National Institute for Health and Care Excellence

Guideline version (Draft)

Diabetic Retinopathy: management and monitoring

[G] Evidence reviews for the effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.1 to 1.5.14 in the NICE guideline

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Draft for Consultation

These evidence reviews were developed by Guideline Development Team

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1.1 Review question

What is the effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema?

1.1.1 Introduction

People with diabetic retinopathy can develop macular oedema, a swelling or thickening of the macula. Diabetic macular oedema is a common complication of diabetic retinopathy and can lead to moderate to severe visual loss. Currently there are several treatment options for people with diabetic macular oedema including macular laser (standard threshold or subthreshold laser), anti-vascular endothelial growth factor agents (anti-VEGFs), intravitreal steroids, or combinations of these treatments. This review aims to compare all treatments to identify the most effective treatment strategy for people with 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: Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

Population	Inclusion: People diagnosed with diabetic macular oedema Exclusion: People who are about to undergo or have undergone cataract surgery

Interventions	• Intravitreal steroid therapy (intravitreal injection or surgical implantation).
	• Macular laser, subclassified as:
	  ○ Standard threshold laser
	  ○ Subthreshold laser
	• Anti-vascular endothelial growth factor agents
	• Anti-vascular endothelial growth factor agents plus intravitreal steroid therapy
	• Anti-vascular endothelial growth factor agents plus macular laser
	• Intravitreal steroid therapy plus macular laser

Comparator	• Another intervention listed above. • Placebo, sham treatment, or no treatment - Trials comparing standard threshold and subthreshold laser will be included. Trials comparing types of standard threshold laser or types of subthreshold laser will not be included. - Trials comparing different Anti-VEGF agents or different intravitreal steroids will be included.

Outcomes	Primary outcomes:
	• Best corrected visual acuity
	  ○ (1) the change from baseline of best-corrected visual acuity (BCVA) as continuous data (converted into logMAR); and
	  ○ (2) three or more lines improvement from baseline (ETDRS, Snellen, or logMAR equivalent; one line improvement analysed if three lines not available).
	
	Outcomes will be assessed at 12 months (plus or minus 6 months) and at the longest timepoint available in the study if 24 months or greater.
	
	Secondary outcomes:
	• Mean change in retinal thickness from baseline.
	• Quality of life (assessed using a validated tool)
	• Adverse events (development of cataract, Intraocular inflammation, raised intraocular pressure, need for glaucoma drainage surgery)
	• Acceptability (additional outcome not assessed in Cochrane reviews). Qualitative or quantitative data on acceptability collected alongside included randomised controlled trials will be included.
	• Driving vision (dichotomous outcome, number of participants with vision sufficient to allow driving)
	• Number of treatments

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.

Results were separated into two populations (people with central-involving macular oedema and people with non-central-involving macular oedema) and were reported at short-term and longer-term time points (12 months and 24 months or longer). As not all studies reported outcomes at these exact time points, it was decided that the 12-month data would include any results from 6 months to 18 months from the beginning of treatment, and 24 months would represent any results reported from 24 months onwards. Results for the primary outcomes of change in visual acuity from baseline and change in central retinal thickness were analysed using network meta-analyses (NMAs) where sufficient data was available. NMAs were therefore used to analyse:

- change in visual acuity from baseline for people with central-involving macular oedema at 12 months and at 24 months.
- change in central retinal thickness for people with central-involving macular oedema at 12 and at 24 months.

Insufficient data was available for an NMA for the other population groups of the primary outcomes, and so results were presented as pairwise meta-analysis for:

- change in visual acuity from baseline for people with non-central-involving macular oedema at 12 months. No data was available for this comparison at 24 months.

Subgroup analysis of the primary NMAs were used to assess the different effects of treatment for people with central retinal thickness greater, or less than, 400 micrometres at baseline. Sufficient data was available for NMAs for:

- change in visual acuity from baseline for people with central-involving macular oedema and central retinal thickness of 400 micrometres or more at 12 months and at 24 months
- change in central retinal thickness from baseline for people with central-involving macular oedema and central retinal thickness of 400 micrometres of more at 12 months.

Insufficient data was available for a network analysis for subgroup analysis of the other population groups, and so results were presented as meta-analysis for:

- change in central retinal thickness at 24 months for people with central-involving macular oedema and central retinal thickness of 400 micrometres or more
- all change in visual acuity and central retinal thickness outcomes for people with central-involving macular oedema and central retinal thickness less than 400 micrometres

All secondary outcomes were presented using meta-analysis as stated in the review protocol. These were performed according to the NICE methods stated in 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

Four Cochrane reviews (Jorge et al. 2018, Mehta et al. 2018, Rittiphairoj et al. 2020, Virgili et al. 2022) were identified which assessed the effects of monotherapy using macular laser, anti-VEGFs or intravitreal steroids for people with diabetic macular oedema. Each review was judged to be high quality and directly applicable to the review (see Appendix D) and so information about these interventions were taken directly from the reviews, rather than undertaking a new literature search (see Table 2 in the methods document).The results of these reviews were combined, and an additional search was conducted for combinations of different treatments that were not included in the Cochrane reviews, plus any studies published after the search dates of the Cochrane reviews. The studies in the Cochrane reviews were assessed to ensure that they met the inclusion criteria for this review.

