chang* or choic* or choos* or mov* or transfer* or sequenc* or sequent* or order* or opt* or success* or unsuccess* or futil* or fail* or remission* or substitut* or replac* or exchang* or swap* or contraindicat* or ending

or ended or end? or stop? or stopping or stopped or terminat* or discontinue* or desist* or cease? or ceasing or halt* or finish* or suspen* or schedule* or plan* or calendar* or itinerary* or program* or timetabl* or alternative* or subsequent* or extend*)).tw. 24205
11 or/5-10 24375
12 4 and 11 54
13 Ophthalmologic Surgical Procedures/ 0
14 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 524
15 Vitrectomy/ or Vitreoretinal Surgery/ 0
16 vitrectom*.tw. 326
17 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 19
18 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 42
19 or/13-18 819
20 exp Light Coagulation/ 0
21 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 641
22 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 1534
23 ((focal or grid) adj3 laser*).tw. 9
24 PRP.tw. 195
25 or/20-24 2243
26 exp Vascular Endothelial Growth Factors/ 0
27 exp Receptors, Vascular Endothelial Growth Factor/ 0
28 (anti adj2 VEGF*).tw. 192
29 (anti-VEGF* or antiVEGF*).tw. 190
30 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 125
31 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 135
32 (vascular proliferation adj4 inhibit*).tw. 0
33 (endothelial adj2 growth adj2 factor*).tw. 659
34 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 0
35 Aflibercept*.tw. 89
36 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 6
37 Bevacizumab/ 0
38 Bevacizumab*.tw. 269
39 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).tw. 10
40 (IVB adj2 inject*).tw. 3

41 Ranibizumab/ 0
42 Ranibizumab*.tw. 92
43 (Lucentis or rhuFab).tw. 2
44 (IVR adj2 inject*).tw. 1
45 (Faricimab or Vabysmo).tw. 3
46 (Pegaptanib* or macugen*).tw. 8
47 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 0
48 Sunitinib/ 0
49 (Sunitinib or Sutent).tw. 61
50 Sorafenib/ 0
51 (Sorafenib or Nexavar).tw. 133
52 Axitinib/ 0
53 (Axitinib or Inlyta).tw. 32
54 (Pazopanib or Votrient).tw. 29
55 or/26-54 1207
56 Intravitreal Injections/ 0
57 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 268
58 Dexamethasone/ or Fluocinolone Acetonide/ or Triamcinolone Acetonide/ 0
59 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 548
60 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 64
61 Iluvien*.tw. 7
62 (Adcortyl* or Kenalog*).tw. 0
63 or/56-62 842
64 19 or 25 or 55 or 63 4700
65 12 and 64 33
66 randomized controlled trial.pt. 1
67 randomi?ed.mp. 12909
68 placebo.mp. 2667
69 or/66-68 13740
70 Observational Studies as Topic/ 0
71 Observational Study/ 2
72 Epidemiologic Studies/ 0
73 exp Case-Control Studies/ 0
74 exp Cohort Studies/ 0
75 Cross-Sectional Studies/ 0
76 Comparative Study.pt. 0
77 case control$.tw. 2252
78 (cohort adj (study or studies)).tw. 8769
79 cohort analy$.tw. 301
80 (follow up adj (study or studies)).tw. 557
81 (observational adj (study or studies)).tw. 3997
82 longitudinal.tw. 6619
83 prospective.tw. 11356
84 retrospective.tw. 17454
85 cross sectional.tw. 10469

86	or/70-85	47342
87	69 or 86	58079
88	65 and 87	14
89	Animals/ not Humans/	0
90	88 not 89	14
91	limit 90 to english language	14
92	limit 91 to (letter or historical article or comment or editorial or news or case reports)	0
93	91 not 92	14

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.

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: Health Technology Assessment (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	

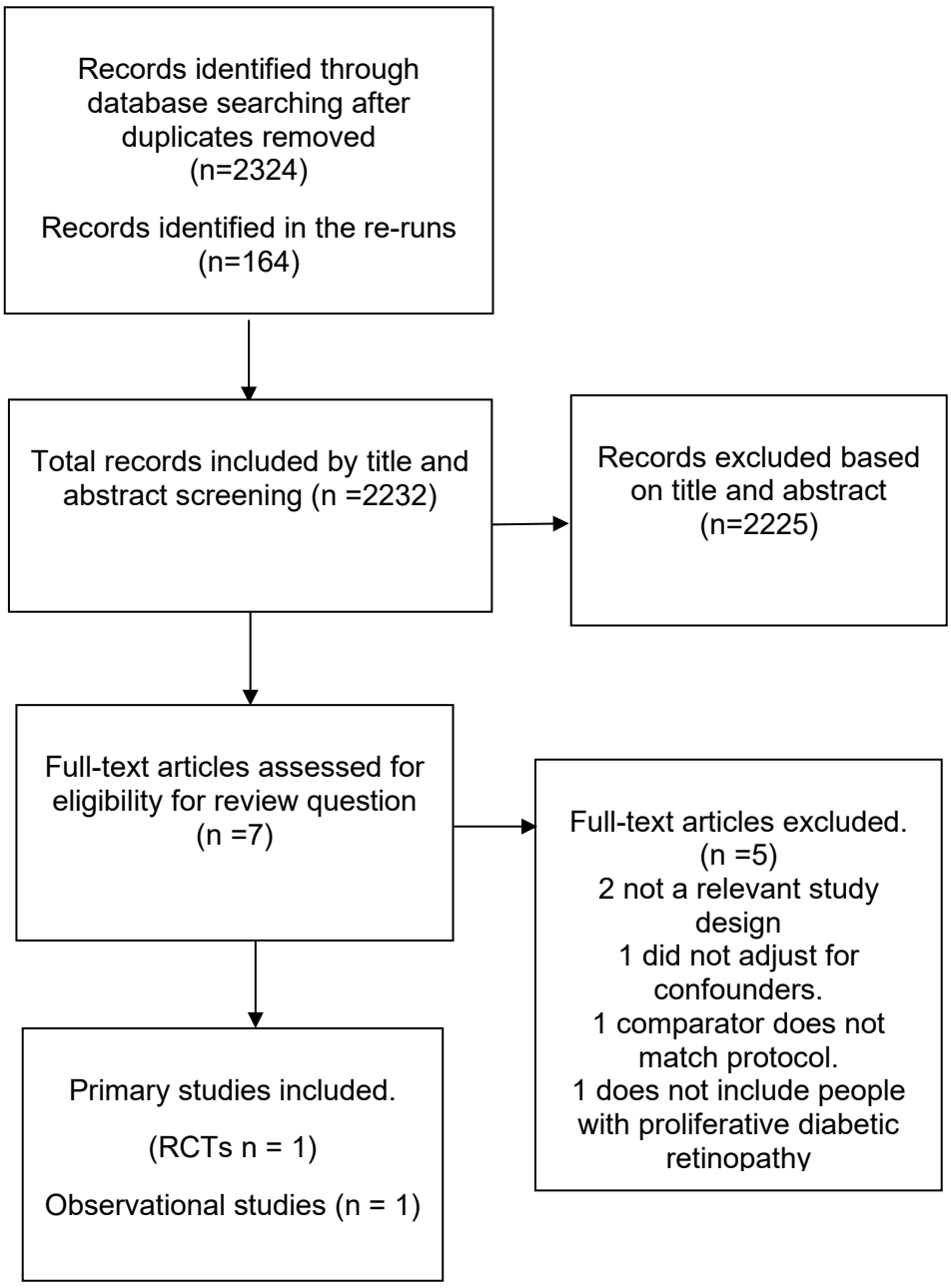
Cohort studies:

