National Institute for Health and Care Excellence

Guideline version (Draft)

Diabetic Retinopathy: management and monitoring

[B] Evidence reviews for effectiveness of different thresholds or criteria for starting treatment for non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular oedema

NICE guideline <number>

Evidence reviews underpinning recommendations 1.4.2 to 1.4.3, 1.4.13 and 1.5.3 to 1.5.4 and research recommendations in the NICE guideline

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Draft for Consultation

These evidence reviews were developed by Guideline Development Team

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Effectiveness of different thresholds or criteria for starting treatment for non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular oedema

1.1 Review question

What is the effectiveness of different thresholds or criteria for starting treatment for non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular oedema?

1.1.1 Introduction

Diabetic retinopathy and macular oedema are progressive conditions that can lead to vision loss if left untreated. Determining appropriate thresholds for when treatment should begin will allow for timely intervention to prevent or slow down disease progression, preserve vision and reduce the risk of severe complications. Different treatment thresholds help in stratifying patients based on the severity of their condition, ensuring that those who are at higher risk or have more advanced disease receive the appropriate level of intervention. This review aims to determine what are the most effective thresholds for people who have been referred to hospital eye services or who are starting treatment for non-proliferative diabetic retinopathy, proliferative 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: Effect of intensive treatments to lower blood glucose levels on progression of diabetic retinopathy and diabetic macular oedema

Population	People with non-proliferative diabetic retinopathy People with proliferative retinopathy People with diabetic macular oedema
Interventions	• Lower or higher thresholds for starting treatment than standard threshold. • Immediate treatment compared with deferred treatment. Limited to the following interventions being considered under other review questions in the guideline: • Blood pressure medicines • Statins • Fibrates • Vitrectomy • Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids • Combinations of the treatments listed above.
Comparator	• Standard threshold for starting treatment (as defined by the study) • Deferred treatment (when compared with immediate treatment)

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.
	• Incidence or progression of proliferative diabetic retinopathy
	• incidence or progression of macular oedema
	• Peripheral vision, assessed using visual field measurement.
	• Quality of life, measured using a validated tool (the overall score as well as mental health domain scores will be reported separately)
	• Central retinal thickness
	• Tractional retinal detachment
	
	Outcomes will be reported at the latest time point reported by the study.

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

After removing duplicate references, 4236 records were identified in the search and screened at title and abstract stage. 2208 records were screened before the stopping criteria specified in the protocol was reached. 37 studies were included for full text screening. These studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A). Six RCTs matched the protocol and were included in the review. 211 additional records were identified when the search was re-run, but none matched the inclusion criteria for the review.

Comparisons (one study compared early vs deferred laser and early vs deferred anti-VEGF, resulting in 7 comparisons from 6 RCTs)

- Early laser photocoagulation versus Deferred laser photocoagulation (Population with non-proliferative diabetic retinopathy) (3 Parallel Group RCTs)
- Early Anti-VEGF versus Deferred Anti-VEGF (Initial observation) (Population with non-proliferative diabetic retinopathy) (1 Parallel Group RCT)
- Early vitrectomy versus Deferred vitrectomy (Population with severe vitreous haemorrhage (1 Parallel Group RCT)
- Anti-VEGF + prompt laser VS Anti-VEGF and deferred laser (Population with non-proliferative diabetic retinopathy) (1 Parallel-Group RCT)
- Early laser photocoagulation versus Deferred laser photocoagulation (Population with diabetic macula oedema) (1 Parallel Group RCT)

1.1.4.2 Excluded studies

Overall, 31 studies were excluded following examination of the full text articles. See Appendix J for the list of excluded studies with reasons for their exclusion.

1.1.5 Summary of studies included in the effectiveness evidence.

Table 2: Table of included studies

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Baker, 2019	Parallel-group RCT 2-year FU	**Inclusion criteria** • Age >= 18 years • Diagnosis of diabetes mellitus (type 1 or type 2) • Best corrected E-ETDRS visual acuity letter score >79 (approximate Snellen equivalent 20/25 or better) at two consecutive visits within 1 to 28 days. • definite retinal thickening due to DMO involving the Center of the macula. • Diabetic macular oedema confirmed on OCT **Key exclusion criteria** • History of chronic renal failure requiring dialysis or kidney transplant. • Initiation of intensive insulin treatment (a pump or multiple daily injections) within 4 months prior • Blood pressure >180/110 (systolic above 180 OR diastolic above 110) • Systemic anti-VEGF or pro-VEGF treatment within	1. **Prompt anti-VEGF group (N = 226)** 2. **Deferred anti-VEGF group (focal/grid photocoagulation): (N = 240)** Participants had 1 study eye Prompt intravitreal anti-VEGF Intravitreal 2.0 mg aflibercept is administered on the day of randomization in eyes assigned to the prompt anti-VEGF group. Prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF Focal/grid photocoagulation is administered on the day of randomization.	**Deferred anti-VEGF group (observation group): (N = 236)** **Participants had 1 study eye with** Observation + deferred intravitreal anti-VEGF Treatment is not administered at baseline.	• Best-corrected Visual acuity • Change from baseline Central retinal thickness (subfield) at two years

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		4 months prior to randomization • Pregnancy • Macular oedema is considered to be due to a cause other than DME. • Any history of prior laser or other surgical, intravitreal, or peribulbar treatment for DME • Any history of vitrectomy • Aphakia.			
Elman, 2015 United States.	Parallel-group RCT 5-year FU	**Inclusion criteria** • 18 years old with type 1 or 2 diabetes. • participants had at least one eye with visual acuity (approximate Snellen equivalent) of 20/32 to 20/320 • DME involving the central macula. • retinal thickness measured on time domain optical coherence tomography (OCT) ≥250µm in the central subfield. **Key exclusion criteria** • treatment for DMO within the prior 4 months, • panretinal photocoagulation within	**(N =180) (per eye)** **A patient could have 2 study eyes in the trial only if both were eligible.** ranibizumab every 4 weeks until no longer improving (with resumption if worsening) and prompt focal/grid laser treatment.	**(N =181) (per eye)** **A patient could have 2 study eyes in the trial only if both were eligible** ranibizumab every 4 weeks until no longer improving (with resumption if worsening) and deferred (>= 24 weeks) focal/grid laser treatment. Laser in the deferral group had to be delayed for at least 24 weeks after initiating anti-VEGF therapy. However, at or after 24 weeks, laser treatment could be given if there was persistent DME involving the central subfield on OCT that had	• Best-corrected visual acuity at the 5-year visit A patient could have 2 study eyes in the trial only if both were eligible at the time of study entry.

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		the prior 4 months or anticipated need for panretinal photocoagulation within the next 6 months, • major ocular surgery within the prior 4 months, • history of open-angle glaucoma or steroid-induced intraocular pressure (IOP) elevation that required IOP-lowering treatment, • IOP ≥25 mmHg. • systolic blood pressure was >180 mmHg or diastolic blood pressure was >110 mmHg, • myocardial infarction,		not improved after at least 2 consecutive injections given at 4-weekly intervals.	
ETDRS, 1985 ETDRS study USA	Parallel-group RCT 4-year FU	**Inclusion criteria** • People with diabetes with early proliferative retinopathy, or moderate-to-severe non-proliferative retinopathy, • DMO in each eye, or a combination of these. **Exclusion criteria** • Right risk proliferative retinopathy (moderate or severe optic nerve neovascularisation	**Early laser photocoagulation (N = 754)** **Within-person RCT; both eyes included in study, eyes received different treatments**	**Deferred argon laser (N = 1490)** **Within-person RCT; both eyes included in study, eyes received different treatments**	• Retinal detachment • Best-corrected visual acuity

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• any neovascularisation with haemorrhage) and other ocular disease or VA < 20/200. • excluded from this report were the results for the eyes with mild-to-moderate retinopathy and macular oedema that were randomly assigned to an initial treatment of PRP and follow-up focal photocoagulation. • if macular oedema persisted. Type of DMO: CSMO			
DRVS, 1990 USA	Parallel-group RCT 2-year FU	**Inclusion criteria** • Adults (age >18) • Diagnosis of diabetes mellitus (either Type 1 or Type 2) • Sudden vision loss due to severe vitreous haemorrhage • BCVA between 5/200 and LP **Key exclusion criteria** • Photocoagulation within three months prior to randomization	**(N =308) Both eyes included in study, eyes received different treatments** Early vitrectomy	**(N =308) Both eyes included in study, eyes received different treatments** Deferral of vitrectomy (could be performed at 1 year)	• Percentage of eyes with visual acuity of 10/20 or better at 24 months • Exploratory Outcome- DME • Retinal detachment Patients with both eyes entered are included in

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• Severe NVI, NVG or IOP more than 30mmHg despite treatment • Total retinal detachment, or macular detachment on ultrasound • History of prior vitrectomy			both early vitrectomy and deferred groups
ETDRS, 1991 ETDRS study USA	Parallel-group RCT 4-year FU	**Inclusion criteria** • Aged 18-70 years • DR in both eyes Each eye either: • with no macular oedema, a visual acuity 20/40 or better and moderate or severe non-proliferative or early PDR, • macular oedema, visual acuity of 20/200 or better and mild, moderate, or severe non-proliferative or early PDR **Key exclusion criteria** • not reported	**(N =3711) Within-person RCT; both eyes included in study, eyes received different treatments** Early argon laser For the intervention group, eyes were also randomly allocated to 'full' or 'mild' PRP	**(N =3711) Within-person RCT; both eyes included in study, eyes received different treatments** Deferred argon laser For the comparator group, argon laser was applied if high risk PDR was detected	Development of severe visual loss which was defined as visual acuity < 5/200 at two consecutive follow-up visits. Follow-up visits were 4 months apart. Visual acuity was measured using an ETDRS chart at a distance of 4 metres and at 1 metre if visual acuity < 20/100 Both eyes included in study, eyes received different treatments
Sato, 2012 Japan	Parallel-group RCT 3-year FU	**Inclusion criteria** • pre-proliferative diabetic retinopathy • no previous photocoagulation • multiple non perfusion areas larger than one disc	**(N =37) One eye per person enrolled: unclear how eye selected** Panretinal Photocoagulation Group	**(N =37) One eye per person enrolled: unclear how eye selected** Non-Panretinal Photocoagulation Group	• Development of proliferative diabetic retinopathy • High risk PDR

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		area on fluorescein angiography images **Key exclusion criteria** • clear fluorescein angiography images could not be obtained due to opaque media • fluorescein angiography could not be performed (e.g., due to allergy) • past history of intraocular surgery (except if 3 or more years after cataract surgery) • PRP indicated	*In both intervention and comparator groups: "photocoagulation for macular oedema was permitted when the ophthalmologist in charge of this study considered it necessary	For the comparator group: "Whenever PDR developed, PRP was performed. The development of PDR was defined as the detection of any of the following: neovascularization detected by ophthalmoscope or FA and preretinal haemorrhage or vitreous haemorrhage. Therefore, in this study, PDR includes not only high-risk PDR, but also early PDR as described by the Early Treatment Diabetic Retinopathy Study Research Group (ETDRS)	• Severe visual loss (BCVA < 0.025)

Notes: Abbreviations: BCVA, best corrected visual acuity; DME, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; FU, follow up; PDR, proliferative diabetic retinopathy.

1.1.6 Summary of the effectiveness evidence

Early laser photocoagulation versus Deferred laser photocoagulation

People with non-proliferative diabetic retinopathy

Table 3:Loss of best corrected visual acuity (BCVA)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Loss of 15 or more letters BCVA at 3 years follow-up.					
2 (ETDRS, 1991 Sato, 2012)	RCT	7458 eyes	Risk Ratio: 0.92 [0.83, 1.03]	Low	Could not differentiate
Loss of 15 or more letters BCVA at 2 years follow-up.					
1(ETDRS, 1991)	RCT	7422 eyes	Risk Ratio: 0.92 [0.82, 1.03]	Moderate	Could not differentiate
Severe visual loss (BCVA < 6/60). at 2 years FU. follow-up.					
22 (ETDRS, 1991 Sato, 2012)	RCT	7458 eyes	Risk Ratio: 0.70 [0.54, 0.90]	Moderate	Favours early laser photocoagulation
Mean BCVA at 12 months follow-up.					
1(Sato, 2012)	RCT	69	Mean difference: 0.02 [-0.23, 0.27]	Moderate	Could not differentiate

Table 4: Progression of diabetic retinopathy at 2 years follow-up.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Progression of diabetic retinopathy. At 2-year follow-up.					
2 ETDRS, 1991 Sato, 2012	RCT	7457 eyes	Risk Ratio: 0.58 [0.54, 0.62]	Moderate	Favours early laser photocoagulation

Early macular laser vs observation

People with non-proliferative diabetic retinopathy with macular oedema
Table 5: Loss of 5 and 15 or more letters BCVA at 2 years follow-up.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Loss of 15 or more letters BCVA at 2 years follow-up.					
1 (Baker,2019)	RCT	420 eyes	Risk Ratio: 0.98 [0.36, 2.66]	Moderate	Could not differentiate
Loss of 5 or more letters BCVA at 2 years follow-up.					
1 (Baker,2019)	RCT	420 eyes	Risk Ratio: 0.91 [0.60, 1.37]	Moderate	Could not differentiate

Table 6: Incidence of Centre-involved diabetic macula oedema and Central retinal thickness (subfield) at 2-year follow-up.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Incidence of Centre-involved diabetic macula oedema and >10% central subfield thickness decrease					
Baker,2019	RCT	420 eyes	Risk Ratio: 1.19 [0.94, 1.52]	Moderate	Could not differentiate
Change from baseline Central retinal thickness (subfield) at two years follow-up.					
Baker,2019	RCT	419 eyes	Mean Difference: -1.00 [-13.00, 11.00][2]	Moderate	Could not differentiate

Early vitrectomy versus deferred vitrectomy

Population with severe vitreous haemorrhage (reducing visual acuity to 5/200)
Table 7: Visual acuity at 2 years follow-up.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best corrected visual acuity (Visual acuity 10/20 or better) at 2 years follow-up.					
1 (DRVS,1990)	RCT	413 eyes	Risk Ratio: 1.62 [1.12, 2.33]	Moderate	Favours early vitrectomy
Best corrected visual acuity (Visual acuity no light perception) at 2 years follow-up.					
1 (DRVS,1990)	RCT	413 eyes	Risk Ratio: 1.29 [0.93, 1.81]	Moderate	Could not differentiate

Table 8: Retinal detachment at 2-year follow-up.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Retinal detachment at 2 year follow-up.					
1 (DRVS,1990)	RCT	412 eyes	Risk Ratio: 0.63 [0.44, 0.91]	Moderate	Favours early vitrectomy

Early Anti-VEGF versus Deferred Anti-VEGF (Initial observation)

Population with non-proliferative diabetic retinopathy with macular oedema

Table 9: Loss of BCVA (letters) at 2 years follow-up.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Loss of 15 or more letters BCVA at 2 years follow-up.					
1 (Baker,2019)	RCT	413 eyes	Risk Ratio: 0.63 [0.21, 1.91]	Moderate	Could not differentiate
Loss of 5 or more letters BCVA at 2 years follow-up..					
1 (Baker,2019)	RCT	413 eyes	Risk Ratio: 0.86 [0.56, 1.31]	Moderate	Could not differentiate

.