Sixty studies were included from the Cochrane reviews (one study was included in both the Mehta et al. 2018 and Rittiphairoi et al. 2020 reviews). The number of primary studies included from each Cochrane review were:

- Jorge et al. 2018 (Monotherapy laser photocoagulation): 16 studies
- Mehta et al. 2018 (Anti-VEGFs with intravitreal steroids): 8 studies
- Rittiphairoj et al. 2020 (Intravitreal steroids): 9 studies
- Virgili et al. 2022 (Anti-VEGFs): 28 studies

In the NICE additional search, a total of 3139 records were screened at title and abstract stage. Following title and abstract screening, 129 studies were included for full text screening. These studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A) and 8 additional RCTs were included. An additional 80 studies were found in the re-run search, of which 1 matched the review protocol and was included in the review. The comparisons from each of the studies identified in the NICE search were for:

- Anti-VEGFs vs macular laser: 1 study

- Anti-VEGFs vs steroids: 2 studies
- Anti-VEGFs vs anti-VEGFs: 2 studies
- Steroids vs sham: 1 study
- Steroids vs macular laser: 1 study
- Steroids with macular laser vs macular laser: 2 studies
- Steroids with macular laser vs steroids: 1 study
- Subthreshold laser vs standard threshold laser: 1 study

This included one study with three arms which compared steroids, macular laser, and steroids with macular laser.

1.1.4.2 Excluded studies

117 studies were excluded following examination of the full text articles. See Appendix I 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.

Studies from NICE additional searches

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Callanan, 2013	Parallel-group RCT 1 year FU	**Inclusion criteria** • At least 18 years of age • Diagnosis of type 1 or type 2 diabetes mellitus • Mean retinal thickness 275 mm by OCT in the 1-mm central macular subfield due to diffuse DME not amenable to laser at • stand-alone treatment (at screening) • Diffuse macular capillary bed leakage evident on FA • BCVA >34 and <70 letters (approximately 20/200 and 20/40Snellen) using the ETDRS method at screening and baseline) **Key exclusion criteria** • Uncontrolled systemic disease • Use of systemic corticosteroid within 12	DEX implant plus laser (N = 126) Dexamethasone Intravitreal Implant Plus Laser	Sham implant and laser (N = 127) Laser Alone	1. Mean of best corrected visual acuity in logMAR 2 Mean of central macular thickness 3. Mean number of treatments

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		weeks prior to baseline or anticipated use during the study • Active ocular infection (either eye) • Glaucoma (either eye) • History of an IOP increase • 10 mm Hg or to 25 mm Hg in response to corticosteroid treatment that required multiple IOP-lowering medications or laser or surgical treatment (either eye) • History or presence of venous occlusive disease, uveitis, Irvine-Gass syndrome, or any condition other than diabetic retinopathy that could contribute to macular oedema • Epiretinal membrane or vitreomacular traction macular oedema • History of pars plana vitrectomy • Active optic disc or retinal neovascularization • History of intravitreal corticosteroid use except dexamethasone			

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Chen, 2020 The VIVID-East study	Parallel-group RCT 1 year FU	• Patients with an ocular condition with a poorer prognosis in the fellow eye than in the study eye • any surgical interventions or laser photocoagulation in the study eye within 120 and 90 days of day 1 • any treatments with corticosteroids or anti-angiogenic drugs in either eye within 90 days of day 1 • active proliferative diabetic retinopathy in the study eye a history of idiopathic or autoimmune uveitis in the study eye	IVT-AFL every 4 weeks (N = 127) or IVT-AFL every 8 weeks (N = 127)	macular laser (N = 127)	mean change in BCVA in ETDRS letter score from baseline. eyes that gained ≥10 ETDRS letters from baseline proportion of eyes that gained ≥15 ETDRS letters from baseline proportion of eyes with a ≥2-step improvement from baseline in the Diabetic Retinopathy Severity Scale (DRSS) change in CRT from baseline Mean number of treatments
Faghihi, 2010	Parallel-group RCT 6 month FU	**Inclusion criteria** • Bilateral non-tractional CSME • 10/10> V.A < 1/10 Controlled blood pressure. **Key exclusion criteria**	IVB plus MPC (N = 40)	IVB (N = 40)	Best corrected visual acuity in logMARMean of central macular thickness Mean number of treatments

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• HRC PDR • Advanced or advanced active PDR • Significant cataract • Glaucoma • History of recent vascular accident (e.g, MI, CVA,) • Previous treatment of CSME or PDR, or pharmacotherapy for CSME. • Macular ischemia • Uncontrolled hypertension			
Fouda, 2017	Parallel-group RCT 1 year FU	**Inclusion criteria** • Patients with type I or II diabetes, • DME in eyes as diagnosed clinically and with OCT • patients with best corrected visual acuity (BCVA) ranged from 0.1 to 0.25 (moderate visual loss) • oedema affecting the central 1 mm of the macula **Key exclusion criteria** • Eyes with vascular retinal disorders other than	IVT-AFL (N = 35) All eyes in group I received an injection of 2 mg/0.05 mL aflibercept (Eylea; Regeneron Pharmaceuticals, NY, USA) and those in	(IVT-RAN (N = 35) group II received an injection of 0.5 mg/0.1 mL ranibizumab (Lucentis; Genentech, USA, Inc., San Francisco, CA, USA)	• Best corrected visual acuity • Central macular thickness • Mean number of treatments