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



Appendix D – Effectiveness evidence

D.1.1 Busch, 2019

Bibliographic Reference	Busch, Catharina; Fraser-Bell, Samantha; Iglicki, Matias; Lupidi, Marco; Couturier, Aude; Chaikitmongkol, Voraporn; Giancipoli, Ermete; Rodriguez-Valdes, Patricio J; Gabrielle, Pierre-Henry; Lains, Ines; Santos, Ana Rita; Cebeci, Zafer; Amphornphruet, Atchara; Degenhardt, Valentin; Unterlauft, Jan-Darius; Cagini, Carlo; Mane-Tauty, Valerie; D'Amico Ricci, Giuseppe; Hindi, Isaac; Agrawal, Kushal; Chhablani, Jay; Loewenstein, Anat; Zur, Dinah; Rehak, Matus; International Retina, Group; Real-world outcomes of non-responding diabetic macular edema treated with continued anti-VEGF therapy versus early switch to dexamethasone implant: 2-year results.; Acta diabetologica; 2019; vol. 56 (no. 12); 1341-1350

Study details

Other publications associated with this study included in review	Busch, C., Zur, D., Fraser-Bell, S. *et al.* Shall we stay, or shall we switch? Continued anti-VEGF therapy versus early switch to dexamethasone implant in refractory diabetic macular edema. *Acta Diabetol* **55**, 789–796 (2018). https://doi.org/10.1007/s00592-018-1151-x
Study type	Retrospective cohort study
Study location	Multiple countries - Consortia For the International Retina Group
Study setting	14 clinical settings (Argentina, Israel, Australia, Turkey, Thailand, India, Germany, Italy, France, Mexico, Italy, Portugal)
Study dates	Medical records of patients from January 1, 2010, to December 31, 2016 with a diagnosis of DME were reviewed
Sources of funding	Not stated
Inclusion criteria	Inclusion (1) age 18 years or older; (2) type 1 or 2 diabetes mellitus; (3) treatment-naïve DME causing visual loss, with study eye VA of 0.1–1.0 logMAR (20/25–20/200 Snellen equivalent); macular oedema defined clinically and by retinal thickness of

	> 300 µm in the central subfield (CST) with intra +/− subretinal fluid on spectral-domain optical coherence tomography (SD-OCT) [15, 16]; (4)Eyes had to be treatment naïve on presentation and initially treated with 3 monthly anti-VEGF injections (aflibercept, ranibizumab or bevacizumab) (i.e., loading phase) leading to a suboptimal response: defined as ≤ 5 letter gain in VA (including vision loss), or reduction of less than 20% of CST on SD-OCT 1 month after the third anti-VEGF injection
Exclusion criteria	Exclusion (1) concomitant ocular disease that could cause macular oedema (including choroidal neovascularization from any cause, retinal vein occlusion, uveitis and recent intraocular surgery); (2) any concomitant ocular or neurological condition that could affect vision except cataract; (3) prior macular laser; (4) treatment with any other intravitreal medication, apart from aflibercept, ranibizumab, bevacizumab or DEX implant during the 12-month period; and (5) switch to DEX implant after > 4 injections of anti-VEGF.
Intervention(s)	anti-VEGF (65.9% Ranibizumab, 15.9% Aflibercept, 18.2% Bevacizumab) with switch to steroids in 2nd year, or early switch to Dex implant (3 months)
Comparator	anti-VEGF (65.9% Ranibizumab, 15.9% Aflibercept, 18.2% Bevacizumab)
Outcome measures	Visual acuity
Number of participants	110 eyes from 105 people with diabetes
Duration of follow-up	2 years
Loss to follow-up	4.3% n=23
Methods of analysis	Retrospective cohort study. The 2-year analysis methods mirrored the 1-year analyses [11]. The demographic and clinical characteristics of our study cohort were evaluated using traditional descriptive methods. The standardized area under the curve (AUC) of VA and CST change was calculated by the trapezoidal rule [13]. Differences in baseline characteristics between matched anti-VEGF and DEX group were assessed by univariable logistic regression model. Differences in outcome measures were analysed by multivariable regression model, including age, gender, stage of diabetic retinopathy, EZ disruption at baseline, lens status at baseline and after 24 months, status post-panretinal photocoagulation at baseline and after 24 months, and baseline visual acuity (for visual acuity outcomes) and baseline CST (for CST outcomes). For continuous outcome variables, a linear regression model, and for a binary outcome, a logistic regression model were

	applied. The last observation carried forward method was used to impute missing data. Statistical analysis was performed with SPSS Statistics 22 (IBM, Armonk, NY, USA)

Study arms

anti-VEGF only (N = 44 eyes)

anti-VEGF switch to steroids 2nd year (N = 14 eyes)

anti-VEGF early switch to DEX implant (N = 29 eyes)

Characteristics

Arm-level characteristics

Characteristic	**anti-VEGF only (N = 44 eyes)**	**anti-VEGF switch to steroids 2nd year (N = 14 eyes)**	**anti-VEGF early switch to DEX implant (N = 29 eyes)**
Mean age (SD) Mean (SD)	60 (10.2)	62.1 (13.1)	64 (12.7)
Duration of diabetes (Months) Mean (SD)	143 (117)	16 (37)	100 (133)
Proliferative diabetic retinopathy, (n (%)) Custom value	12 (27.3%)	5 (35.7%)	13 (44.8%)
VA at baseline (logMAR)	0.47 (0.25)	0.59 (0.22)	0.57 (0.23)