Table 10: Incidence of Centre-involved diabetic macula oedema and Central retinal thickness (subfield) at 2-year follow-up.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Incidence of Centre-involved diabetic macula oedema and >10% central subfield thickness decrease					
Baker,2019	RCT	412 eyes	Risk Ratio: 1.30 [1.03, 1.64]	Moderate	Favours Deferred Anti-VEGF (Initial observation)
Change from baseline Central retinal thickness (subfield) at two years follow-up.					
Baker,2019	RCT	412 eyes	Mean Difference: -13.00 [-27.00, 1.00][3]	Moderate	Could not differentiate

Anti-VEGF + prompt laser vs Anti-VEGF + deferred laser

Population with non-proliferative diabetic retinopathy

Table 11: Best-corrected visual acuity (letter score) at 5-year follow-up.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Best-corrected visual acuity (letter score) at 5-year FU					
1 (Elman, 2015)	RCT	235 eyes	Mean Difference: 2.60 [-0.40, 5.60][2]	High	Could not differentiate

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Loss of 15 or more letters BCVA at 5 years.					
1 (Elman, 2015)	RCT	235 eyes	Risk Ratio 1.04 [0.36, 3.01]	High	Could not differentiate

Table 11: Change in Central Retinal Thickness from Baseline to Five Year (retinal thickness <250 with at least a 25µm decrease)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in Central Retinal Thickness from Baseline to Five Year follow-up. (Retinal thickness <250 with at least a 25µm decrease)					
Elman, 2015	RCT	235 eyes	Risk Ratio: 0.97 [0.79, 1.19]	High	Could not differentiate

Early laser versus Deferred laser

People with diabetic macular oedema

Table 12: Worsening of best-corrected visual acuity.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Worsening of best-corrected visual acuity (≥ 15 letters) at 3 years follow-up.					
1 (ETDRS, 1985)	RCT	3148 eyes	Risk Ratio: 0.68 [0.58, 0.80]	High	Favours Early laser
Worsening of best-corrected visual acuity (≥ 15 letters) at 2 years					
1 (ETDRS, 1985)	RCT	3293 eyes	Risk Ratio: 0.66 [0.55, 0.79]	High	Favours Early laser

Table 13: number of eyes with non/clinically significant macular oedema at 3 years follow-up.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Eyes with clinically significant macular oedema at 3 years follow-up.					
1 (ETDRS, 1985)	RCT	350	Risk Ratio: 0.44 [0.32, 0.62]	Moderate	Favours Early laser
Eyes with not clinically significant macular oedema at 3 years follow-up.					
1 (ETDRS, 1985)	RCT	254	Risk Ratio: 0.65 [0.37, 1.13]	Moderate	Could not differentiate

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies.

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see **Error! Reference source not found.**). This search retrieved 672 studies. Based on title and abstract screening, 669 of the studies could confidently be excluded for this review question. Three studies were 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 prioritised for this review question.

1.1.10 Evidence statements

No relevant health economic studies were identified to be included.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

Change in visual acuity was identified as a crucial outcome. The committee acknowledged that preserving and improving visual acuity is a primary concern for patients. Loss of visual acuity can significantly impact an individual's daily activities and overall quality of life.

The incidence of clinically significant and non-clinically significant macular oedema was also considered important. Macular oedema in the central part of the retina can cause vision impairment and so it is important to reduce the incidence of this wherever possible. Although the committee recognised the importance of health-related quality of life and changes in peripheral vision, none of the included studies reported on these measures.

1.1.11.2 The quality of the evidence

Six RCTs met the inclusion criteria for this review. The studies included different patient populations, including people with non-proliferative diabetic retinopathy, people with vitreous haemorrhage and people with diabetic macular oedema.

Each study assessed different interventions for the management of diabetic retinopathy or macular oedema. While each intervention was relevant to current practice, this also meant that the results of different studies could not be pooled, and so most of the outcomes were based on individual study analysis. These limitations also meant that there were different comparisons for each population group. For instance, while there were comparisons between early and deferred anti-VEGFs for people with non-proliferative diabetic retinopathy, there was no similar comparison for people who have diabetic macular oedema. This made it difficult to

determine whether a certain threshold for starting treatment would be as effective for different populations.

The committee discussed how some of the studies were conducted a number of years ago when clinical practice might have differed from current standards. However, the committee still considered this evidence to be relevant, as it used treatments that are still used in current practice and included relevant populations. Others, such as Baker 2019, were more recent but had other limitations. This study compared laser photocoagulation, anti-VEGFs and initial observation (deferred anti-VEGFs) in people who have non-proliferative diabetic retinopathy and macular oedema. The population for this study had better vision than many people who have retinopathy, and so represent a small subgroup of the population. However, the committee thought these were still important results. The committee therefore considered these limitations when comparing the results to their clinical experience and knowledge to develop recommendations that align with current standards of care and a range of patient needs.

The committee identified several population subgroups that might influence treatment effectiveness. These subgroups included people who are pregnant and people from different age groups, varying disease severities, and those from different ethnic backgrounds. The committee thought that these factors could potentially impact the response to treatments, and therefore influence when treatment should be started. However, no evidence was available for analyses of any of these subgroups. These groups were therefore highlighted as potential subgroups in the research recommendation (see Appendix K).

1.1.11.3 Imprecision and clinical importance of effects

The committee thought that the evidence for the effects of macular laser compared to deferred treatment and early anti-VEGF compared to deferred treatment for people with macular oedema was precise enough to draw meaningful conclusions. The committee believed that early macular laser was likely to have clinically important effects in this population. However, they were less confident in the effects for people with non-proliferative or proliferative diabetic retinopathy.

The evidence for people with non-proliferative retinopathy and people with proliferative diabetic retinopathy mostly came from small trials, with wide confidence intervals for many of the outcomes. This made it difficult for the committee to draw any strong conclusions about the best thresholds at which to start treatment for these groups of people.

1.1.11.4 Benefits and harms

For people with non-proliferative and proliferative diabetic retinopathy

Given the limited number of studies, lack of meta-analysis, and the age of some of the studies, the committee decided that they were limited in the recommendations they could make for people with non-proliferative or proliferative diabetic retinopathy. However, they thought that the results from comparisons between early and deferred panretinal photocoagulation for people with diabetic retinopathy should be considered. The evidence indicated potential benefits in terms of reducing severe visual loss and progression of retinopathy at 2-year follow-up if panretinal photocoagulation was provided early. Based on this evidence, the committee recommended that panretinal photocoagulation should be offered when people first develop signs of proliferative diabetic retinopathy. They used their clinical experience to recommend how soon treatment should start after it is offered (see section 1.1.12.4 in evidence review E).

There was limited evidence for people with non-proliferative diabetic retinopathy either in this review, or in the review on treatment strategies for diabetic retinopathy (see evidence review E) and so the committee did not think they could make recommendations for this group. The committee recognised the limited evidence available for people with non-proliferative diabetic

retinopathy and acknowledged the need for further research to identify the best treatment strategies for this group, and so they made a research recommendation on this (see Appendix K).

For people with diabetic macular oedema

The committee reviewed the effectiveness of early macular laser treatment compared to deferred macular laser treatment for people with diabetic macular oedema. The evidence primarily relied on one large study, which demonstrated that early macular laser slowed the worsening of best-corrected visual acuity at 2 and 3 years of follow-up. Additionally, eyes receiving early laser treatment had a lower likelihood of developing clinically significant macular oedema compared to those receiving deferred treatment. The committee considered these improved outcomes consistent with their clinical experience, highlighting the importance of early intervention for diabetic macular oedema.

The committee highlighted that the evidence for people with diabetic macular oedema is for a population with good vision. Therefore, they felt that the evidence on the benefits of early laser mostly applied to people who do not have visual impairment. This study also showed that initial observation (deferred anti-VEGF treatment) did not result in worse outcomes than when people were given early anti-VEGF treatment or macular laser. For this reason, the committee decided to recommend that the options of macular laser and observation are considered for people who have centre-involving diabetic macular oedema and good vision. The decision between the two options should be made based on a discussion between the patient and the clinician to determine which option best meets their personal needs.

Although some people may prefer the option of observation over treatment at a stage when they do not have visual impairment, the committee noted that the option to choose early macular laser addresses the issue of delayed treatment and the potential missed opportunity for macular laser. They noted that in clinical practice, there are cases where treatment is deferred until the disease progresses, resulting in the need for anti-VEGF treatment. By initiating early laser treatment, fewer individuals may progress to the point of requiring anti-VEGF treatment, or they will take longer to reach this more severe stage of disease. This approach aims to prevent disease progression and reduce the need for more costly anti-VEGF treatments.

The committee were concerned about the variability in patient characteristics and the limitations of randomised controlled trials. While the studies included patients with centre involving diabetic macular oedema and central macular thickness above a certain threshold, they did not provide information on the effectiveness of macular laser treatment in selected cases. Structural variability, including differences in central retinal thickness, can impact the response to treatment and the effectiveness of interventions. The committee highlighted that there needs to be some consideration for genders and ethnicities. These groups were therefore added as potential subgroups in the research recommendations (Appendix K).

1.1.11.5 Cost effectiveness and resource use

No economic evidence was identified which addressed the cost-effectiveness of different thresholds or criteria for starting treatment for non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, or diabetic macula oedema. No recommendations were made for patients with non-proliferative diabetic retinopathy due to a lack of evidence in this area.

The committee discussed that timeliness of treatment is important for those with active proliferative diabetic retinopathy and recommended that panretinal photocoagulation is offered when individuals first develop signs of proliferative diabetic retinopathy and for treatment to start within 2 weeks of being offered. The committee discussed the resource implications of this recommendation, and considered there may be capacity constraints faced in clinical

practice such as additional staff time required on delivery and organisation of this more prompt treatment. The committee expressed the importance of panretinal photocoagulation being offered promptly whilst allowing for some flexibility up to two weeks to allow for capacity challenges some clinics may face. Although this is a slight change to overall practice in terms of offering treatment earlier, the committee did not expect there to be a major resource impact associated with this recommendation because the prompt offering of treatment is likely to reduce the risk of disease progression which would subsequently require more monitoring and potentially more interventions.

Given there was no economic evidence identified for people with diabetic macular oedema, the committee did not feel they could make specific recommendations on timing of treatment for this population. However, for people with non-centre involving clinically significant macular oedema and good vision the committee discussed that, based on the clinical evidence and their clinical expertise, laser treatment could be beneficial for this population and this could be considered 'early' laser treatment given it is likely to be earlier in the disease pathway. The committee noted that there is currently variation in practice as laser treatment is not used by all clinicians in all areas, and in these circumstances it is likely that there would be a need for anti-VEGF treatment to be started earlier and continue for a longer duration. The recommendation for timely use of macular laser treatment before vision loss is therefore expected to have a positive impact on resource implications as it is anticipated that the additional patient burden and longer treatment duration and therefore high costs associated with anti-VEGF treatment will be delayed or avoided.

1.1.12 Recommendations supported by this evidence review.

This evidence review supports recommendations 1.4.2 to 1.4.3, 1.4.13 and 1.5.3 to 1.5.4 and the research recommendation on effectiveness of different thresholds or criteria for starting treatment for non-proliferative diabetic retinopathy.

1.1.13 References – included studies.

1.1.13.1 Effectiveness

(1990) Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Four-year results of a randomized trial: Diabetic Retinopathy Vitrectomy Study Report 5. Archives of ophthalmology (Chicago, Ill. : 1960) 108(7): 958-964

Sato Y, Kojimahara N et al. (2012) Multicenter randomized clinical trial of retinal photocoagulation for preproliferative diabetic retinopathy.Japanese journal of ophthalmology 56(1): 52-59

Anonymous (1991) Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 98(5suppl): 766-85

Anonymous (1985) Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Archives of ophthalmology (Chicago, Ill. : 1960) 103(12): 1796-806

Baker, C.W., Glassman, A.R., Beaulieu, W.T. et al. (2019) Effect of Initial Management with Aflibercept vs Laser Photocoagulation vs Observation on Vision Loss among Patients with Diabetic Macular Edema Involving the Center of the Macula and Good Visual Acuity: A

Randomized Clinical Trial. JAMA - Journal of the American Medical Association 321(19): 1880-1894

Elman, Michael J, Ayala, Allison, Bressler, Neil M et al. (2015) Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. Ophthalmology 122(2): 375-81

1

2 **1.1.13.2 Economic**

3 No economic evidence was included.

4 **1.1.13.3 Other**

5

Appendices

Appendix A – Review protocols

Review protocol for the most effective thresholds or criteria for starting treatment for non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular oedema?

ID	Field	Content
0.	PROSPERO registration number	CRD42022354242
1.	Review title	Q2: The effectiveness of different thresholds or criteria for starting treatment for non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular oedema?
2.	Review question	What is the effectiveness of different thresholds or criteria for starting treatment for non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular oedema?
3.	Objective	To determine what are the most effective threshold for people who have been referred to hospital eye services or starting treatment for non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular oedema. The aim is to inform recommendations for the early or deferred treatment of Diabetic Retinopathy and diabetic macular oedema managed

		under hospital eye services and the population outlined in this protocol broadly matches that group.
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 with: • non-proliferative diabetic retinopathy

		• proliferative diabetic retinopathy • diabetic macular oedema.
7.	Intervention	• Lower or higher thresholds for starting treatment than standard threshold. • Immediate treatment compared with deferred treatment. Limited to the following interventions being considered under other review questions in the guideline: • Blood pressure medicines • Statins • Fibrates • Vitrectomy • Laser photocoagulation • Anti-VEGF agents • Intravitreal steroids • Combinations of the treatments listed above
8.	Comparators	• Standard threshold for starting treatment (as defined by the study) • Deferred treatment (when compared with immediate treatment)
9.	Types of study to be included	- Randomised controlled trials - Comparative observational studies with a concurrent control group. - Within person studies comparing treatment thresholds between eyes will be included.
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.
		  ○

13.	Secondary outcomes (important outcomes)	• Incidence or progression of proliferative diabetic retinopathy • Incidence or progression of macular oedema • Peripheral vision, assessed using visual field measurement • Quality of life, measured using a validated tool (the overall score as well as mental health domain scores will be reported separately) • Central retinal thickness • Tractional retinal detachment 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. The unit of analysis will be the eye. Studies that have included more than 1 eye per participant should have adjusted for the within-person correlation in their analysis. Adjusted effect estimates will be incorporated using the generic inverse variance function in RevMan. If only unadjusted data are available this will be incorporated and the implications with the committee will be discussed.
17.	Analysis of sub-groups	Data will be presented separately for the following groups: • Pregnant women • Non-proliferative diabetic retinopathy, proliferative retinopathy, diabetic macular oedema If data is available a subgroup analysis will be conducted by: • Ethnicity • People with a learning disability • Socioeconomic status

		• Age: (People under the age of 18, people aged 18 to 80, people aged greater than 80) • Severity of non-proliferative retinopathy (moderate, severe and very severe). Severity of proliferative retinopathy (low risk, high risk), Severity of diabetic macular oedema (non-centre involving, centre involving)
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

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

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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)	14/09/2022	Wiley	Issue 8 of 12, August 2022
Cochrane Database of Systematic Reviews (CDSR)	14/09/2022	Wiley	Issue 9 of 12, September 2022
Embase	14/09/2022	OVID	1974 to 2022 September 13
Epistemonikos	14/09/2022	N/A	Search run on 14 September 2022
HTA	14/09/2022	CRD	Search run on 14 September 2022
INAHTA	14/09/2022	INAHTA	Search run on 14 September 2022
MEDLINE	14/09/2022	OVID	1946 to September 13, 2022
MEDLINE-in-Process	14/09/2022	OVID	1946 to September 13, 2022
MEDLINE ePub Ahead-of-Print	14/09/2022	OVID	September 13, 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 5625
#4 {or #1-#3} 6068
#5 MeSH descriptor: [Treatment Outcome] this term only 145845
#6 MeSH descriptor: [Time Factors] this term only 67162
#7 MeSH descriptor: [Time-to-Treatment] this term only 453
#8 ((prompt* or defer* or delay* or reduc* or extend* or start* or stop* or earl* or late*) near/2 treat*):ti,ab,kw 41035
#9 ((treat* or dos* or low* or high*) near/2 (regimen* or threshold*)):ti,ab,kw 29471
#10 {or #5-#9} 249116
#11 #4 and #10 1776