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		diabetic retinopathy (eg, choroidal neovascularization) • eyes that received previous intravitreal injection of any agents			
Gillies, 2009	Parallel-group RCT 5 year FU	**Inclusion criteria** • Diabetes mellitus (type 1 or 2) • Diabetic macular oedema in study eye associated to diabetic retinopathy • Diffuse macular oedema defined as macular thickening determined by biomicroscopy and fluorescein angiography. • Best corrected visual acuity between 34 (20/200) and 68 letters (20/50). • Macular thickness greater than 300 mcm on OCT. **Key exclusion criteria** • Uncontrolled systemic disease • Start of medical therapy for diabetes or change in treatment from oral to insulin four months before initial visit. • HbA1c levels greater than	Initial Triamcinolone (N = 23)	Initial Placebo (N = 21)	best corrected visual acuity in logMAR

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		10% • Presence of retinal venous occlusion, cystoid macular oedema, or other condition that would contribute to macular oedema. • Presence of epiretinal membrane • Presence of vitreomacular traction in the study eye. • Aphakic or anterior chamber intraocular lens in the study eye. • Neovascularization of disc or elsewhere in the study eye. • History or presence of choroidal neovascularization in the study eye. • Presence of rubeosis irides in the study eye. • Eye opacity that interfere with clinical documentation and photography. • Intra-ocular surgery 90 days before initial visit. • Previous vitrectomy in study eye. • Previous history of intravitreal or periocular corticoid or any other intravitreal drug in study eye.			

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• Scheduled surgery for study eye. • Patients with known allergies to fluorescein, iodo-povidone or any component of study drug.			
Lam, 2007	Parallel-group RCT 6 monthFU	**Inclusion criteria** • Patients 18 years or older with type I or II diabetes mellitus • Eyes had DME involving the fovea, as defined by clinically significant macular oedema according to ETDRS guidelines. • central foveal thickness (CFT) >250 um, • **Key** macular oedema secondary to causes other than diabetic maculopathy • signs of vitreomacular traction • proliferative diabetic retinopathy • Patients who had phakia • history of glaucoma or ocular hypertension • macular ischemia (1-disc diameters of capillary closure at the macula on fluorescein angiography).	4 mg of intravitreal TA (N = 38) OR 4 mg of intravitreal TA + grid laser (N = 36)	grid laser (N = 37)	Central foveal thickness (logMAR) best-corrected visual acuity

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• Patients who had any laser procedure within 3 months			
Lois,2023	RCT 24 months follow up	**Inclusion criteria** • centre-involving DMO, as determined by slit-lamp biomicroscopy and SD-OCT • in one or both eyes, with either: • a CRT of > 300 µm but < 400 µm in the central subfield (central 1 mm) owing to DMO as determined by SD-OCT • a CRT of < 300 µm provided that intra-retinal and/or subretinal fluid was present in the central subfield (central 1 mm) owing to DMO. • The following conditions also had to be met: • visual acuity of > 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent > 20/320) • amenable to laser treatment, as judged by the treating ophthalmologist	subthreshold micropulse laser 577 nm SML (n = 133;	Standard threshold laser [e.g. argon, frequency doubled neodymium-doped yttrium aluminium garnet (Nd:YAG) 532 nm laser]. (n = 133)	• Mean change in BCVA • Mean change in CRT • Number meeting driving standards • Number of laser treatments used

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		• aged ≥ 18 years. **Exclusion criteria** • A patient's eyes were not eligible for the study if their macular oedema was owing to causes other than DMO o • ineligible for macular laser, as judged by the treating ophthalmologist • DMO with a CRT of ≥ 400 µm • active PDR requiring treatment • received intravitreal anti-VEGF therapy within the previous 2 months • received macular laser treatment within the previous 12 months • received intravitreal injection of steroids • cataract surgery within the previous 6 weeks panretinal photocoagulation (PRP) within the previous 3 months.			

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
Ozsaygili, 2020	Parallel-group RCT 1 year FU	• Patients older than 18 years of age diagnosed with Type 1 or Type 2 DM • Treatment-naïve DME with SRD and hyperreflective foci • BCVA letter score between 73 and 34 (Snellen equivalent 20/40–20/200); • The CRT obtained from the 1-mm central macular subfield greater than 450 mm by SD-OCT. **Key exclusion criteria** • Previous history of intraocular anti-VEGF or steroid injection • macular ischemia defined by fundus fluorescein angiogram • any other ocular pathologies causing visual impairment • recent (within 3 months) serious cardiovascular or cerebrovascular events • IOP over 23mmHg without treatment or IOP over 21 mmHg with one antiglaucoma medication • presence of vitreomacular	3 monthly injections of 2 mg of aflibercept as a loading phase in the anti–vascular endothelial growth factor group	0.7 mg of DEX implant in the DEX group and then pro re nata treatment.	• Best corrected visual acuity • Mean number of treatments • Adverse events

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		interface abnormalities • aphakia or an anterior chamber intraocular lens • active proliferative diabetic retinopathy.			
Vader, 2020	Parallel-group RCT 6 months FU	**Inclusion criteria** • patients were older than 18 years, • diagnosed with type 1 or type 2 diabetes mellitus and with a glycosylated haemoglobin of less than 12%, • central area thickness on (OCT) of more than 325 mm • visual impairment resulting from DME • best-corrected visual acuity (BCVA) outcome of at least 24 letters and less than 79 letters on standardized ETDRS **Key exclusion criteria** • Untreated PDR was defined as leakage on • fluorescein angiogram resulting from a	**1.25 mg bevacizumab (N = 86)**	**0.5 mg ranibizumab (N = 84)**	Mean of best corrected visual acuity in logMAR Mean of central macular thickness Mean number of treatments

Study Country	Study type and follow-up (FU) time	Population	Intervention	Comparator	Outcomes
		neovascularization • the presence of preretinal haemorrhages • vitreous haemorrhages, • Structural damage included the presence of laser scars, retinal pigment epithelium • atrophy organized hard exudate plaques close to the macula			

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

See Appendix D for full evidence tables.