Characteristic	anti-VEGF only (N = 44 eyes)	anti-VEGF switch to steroids 2nd year (N = 14 eyes)	anti-VEGF early switch to DEX implant (N = 29 eyes)
Mean (SD)			

Critical appraisal - GDT Crit App - ROBINS-I: a tool for non-randomised studies of interventions

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *Serious bias found in classification of interventions: In those who switched in second year, some switched to DEX implant and some to fuocinolone acetonide. In those who switched to DEX early, 76% continued with implants in second year but 10.3% switched to fuocinolone acetonide implant. Four eyes (13.8%) received additional anti-VEGF injections in the second year. Six eyes (20.7%) did not receive further DME therapy in the second year. Moderate bias arising from unknown confounders in observational evidence which can't be controlled for.)*
Overall bias	Directness	Directly applicable

D.1.2 Jhaveri, 2022

Bibliographic Reference Jhaveri, Chirag D; Glassman, Adam R; Ferris, Frederick L 3rd; Liu, Danni; Maguire, Maureen G; Allen, John B; Baker, Carl W; Browning, David; Cunningham, Matthew A; Friedman, Scott M; Jampol, Lee M; Marcus, Dennis M; Martin, Daniel F; Preston, Carin M; Stockdale, Cynthia R; Sun, Jennifer K; DRCR Retina, Network; Aflibercept Monotherapy or Bevacizumab First for Diabetic Macular Edema.; The New England journal of medicine; 2022; vol. 387 (no. 8); 692-703

Study details

Trial registration number and/or trial name	NCT03321513

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	54 clinical sites
Study dates	December 8, 2017, and November 25, 2019
Sources of funding	Supported by a grant (UG1EY014231) from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.
Inclusion criteria	Inclusion 18 years of age and had type 1 or 2 diabetes, at least one eye with a best-corrected Electronic Early Treatment Diabetic Retinopathy Study visual-acuity letter score of 24 to 69 (on a scale from 0 to 100, with higher scores indicating better visual acuity; Snellen equivalent, 20/320 to 20/50), centre-involved diabetic macular oedema on ophthalmoscopic examination, and central subfield thickness values greater than machine- and sex-specific thresholds on optical coherence tomography (OCT).
Exclusion criteria	Exclusion Eyes that had received anti-VEGF treatment for diabetic macular oedema in the previous 12 months or any treatment for diabetic macular oedema within the previous 4 months were excluded
Intervention(s)	- Aflibercept-Monotherapy Group - mean of 14.6±4.1 injections
Comparator	Bevacizumab-First Group - 16.1±4.1 injections (adjusted difference, −1.5 injections; 95% confidence interval −2.4 to −0.5 Eyes in the bevacizumab-first group received a mean of 9.2±5.2 bevacizumab injections and 6.9±5.8 aflibercept injections over the 2-year period. 70% (95% CI, 62 to 77) switch to aflibercept over the 2-year period. Among the 100 eyes that were switched to aflibercept therapy, 57 (57%) met the criteria between 12 weeks and 24 weeks. Criteria for switching:

	Persistent centre-involved diabetic macular oedema - Central subfield thickness on OCT greater than sex- and device-specific threshold Recent treatment of eye - Receipt of injection with bevacizumab at the last two trial visits No recent improvement in eye condition - Visual-acuity letter score not improved by ≥5 letters and central subfield thickness on OCT not improved by ≥10% as compared with each of the two preceding visits or between each of the two preceding visits. Suboptimal vision - Approximate Snellen score of 20/50 or worse (≤68 letters) before 24 week or 20/32 or worse (≤78 letters) at 24 weeks or later
Number of participants	Visual Acuity Letter Score (included in this review) Central subfield thickness on OCT No of trial visits No of injections
Duration of follow-up	2 years
Loss to follow-up	Aflibercept - 132 (84%) completed 2-year visit. 11 died 5 withdrew from study 10 lost to follow-up Bevacizumab First - 128 (83%) completed 2-year visit. 5 died 10 withdrew from study 11 lost to follow-up.
Methods of analysis	The primary analysis followed the intention to-treat principle according to treatment group and included all the eyes that had undergone randomization. Missing values for visual acuity at follow-up visits were imputed with Markov chain Monte Carlo multiple imputation. Outlying values were truncated to ±3 SD from the mean of the visual-acuity distribution at 104 weeks. The primary analysis of the time-averaged mean score used a linear mixed-effects model with robust variance estimation and a random intercept to account for the correlation in outcome between two eyes in a patient, with adjustment for baseline visual acuity and number of study eyes in the same patient. Prespecified subgroup analyses evaluated the effects of baseline central subfield thickness and visual acuity. Secondary outcomes were compared with the use of linear mixed models or logistic regression with a random intercept term or a student's t-test for two independent samples (number of visits). Systemic safety outcomes were compared among three groups with the use of Fisher's exact test, and global P

	values are reported. Ocular safety outcomes were compared with the use of Barnard's unconditional exact test. Means with standard deviations or medians with interquartile ranges are reported. All P values and 95% confidence intervals are two-sided. As prespecified, no P values are presented for secondary efficacy outcome measures. No adjustment for multiplicity in sensitivity, subgroup, or safety analyses was implemented. The widths of the confidence intervals are not adjusted for multiple comparisons and should not be used to infer treatment effects.

Study arms

Aflibercept-monotherapy (N = 158)
n = Number of eyes

Bevacizumab-First (N = 154)
n= No of eyes. Beginning at 12 weeks, eyes in the bevacizumab-first group were switched to aflibercept therapy if protocol-specified criteria were met. Criteria for switching: 1) Persistent centre-involved diabetic macular oedema 2) Recent treatment of eye, 3) No recent improvement in eye condition 4) Suboptimal vision.