Database: Embase

1 diabetic retinopathy/ 47121
2 macular edema/ 6291
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 52113

4 or/1-3 70817
5 treatment outcome/ 933197
6 time factor/ 45743
7 time to treatment/ 23655
8 ((prompt* or defer* or delay* or reduc* or extend* or start* or stop* or earl* or late*) adj2 treat*).tw. 307946
9 ((treat* or dos* or low* or high*) adj2 (regimen* or threshold*)).tw. 155117
10 or/5-9 1415424
11 4 and 10 7572
12 exp hydroxymethylglutaryl coenzyme A reductase inhibitor/ 179101
13 Statin*.tw. 81162
14 atorvastatin/ or simvastatin/ or fluindostatin/ or pravastatin/ or rosuvastatin/ 84778
15 (atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or fluindostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or dorisin* or nandovar*).tw. 41907
16 ((hmgcoa reductase* or hmg-coa reductase*) adj4 inhibitor*).tw. 6526
17 (hydroxymethylglutary* adj3 (inhibit* or reductase*)).tw. 980
18 or/12-17 199707
19 bezafibrate/ 5592
20 (Bezafibrate* or Fibrazate*).tw. 2217
21 ciprofibrate/ 1359
22 (ciprofibrate* or lipanor*).tw. 625
23 gemfibrozil/ 9168
24 (gemfibrozil* or lopid*).tw. 2912
25 or/19-24 13883
26 18 or 25 207193
27 11 and 26 171
28 exp vasculotropin/ 152599
29 exp vasculotropin receptor/ 12648
30 (anti adj2 VEGF*).tw. 14389
31 (anti-VEGF* or antiVEGF*).tw. 14018
32 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 6577
33 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 16440
34 (vascular proliferation adj4 inhibit*).tw. 44
35 or/28-34 172459
36 Aflibercept*.tw. 4397
37 aflibercept/ 7987
38 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 1602
39 bevacizumab/ 68296
40 Bevacizumab*.tw. 33900
41 (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. 10648
42 (IVB adj2 inject*).tw. 383
43 ranibizumab/ 11630
44 Ranibizumab*.tw. 6917
45 (Lucentis or rhuFab).tw. 3053
46 (IVR adj2 inject*).tw. 190
47 (Faricimab or Vabysmo).tw. 76

48 faricimab/ 151
49 Pegaptanib*.tw. 577
50 pegaptanib/ 2399
51 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 1240
52 sunitinib/ 25870
53 (Sunitinib or Sutent).tw. 13893
54 sorafenib/ 34748
55 (Sorafenib or Nexavar).tw. 20361
56 axitinib/ 6367
57 (Axitinib or Inlyta).tw. 2627
58 pazopanib/ 9767
59 (Pazopanib or Votrient).tw. 4430
60 or/36-59 123887
61 laser coagulation/ 23260
62 ((Laser* or panretinal* or pan-retinal*) adj4 (coagulat* or co-agulat* or photocoagulat* or thermocoagulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 66002
63 PRP.tw. 24511
64 or/61-63 101232
65 35 or 60 or 64 364373
66 11 and 65 3218
67 dexamethasone/ or fluocinolone acetonide/ or triamcinolone acetonide/ 190075
68 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 90967
69 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 6955
70 angiogenesis/ or angiogenesis inhibitor/ or angiogenic factor/ or endothelial cell growth factor/ 162649
71 macugen*.tw. 1190
72 (anti adj2 VEGF*).tw. 14389
73 (endothelial adj2 growth adj2 factor*).tw. 87660
74 exp laser coagulation/ 23260
75 (photocoagulat* or argon or diode or micropulse).tw. 58282
76 ((photo or light) adj1 (coagulat* or co-agulat*)).tw. 210
77 ((focal or grid) adj3 laser*).tw. 1448
78 or/67-77 493765
79 11 and 78 2816
80 eye surgery/ 20317
81 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 42978
82 vitrectomy/ or vitreoretinal surgery/ 26217
83 vitrectom*.tw. 21997
84 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 3391
85 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 3210
86 or/80-85 84261
87 11 and 86 1286
88 27 or 66 or 79 or 87 4346
89 random:.tw. 1832912
90 placebo:.mp. 501148
91 double-blind:.tw. 233566
92 or/89-91 2102774
93 Clinical study/ 160312
94 Case control study/ 192677
95 Family study/ 25688

96 Longitudinal study/ 178031
97 Retrospective study/ 1305638
98 comparative study/ 967863
99 Prospective study/ 793999
100 Randomized controlled trials/ 234315
101 99 not 100 784636
102 Cohort analysis/ 893939
103 cohort analy$.tw. 17297
104 (Cohort adj (study or studies)).tw. 411410
105 (Case control$ adj (study or studies)).tw. 161174
106 (follow up adj (study or studies)).tw. 70317
107 (observational adj (study or studies)).tw. 225990
108 (epidemiologic$ adj (study or studies)).tw. 117376
109 (cross sectional adj (study or studies)).tw. 301293
110 prospective.tw. 1023625
111 retrospective.tw. 1136239
112 or/93-98,101-111 4909541
113 92 or 112 6501156
114 88 and 113 2699
115 Nonhuman/ not Human/ 5051072
116 114 not 115 2691
117 limit 116 to english language 2495
118 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5310614
119 117 not 118 2063

1

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:(treatment) OR abstract:(treatment))

AND

(title:((time OR factor OR outcome OR regimen* OR threshold* OR prompt* OR defer* OR delay* OR reduc* OR extend* OR start* OR stop* OR earl* OR late*)) OR abstract:((time OR factor OR outcome OR regimen* OR threshold* OR prompt* OR defer* OR delay* OR reduc* OR extend* OR start* OR stop* OR earl* OR late*)))

2

Database: Health Technology Assessment (HTA)

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118 Delete

2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82 Delete
3 ((diabet* near (retin* or eye* or macular* or maculopath*))) 225 Delete
4 #1 OR #2 OR #3 254 Delete
5 MeSH DESCRIPTOR Treatment Outcome EXPLODE ALL TREES 14294 Delete
6 MeSH DESCRIPTOR Time Factors EXPLODE ALL TREES 3076 Delete
7 MeSH DESCRIPTOR Time-to-Treatment EXPLODE ALL TREES 19 Delete
8 (((prompt* or defer* or delay* or reduc* or extend* or start* or stop* or earl* or late*) near treat*)) 2532 Delete
9 (((treat* or dos* or low* or high*) near (regimen* or threshold*))) 1857 Delete
10 #5 OR #6 OR #7 OR #8 OR #9 18917 Delete
11 #4 AND #10 58 Delete
12 * IN HTA 17351 Delete
13 #11 AND #12 3 Delete

1

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

11 #10 AND #4 95
10 #9 OR #8 OR #7 OR #6 OR #5 3577
9 (((treat* or dos* or low* or high*) AND (regimen* or threshold*))) 520
8 (((prompt* or defer* or delay* or reduc* or extend* or start* or stop* or earl* or late*) AND treat*)) 2840
7 "Time-to-Treatment"[mh] 6
6 "Time Factors"[mh] 73
5 "Treatment Outcome"[mh] 441
4 #3 OR #2 OR #1 95
3 ((diabet* AND (retin* or eye* or macular* or maculopath*)) 87
2 "Macular Edema"[mh] 28
1 "Diabetic Retinopathy"[mh] 40

2

Database: Ovid MEDLINE(R)

1 Diabetic Retinopathy/ 28376
2 Macular Edema/ 8527
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 32693
4 1 or 2 or 3 43039
5 Treatment Outcome/ 1118485
6 Time Factors/ 1228203
7 Time-to-Treatment/ 9683

8 ((prompt* or defer* or delay* or reduc* or extend* or start* or stop* or earl* or late*) adj2 treat*).tw. 172501
9 ((treat* or dos* or low* or high*) adj2 (regimen* or threshold*)).tw. 92379
10 or/5-9 2418667
11 4 and 10 7240
12 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ 45294
13 Statin*.tw. 43378
14 Atorvastatin/ or Simvastatin/ or Fluvastatin/ or Pravastatin/ or Rosuvastatin Calcium/ 20063
15 (atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or fluindostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or dorisin* or nandovar*).tw. 21943
16 ((hmgcoa reductase* or hmg-coa reductase*) adj3 inhibit*).tw. 4930
17 (hydroxymethylglutary* adj3 (inhibit* or reductase*)).tw. 852
18 or/12-17 65872
19 Bezafibrate/ 1261
20 (Bezafibrate* or Fibrazate*).tw. 1561
21 (ciprofibrate* or lipanor*).tw. 475
22 Gemfibrozil/ 1402
23 (gemfibrozil* or lopid*).tw. 1847
24 or/19-23 4102
25 18 or 24 69114
26 11 and 25 48
27 exp Vascular Endothelial Growth Factors/ 62005
28 exp Receptors, Vascular Endothelial Growth Factor/ 17799
29 (anti adj2 VEGF*).tw. 7055
30 (anti-VEGF* or antiVEGF*).tw. 6815
31 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 4233
32 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 9373
33 (vascular proliferation adj4 inhibit*).tw. 29
34 or/27-33 75164
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/ 13584
38 Bevacizumab*.tw. 15321
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/ 4485
42 Ranibizumab*.tw. 3755
43 (Lucentis or rhuFab).tw. 362
44 (IVR adj2 inject*).tw. 105
45 (Faricimab or Vabysmo).tw. 34
46 Pegaptanib*.tw. 420
47 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 118
48 Sunitinib/ 4028
49 (Sunitinib or Sutent).tw. 5364
50 Sorafenib/ 5930
51 (Sorafenib or Nexavar).tw. 7950
52 Axitinib/ 669

53 (Axitinib or Inlyta).tw. 956
54 (Pazopanib or Votrient).tw. 1589
55 or/35-54 35510
56 Laser Coagulation/ 8108
57 ((Laser* or panretinal* or pan-retinal*) adj4 (coagulat* or co-agulat* or photocoagulat* or thermocoagulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 44556
58 PRP.tw. 15472
59 or/56-58 62859
60 34 or 55 or 59 159241
61 11 and 60 2573
62 Dexamethasone/ or Fluocinolone Acetonide/ or Triamcinolone Acetonide/ 61534
63 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 57182
64 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 4933
65 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 113033
66 macugen*.tw. 107
67 (anti adj2 VEGF*).tw. 7055
68 (endothelial adj2 growth adj2 factor*).tw. 61410
69 exp light coagulation/ 13108
70 (photocoagulat* or argon or diode or micropulse).tw. 35271
71 ((photo or light) adj1 (coagulat* or co-agulat*)).tw. 326
72 ((focal or grid) adj3 laser*).tw. 859
73 or/62-72 249914
74 11 and 73 3044
75 Ophthalmologic Surgical Procedures/ 13038
76 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 30310
77 Vitrectomy/ or Vitreoretinal Surgery/ 15840
78 vitrectom*.tw. 15058
79 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 2238
80 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 2278
81 or/75-80 57829
82 11 and 81 1085
83 26 or 61 or 74 or 82 3783
84 randomized controlled trial.pt. 576794
85 randomi?ed.mp. 931738
86 placebo.mp. 219275
87 or/84-86 987997
88 Observational Studies as Topic/ 8134
89 Observational Study/ 132223
90 Epidemiologic Studies/ 9185
91 exp Case-Control Studies/ 1353189
92 exp Cohort Studies/ 2394292
93 Cross-Sectional Studies/ 440197
94 Comparative Study.pt. 1911548
95 case control$.tw. 132857
96 (cohort adj (study or studies)).tw. 246243
97 cohort analy$.tw. 9350
98 (follow up adj (study or studies)).tw. 50057
99 (observational adj (study or studies)).tw. 121615
100 longitudinal.tw. 257535

101 prospective.tw. 595827
102 retrospective.tw. 582780
103 cross sectional.tw. 385793
104 or/88-103 4942783
105 87 or 104 5538483
106 83 and 105 2875
107 animals/ not humans/ 5012420
108 106 not 107 2859
109 limit 108 to english language 2645
110 limit 109 to (letter or historical article or comment or editorial or news or case reports) 105
111 109 not 110 2540

1

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 1 or 2 or 3 1
5 Treatment Outcome/ 0
6 Time Factors/ 0
7 Time-to-Treatment/ 0
8 ((prompt* or defer* or delay* or reduc* or extend* or start* or stop* or earl* or late*) adj2 treat*).tw. 54
9 ((treat* or dos* or low* or high*) adj2 (regimen* or threshold*)).tw. 31
10 or/5-9 84
11 4 and 10 0
12 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ 0
13 Statin*.tw. 9
14 Atorvastatin/ or Simvastatin/ or Fluvastatin/ or Pravastatin/ or Rosuvastatin Calcium/ 0
15 (atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or fluindostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or dorisin* or nandovar*).tw. 6
16 ((hmgcoa reductase* or hmg-coa reductase*) adj3 inhibit*).tw. 1
17 (hydroxymethylglutary* adj3 (inhibit* or reductase*)).tw. 0
18 or/12-17 12
19 Bezafibrate/ 0
20 (Bezafibrate* or Fibrazate*).tw. 0
21 (ciprofibrate* or lipanor*).tw. 0
22 Gemfibrozil/ 0
23 (gemfibrozil* or lopid*).tw. 0
24 or/19-23 0
25 18 or 24 12
26 11 and 25 0
27 exp Vascular Endothelial Growth Factors/ 0
28 exp Receptors, Vascular Endothelial Growth Factor/ 0
29 (anti adj2 VEGF*).tw. 0
30 (anti-VEGF* or antiVEGF*).tw. 0
31 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 0

32 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 0
33 (vascular proliferation adj4 inhibit*).tw. 0
34 or/27-33 0
35 Aflibercept*.tw. 0
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. 5
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. 1
46 Pegaptanib*.tw. 0
47 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 0
48 Sunitinib/ 0
49 (Sunitinib or Sutent).tw. 2
50 Sorafenib/ 0
51 (Sorafenib or Nexavar).tw. 1
52 Axitinib/ 0
53 (Axitinib or Inlyta).tw. 1
54 (Pazopanib or Votrient).tw. 1
55 or/35-54 9
56 Laser Coagulation/ 0
57 ((Laser* or panretinal* or pan-retinal*) adj4 (coagulat* or co-agulat* or photocoagulat* or thermocoagulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 16
58 PRP.tw. 4
59 or/56-58 20
60 34 or 55 or 59 29
61 11 and 60 0
62 Dexamethasone/ or Fluocinolone Acetonide/ or Triamcinolone Acetonide/ 0
63 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 5
64 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 0
65 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 0
66 macugen*.tw. 0
67 (anti adj2 VEGF*).tw. 0
68 (endothelial adj2 growth adj2 factor*).tw. 5
69 exp light coagulation/ 0
70 (photocoagulat* or argon or diode or micropulse).tw. 5
71 ((photo or light) adj1 (coagulat* or co-agulat*)).tw. 0
72 ((focal or grid) adj3 laser*).tw. 0
73 or/62-72 15
74 11 and 73 0
75 Ophthalmologic Surgical Procedures/ 0
76 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 3