Table 3: Summary of Cochrane reviews used for clinical effectiveness evidence

Study	Number of included studies	Inclusion criteria	Exclusion criteria	Interventions	Comparison	Outcomes
Jorge et al-2018	15 studies	Randomised controlled trials (RCTs) comparing any type of focal/grid macular laser versus another type or technique of laser treatment and no intervention	Excluded studies comparing laser with other interventions	Different macular laser as monotherapy in the treatment of diabetic macular oedema.	another type or technique of laser treatment and no intervention	• Gain or loss of 3 lines (0.3 logMAR or 15 ETDRS letters) of best-corrected visual acuity (BCVA) at one year of follow-up (plus or minus six months) after treatment initiation. • Mean change in BCVA. • Resolution of macular oedema • Central retinal thickness • Quality of life • Adverse events, all at one year
Mehta et al-2018	8	Randomised controlled trials (RCTs) comparing intravitreal anti-VEGF combined with intravitreal steroids versus	NR	intravitreal anti-VEGF combined with intravitreal steroids	intravitreal anti-VEGF alone, intravitreal steroids alone or macular laser alone	• Change in best corrected visual acuity (BCVA) between baseline and one year • Change in central

Study	Number of included studies	Inclusion criteria	Exclusion criteria	Interventions	Comparison	Outcomes
		intravitreal anti-VEGF alone, intravitreal steroids alone or macular laser alone for managing DMO				macular thickness (CMT) • Quality of life. • Adverse events including intraocular inflammation, raised intraocular pressure (IOP) and development of cataract
Rittiphairoj et al-2020	9	Randomised controlled trials (RCTs) comparing intravitreal steroid therapies versus other treatments, including intravitreal anti-VEGF therapy, laser photocoagulation, and sham injection	NR	any type of intravitreal steroids as monotherapy against	any other intervention (e.g., observation, laser, anti-vascular endothelial growth factor (anti-VEGF) for DMO	
Virgili et al-2022	29	Randomised controlled trials (RCTs) comparing any anti-angiogenic drug with an anti-VEGF mechanism of action versus another anti-VEGF drug, another treatment, sham or no treatment in people with DMO	People with normal best corrected visual acuity (BCVA) were not included	any anti-angiogenic drug with an anti-VEGF mechanism of action	another anti-VEGF drug, another treatment, sham, or no treatment	• Change in best corrected visual acuity (BCVA) between baseline and one year • Change of BCVA at 24 months. • Improvement of three or more lines of visual acuity

Study	Number of included studies	Inclusion criteria	Exclusion criteria	Interventions	Comparison	Outcomes
						• Change in central macular thickness (CMT)

Summary of included primary studies from Cochrane systematic review

Table 4: Randomised controlled trials (for full study details, see Virgili et al. 2022)

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
Randomised controlled trials (from Virgili et al 2022 Cochrane systematic review)					
Azad 2012	6 months	Inclusion: • Diffuse DMO with at least two prior sessions of macular laser photocoagulation • CRT > 250 µm Exclusion: History of having received prior intraocular, peribulbar, or systemic steroids or prior anti-VEGF therapy	Bevacizumab (1.25 mg) [Triamcinolone acetonide arm – not reported in Virgili 2018]	Macular grid augmentation	
Baker 2019	24 months and 5 years	Inclusion criteria: • Age ≥ 18 years. • Diagnosis of diabetes mellitus (type 1 or type 2). Exclusion criteria: • History of chronic renal failure requiring dialysis or kidney transplant.	Aflibercept (n=236) Macular laser (n=240	Observation (n=236)	• mean change in visual acuity from baseline, • visual acuity of at least 84 letters (Snellen equivalent of 20/20), loss of at least 10 • gain of at least 5 letters of visual acuity • mean change in CST from baseline • proportion of eyes with at least

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		• unstable medical status including blood pressure, cardiovascular disease, and glycaemic control). • Initiation of intensive insulin treatment (a pump or multiple daily injections) within 4 months prior to randomization			10% CST change from baseline • incidence of cataracts • adverse events (increased intraocular pressure, vitreous haemorrhage)
BOLT 2010 (Michaelides 2010)		Inclusion criteria: • Centre-involving CSMO • CRT of ≥ 270 µm • BCVA in the study eye between 35 and 69 ETDRS letters at 4 m (Snellen equivalent 6/60 or 6/12) • At least 1 prior macular laser therapy Exclusion criteria: PDR except for tufts of new vessels elsewhere < 1 disc in area with no vitreous haemorrhage	Bevacizumab (1.25 mg) n = 42 (42 eyes	Macular laser therapy n = 38 (38 eyes)	• mean CRT • mean change in CRT • gain and loss of 15 and 10 letters of ETDRS • loss of 30 ETDRS letters • VA 3 or more lines improvement • retinopathy severity (ETDRS grading • number of treatments • adverse events (increased intraocular pressure, vitreous haemorrhage)
Brown 2015	12 months FU	• Adult patients with type 1 or 2 diabetes mellitus • central-involved DME (defined as retinal thickening involving the 1-mm central [OCT] • subfield thickness [CST]) were if best-corrected visual acuity (BCVA) was	VISTA: 154 IAI 2q4, or 151 IAI 2q8 VIVID: 136 IAI 2q4, or 135 IAI 2q8	VISTA: 154 Laser control VIVID: 132 Laser control	• mean change from baseline in best-corrected visual acuity (BCVA) at week 52. • change from baseline in CST,as determined by optical coherence tomography, • number of treatments