Characteristics

Arm-level characteristics

Characteristic	Aflibercept-monotherapy (N = 158)	Bevacizumab-First (N = 154)
% Female Custom value	48%	48%
Race - white Custom value	52%	54%
Race - Black or African American Custom value	20%	17%

Characteristic	Aflibercept-monotherapy (N = 158)	Bevacizumab-First (N = 154)
Race - Hispanic or Latino Custom value	25%	27%
Race - Asian Custom value	1%	1%
Age - median Median (IQR)	60 (55 to 66)	61 (54 to 67)
Median visual acuity letter score Median (IQR)	61 (65 to 54)	60 (65 to 51)
Type 1 diabetes Custom value	4%	5%
Type 2 diabetes Custom value	96%	95%
Race - Native Hawaiian or another Pacific Islander Custom value	1%	1%

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Some concerns around a lack of information about blinding and imputed missing data)*

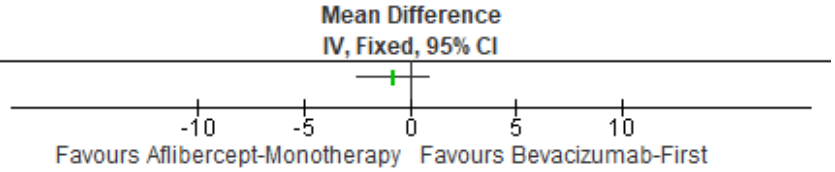
Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plots

E.1.1 Switching criteria: Persistent centre-involved diabetic macular oedema, Recent treatment of eye no recent improvement in eye condition and or Suboptimal vision (Bevacizumab first with switch to Aflibercept at week 12 vs Aflibercept monotherapy)

Figure 1: Visual acuity - Mean change in letters from baseline over 2-year period

	Bevucizumab-First			Aflibercept mono				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Jhaveri 2022 (1)	14.2	6.9921	128	15	6.9921	132		-0.80 [-2.50, 0.90]



Footnotes
(1) Adjusted MD for baseline visual acuity and number of study eyes in the same patient. Mean scores in each arm will differ from raw data.

Figure 2: Visual acuity (letter score) at 2 years

	Bevacizumab-First			Aflibercept-Mono				Mean Difference
Study or Subgroup	Mean [Letter]	SD [Letter]	Total	Mean [Letter]	SD [Letter]	Total	Weight	IV, Fixed, 95% CI [Letter]
Jhaveri 2022	73	13	128	72	15	132		1.00 [-2.41, 4.41]

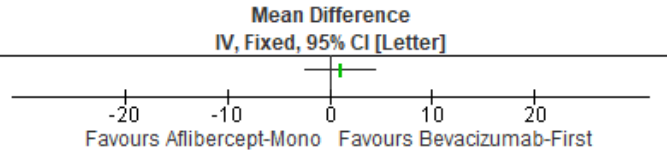


Figure 3: Visual acuity – number of eyes 20/20 or better

	Bevacizumab-First		Aflibercept-Monotherapy			Risk Ratio (Non-event)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Jhaveri 2022	28	128	29	132		1.00 [0.88, 1.14]

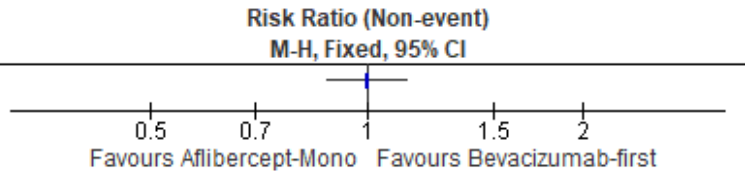


Figure 4: Visual acuity – number of eyes 20/40 or better

Study or Subgroup	Bevacizumab-First Events	Total	Aflibercept Monotherapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jhaveri 2022	95	128	96	132		1.02 [0.88, 1.18]

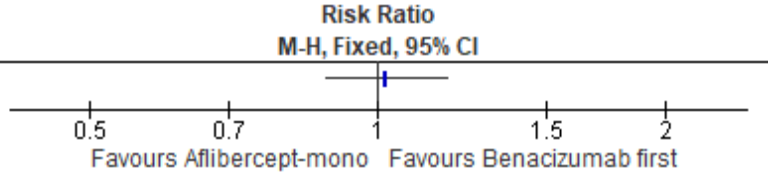


Figure 5: Visual acuity – number of eyes 20/200 or worse

Study or Subgroup	Bevacizumab-First Events	Total	Aflibercept-Monotherapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jhaveri 2022	2	128	6	132		0.34 [0.07, 1.67]

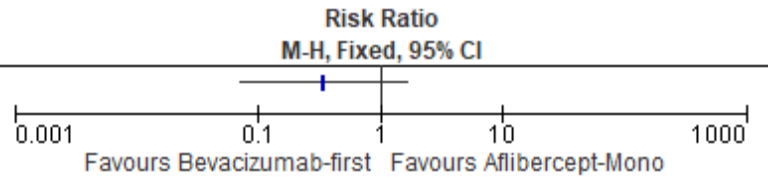
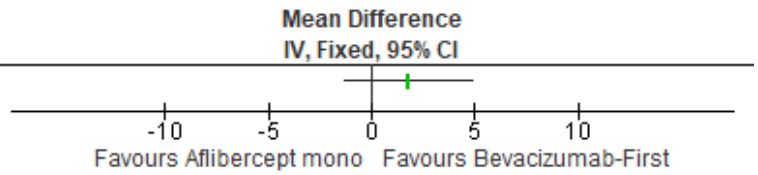


Figure 6: Visual acuity – mean change from baseline to 2 years in letter score

Study or Subgroup	Bevacizumab-First Mean	SD	Total	Aflibercept-Monotherapy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Jhaveri 2022 (1)	16.5	12.7503	128	14.7	12.7503	132		1.80 [-1.30, 4.90]



Footnotes
(1) Adjusted MD for baseline visual acuity and number of study eyes in the same patient. Mean scores in each arm will differ from raw data.