77 Vitrectomy/ or Vitreoretinal Surgery/ 0
78 vitrectom*.tw. 0
79 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 0
80 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or re-sect* or remov*)).tw. 0
81 or/75-80 3
82 11 and 81 0
83 26 or 61 or 74 or 82 0
84 randomized controlled trial.pt. 0
85 randomi?ed.mp. 163
86 placebo.mp. 31
87 or/84-86 169
88 Observational Studies as Topic/ 0
89 Observational Study/ 0
90 Epidemiologic Studies/ 0
91 exp Case-Control Studies/ 0
92 exp Cohort Studies/ 0
93 Cross-Sectional Studies/ 0
94 Comparative Study.pt. 0
95 case control$.tw. 25
96 (cohort adj (study or studies)).tw. 137
97 cohort analy$.tw. 7
98 (follow up adj (study or studies)).tw. 9
99 (observational adj (study or studies)).tw. 53
100 longitudinal.tw. 89
101 prospective.tw. 145
102 retrospective.tw. 231
103 cross sectional.tw. 113
104 or/88-103 606
105 87 or 104 740
106 83 and 105 0
107 animals/ not humans/ 0
108 106 not 107 0
109 limit 108 to english language 0
110 limit 109 to (letter or historical article or comment or editorial or news or case reports) 0
111 109 not 110 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. 491
4 1 or 2 or 3 491
5 Treatment Outcome/ 0
6 Time Factors/ 0
7 Time-to-Treatment/ 0
8 ((prompt* or defer* or delay* or reduc* or extend* or start* or stop* or earl* or late*) adj2 treat*).tw. 2728
9 ((treat* or dos* or low* or high*) adj2 (regimen* or threshold*)).tw. 1270
10 or/5-9 3962

1 11 4 and 10 45
2 12 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ 0
3 13 Statin*.tw. 700
4 14 Atorvastatin/ or Simvastatin/ or Fluvastatin/ or Pravastatin/ or Rosuvastatin
5 Calcium/ 0
6 15 (atorvastatin* or lipitor* or simvastatin* or zocor* or fluvastatin* or
7 fluindostatin* or lescol* or pravastatin* or lipostat* or rosuvastatin* or crestor* or
8 dorisin* or nandovar*).tw. 210
9 16 ((hmgcoa reductase* or hmg-coa reductase*) adj3 inhibit*).tw. 39
10 17 (hydroxymethylglutary* adj3 (inhibit* or reductase*)).tw. 7
11 18 or/12-17 843
12 19 Bezafibrate/ 0
13 20 (Bezafibrate* or Fibrazate*).tw. 5
14 21 (ciprofibrate* or lipanor*).tw. 0
15 22 Gemfibrozil/ 0
16 23 (gemfibrozil* or lopid*).tw. 13
17 24 or/19-23 18
18 25 18 or 24 858
19 26 11 and 25 1
20 27 exp Vascular Endothelial Growth Factors/ 0
21 28 exp Receptors, Vascular Endothelial Growth Factor/ 0
22 29 (anti adj2 VEGF*).tw. 187
23 30 (anti-VEGF* or antiVEGF*).tw. 185
24 31 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 121
25 32 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or
26 vascular permeability factor* or VPF) adj2 (trap* or inhibit* or
27 antagonist*)).tw. 133
28 33 (vascular proliferation adj4 inhibit*).tw. 0
29 34 or/27-33 335
30 35 Aflibercept*.tw. 85
31 36 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005"
32 or AVE005).tw. 6
33 37 Bevacizumab/ 0
34 38 Bevacizumab*.tw. 271
35 39 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas
36 or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or
37 NSC704865).tw. 9
38 40 (IVB adj2 inject*).tw. 3
39 41 Ranibizumab/ 0
40 42 Ranibizumab*.tw. 91
41 43 (Lucentis or rhuFab).tw. 2
42 44 (IVR adj2 inject*).tw. 1
43 45 (Faricimab or Vabysmo).tw. 3
44 46 Pegaptanib*.tw. 8
45 47 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 0
46 48 Sunitinib/ 0
47 49 (Sunitinib or Sutent).tw. 61
48 50 Sorafenib/ 0
49 51 (Sorafenib or Nexavar).tw. 138
50 52 Axitinib/ 0
51 53 (Axitinib or Inlyta).tw. 33
52 54 (Pazopanib or Votrient).tw. 27
53 55 or/35-54 590
54 56 Laser Coagulation/ 0

1 57 ((Laser* or panretinal* or pan-retinal*) adj4 (coagulat* or co-agulat* or
2 photocoagulat* or thermocoagulat* or surg* or treat* or procedure* or therap* or
3 cauteri*)).tw. 635
4 58 PRP.tw. 194
5 59 or/56-58 821
6 60 34 or 55 or 59 1582
7 61 11 and 60 19
8 62 Dexamethasone/ or Fluocinolone Acetonide/ or Triamcinolone
9 Acetonide/ 0
10 63 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 548
11 64 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 65
12 65 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or
13 endothelial cell growth factor/ or exp vasculotropin/ 0
14 66 macugen*.tw. 0
15 67 (anti adj2 VEGF*).tw. 187
16 68 (endothelial adj2 growth adj2 factor*).tw. 649
17 69 exp light coagulation/ 0
18 70 (photocoagulat* or argon or diode or micropulse).tw. 636
19 71 ((photo or light) adj1 (coagulat* or co-agulat*)).tw. 0
20 72 ((focal or grid) adj3 laser*).tw. 9
21 73 or/62-72 1921
22 74 11 and 73 19
23 75 Ophthalmologic Surgical Procedures/ 0
24 76 ((ophthalm* or ocular* or eye*) adj4 (surg* or operat* or proced* or resect* or
25 re-sect* or remov*)).tw. 525
26 77 Vitrectomy/ or Vitreoretinal Surgery/ 0
27 78 vitrectom*.tw. 321
28 79 (vitreous* adj4 (surg* or operat* or proced* or resect* or re-sect* or
29 remov*)).tw. 18
30 80 ((vitreoretinal* or vitreo-retinal*) adj4 (surg* or operat* or proced* or resect* or
31 re-sect* or remov*)).tw. 42
32 81 or/75-80 816
33 82 11 and 81 3
34 83 26 or 61 or 74 or 82 25
35 84 randomized controlled trial.pt. 1
36 85 randomi?ed.mp. 12953
37 86 placebo.mp. 2654
38 87 or/84-86 13774
39 88 Observational Studies as Topic/ 0
40 89 Observational Study/ 2
41 90 Epidemiologic Studies/ 0
42 91 exp Case-Control Studies/ 0
43 92 exp Cohort Studies/ 0
44 93 Cross-Sectional Studies/ 0
45 94 Comparative Study.pt. 0
46 95 case control$.tw. 2275
47 96 (cohort adj (study or studies)).tw. 8814
48 97 cohort analy$.tw. 302
49 98 (follow up adj (study or studies)).tw. 559
50 99 (observational adj (study or studies)).tw. 4020
51 100 longitudinal.tw. 6616
52 101 prospective.tw. 11355
53 102 retrospective.tw. 17603
54 103 cross sectional.tw. 10484
55 104 or/88-103 47563

105	87 or 104	58302
106	83 and 105	14
107	animals/ not humans/	0
108	106 not 107	14
109	limit 108 to english language	14
110	limit 109 to (letter or historical article or comment or editorial or news or case reports)	0
111	109 not 110	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)

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

Database: EconLit

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 14
4 1 or 2 or 3 14

Database: Embase

Cost utility search:

1 diabetic retinopathy/ 45217
2 macular edema/ 5687
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47443
4 1 or 2 or 3 65931
5 cost utility analysis/ 10912
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 26154
7 ((incremental* adj2 cost*) or ICER).tw. 26757
8 (cost adj2 utilit*).tw. 9655
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 2715
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 31906
11 (cost and (effect* or utilit*)).ti. 51363
12 or/5-11 81030
13 4 and 12 417

14 nonhuman/ not human/ 4929899
15 13 not 14 415
16 (conference abstract or conference paper or conference proceeding or "conference review").pt. 5091583
17 15 not 16 302

Cohort studies:

1 diabetic Retinopathy/ 45440
2 macular Edema/ 5828
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47762
4 or/1-3 66388
5 cohort analysis/ 811098
6 Retrospective study/ 1206857
7 Prospective study/ 748103
8 (Cohort adj (study or studies)).tw. 380594
9 (cohort adj (analy* or regist*)).tw. 16437
10 (follow up adj (study or studies)).tw. 68508
11 longitudinal.tw. 384899
12 prospective.tw. 981024
13 retrospective.tw. 1068301
14 or/5-13 3358085
15 4 and 14 13743
16 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or

south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ 1511773

17 exp "organisation for economic co-operation and development"/ 1933

18 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ 3545238

19 european union/ 29144

20 developed country/ 34415

21 or/17-20 3576072

22 16 not 21 1373176

23 15 not 22 12938

24 limit 23 to english language 12133

25 nonhuman/ not human/ 4938000

26 24 not 25 12067

27 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 7072757

28 26 not 27 8733

29 limit 28 to dc=20120101-20220228 6467

Database: HTA

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118

2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82

3 ((diabet* adj4 (retin* or eye* or macular*))) 216

4 #1 OR #2 OR #3 245

5 * IN HTA FROM 2012 TO 2022 5598

6 #4 AND #5 26

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

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

1

2

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
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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

1

2

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

Cost utility search:

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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
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4	or/1-3	336
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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

3

4

Database: Ovid MEDLINE(R) Epub Ahead of Print

Cost utility search:

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2 Macular Edema/ 0
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4 1 or 2 or 3 585
5 Cost-Benefit Analysis/ 0
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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:

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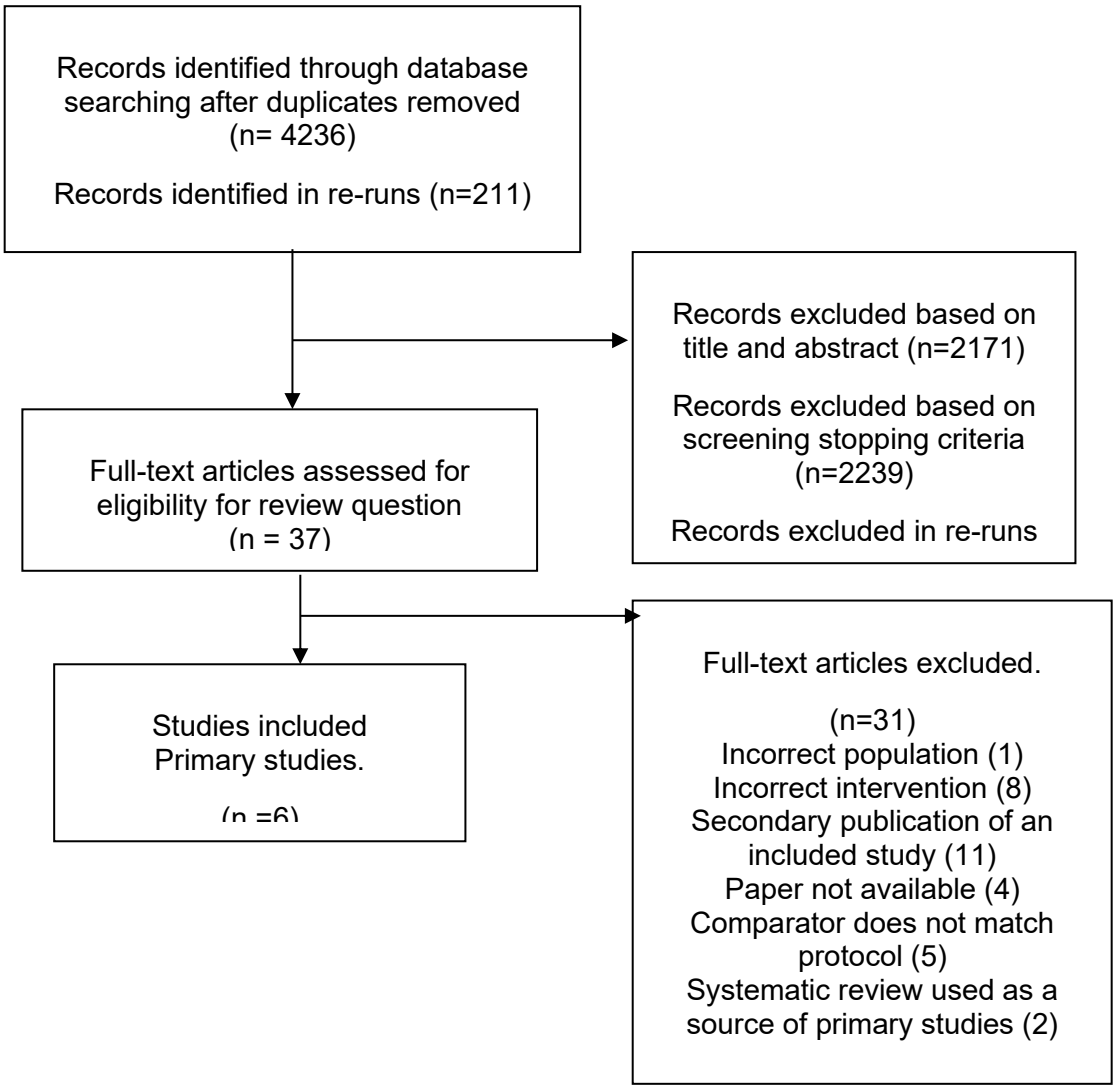
7 (cohort adj (analy* or regist*)).tw. 349
8 (follow up adj (study or studies)).tw. 607
9 longitudinal.tw. 6722
10 prospective.tw. 12241
11 retrospective.tw. 18324
12 or/5-11 37987
13 4 and 12 147
14 limit 13 to english language 147

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



1 Appendix D – Effectiveness evidence

2 Baker, 2019

Bibliographic Reference	Baker, C.W.; Glassman, A.R.; Beaulieu, W.T.; Antoszyk, A.N.; Browning, D.J.; Chalam, K.V.; Grover, S.; Jampol, L.M.; Jhaveri, C.D.; Melia, M.; Stockdale, C.R.; Martin, D.F.; Sun, J.K.; Effect of Initial Management with Aflibercept vs Laser Photocoagulation vs Observation on Vision Loss among Patients with Diabetic Macular Edema Involving the Center of the Macula and Good Visual Acuity: A Randomized Clinical Trial; JAMA - Journal of the American Medical Association; 2019; vol. 321 (no. 19); 1880-1894

3 Study details

Study dates	November 8, 2013, to September 26, 2016
Inclusion criteria	• Age >= 18 years • Diagnosis of diabetes mellitus (type 1 or type 2) • Best corrected E-ETDRS visual acuity letter score >79 (approximate Snellen equivalent 20/25 or better) at two consecutive visits within 1 to 28 days. • definite retinal thickening due to DME involving the centre of the macula. • Diabetic macular oedema confirmed on OCT
Exclusion criteria	• History of chronic renal failure requiring dialysis or kidney transplant. • Initiation of intensive insulin treatment (a pump or multiple daily injections) within 4 months prior to randomization or plans to do so in the next 4 months. • Blood pressure >180/110 (systolic above 180 OR diastolic above 110) • Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization • Pregnancy • Macular oedema is considered to be due to a cause other than DME. • Any history of prior laser or other surgical, intravitreal, or peribulbar treatment for DME • Any history of vitrectomy • Aphakia.
Intervention(s)	Prompt intravitreal anti-VEGF Intravitreal 2.0 mg aflibercept is administered on the day of randomization in eyes assigned to the prompt anti-VEGF group.
Comparator	• Prompt focal/grid photocoagulation + deferred intravitreal anti-VEGF Focal/grid photocoagulation is administered on the day of randomisation.

	• Observation + deferred intravitreal anti-VEGF Treatment is not administered at baseline. For eyes in the deferred anti-VEGF groups (either observation or focal/grid), if there is a decrease in visual acuity presumed to be due to DME of at least 10 letters compared with the baseline visual acuity (mean of the screening and randomization visual acuity) at a single visit or 5 to 9 letters decrease compared with baseline visual acuity at two consecutive visits, an injection of anti-VEGF will be given. Once anti-VEGF injections are initiated, retreatment will follow the criteria
Number of participants	702 (per eye)
Duration of follow-up	2-year follow-up
Loss to follow-up	Excluding deaths, the 2-year completion rate was 92% (625/681).