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		between 73 and 24 letters (20/40 to 20/320 Snellen equivalent) in the study eye. • Only 1 eye per patient			
Brown 2022	12 months	Inclusion criteria: • aged ≥18 years with type 1 or 2 diabetes mellitus • glycosylated haemoglobin (HbA1c) ≤ 10% • BCVA score between 78 and 23 letters • Snellen equivalent of 20/32 to 20/320) at screening • central-involved DME with CSFT of ≥320µm Exclusion criteria: • active proliferative diabetic retinopathy in the study eye •received intraocular or periocular corticosteroids in the 6 months prior to baseline or prior anti-VEGF	Brolucizumab 3 mg, brolucizumab 6 mg, (KESTREL) or brolucizumab 6 mg (KITE)	Aflibercept 2mg (KESTREL and KITE)	• BCVA change from baseline • incidence of ocular and non-ocular adverse events. • mean number of treatments
Chatzirallis 2020	12- & 18-months FU	Inclusion criteria: • Type 2 diabetes mellitus • Central involved DME • Central retinal thickness (CRT) ≥320 µm	0.5 mg Ranibizumab n = 54 (54 eyes)	Aflibercept 2 mg n = 58 (58 eyes)	• change in BCVA and CRT at month 12 and 18 • mean number of treatments

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		Exclusion criteria: • AMD • Retinal vein occlusion Vitreomacular traction Intraocular inflammation Cornea disorders • Media opacities Uncontrolled glaucoma High myopia >6D Previous trauma Intraocular surgery within the last 6 month			
DA VINCI 2011 (Do 2012)	6, 12-month FU	Inclusion criteria: • DMO involving central macula • CRT ≥ 250 µm in central subfield • BCVA letter score at 4 m of 73-24 (Snellen equivalent: 20/40–20/320) Exclusion criteria: PDR (unless regressed and currently inactive)	VEGF Trap-Eye n = 177 (177 eyes)	Standard threshold laser n = 44 (44 eyes)	• retinal thickness assessed by OCT • safety and tolerability • change in BCVA from baseline at week 52 • proportion of eyes that gained at least 15 ETDRS letters in BCVA compared with baseline at weeks 24 and 52 • the change in CRT (central subfield on OCT) from baseline to weeks 24 and 52 • number of focal laser treatments given • incidence of cataracts • adverse events (increased intraocular pressure, vitreous haemorrhage)
DRCRnet 2010	12 months	Inclusion criteria: • Retinal thickness of ≥ 250 µm in the central subfield • Best-corrected ETDRS VA letter score 78-24 (20/32–	Ranibizumab (0.5 mg) and standard threshold laser (macular laser) (375 eyes)	Sham injection and standard threshold laser (macular laser) (293 eyes)	• BCVA and CRT at 12 months

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		20/320) Retinal thickening due to DME involving the centre of the macula	[Triamcinolone with prompt laser photocoagulation – not included in Virgili 2018]		
DRCRnet 2015	12 months	Inclusion criteria: • Definite retinal thickening due to DMO involving the centre of the macular • Retinal thickness of ≥ 250 µm in the central subfield • ETDRS BCVA 78-24 (20/32 - 20/320)	• Aflibercept (2 mg) 224 eyes • Ranibizumab (0.3 mg) 218 Eyes	• Bevacizumab (1.25 mg) 218 eyes	• BCVA and CRT at 12 months
Ekinci 2014	12 months	Inclusion criteria: • CSMO • CRT>300 µm [Unclear whether DMO is centre involving]	Bevacizumab (1.25 mg) n = 50 (50 eyes)	Ranibizumab (0.05 mg) n = 50 (50 eyes)	• BCVA using the Snellen chart • CRT assessed with OCT • IOP assessed with applanation tonometry
Korobelnik 2014 (1)		Inclusion criteria: • Central DMO involvement (defined as retinal thickening involving the 1 mm central (OCT) subfield thickness) • Retinal thickness ≥ 300 µm • BCVA ETDRS letter score of 73-24 (20/40-20/320) in the study eye • Type I or type II Exclusion criteria: Active PDR in the study eye with the exception of inactive, regressed PDR	• aflibercept 2q4 n = 290 (290 eyes): aflibercept 2 mg every 4 weeks • • aflibercept 2q8 n = 286 (286 eyes): aflibercept 2 mg monthly for 5 months, then every 8 weeks	Standard threshold laser and sham monthly injection = 286 (286 eyes)	• proportion of eyes that gained at least 10 ETDRS letters in BCVA at week 52 compared with baseline • proportion of eyes that gained at least 15 ETDRS letters in BCVA compared with baseline • change in CRT (central subfield on OCT) from baseline to week 52 • proportion of eyes with a 2-step improvement in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score • change from baseline in the National Eye Institute Visual FunctionQuestionnaire-25 (NEI VFQ-25) near activities subscale score • change from baseline in the NEI VFQ-25 distance activities subscale score • Number of treatments • Incidence of cataracts
Li 2019	Follow-up: 12	Patients with visual	ranibizumab 0.5mg	Macular laser	Mean change in BCVA from baseline