Figure 7: Visual acuity – improvement by ≥15 letters

Study or Subgroup	Bevacizumab-First Events	Total	Aflibercept-Monotherapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jhaveri 2022	74	128	70	132		1.09 [0.88, 1.36]

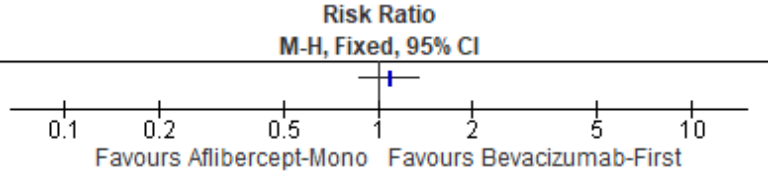


Figure 8: Visual acuity – improvement by ≥10 letters

Study or Subgroup	Bevacizumab-First Events	Total	Aflibercept-Mono Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jhaveri 2022	98	128	101	132		1.00 [0.87, 1.14]

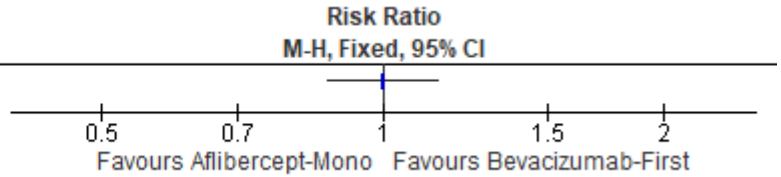


Figure 9: Visual acuity – worsening by ≥10 letters

Study or Subgroup	Bevacizumab-First Events	Total	Aflibercept-Monotherapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jhaveri 2022	5	128	9	132		0.57 [0.20, 1.66]

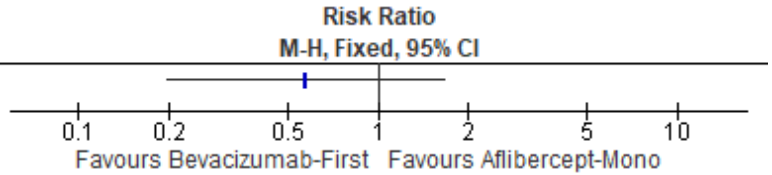
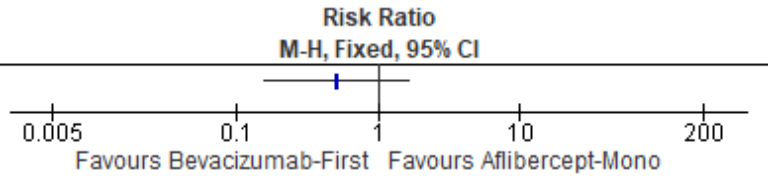


Figure 10: Visual acuity – worsening by ≥15 letters

Study or Subgroup	Bevacizumab-First Events	Total	Aflibercept-Monotherapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jhaveri 2022	4	128	8	132		0.52 [0.16, 1.67]



E.1.2 Switching criteria: Suboptimal response to anti-VEGF loading phase (Anti-VEGF vs switch to steroids in 2nd year)

Figure 11: Visual acuity logMAR – 24 months

	Switch to steroids year 2			Anti-VEGF				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Busch 2019	0.44	0.21	14	0.39	0.29	44		0.05 [-0.09, 0.19]

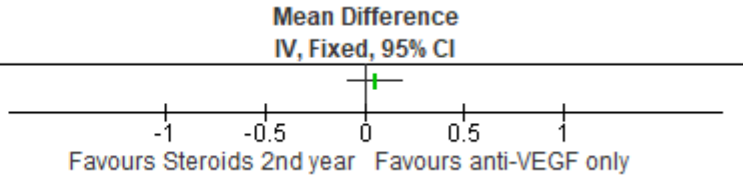


Figure 12: Visual acuity – mean change in letters from month 3 to 24

	Switch to steroids 2nd yr			Anti-VEGF				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Busch 2019	7.2	8.3	14	2.8	12.9	44		4.40 [-1.38, 10.18]

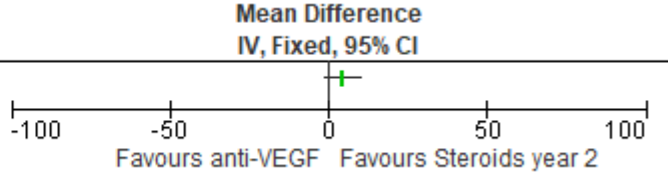


Figure 13: Visual acuity gain ≥5 letters at month 24 from month 3

	Switch to steroids year 2		Anti-VEGF			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Busch 2019	8	14	19	44		1.32 [0.75, 2.33]

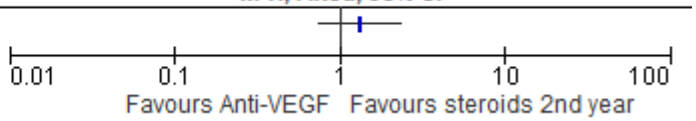


Figure 14: Visual acuity gain ≥10 letters at month 24 from month 3

	Switch to steroids year 2		Anti-VEGF			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Busch 2019	7	14	11	44		2.00 [0.96, 4.16]

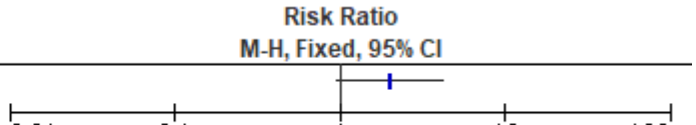
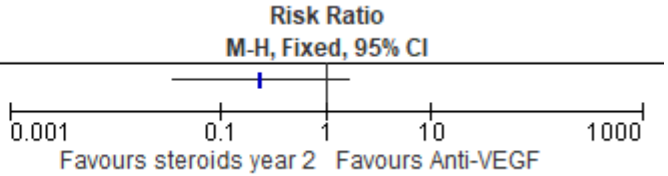


Figure 15: Visual acuity loss ≥5 letters at month 24 from month 3

Study or Subgroup	Switch to steroids year 2 Events	Total	Anti-VEGF Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Busch 2019	1	14	13	44		0.24 [0.03, 1.69]



E.1.3 Switching criteria: Suboptimal response to anti-VEGF loading phase (Anti-VEGF vs early switch (3 months) to DEX implant)

Figure 16: Visual acuity – mean logMAR at 24 months

Study or Subgroup	Early swtich to DEX Mean [logMAR]	SD [logMAR]	Total	anti-VEGF only Mean [logMAR]	SD [logMAR]	Total	Weight	Mean Difference IV, Fixed, 95% CI
Busch 2019	0.37	0.18	29	0.39	0.29	44		-0.02 [-0.13, 0.09]

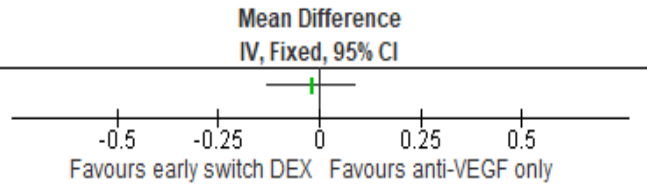


Figure 17: Visual acuity – change in letters from month 3 to month 24

Study or Subgroup	Early swtich to DEX Mean	SD	Total	anti-VEGF only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Busch 2019	8.9	13.2	29	2.8	12.9	44		6.10 [-0.03, 12.23]