Study arms

Prompt anti-VEGF group (N = 226)
Deferred anti-VEGF group (focal/grid photocoagulation): (N = 240)
Deferred anti-VEGF group (observation group): (N = 236)

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 (The study included a specific population)
Overall bias and Directness	Overall Directness	Directly applicable

Elman, 2015

Bibliographic Reference	Elman, Michael J; Ayala, Allison; Bressler, Neil M; Browning, David; Flaxel, Christina J; Glassman, Adam R; Jampol, Lee M; Stone, Thomas W; Diabetic Retinopathy Clinical Research, Network; Intravitreal Ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results.; Ophthalmology; 2015; vol. 122 (no. 2); 375-81

Study details

Study type	Randomised controlled trial (RCT)
Study setting	52 clinical sites in the United States.
Sources of funding	The Johns Hopkins University sponsored by the Bayer; Genentech, Inc, Novartis Pharma AG, Regeneron, and The Emmes Corporation through the Office of Research Administration of the Johns Hopkins University School of Medicine and has a contract agreement from the American Medical Association to the Johns Hopkins University School of Medicine.

Inclusion criteria	• 18 years old with type 1 or 2 diabetes. • participants had at least one eye with visual acuity (approximate Snellen equivalent) of 20/32 to 20/320 • DME involving the central macula • retinal thickness measured on time domain optical coherence tomography (OCT) ≥250 μm in the central subfield. A patient could have 2 study eyes in the trial only if both were eligible at the time of study entry.
Exclusion criteria	• treatment for DME within the prior 4 months, • panretinal photocoagulation within the prior 4 months or anticipated need for panretinal photocoagulation within the next 6 months, • major ocular surgery within the prior 4 months, • history of open-angle glaucoma or steroid-induced intraocular pressure (IOP) elevation that required IOP-lowering treatment, • IOP ≥25 mmHg. • systolic blood pressure was >180 mmHg or diastolic blood pressure was >110 mmHg, • myocardial infarction,
Intervention(s)	ranibizumab every 4 weeks until no longer improving (with resumption if worsening) and prompt focal/grid laser treatment. 180 eyes were assigned to ranibizumab plus prompt focal/grid laser treatment
Comparator	ranibizumab every 4 weeks until no longer improving (with resumption if worsening) and deferred (>= 24 weeks) focal/grid laser treatment. 181 eyes to ranibizumab plus deferred laser treatment. Laser in the deferral group had to be delayed for at least 24 weeks after initiating anti-VEGF therapy. However, at or after 24 weeks, laser treatment could be given if there was persistent DME involving the central subfield on OCT that had not improved after at least 2 consecutive injections given at 4-weekly intervals
Outcome measures	Best-corrected visual acuity at the 5-year visit. OCT Central Subfield Thickness
Number of participants	235
Duration of follow-up	Visits occurred every 4 weeks through year 1 and then every 4 to 16 weeks through year 5
Loss to follow-up	Excluding deaths, the 5-year completion rate was 76% of the 163 original participants randomized to the ranibizumab + prompt laser group and 74% of the 150 original participants randomized to the ranibizumab + deferred laser group.

Study arms

Ranibizumab + Prompt Laser treatment (N = 124)

Ranibizumab + Deferred Laser treatment (N = 111)

Characteristics

Study-level characteristics

Characteristic	Study (N = 235)
% Female Sample size	n = 102 (43%)

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	Low
Overall bias and Directness	Overall Directness	Directly applicable

ETDRS, 1985

Bibliographic Reference	Anonymous; Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group.; Archives of ophthalmology (Chicago, Ill. : 1960); 1985; vol. 103 (no. 12); 1796-806

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	23 centres
Study dates	April 1980-August1985
Sources of funding	not reported
Inclusion criteria	• People with diabetes with early proliferative retinopathy, or moderate-to-severe non-proliferative retinopathy, • DMO in each eye, or a combination of these.
Exclusion criteria	• Right risk proliferative retinopathy (moderate or severe optic nerve neovascularisation • any neovascularisation with haemorrhage) and other ocular disease or VA < 20/200. E • excluded from this report were the results for the eyes with mild-to-moderate retinopathy and macular oedema that were randomly assigned to an initial treatment of PRP and follow-up focal photocoagulation if macular oedema persisted. Type of DMO: CSMO
Intervention(s)	immediate photocoagulation laser
Comparator	deferred argon laser
Outcome measures	retinal detachment Best-corrected visual acuity

Number of participants	1122 participants (2244 eyes)
Duration of follow-up	4 years follow up
Loss to follow-up	not reported

Study arms

deferred argon laser (N = 1490)

early laser photocoagulation (N = 754)

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 (The study population consisted of individuals with specific characteristics)
Overall bias and Directness	Overall Directness	Directly applicable

DRVS, 1990

Bibliographic Reference	Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Four-year results of a randomized trial: Diabetic Retinopathy Vitrectomy Study Report 5.; Archives of ophthalmology (Chicago, Ill. : 1960); 1990; vol. 108 (no. 7)

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	multicentre, interventional clinical trial DRVS sites
Study dates	
Inclusion criteria	• Adults (age >18) • Diagnosis of diabetes mellitus (either Type 1 or Type 2) • Sudden vision loss due to severe vitreous haemorrhage • BCVA between 5/200 and LP
Exclusion criteria	• Photocoagulation within three months prior to randomization • Severe NVI, NVG or IOP more than 30mmHg despite treatment • Total retinal detachment, or macular detachment on ultrasound • History of prior vitrectomy
Intervention(s)	Early vitrectomy
Comparator	Deferral of vitrectomy (could be performed at 1 year)
Outcome measures	Percentage of eyes with visual acuity of 10/20 or better at 24 months

	Exploratory Outcome- DME retinal detachment
Number of participants	616 eyes from 594 patients randomized, 308 early vitrectomy, 308 deferred vitrectomy Patients with both eyes entered are included in both early vitrectomy and deferred groups
Duration of follow-up	2 Years and 4 years

Study arms

Early vitrectomy (N = 308)
Deferred vitrectomy (N = 308)
Deferral of vitrectomy for 1 year.

Characteristics

Study-level characteristics

Characteristic	**Study (N = 616)**
% Female Sample size	% = 51.9
Mean age (SD) Mean (SD)	48.9 (16)

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 (study population consisted of individuals with severe vitreous haemorrhage in diabetic retinopathy. The findings may not be directly applicable to individuals with different disease severity, The participants in the study were selected based on specific inclusion criteria, and not all individuals with severe vitreous haemorrhage were included the study did not account for potential confounding factors, such as variations in surgical technique or individual patient characteristics, which may influence the outcomes.
Overall bias and Directness	Overall Directness	Directly applicable

ETDRS, 1991

Bibliographic Reference	Anonymous; Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group.; Ophthalmology; 1991; vol. 98 (no. 5suppl); 766-85

1 **Study details**

Study type	Within-person Randomised controlled trial (RCT)
Study location	USA
Study setting	
Study dates	Date conducted: April 1980 to June 1985
Sources of funding	Sources of funding: NEI Declaration of interest: not reported
Inclusion criteria	• Aged 18-70 years. • DR in both eyes each eye either: • with no macular oedema, a visual acuity 20/40 or better and moderate or severe non-proliferative or early PDR, • macular oedema, visual acuity of 20/200 or better and mild, moderate, or severe non-proliferative or early PDR
Exclusion criteria	not reported
Intervention(s)	(n = 3711 eyes) early argon laser For the intervention group, eyes were also randomly allocated to 'full' or 'mild' PRP
Comparator	(n = 3711 eyes) deferred argon laser For the comparator group, argon laser was applied if high risk PDR was detected
Outcome measures	development of severe visual loss which was defined as visual acuity < 5/200 at two consecutive follow-up visits. Follow-up visits were 4 months apart. Visual acuity was measured using an ETDRS chart at a distance of 4 metres and at 1 metre if visual acuity < 20/100
Number of participants	Number of participants (eyes): 3711 (7422) both eyes included in study, eyes received different treatments.
Duration of follow-up	unknown

2

3 **Characteristics**

Study-level characteristics

Characteristic	Study (N = 3711)
% Female Sample size	% = 44
Mean age (SD) Range	18 to 70

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	High – high attrition rate
Overall bias and Directness	Overall Directness	Directly applicable

Sato, 2012

Bibliographic Reference	; Sato Y; Kojimahara N; Kitano S; Kato S; Ando N; Yamaguchi N; Hori S; Multicenter randomized clinical trial of retinal photocoagulation for preproliferative diabetic retinopathy.; Japanese journal of ophthalmology; 2012; vol. 56 (no. 1)

Study details

Study type	Randomised controlled trial (RCT)
Study location	Japan
Study dates	February 2004-December 2008
Sources of funding	This study was supported by a Grant-in-Aid for Scientific Research C (no. 17591856), 2005, from the Japan Society for the Promotion of Science. The following authors have indicated that they have received grants from the Japanese Government: Sadao Hori and Naohito Yamaguchi
Inclusion criteria	• pre-proliferative diabetic retinopathy • no previous photocoagulation • multiple non perfusion areas larger than one disc area on fluorescein angiography images
Exclusion criteria	• clear fluorescein angiography images could not be obtained due to opaque media • fluorescein angiography could not be performed (e.g. due to allergy) • past history of intraocular surgery (except if 3 or more years after cataract surgery) • PRP indicated
Intervention(s)	(n = 32)

	selective photocoagulation of nonperfusion areas In both intervention and comparator groups: "photocoagulation for macular oedema was permitted when the ophthalmologist in charge of this study considered it necessary
Comparator	(n = 37) deferred panretinal laser photocoagulation For the comparator group: "Whenever PDR developed, PRP was performed. The development of PDR was defined as the detection of any of the following: neovascularization detected by ophthalmoscope or FA and preretinal haemorrhage or vitreous haemorrhage. Therefore, in this study, PDR includes not only high-risk PDR, but also early PDR as described by the Early Treatment Diabetic Retinopathy Study Research Group (ETDRS)
Outcome measures	development of proliferative diabetic retinopathy high risk PDR severe visual loss (BCVA < 0.025)
Number of participants	Number of participants (eyes): 69 (69)
Duration of follow-up	Follow-up: 3 years

Study arms

Panretinal photocoagulation group (N = 32)

Non-panretinal photocoagulation group (N = 37)

Characteristics

Study-level characteristics

Characteristic	Study (N = 69)
% Female Custom value	25%
Mean age (SD) Custom value	Average age 60 years

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	High (had high loss to follow-up)

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

1

Appendix E – Forest plots

E.1.1 Population with non-proliferative diabetic retinopathy

Early laser photocoagulation versus Deferred laser photocoagulation
Figure 1: Loss of 15 or more letters Best Corrected Visual Acuity (BCVA) at 3 years.

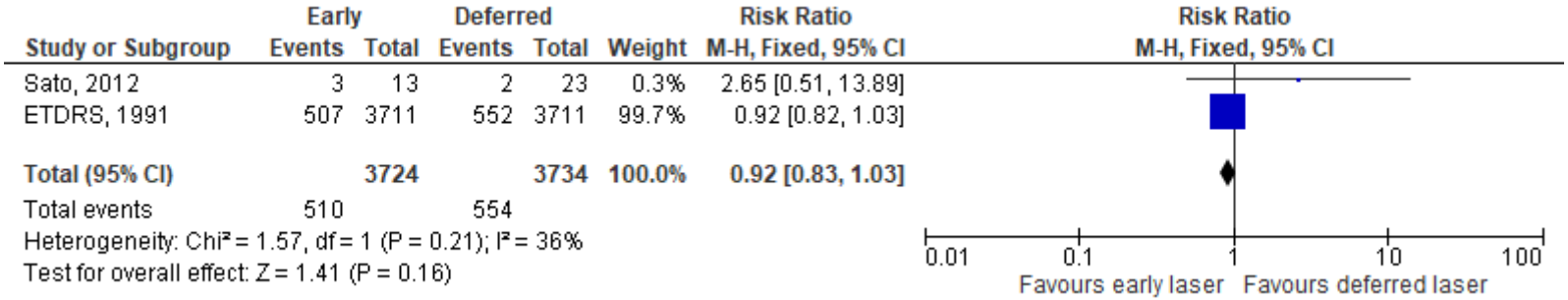


Figure 2: Loss of 15 or more letters Best Corrected Visual Acuity (BCVA) at 2 years.

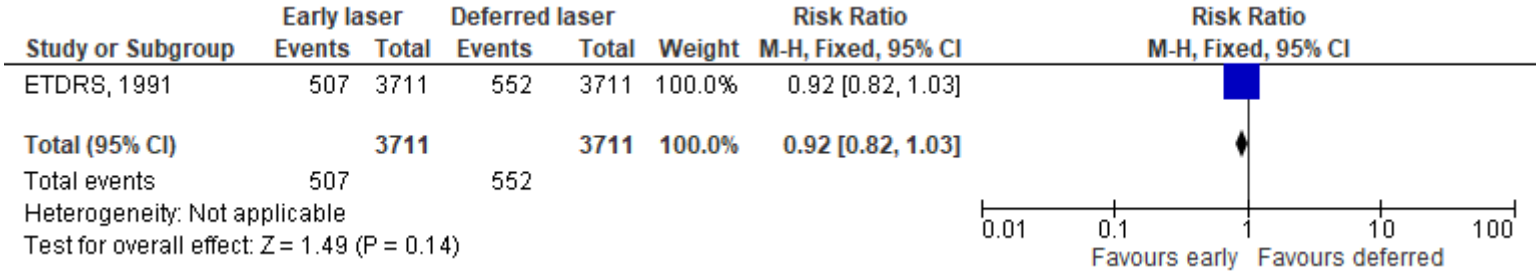


Figure 3: Severe visual loss Best Corrected Visual Acuity (BCVA)

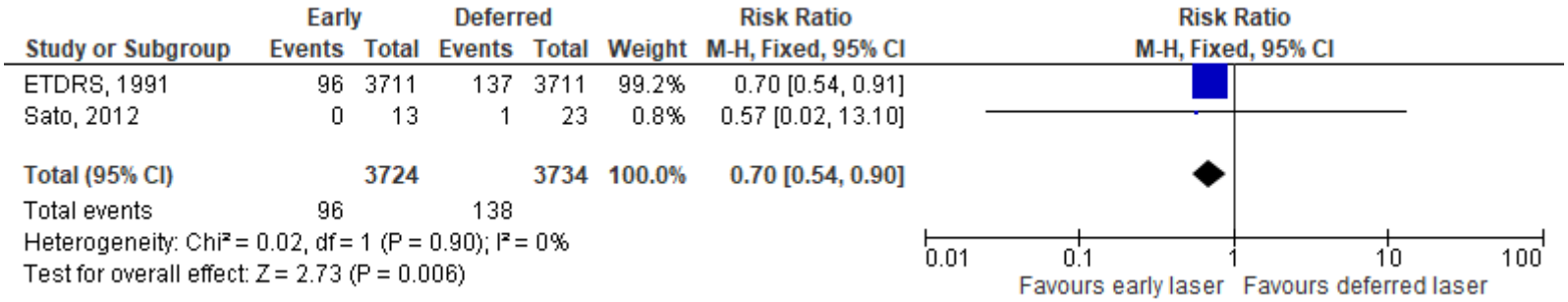


Figure 4: Mean Best Corrected Visual Acuity (BCVA) at 12 months.