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
	months	impairment due to focal or diffuse DME in at least one eye. • BCVA score at both screening and baseline between 78 and 39 letters as measured by ETDRS- (Approximately 20/32 to 20/160 Snellen equivalent).			• Mean change in CSFT from baseline • Proportion of patients with BCVA gain of ≥ 10 and ≥ 15 letters and loss of <10 and <15 letters from baseline • Proportion of patients with BCVA ≥ 73 letters (approximate20/40 Snellen chart equivalent) • treatment exposure, number of retreatments, ocular and non-ocular adverse events (AEs) and serious AEs (SAEs) over 12 months (increased intraocular pressure, vitreous haemorrhage)
Liu 2022	Follow-up: 12 months	• >18 years of age. • type I or II diabetes mellitus. • haemoglobin A1c (HbA1c) 10%. • CRT 300 µm according to (OCT) imaging, • clear ocular media and adequate pupil dilation for examination • ETDRS BCVA of the subject's non-target eye of ≥24 letters (equivalent to 20/320 of the Snellen vision).	Conbercept (n=76)	Macular laser (n=80)	• mean change in BCVA from baseline to month 12 • change in CRT from baseline to month 12 • ocular and non-ocular adverse events (vitreous haemorrhage) • serious adverse events (SAEs) • number of treatments
Prunte 2016	24-month FU	• 18 years with either type I or II diabetes mellitus • glycosylated haemoglobin (HbA1c) values of ≤12% at screening	Ranibizumab 0.5 mg with laser	Ranibizumab 0.5 mg	• mean average change in BCVA from baseline to months 1-12 (primary), • mean BCVA change from baseline to months 12 and 24,

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		• (ETDRS) BCVA letter score ranging from 78 to 39, inclusive (approximate Snellen equivalent of 20/32–20/160) • those with visual impairment due to focal or diffuse DMO of any extent or thickness in at least one eye who were eligible for laser treatment • One eye was treated as the study eye.			• treatment exposure • safety profile.
LUCIDATE 2014 (Comyn 2014)	12 month follow up	Inclusion criteria: • Central subfield thickness of 300 µm or more • BCVA of 55-79 ETDRS (Snellen equivalent, 20/30-20/80) • Type I or type II diabetes • Centre-involving DMO Exclusion criteria: • PDR either active or treatment within previous 3 months Cataract precluding fundus photography	Ranibizumab (0.5 mg) N= 25	Macular laser N=12	• change in ETDRS BCVA • macular thickness and volume • change in ETDRS severity grade of diabetic retinopathy from fundus photographs • number of treatments
Macugen 2005	12 months FU	Inclusion criteria: • An area of retinal thickening of at least half a disc area involving the central macula • BCVA letter scores between 68-25 inclusive (approximate Snellen equivalent, 20/50–20/320)	Pegaptanib (0.3 mg, 1 mg, or 3 mg)	Sham injection	•BCVA (standardised ETDRS refraction protocol) • retinal thickness (using OCT)

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		• MO involving the centre of the macula – demonstrated on OCT Exclusion criteria: • History of PRP or focal photocoagulation Cataract surgery within 12 months			
Macugen 2011 (Sultan 2011)	12 months 24 ,months FU	Inclusion criteria: • Foveal thickness of ≥ 250 µm • BCVA with a letter score of 65-35 (20/50–20/200 Snellen equivalents) DMO involving centre of macula	Pegaptanib sodium (0.3 mg) n = 133	Sham injection N = 127	• BCVA (standardised ETDRS refraction protocol) • retinal thickness (using OCT)
Nepomuceno 2013		Inclusion criteria: • Central subfield thickness > 300 µm • BCVA ETDRS measurement between 0.3 logMAR (Snellen equivalent: 20/40) and 1.6 logMAR (Snellen equivalent: 20/800) • At least 1 session of macular laser photocoagulation performed at least 3 months previously • Centre-involved DMO Exclusion criteria: • PDR needing PRP or anticipated to need PRP in the next 12 months	Bevacizumab (1.5 mg) 32 eyes	Ranibizumab (0.5 mg) 28 eyes	• BCVA • retinal thickness • Mean number of treatments
READ2 2009 (Nguyen 2009)	12 months 24 months	Inclusion criteria: • Centre subfield thickness of ≥250 µm Reduction in VA between	• Ranibizumab (0.5 mg) n = 42 (42 eyes) • Ranibizumab (0.5	Standard threshold laser n = 42 (42 eyes)	• change in BCVA between baseline and month 24 • 3 or more lines or 2 or more lines improvement at month 24