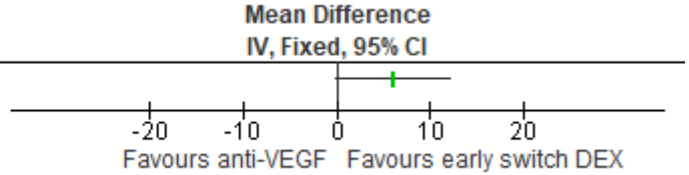


Figure 18: Visual acuity gain ≥5 letters at month 24 from month 3

Study or Subgroup	Early swtich to DEX Events	Total	anti-VEGF only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Busch 2019	20	29	19	44		1.60 [1.05, 2.43]

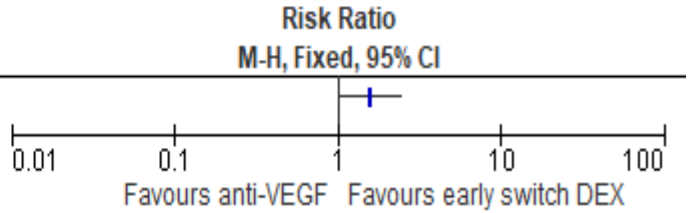


Figure 19: Visual acuity gain >10 letters at month 24 from month 3

	Early swtich to DEX		anti-VEGF only			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Busch 2019	17	29	11	44		2.34 [1.29, 4.26]

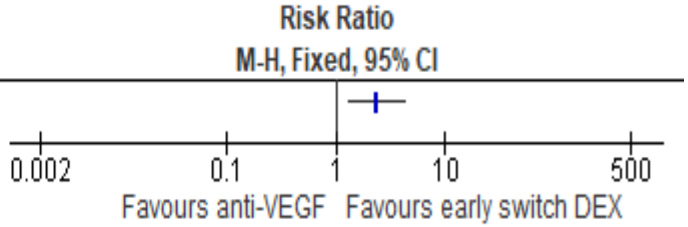
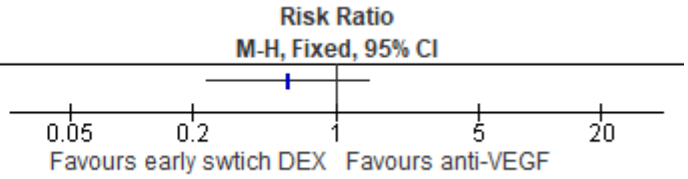


Figure 20: Visual acuity loss >5 letters at month 24 from month 3

	Early swtich to DEX		anti-VEGF only			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Busch 2019	5	29	13	44		0.58 [0.23, 1.46]



Appendix F – GRADE tables

F.1.1 Switching criteria: Persistent centre-involved diabetic macular oedema, Recent treatment of eye no recent improvement in eye condition and or Suboptimal vision (Bevacizumab first with switch to Aflibercept at week 12 vs Aflibercept monotherapy)

Table 5. Outcomes for switching criteria: Persistent centre-involved diabetic macular oedema, Recent treatment of eye no recent improvement in eye condition and or Suboptimal vision (Bevacizumab first with switch to Aflibercept at week 12 vs Aflibercept monotherapy)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Absolute risk difference	Risk of bias	Inconsistency	Indirectness	Quality
Bevacizumab first with switch to Aflibercept at week 12 Vs Aflibercept monotherapy (n = number of eyes)										
Visual acuity - Mean change in letters from baseline over 2-year period [4] (MD greater than 0 favours Bevacizumab first with switch to Aflibercept at week 12)										
1[1]	RCT	260	MD -0.80 (-2.50, 0.90)[2]	-	-	-	Serious[3]	N/A	Not Serious	Moderate
Visual acuity (letter score) at 2 years[4] (MD greater than 0 favours Bevacizumab first with switch to Aflibercept at week 12)										
1[1]	RCT	260	MD 1.00 (-2.41, 4.41)	-	-	-	Serious[3]	N/A	Not Serious	Moderate
Visual acuity – number of eyes 20/20 or better (RR greater than 1 favours Bevacizumab first with switch to Aflibercept at week 12)										
1[1]	RCT	260	RR 1.00 (0.88,1.14)	220 per 1000	220 per 1000	0 more (26 fewer to 31 more)	Serious[3]	N/A	Not Serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Absolute risk difference	Risk of bias	Inconsistency	Indirectness	Quality
Visual acuity – number of eyes 20/40 or better (RR greater than 1 favours Bevacizumab first with switch to Aflibercept at week 12)										
1[1]	RCT	260	RR 1.02 (0.88,1.18)	727 per 1000	742 per 1000	15 more (87 fewer to 131 more)	Serious[3]	N/A	Not Serious	Moderate
Visual acuity – number of eyes 20/200 or worse (RR less than 1 favours Bevacizumab first with switch to Aflibercept at week 12)										
1[1]	RCT	260	RR 0.34 (0.07,1.67)	45 per 1000	15 per 1000	30 fewer (42 fewer to 30 more)	Serious[3]	N/A	Not Serious	Moderate
Visual acuity - Mean change from baseline in letter score at 2 years[4] (MD greater than 0 favours Bevacizumab first with switch to Aflibercept at week 12)										
1[1]	RCT	260	MD 1.80 (-1.30, 4.90)	-	-	-	Serious[3]	N/A	Not Serious	Moderate
Visual acuity - Improvement by ≥ 15 letters (RR greater than 1 favours Bevacizumab first with switch to Aflibercept at week 12)										
1[1]	RCT	260	RR 1.09 (0.88, 1.36)	530 per 1000	578 per 1000	48 more (64 fewer to 191 more)	Serious[3]	N/A	Not Serious	Moderate
Visual acuity - Improvement by ≥ 10 letters (RR greater than 1 favours Bevacizumab first with switch to Aflibercept at week 12)										
1[1]	RCT	260	RR 1.00 (0.87,1.14)	765 per 1000	765 per 1000	0 more (99 fewer to 107 more)	Serious[3]	N/A	Not Serious	Moderate
Visual acuity - Worsening by ≥ 10 letters (RR less than 1 favours Bevacizumab first with switch to Aflibercept at week 12)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Absolute risk difference	Risk of bias	Inconsistency	Indirectness	Quality
1[1]	RCT	260	RR 0.57 (0.20, 1.66)	68 per 1000	39 per 1000	29 fewer (54 fewer to 45 more)	Serious[3]	N/A	Not Serious	Moderate
Visual acuity - Worsening by ≥ 15 letters (RR less than 1 favours Bevacizumab first with switch to Aflibercept at week 12)										
1[1]	RCT	260	RR 0.52 (0.16, 1.67)	61 per 1000	32 per 1000	29 fewer (51 fewer to 41 more)	Serious[3]	N/A	Not Serious	Moderate

1. Jhaveri 2022
2. Adjusted MD for baseline visual acuity and number of study eyes in the same patient. Mean scores in each arm will differ from raw data.
3. Moderate risk of bias rating
4. Higher scores are better.