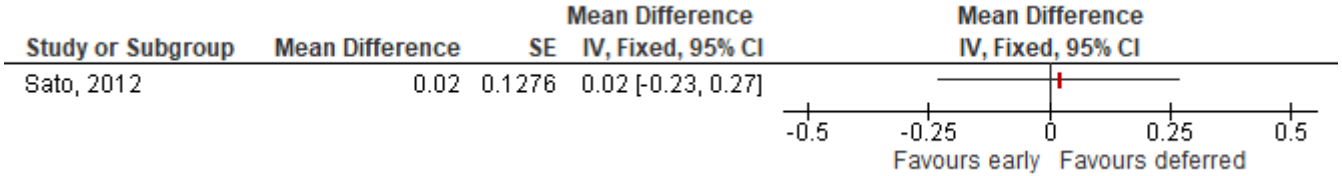
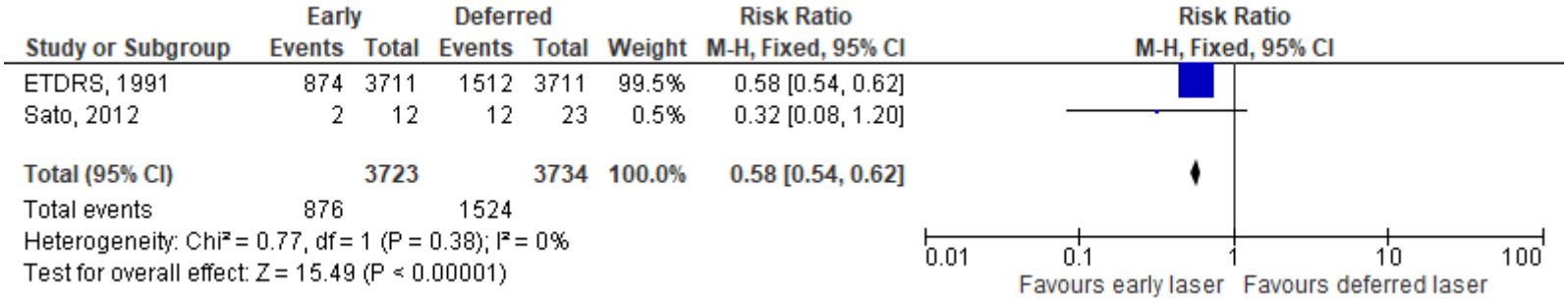


Figure 5: Progression of diabetic retinopathy at 2 years follow up

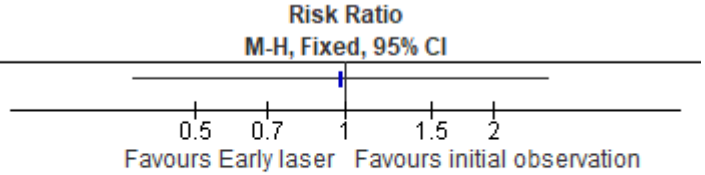


E.1.2 Population with non-proliferative diabetic retinopathy with macula oedema

Early laser photocoagulation versus initial observation (deferred Anti-VEGF)

Figure 6: Loss of 15 or more letters Best Corrected Visual Acuity (BCVA) at 2 years.

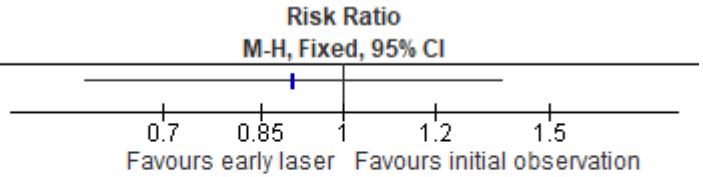
	Early laser		initial observation		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Baker,2019 (1)	8	212	8	208	0.98 [0.38, 2.57]



Footnotes
(1) inital observation (deferred anti-VEGFs)

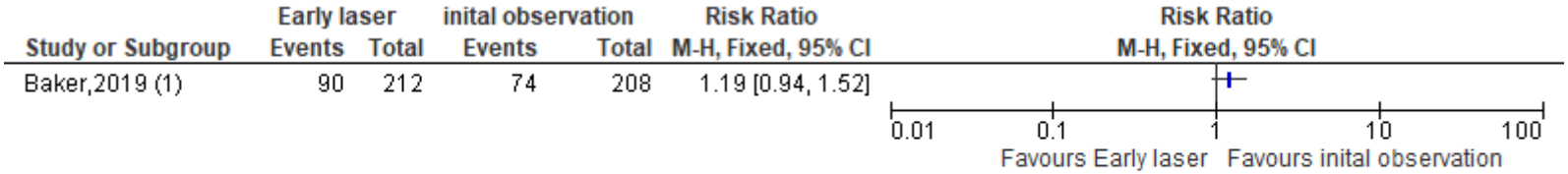
Figure 7: Loss of 5 or more letters Best Corrected Visual Acuity (BCVA) at 2 years

	Early laser		initial observation		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Baker,2019 (1)	36	212	39	208	0.91 [0.60, 1.37]



Footnotes
(1) inital observation (deferred anti-VEGFs)

Figure 8: Incidence of centre-involved diabetic macula oedema and >10% central subfield thickness decrease



Footnotes
(1) inital observation (deferred anti-VEGFs)

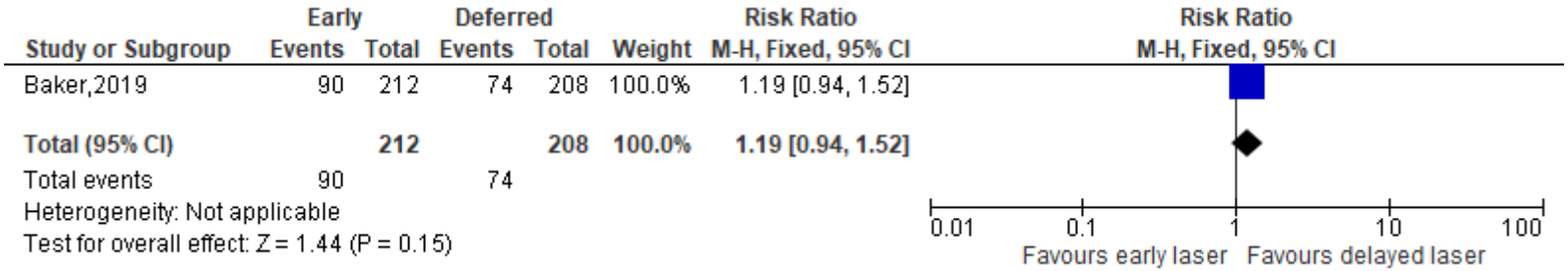
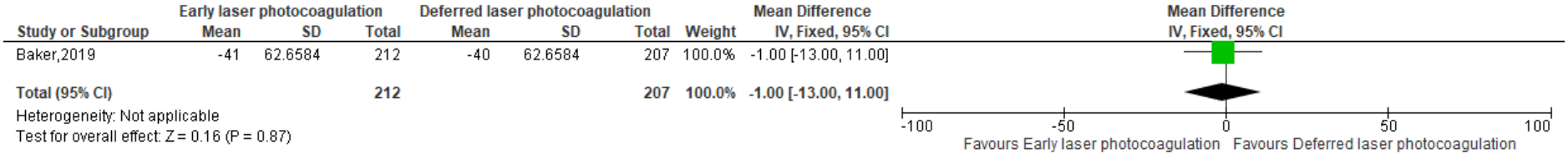


Figure 9: Change from baseline Central retinal thickness (subfield) at two years



Early vitrectomy versus Deferred vitrectomy (Population with severe vitreous haemorrhage reducing Visual acuity to 5/200)

Figure 10: Best corrected visual acuity (Visual acuity 10/20 or better) at 2 years

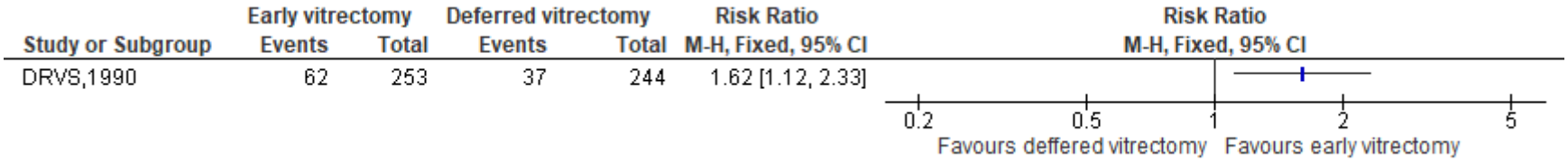


Figure 11: Best corrected visual acuity: no light perception at 2 years

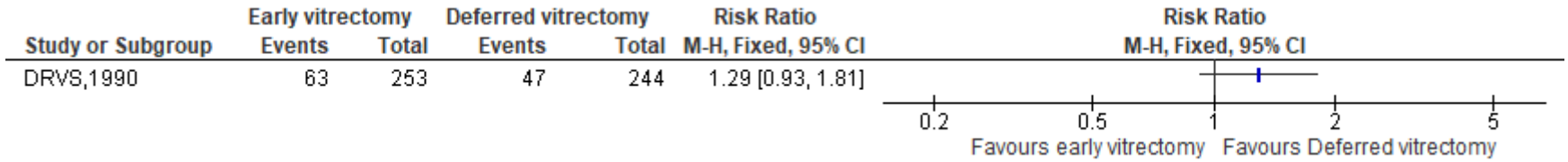
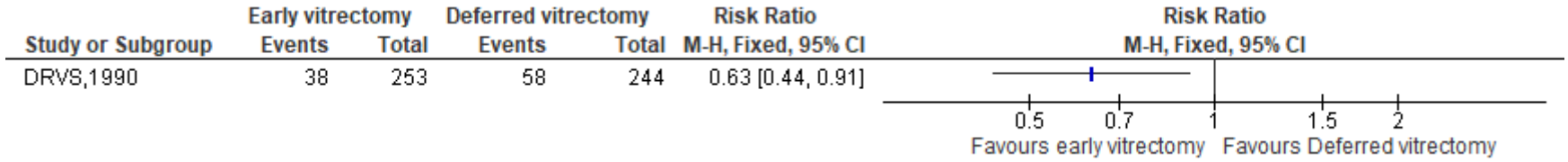


Figure 12: Retinal detachment at 2 years



Early Anti-VEGF versus Deferred Anti-VEGF (Initial observation) (Population with non-proliferative diabetic retinopathy with macular oedema)

Figure 13: Loss of 15 or more letters Best Corrected Visual Acuity (BCVA) at 2 years.

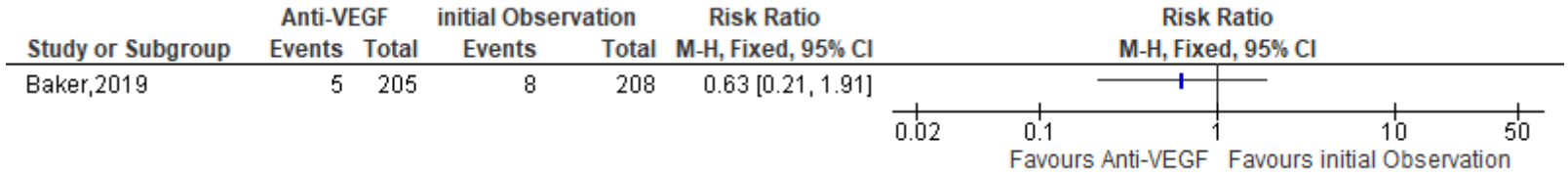


Figure 14: Loss of 5 or more letters Best Corrected Visual Acuity (BCVA) at 2 years.

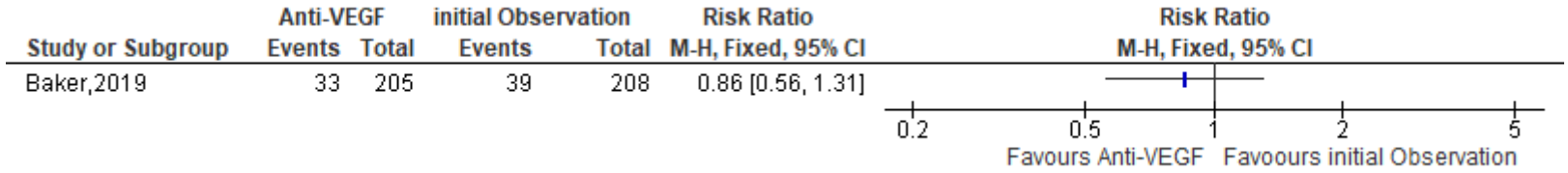


Figure 15: Incidence of centre-involved diabetic macula oedema and >10% central subfield thickness decrease

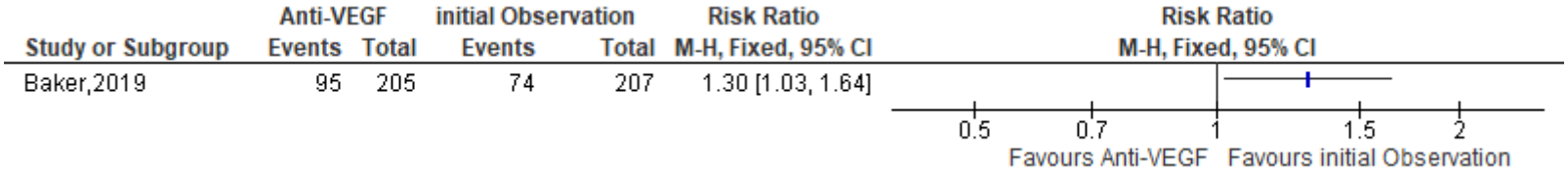
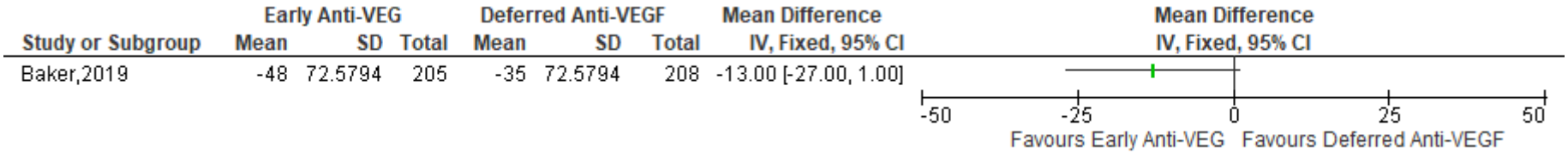


Figure 16: Change from baseline Central retinal thickness (subfield) at two years



Anti-VEGF + prompt laser VS Anti-VEGF + deferred laser (Population with non-proliferative diabetic retinopathy)
Figure 17: Best-corrected visual acuity (letter score) at 5-year FU

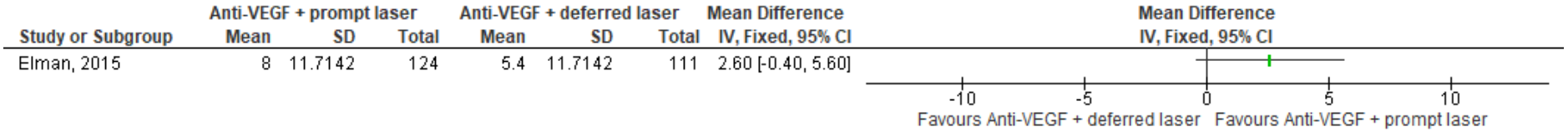


Figure 18: Loss of 15 or more letters Best Corrected Visual Acuity (BCVA) at 5 years

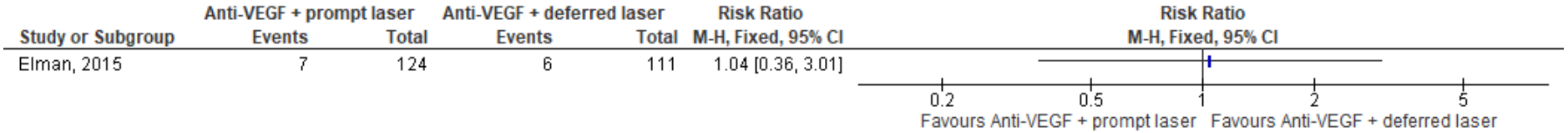
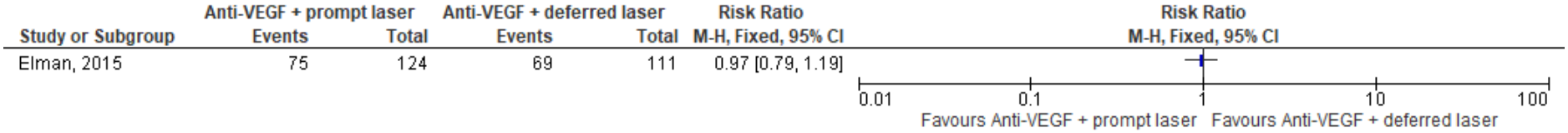


Figure 19: Change in Central Retinal Thickness from Baseline to Five Year (retinal thickness <250 with at least a 25µm decrease)



Early laser photocoagulation versus Deferred laser photocoagulation for people with diabetic macular oedema

Figure 20: Worsening of best-corrected visual acuity (≥ 15 letters) at 3 years.