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		20/40-20/320	mg) plus macular laser n = 42 (42 eyes)		• change in foveal thickness between baseline and month 24 • elimination of 90% or 50% excess foveal thickness
RELATION 2012	12 months FU	Inclusion criteria: • Focal or diffuse macular oedema • BCVA between 78-39 letters	Ranibizumab (0.5 mg) plus laser n = 85 (85 eyes)	Laser plus sham injection n = 85 (85 eyes)	• mean change in BCVA from baseline to month 12 (ETDRS chart, 4 m) • adverse events
RESOLVE 2010 (Massin 2010)	12 Month FU	Inclusion criteria: • CRT ≥ 300 µm • BCVA score between 73-39 letters (approximate Snellen equivalent of 20/40-20/160) • DMO with centre involvement Exclusion criteria: PDR in the study eye, with the exception of tufts of neovascularization < 1 disc area with no vitreous haemorrhage	Ranibizumab (0.3 mg or 0.5 mg) n = 102 (102 eyes)	Sham injection n = 49 (49 eyes)	• mean change in BCVA and CRT from baseline at 12 months • safety
RESPOND 2013	12 Month FU	Inclusion criteria: • Stable type I or type II diabetes • Focal or diffuse DMO	• Ranibizumab (0.5 mg) n = 80 (80 eyes) • Ranibizumab (0.5 mg) plus laser n = 78 (78 eyes)	Laser n = 81 (81 eyes)	• mean change from baseline in Best Correct Visual Acuity (BCVA) • number of patients with improvement in BCVA • change in central retinal thickness and other anatomical changes
RESTORE 2011 (Mitchell 2011)	12 Month FU	Inclusion criteria: • Focal or diffuse MO • BCVA letter score between 78-39 (approximate Snellen equivalent 20/32-20/160)	• Ranibizumab (0.5 mg) plus sham laser n = 116 (116 eyes) • Ranibizumab (0.5 mg) plus laser118 (118 eyes)	Laser treatment plus sham injections n = 111 (111 eyes	• mean average change in BCVA from baseline over 12 months • VA improvement • BCVA letter score 73 (20/40 Snellen equivalent) at month 12 • mean change in BCVA letter score • mean change in central retinal (subfield) thickness • patient-reported outcomes

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
					• safety • number of treatments • incidence of cataracts
REVEAL 2015 (Ishibashi 2015)	12- months FU	Inclusion criteria: • Focal or diffuse macular oedema • BCVA letter score between 78-39 (approximate Snellen equivalent 20/32-20/160)	• Ranibizumab sham laser (n = 133) • Ranibizumab + active laser (n =132)	Sham injection + active laser (n = 131).	• mean change in BCVA from baseline over 12 months • mean change in central retinal (subfield) thickness • safety • number of treatments
RISE-RIDE (Nguyen 2012)	24 Month FU	Inclusion criteria: • Central subfield thickness ≥ 275 µm BCVA, 20/40–20/320 Snellen equivalent using ETDRS testing	• Ranibizumab (0.3 mg or 0.5 mg) n = 244 (244 eyes)	Sham injection (n = 122)	• gain of 15 or more ETDRS letters in BCVA score from baseline at 24 months (corresponding to 3 lines on the eye chart) • mean change from baseline BCVA score over time • proportion of participants with BCVA Snellen equivalent of 20/40 • mean change from baseline BCVA score over time in participants with focal oedema as assessed on • fluorescein angiography • proportion of participants losing 15 letters in BCVA score from baseline • mean change from baseline in OCT CFT over time • proportion of participants with a 3-step progression from baseline in ETDRS retinopathy severity on • fundus photography proportion of participants with resolution of leakage on FA • mean number of macular laser treatments

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
Soheilian 2007	12 Month FU	• Inclusion criteria: • Clinically significant DMO • Exclusion criteria: • Previous PRP or focal laser photocoagulation • High-risk PDR • Significant media opacities • VA of 20/40 or better, or worse than 20/300	Bevacizumab (1.25 mg)	Macular laser	• mean change from baseline BCVA • proportion of participants with BCVA Snellen equivalent of 20/40 • Number of treatments
Turkoglu 2015	12-month FU	Inclusion criteria: • CSMO Exclusion criteria: • History of intravitreal injection and laser photocoagulation for PDR or CSMO	Focal or grid laser treatment	Initial injection of ranibizumab 0.5 mg/0.05 mL	
Wykoff 2022	12 Months FU	• Age ≥18 years • DM type 1 or 2 • Current regular use of insulin • Current regular use of oral anti-hyperglycaemic agents • HbA1c of ≤10% within 2 months before day	Intravitreal Faricimab 6·0 mg every 8 weeks, intravitreal Faricimab 6·0 mg	Intravitreal aflibercept 2·0 mg every 8 weeks	• BCVA outcomes • DR severity outcomes • patient-reported vision-related functioning and quality of life

BCVA: best-corrected visual acuity; CMT: central macular thickness; CRT: central retinal thickness; CSMO: clinically significant macular oedema; CSRT: central subfield retinal thickness; DME: diabetic macular oedema; DMO: diabetic macular oedema; DR: diabetic retinopathy; ETDRS: Early Treatment Diabetic Retinopathy Study; FAZ: foveal avascular zone; IVS: intravitreal steroid; logMAR: log of the Minimum Angle of Resolution; mETDRS: modified Early Treatment of Diabetic Retinopathy Study; MMG: mild macular grid; MO: macular oedema; NPDR: non-proliferative diabetic retinopathy; NR: not reported; OCT: optical coherence tomography; PDR: proliferative diabetic retinopathy; PR: proliferative retinopathy; PRN: pro-re-nata (i.e. as needed); PRP: panretinal photocoagulation; SDM: subthreshold micropulse diode; VA: visual acuity; VEGF: vascular endothelial growth factor

Table 5: Randomised controlled trials (for full study details, see Jorge et al. 2018)