F.1.2 Switching criteria: Suboptimal response to anti-VEGF loading phase (Anti-VEGF vs switch to steroids in 2nd year)

Table 6. Outcomes for switching criteria: Suboptimal response to anti-VEGF loading phase (Anti-VEGF vs switch to steroids in 2nd year)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Absolute risk difference	Risk of bias	Inconsistency	Indirectness	Quality
Switch to steroids in 2nd year vs Anti-VEGF (n = number of eyes)										
Visual acuity logMAR – 24 months[3] (MD less than 0 favours Switch to steroids in 2nd year)										
1[1]	Observational	58	MD 0.05 (-0.09, 0.19)	-	-	-	Very serious[2]	N/A	Not serious	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Absolute risk difference	Risk of bias	Inconsistency	Indirectness	Quality
Visual acuity – mean change in letters from month 3-24[4] (MD greater than 0 favours Switch to steroids in 2nd year)										
1[1]	Observational	58	MD 4.40 (-1.38, 10.18	-	-	-	Very serious[2]	N/A	Not serious	Low
Visual acuity gain ≥ 5 letters at month 24 (from month 3) (RR greater than 1 favours Switch to steroids in 2nd year)										
1[1]	Observational	58	RR 1.32 (0.75, 2.33)	432 per 1000	570 per 1000	138 more (108 fewer to 575 more)	Very serious[2]	N/A	Not serious	Low
Visual acuity gain ≥ 10 letters at month 24 (from month 3) (RR greater than 1 favours Switch to steroids in 2nd year)										
1[1]	Observational	58	RR 2.00 (0.96, 4.16)	250 per 1000	500 per 1000	250 more (10 fewer to 790 more)	Very serious[2]	N/A	Not serious	Low
VA loss ≥ 5 letters at month 24 (from month 3) (RR less than 1 favours Switch to steroids in 2nd year)										
1[1]	Observational	58	RR 0.24 (0.03, 1.69)	295 per 1000	71 per 1000	224 fewer (286 fewer to 204 more)	Very serious[2]	N/A	Not serious	Low

1. Busch 2019
2. Observational study assessed as high risk of bias
3. Lower scores are better
4. Higher scores are better

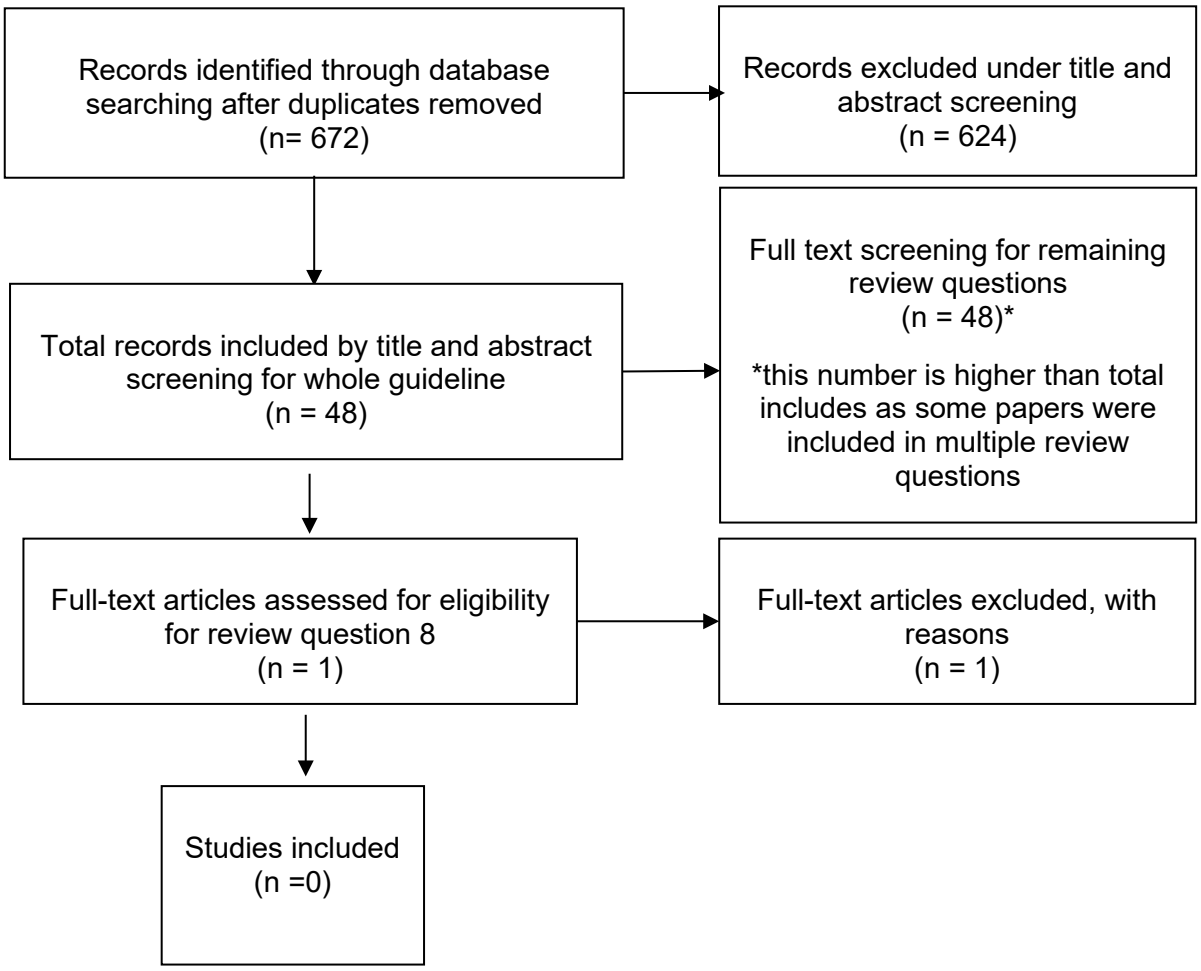
Table 7. Outcomes for switching criteria: Suboptimal response to anti-VEGF loading phase (Anti-VEGF vs early switch (3 months) to DEX implant)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Absolute risk difference	Risk of bias	Inconsistency	Indirectness	Quality
Anti-VEGF only vs early switch (3 months) to DEX implant										
Visual acuity – mean logMAR at 24 months[3] (MD less than 0 favours Switch to steroids in 2nd year)										
1[1]	Observational	73	MD -0.02 (-0.13, 0.09)	-	-	-	Very serious[2]	N/A	Not serious	Low
Visual acuity – change in letters from month 3-24[4] (MD greater than 0 favours Switch to steroids in 2nd year)										
1[1]	Observational	73	MD 6.10 (-0.03, 12.23)	-	-	-	Very serious[2]	N/A	Not serious	Low
Visual acuity gain ≥ 5 letters at month 24 (from month 3) (RR greater than 1 favours Switch to steroids in 2nd year)										
1[1]	Observational	73	RR 1.60 (1.05, 2.43)	432 per 1000	691 per 1000	259 more (22 more to 618 more)	Very serious[2]	N/A	Not serious	Low
Visual acuity gain ≥ 10 letters at month 24 (from month 3) (RR greater than 1 favours Switch to steroids in 2nd year)										
1[1]	Observational	73	RR 2.34 (1.29, 4.26)	250 per 1000	585 per 1000	335 more (73 more to 815 more)	Very serious[2]	N/A	Not serious	Low
Visual acuity loss ≥ 5 letters at month 24 (from month 3) (RR less than 1 favours Switch to steroids in 2nd year)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Absolute risk difference	Risk of bias	Inconsistency	Indirectness	Quality
1[1]	Observational	73	RR 0.58 (0.23, 1.46)	295 per 1000	171 per 1000	124 fewer (227 fewer to 136 more)	Very serious[2]	N/A	Not serious	Low