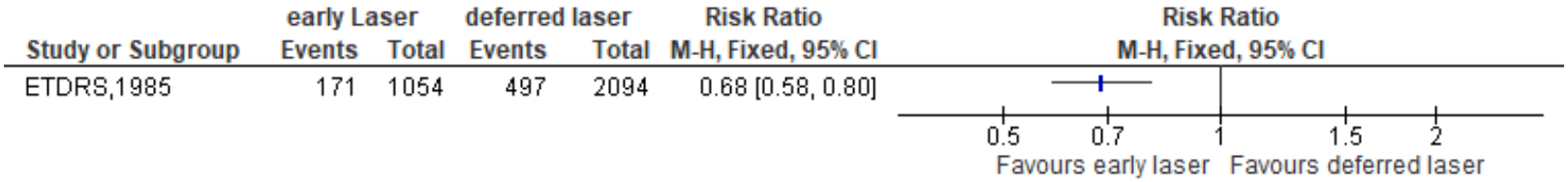


Figure 21: Worsening of best-corrected visual acuity (≥ 15 letters) at 2 years.

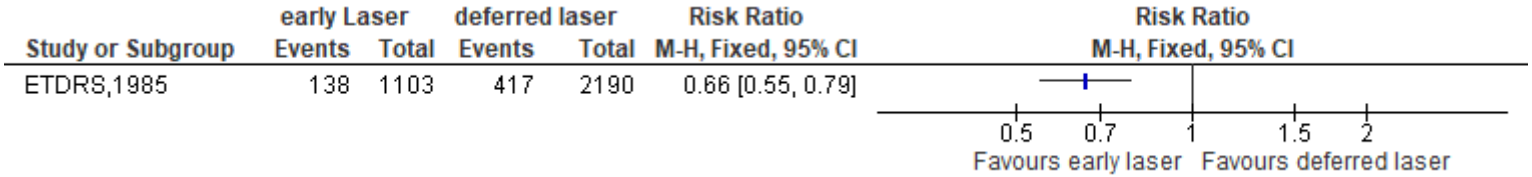


Figure 22: Eyes with clinically significant macular oedema at 3 years

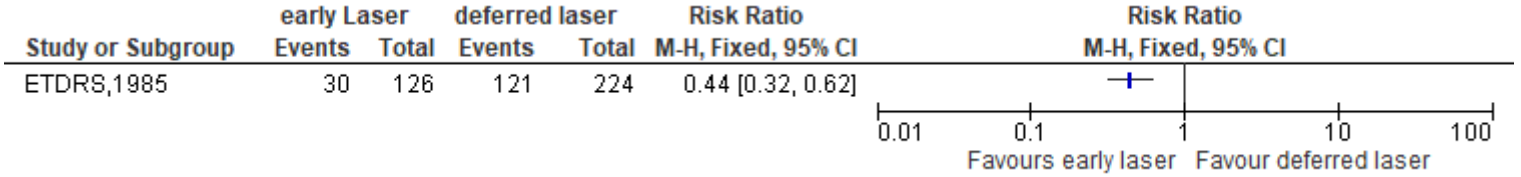
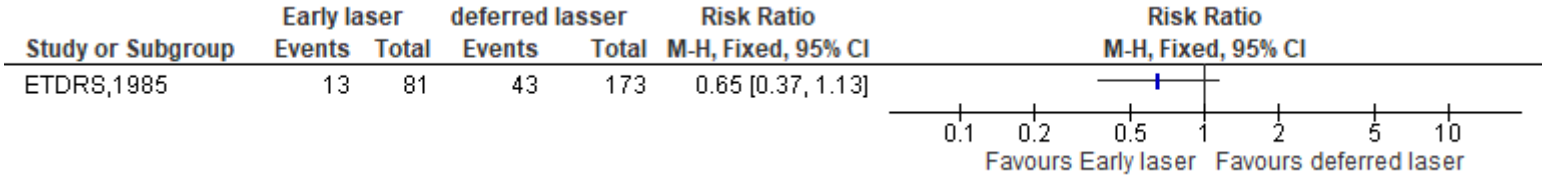


Figure 23: Eyes with not clinically significant macular oedema at 3 years



Appendix F – GRADE Tables

F.1.1 Population with non-proliferative diabetic retinopathy

Early laser photocoagulation versus Deferred laser photocoagulation

Table 12: Loss of BCVA (Letters) at follow-up

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred laser	Risk with Early laser					
Loss of 15 or more letters BCVA at 3 years follow-up. RR greater than 1 favour early laser photocoagulation									
2 (ETDRS, 1991 Sato, 2012)	RCT	7458	15 per 100	14 per 100 (12 lower 15 higher)	Risk Ratio: 0.92 [0.83, 1.03][5]	serious[1]	serious [2]	No serious	Low
Loss of 15 or more letters BCVA at 2 years follow-up. RR greater than 1 favour early laser photocoagulation									
1(ETDRS, 1991)	RCT	7442			Risk Ratio:0.92 [0.82, 1.03]	serious[1]	N/A	No serious	Moderate
Severe visual loss (BCVA < 6/60). at 2 years follow-up. RR greater than 1 favour early laser photocoagulation									
2 (ETDRS, 1991 Sato, 2012)	RCT	7458	4 per 100	3 Per 100 (2 lower 3 higher)	Risk Ratio: 0.70 [0.54, 0.90]	serious[1]	No serious	No serious	Moderate
Mean BCVA at 12 months follow-up.									
1 (Sato, 2012)	RCT	-	-	-	Mean Difference: 0.02 [-0.23, 0.27][4]	serious[1]	N/A	No serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias due to blinding, detection bias, selective reporting of outcomes
2 downgraded by one increment for heterogeneity I2 value= >33%
Abbreviations: FU, follow up.

Table 13:Progression of diabetic retinopathy at 2 years follow-up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred laser	Risk with Early laser					
Progression of diabetic retinopathy at 2 years follow-up. RR greater than 1 favour early laser photocoagulation									
2 ETDRS, 1991 Sato, 2012	RCT	7457	41 per 100	24 Per 100 (22 lower 25 higher)	Risk Ratio: 0.58 [0.54, 0.62]	serious[1]	No serious	No serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias due to blinding, detection bias, selective reporting of outcomes

Abbreviations: FU, follow up.

F.1.2 Population with non-proliferative diabetic retinopathy with macular oedema

Early Laser versus Deferred Anti-VEGF (Initial observation) (Population with non-proliferative diabetic retinopathy with macular oedema)

Table 14: Loss of 5 and 15 or more letters BCVA at 2 years follow-up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred laser	Risk with Early laser					
Loss of 15 or more letters BCVA at 2 years follow-up. RR greater than 1 favour early laser photocoagulation									
1 (Baker,2019)	RCT	420			Risk Ratio: 0.98 [0.36, 2.66]	serious[1]	N/A	No serious	Moderate
Loss of 5 or more letters BCVA at 2 years follow-up. RR greater than 1 favour early laser photocoagulation									
1 (Baker,2019)	RCT	420	19 per 100	17 Per 100 (11 lower 26 higher)	Risk Ratio: 0.91 [0.60, 1.37]	serious[1]	N/A	No serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias due high attrition

Table 15:Incidence of Centre-involved diabetic macula oedema and Central retinal thickness (subfield) at 2 years follow-up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred laser	Risk with Early laser					
Incidence of Centre-involved diabetic macula oedema and >10% central subfield thickness decrease RR greater than 1 favours early laser photocoagulation									
Baker, 2019	RCT	420	36 per 100	42 Per 100 (33 lower 54 higher)	Risk Ratio: 1.19 [0.94, 1.52]	serious[1]	N/A	No serious	Moderate
Change from baseline Central retinal thickness (subfield) at 2 years follow-up. (MD greater than 0 favours early laser photocoagulation)									
Baker, 2019	RCT	419	-	-	Mean Difference: -1.00 [-13.00, 11.00][2]	serious[1]	N/A	No serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias due to due to high attrition
2 Adjusted MD for visual acuity at baseline, mean scores in each arm will differ from raw data

Abbreviations: FU, follow up

Early vitrectomy versus Deferred vitrectomy (Population with severe vitreous haemorrhage reducing Visual acuity to 5/200)

Table 16: Visual acuity at 2 years follow-up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred vitrectomy	Risk with Early vitrectomy					
Best corrected visual acuity (Visual acuity 10/20 or better) at 2 years follow-up. RR less than 1 favour early vitrectomy									
1 (DRVS,1990)	RCT	413	15 per 100	23 Per 100 (17 lower 35 higher)	Risk Ratio: 1.62 [1.12, 2.33]	serious [1]	N/A	No serious	Moderate
Best corrected visual acuity (Visual acuity no light perception) at 2 years follow-up. RR greater than 1 favour early vitrectomy									
1 (DRVS,1990)	RCT	413	15 per 100	20 Per 100 (14 lower 27 higher)	Risk Ratio: 1.29 [0.93, 1.81]	serious [1]	N/A	No serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias due to due to high attrition
Abbreviations: FU, follow up.

Table 17:Retinal detachment at 2-year follow-up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred laser	Risk with Early laser					
Retinal detachment RR greater than 1 favour early vitrectomy									
1 (DRVS,1990)	RCT	412	24 per 100	15 Per 100 (10 lower 22 higher)	Risk Ratio: 0.63 [0.44, 0.91]	serious[1]	N/A	No serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias due to due to high attrition
Abbreviations: FU, follow up.

Early Laser versus Deferred Anti-VEGF (Initial observation) (Population with non-proliferative diabetic retinopathy with macular oedema)

Table 18:Loss of BCVA letters at 2 years follow-up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred Anti-VEGF	Risk with Early Anti-VEGF					
Loss of 15 or more letters BCVA at 2 years follow-up. RR greater than 1 favour early Anti-VEGF									
1 (Baker,2019)	RCT	413	4 per 100	2 Per 100 (1 lower 7 higher)	Risk Ratio: 0.63 [0.21, 1.91]	serious[1]	N/A	No serious	Moderate
Loss of 5 or more letters BCVA at 2 years follow-up. RR greater than 1 favour early Anti-VEGF									
1 (Baker,2019)	RCT	413	19 per 100	16 Per 100 (11 lower 25 higher)	Risk Ratio: 0.86 [0.56, 1.31]	serious[1]	N/A	No serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias due to due to high attrition
Abbreviations: FU, follow up.

Table 19:Incidence of Centre-involved diabetic macula oedema and Central retinal thickness (subfield) at 2 years follow-up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred laser	Risk with Early laser					
Incidence of Center-involved diabetic macula oedema and >10% central subfield thickness decreases RR greater than 1 favour early Anti-VEGF									
Baker,2019	RCT	412	36 per 100	46 Per 100 (37 lower 59 higher)	Risk Ratio: 1.30 [1.03, 1.64]	serious[1]	N/A	No serious	Moderate
Change from baseline Central retinal thickness (subfield) at two years follow-up (MD greater than 0 favours early Anti-VEGF)									
Baker,2019	RCT	412	-	-	Mean Difference: -13.00 [-27.00, 1.00][2]	serious[1]	N/A	No serious	Moderate

1 >33% of weighted data from studies at moderate or high risk of bias due to due to high attrition
2 Adjusted MD for visual acuity at baseline, mean scores in each arm will differ from raw data
Abbreviations: FU, follow up

Anti-VEGF + prompt laser VS Anti-VEGF + deferred laser (Population with non-proliferative diabetic retinopathy)

Table 20:Best-corrected visual acuity (letter score) at 5-year follow-up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred laser	Risk with Early laser					
Best-corrected visual acuity (letter score) at 5-year follow-up. (MD greater than 0 favours Anti-VEGF + prompt laser)									
1 (Elman, 2015)	RCT	235	-	-	Mean Difference: 2.60 [-0.40, 5.60][1]	No serious	N/A	No serious	High
Loss of 15 or more letters BCVA at 5-year follow-up. RR greater than 1 favour Anti-VEGF + prompt laser									
1 (Elman, 2015)	RCT	235	7 per 100	7 Per 100 (3 lower 22 higher)	Risk Ratio 1.04 [0.36, 3.01]	No serious	N/A	No serious	High

1 Adjusted MD for visual acuity at baseline, mean scores in each arm will differ from raw data
Abbreviations: FU, follow up

Table 21:Change in Central Retinal Thickness from Baseline to Five Year (retinal thickness <250 with at least a 25µm decrease)

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred laser	Risk with Early laser					
Change in Central Retinal Thickness from Baseline to Five Year (retinal thickness <250 with at least a 25µm decrease) RR greater than 1 favour Anti-VEGF + prompt laser									
Elman, 2015	RCT	235	62 per 100	60 Per 100 (49 lower 74 higher)	Risk Ratio: 0.97 [0.79, 1.19]	No serious	N/A	No serious	High