1. Busch 2019
2. Observational study assessed as high risk of bias
3. Lower scores are better
4. Higher scores are better

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

There are no included studies for this review question.

Appendix I – Health economic model

Original health economic modelling has not been conducted for this review question.

Appendix J – Excluded studies

Clinical evidence

Study	Reason for exclusion
Blanc, Julie, Deschasse, Clemence, Kodjikian, Laurent et al. (2018) Safety and long-term efficacy of repeated dexamethasone intravitreal implants for the treatment of cystoid macular edema secondary to retinal vein occlusion with or without a switch to anti-VEGF agents: a 3-year experience. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 256(8): 1441-1448	- Not a relevant study design Non comparative study
Hogg, Hd Jeffry; Di Simplicio, Sandro; Pearce, Mark S (2021) Ranibizumab and aflibercept intravitreal injection for treatment naïve and refractory macular oedema in branch retinal vein occlusion. European journal of ophthalmology 31(2): 548-555	- Does not contain a population of people with diabetic retinopathy or diabetic macular oedema
Liu, Y., Cheng, J., Gao, Y. et al. (2020) Efficacy of switching therapy to aflibercept for patients with persistent diabetic macular edema: A systematic review and meta-analysis. Annals of Translational Medicine 8(6): 382	- Not a relevant study design Systematic review
Rush, R.B. and Rush, S.W. (2022) Faricimab for Treatment-Resistant Diabetic Macular Edema. Clinical Ophthalmology 16: 2797-2801	- Did not adjust for confounding
Sarao, Valentina, Veritti, Daniele, Furino, Claudio et al. (2017) Dexamethasone implant with fixed or individualized regimen in the treatment of diabetic macular oedema: six-month outcomes of the UDBASA study. Acta ophthalmologica 95(4): e255-e260	- Comparator in study does not match that specified in protocol

Economic evidence

Title	Reason for exclusion
Ramsey, D.J., Poulin, S.J., Lamonica, L.C. et al. (2021) Early conversion to aflibercept for persistent diabetic macular edema results in better visual outcomes and lower	- Exclude - not relevant comparator

Title	Reason for exclusion
treatment costs. Clinical Ophthalmology 15: 31-39	

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

What are the clinical features or factors that suggest treatment should be switched or stopped for people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema?

K.1.2 Why this is important.

There are several treatment strategies for people with proliferative diabetic retinopathy or diabetic macular oedema. It is still unclear how to assess non responsiveness to the various treatments, and it is important for clinicians to know when to consider switching someone to another form of treatment, or when they should stop treatment. A better understanding of which clinical, biochemical, and anatomical characteristics indicate that someone would benefit from a change in treatment will help clinicians to provide patients with the most effective treatment options and reduce the complications associated with proliferative diabetic retinopathy and diabetic macular oedema.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	By understanding what characteristics indicate that a patient is not responding sufficiently to treatment, clinicians can ensure that patients are given the most effective treatment. This can reduce the long-term effects associated with the progression of diabetic retinopathy and macular oedema.
Relevance to NICE guidance	Stopping and switching criteria for treatment of diabetic retinopathy and macular oedema has been considered in this guideline and there is a lack of data on the most effective criteria to determine if someone should switch or stop treatment.
Relevance to the NHS	The outcome would affect the types of treatment that people receive. It will reduce the risk of someone who has a suboptimal response to treatment experiencing further progression of diabetic retinopathy or macular oedema and requiring additional treatment.
National priorities	Moderate
Current evidence base	No studies for diabetic retinopathy. 2 studies for macular oedema – 1 RCT and 1 retrospective cohort study. None of the evidence is based in the UK.
Equality considerations	None known

K.1.4 Modified PICO table

Population	People with proliferative diabetic retinopathy People with diabetic macular oedema
Intervention	Either: • Initial treatment with Anti-VEGF then switched to intravitreal steroids after suboptimal response. or: • Initial treatment with one Anti-VEGF then switched to a different Anti-VEGF after suboptimal response. when sub-optimal response is defined and identified by criteria related to the following (either alone or a combination of factors): • imaging biomarkers • biochemical factors– (such as HbA1c) • functional characteristics • anatomical characteristics
Comparator	People continued on anti-VEGF monotherapy
Outcome	Visual acuity Quality of life
Study design	RCT
Timeframe	Long term and short-term evidence
Additional information	Subgroups could be used to determine whether different populations (such as different genders, ethnicities, or ages) have different switching criteria