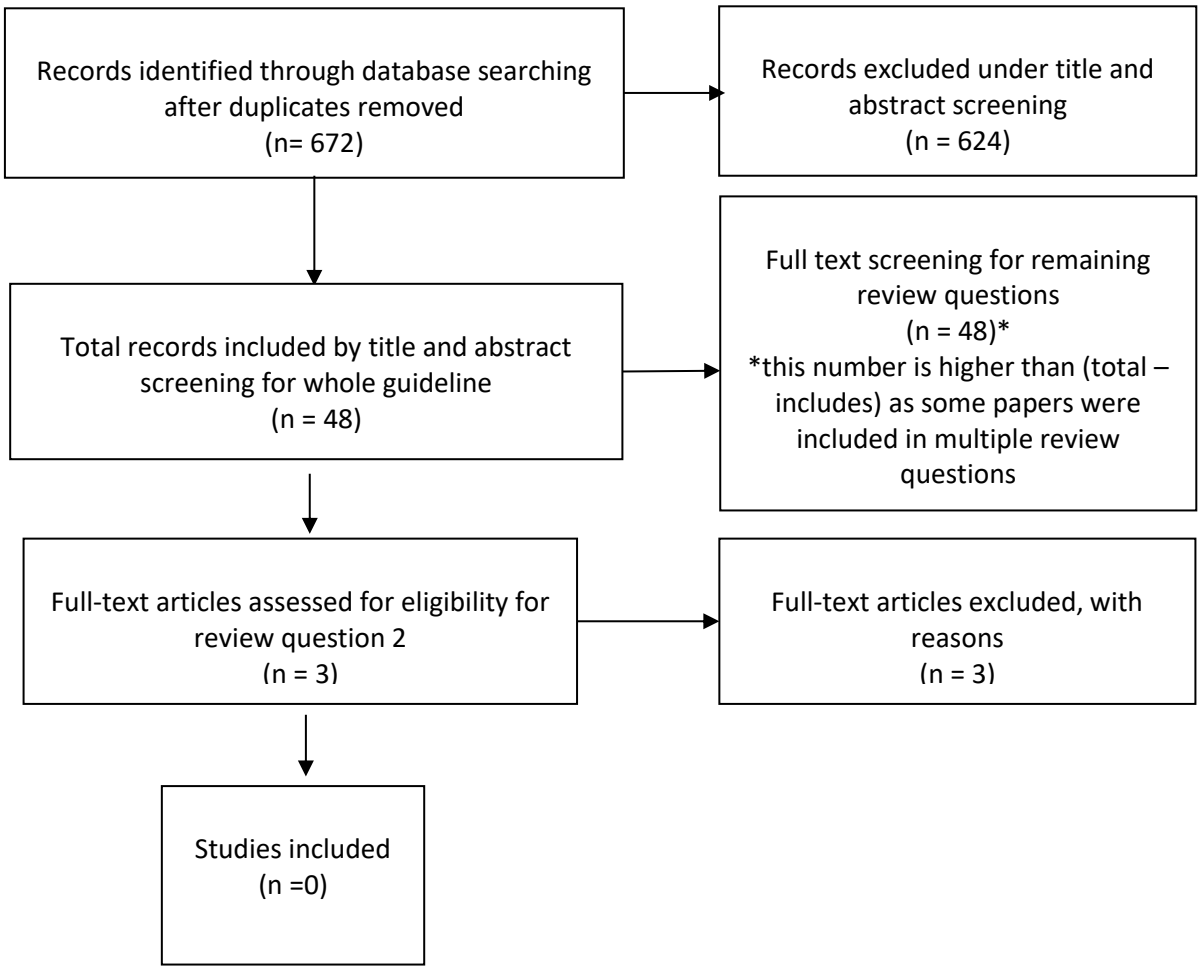
Early laser photocoagulation versus Deferred laser photocoagulation for people with diabetic macular oedema
Table 22: Worsening of best-corrected visual acuity (≥ 15 letters) at 2 and 3 years follow-up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred laser	Risk with Early laser					
Worsening of best-corrected visual acuity (≥ 15 letters) at 3 years follow-up. RR greater than 1 favour early laser photocoagulation									
1 (ETDRS, 1985)	RCT	7458	24 per 100	16 per 100 (14 lower 19 higher)	Risk Ratio: 0.68 [0.58, 0.80]	No serious	N/A	No serious	High
Worsening of best-corrected visual acuity (≥ 15 letters) at 2-year **follow**-up. RR greater than 1 favour early laser photocoagulation									
1 (ETDRS, 1985)	RCT	7842	19 per 100	13 Per 100 (10 lower 15 higher)	Risk Ratio 0.66 [0.55, 0.79]	No serious	N/A	No serious	High

Table 23:Number of eyes with non/clinically significant macular oedema at 3 years follow-up.

No. of studies	Study design	Sample size	Anticipated absolute effects*		Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
			Risk with Deferred laser	Risk with Early laser					
Eyes With Clinically Significant Macular Oedema At 3 Year follow-up. RR greater than 1 favour early laser photocoagulation									
1 (ETDRS, 1985)	RCT	420	54 per 100	24 Per 100 (17 lower 34 higher)	Risk Ratio: 0.44 [0.32, 0.62]	No serious	N/A	No serious	High
Eyes With Not Clinically Significant Macular Oedema At 3 Year follow-up. RR greater than 1 favour early laser photocoagulation									
1 (ETDRS, 1985)	RCT	419	25 per 100	16 Per 100 (9 lower 28 higher)	Risk Ratio: 0.65 [0.37, 1.13]	No serious	N/A	No serious	High

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 was not conducted for this review question.

Appendix J – Excluded studies

Clinical evidence

Study	Reason
Abd Elhamid, Ahmed Hosni; Mohamed, Ahmed Abd El Alim; Khattab, Abeer Mohamed (2020) Intravitreal Aflibercept injection with Panretinal photocoagulation versus early Vitrectomy for diabetic vitreous hemorrhage: randomized clinical trial. BMC ophthalmology 20(1): 130	- Comparator in study does not match that specified in protocol
Anonymous (1985) Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Two-year results of a randomized trial. Diabetic Retinopathy Vitrectomy Study report 2. The Diabetic Retinopathy Vitrectomy Study Research Group. Archives of ophthalmology (Chicago, Ill. : 1960) 103(11): 1644-52	- Secondary publication of an included study that does not provide any additional relevant information
Anonymous (1995) Focal photocoagulation treatment of diabetic macular edema. Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report no. 19. Early Treatment Diabetic Retinopathy Study Research Group. Archives of ophthalmology (Chicago, Ill. : 1960) 113(9): 1144-55	- Secondary publication of an included study that does not provide any additional relevant information
Anonymous. (2014) Erratum: Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: Three year randomized trial results (Ophthalmology (2012) 119 (2312-2318)). Ophthalmology 121(3): 805	- Full text paper not available
Ashraf, Mohammed; Souka, Ahmed A R; ElKayal, Hassan (2017) Short-Term Effects of Early Switching to Ranibizumab or Aflibercept in Diabetic Macular Edema Cases With Non-Response to Bevacizumab. Ophthalmic surgery, lasers & imaging retina 48(3): 230-236	- Study does not contain a relevant intervention
Bressler, S.B., Melia, M., Glassman, A.R. et al. (2015) Ranibizumab plus prompt or deferred laser for diabetic macular edema in eyes with vitrectomy before anti-vascular endothelial growth factor therapy. Retina 35(12): 2516-2528	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason
Bressler, Susan B, Glassman, Adam R, Almukhtar, Talat et al. (2016) Five-Year Outcomes of Ranibizumab With Prompt or Deferred Laser Versus Laser or Triamcinolone Plus Deferred Ranibizumab for Diabetic Macular Edema. American journal of ophthalmology 164: 57-68	- Comparator in study does not match that specified in protocol
Campochiaro, Peter A, Wykoff, Charles C, Singer, Michael et al. (2014) Monthly versus as-needed ranibizumab injections in patients with retinal vein occlusion: the SHORE study. Ophthalmology 121(12): 2432-42	- Study does not contain a relevant intervention
Campos, Antonio, Beselga, Diana, Mendes, Silvia et al. (2014) Deferred intravitreal triamcinolone in diabetic eyes after phacoemulsification. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics 30(9): 717-28	- Study does not contain a relevant intervention
Cazet-Supervielle, A, Boissonnot, M, Rouissi, S et al. (2014) Intravitreal injections of ranibizumab with deferred laser grid laser photocoagulation for the treatment of diabetic macular edema with visual impairment: results at 1 year of LLOMD study. Investigative ophthalmology and visual science. Conference: 2014 annual meeting of the association for research in vision and ophthalmology, ARVO 2014. United states 55(13): 1772	- Full text paper not available
Chew, Emily Y, Ferris, Frederick L 3rd, Csaky, Karl G et al. (2003) The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the early treatment diabetic retinopathy follow-up study. Ophthalmology 110(9): 1683-9	- Secondary publication of an included study that does not provide any additional relevant information
Corbelli, Eleonora, Fasce, Francesco, Iuliano, Lorenzo et al. (2020) Cataract surgery with combined versus deferred intravitreal dexamethasone implant for diabetic macular edema: long-term outcomes from a real-world setting. Acta diabetologica 57(10): 1193-1201	- Comparator in study does not match that specified in protocol
Diabetic Retinopathy Clinical Research, Network, Elman, Michael J, Aiello, Lloyd Paul et al. (2010) Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 117(6): 1064-1077e35	- Secondary publication of an included study that does not provide any additional relevant information
Diabetic Retinopathy Clinical Research, Network, Elman, Michael J, Qin, Haijing et al. (2012) Intravitreal ranibizumab for diabetic	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason
macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmology 119(11): 2312-8	
Diabetic Retinopathy Clinical Research, Network, Writing, Committee, Aiello, Lloyd Paul et al. (2011) Rationale for the diabetic retinopathy clinical research network treatment protocol for center-involved diabetic macular edema. Ophthalmology 118(12): e5-14	- Secondary publication of an included study that does not provide any additional relevant information
Dugel, Pravin U, Campbell, Joanna H, Kiss, Szilard et al. (2019) ASSOCIATION BETWEEN EARLY ANATOMIC RESPONSE TO ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY AND LONG-TERM OUTCOME IN DIABETIC MACULAR EDEMA: An Independent Analysis of Protocol i Study Data. Retina (Philadelphia, Pa.) 39(1): 88-97	- Secondary publication of an included study that does not provide any additional relevant information
Elman, M.J., Bressler, N.M., Qin, H. et al. (2011) Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 118(4): 609-614	- Secondary publication of an included study that does not provide any additional relevant information
Evans, Jennifer R; Michelessi, Manuele; Virgili, Gianni (2014) Laser photocoagulation for proliferative diabetic retinopathy. The Cochrane database of systematic reviews: cd011234	- Systematic review used as source of primary studies
Glassman, Adam R, Baker, Carl W, Beaulieu, Wesley T et al. (2020) Assessment of the DRCR Retina Network Approach to Management With Initial Observation for Eyes With Center-Involved Diabetic Macular Edema and Good Visual Acuity: A Secondary Analysis of a Randomized Clinical Trial. JAMA ophthalmology 138(4): 341-349	- Secondary publication of an included study that does not provide any additional relevant information
Hayashida, Mayuka, Miki, Akiko, Imai, Hisanori et al. (2019) Impact of Early Vitrectomy for Dense Vitreous Hemorrhage of Unknown Etiology. Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde 242(4): 234-238	- Study does not contain a relevant intervention
Khan, M A; Mallika, Varakutti; Joshi, Dattakiran (2018) Comparison of immediate versus deferred intravitreal Bevacizumab in macular oedema due to branch retinal vein occlusion: a pilot study. International ophthalmology 38(3): 943-949	- Does not contain a population of people with PDR
Maturi, RK (2021) A Randomized Trial of Intravitreous AntiVEGF for Prevention of Vision Threatening Complications of Diabetic	- Comparator in study does not match that specified in protocol

Study	Reason
Retinopathy (Protocol W). Investigative ophthalmology & visual science 62(8)	
Patz, A.; Rice, T.A.; Murphy, R.P. (1985) Photocoagulation for diabetic macular edema. Archives of Ophthalmology 103(12): 1796-1806	- Secondary publication of an included study that does not provide any additional relevant information
Pearce, IA (2014) Ranibizumab treatment of diabetic macular edema with bimonthly monitoring: 18-month outcomes of the Phase IIIb multicenter RELIGHT study. Investigative ophthalmology and visual science. Conference: 2014 annual meeting of the association for research in vision and ophthalmology, ARVO 2014. United states 55(13): 1701	- Full text paper not available
Rauser, ME (2013) Intravitreal ranibizumab for diabetic macular edema with prompt vs deferred laser treatment: 3-year Randomized Trial Results. Investigative ophthalmology & visual science 54(15)	- Secondary publication of an included study that does not provide any additional relevant information
Schefler, AC, Fuller, D, Anand, R et al. (2018) Ranibizumab for radiation retinopathy (RRR): a prospective, multicenter trial of monthly versus PRN dosing for radiation retinopathy-related cystoid macular edema. Investigative ophthalmology & visual science 59(9)	- Full text paper not available
Singer, Michael A, Miller, Dan M, Gross, Jeffrey G et al. (2018) Visual Acuity Outcomes in Diabetic Macular Edema With Fluocinolone Acetonide 0.2 mug/Day Versus Ranibizumab Plus Deferred Laser (DRCR Protocol I). Ophthalmic surgery, lasers & imaging retina 49(9): 698-706	- Secondary publication of an included study that does not provide any additional relevant information
Wykoff, Charles C and Hariprasad, Seenu M (2016) DRCR Protocol-T: Reconciling 1- and 2-Year Data for Managing Diabetic Macular Edema. Ophthalmic surgery, lasers & imaging retina 47(4): 308-12	- Secondary publication of an included study that does not provide any additional relevant information
Wykoff, Charles C, Nittala, Muneeswar G, Zhou, Brenda et al. (2019) Intravitreal Aflibercept for Retinal Nonperfusion in Proliferative Diabetic Retinopathy: Outcomes from the Randomized RECOVERY Trial. Ophthalmology. Retina 3(12): 1076-1086	- Study does not contain a relevant intervention
Yu, Hannah J, Fuller, Dwain, Anand, Rajiv et al. (2022) Two-year results for ranibizumab for radiation retinopathy (RRR): a randomized, prospective trial. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 260(1): 47-54	- Study does not contain a relevant intervention

Study	Reason
Zucchiatti, Ilaria and Bandello, Francesco (2017) Intravitreal Ranibizumab in Diabetic Macular Edema: Long-Term Outcomes. Developments in ophthalmology 60: 63-70	- Study does not contain a relevant intervention

Economic evidence

Title	Reason for exclusion
Dewan, Vinay, Lambert, Dennis, Edler, Joshua et al. (2012) Cost-effectiveness analysis of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 119(8): 1679-84	- Exclude - did not compare thresholds for starting treatment
Romero-Aroca, Pedro, de la Riva-Fernandez, Sofia, Valls-Mateu, Aida et al. (2016) Cost of diabetic retinopathy and macular oedema in a population, an eight year follow up. BMC ophthalmology 16: 136	- Exclude - population was people with diabetes, not specifically diabetic retinopathy or DMO - Exclude - did not compare thresholds for starting treatment
Sharma, S, Hollands, H, Brown, G C et al. (2001) The cost-effectiveness of early vitrectomy for the treatment of vitreous hemorrhage in diabetic retinopathy. Current opinion in ophthalmology 12(3): 230-4	- Exclude - for-profit insurer perspective - Exclude - did not compare thresholds for starting treatment

Appendix K – Research recommendations – full details

K.1.1.1 Research recommendation

What is the effectiveness of different thresholds or criteria for starting treatment for people with non-proliferative diabetic retinopathy?

K.1.1.2 Why this is important

The effectiveness of different thresholds or criteria for starting treatment in individuals with non-proliferative diabetic retinopathy is an important question in the management of diabetic retinopathy. The decision to initiate treatment aims to prevent or delay the progression of the disease and reduce the risk of vision loss. Determining the appropriate thresholds or criteria at which to start treatment is therefore crucial. Research is therefore needed to help clinicians understand when treatment should begin so that people with diabetic retinopathy can have the best possible outcome.

K.1.1.3 Rationale for research recommendation

Importance to 'patients' or the population	By understanding when treatment for people who have non-proliferative diabetic retinopathy should begin, patients will be less likely to progress to proliferative diabetic retinopathy or diabetic macular oedema, and experience complications such as vision loss.
Relevance to NICE guidance	Treatment initiation and stopping criteria has been considered in this guideline and there is a lack of data on specific thresholds for initiation of treatment
Relevance to the NHS	The outcomes will inform when treatment for people with non-proliferative diabetic retinopathy should begin. By starting treatment at the most effective time, fewer people will progress to proliferative retinopathy or macular oedema. This will reduce both the time and costs associated with additional treatment.
National priorities	Moderate
Current evidence base	Minimal long-term data
Equality considerations	None known

K.1.1.4 Modified PICO table.

Population	People with non-proliferative diabetic retinopathy
Intervention	• Lower or higher thresholds for starting treatment than standard threshold. • Immediate treatment compared with deferred treatment
Comparator	• Standard threshold for starting treatment • Deferred treatment (when compared with immediate treatment)

Outcome	• Best corrected visual acuity • Progression to proliferative diabetic retinopathy or diabetic macular oedema. • Change in visual acuity • Treatment-related adverse events • Quality of life • Central retinal thickness • Tractional retinal detachment
Study design	RCT Comparative observational studies with a concurrent control group.
Timeframe	Long term
Additional information	Subgroup analysis based on: • people who are pregnant • age groups • disease severity • ethnicity