Study	Follow-up time	Population	Intervention	Comparator	Outcomes

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
Randomised controlled trials (from Jorge et al. 2018 Cochrane systematic review)					
Bandello 2005	12 Months FU	Inclusion criteria: • CSMO • NPDR • Foveal thickness exceeding 2 SD normal mean value • VA≥20/200 of ETDRS chart • Type I or type II diabetes Exclusion criteria: • Cataract extraction within the past 12 months • PDR • Significant media opacities • Previous laser	Standard threshold laser "Classic" Nd:Yag 532 nm laser treatment	Subthreshold laser "Light" Nd:Yag 532 nm laser treatment	• significant decrease in FTH on OCT retina thickness • eyes that experienced a visual gain or loss of ≥ 5 letters (approximately 1 line) on the ETDRS chart • mean changes in VA
Blankenship 1979	12 Months FU	Inclusion criteria: • Diffuse and cystoid MO • BCVA ≥ 20/100 (0.7 logMAR) Exclusion: • PDR • Previous photocoagulation	Argon laser	No treatment	• Changes of VA
Casson 2012	6 Months FU	Inclusion criteria: • Focal or diffuse MO • CSRT ≥ 250 µm or ≥ 300 µm in ≥ 1 of the 4 inner subfields • Best-corrected ETDRS VA score ≥ 19 letters • Type I or type II diabetes	Subthreshold laser Nanopulse (2RT) laser treatment	Standard threshold laser	• Changes of VA • Changes of CRT
DRCNET 2007	12 Months FU	Inclusion criteria: • CSMO • Definite retinal thickening due to previously untreated DMO within 500µm of the macular centre	Standard threshold laser (mETDRS style focal laser) (162 eyes)	Subthreshold laser (MMG laser) (161 eyes)	• change in retinal thickening in the central subfield on OCT. • Change in VA • adverse events

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		• Retinal thickness ≥ 250µm in central subfield or ≥ 300µm in ≥ 1 of the 4 inner subfields • Best-corrected electronic ETDRS VA score ≥ 19 (approximately 20/400 or better) • Type I or type II diabetes • No prior laser or other treatment for DMO Exclusion criteria: • Cataract surgery within prior 6 months			
ETDRS 1985	12 Months FU	Inclusion criteria: • CSMO • Early PR and moderate-to-severe non-proliferative retinopathy Exclusion criteria: • Right risk proliferative retinopathy • VA<20/200	Immediate standard threshold laser (argon laser) 754 eyes	Deferred standard threshold laser = (no intervention)) (1490)	• Outcomes VA and occurrence of retinal thickening
Figueira 2009	12 Months FU	Inclusion criteria: • CSMO • BCVA ≥ 55 letters on the modified ETDRS chart (equivalent to 20/80 or better) • Type II diabetes Exclusion criteria: • Significant cataract • Previous laser treatment	Subthreshold laser (Micropulse diode) 44 Eyes	Standard threshold laser (argon green) 40 eyes	• BCVA • CMT
Ishibashi 2014	12 Months FU	Inclusion criteria: • Macular oedema involving central fovea • Retinal thickening ≥ 250 µm	Pegaptanib sodium	Sham injection	• Mean (SD) visual acuity • Mean (SD) retinal thickness

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		Corrected VA is 35-68 letters by ETDRS charts			
Ladas 1993	12 Months FU	Inclusion criteria: • CSMO • Background DR • Diffuse MO [defined as having 2 or more-disc areas of diffuse fluorescein involving some portion of the FAZ – indicating that DMO is centre-involving] Exclusion criteria: • Significant media opacities • Previous treatment with PRP or photocoagulation to within 2-disc diameters of the foveola • BCVA ≤ 0.1	Standard threshold laser (Blue-green argon laser) (27 eyes)	control (23 eyes)	• Change in VA defined as a difference of ≥ 2 lines on the standard Snellen's VA charts
Laursen 2004	12 Months FU	Inclusion criteria: • CSMO • Type I or type II diabetes Exclusion criteria: • Cataract extraction within past 12 months • PDR • Significant media opacities • Previous laser photocoagulation for DR [Included diffuse (12 eyes) and focal (11	Subthreshold laser (MPDL) n=12	Standard threshold laser (argon laser) n=11	• Visual improvement/loss by > 2 lines on ETDRS chart and reduction/elimination of macular oedema evaluated by OCT
Lavinsky 2011	12 Months FU	Inclusion criteria: • CSMO • Retinal thickening within 500 µm of macular centre and CMT ≥ 250 µm BCVA > 20/400 and < 20/40 by the ETDRS protocol	• Standard threshold laser (mETDRS focal/grid) (42 eyes)	Subthreshold laser • normal-density SDM laser high-density SDM laser (42 eyes)	• changes from baseline in ETDRS BCVA and in CMT assessed by OCT;

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		Exclusion criteria: • No prior laser or drug treatment for DMO			
Olk 1986	12 Months FU	Inclusion criteria: • Diffuse with or without cystoid macular oedema • ≥ 2-disc areas of retinal thickening • Retinal thickening that involved the centre of the macular • BCVA < 20/32+2 and better than 20/200-3 Exclusion criteria: • Cataract extraction within previous 12 months • Significant media opacities Previous laser photocoagulation to within 2-disc diameters of the centre of the FAZ	Standard threshold laser Grid with PRP 82 eyes	No treatment 78 eyes	• improvement or worsening of visual acuity and reduction of macular oedema and/or cystoid macular oedema
Pei-Pei 2015	12 Months FU	Inclusion criteria: • Diffuse and cystoid MO • Newly diagnosed severe NPDR • Mean CRT > 300 µm • ETDRS VA > 19 letters (Snellen's equivalent of 20/400 or better) • Type II diabetes Exclusion criteria: • Previous retinal treatment: laser, drug, or surgery	Subthreshold laser 21 eyes 543 nm subthreshold laser (laser grid)	Standard threshold laser 21 eyes	• VA as determined by the ETDRS vision chart • mean CMT as determined by OCT,
Tewari 1998	12 Months FU	Inclusion criteria: • CSMO • BCVA of 6/60 or better in	Subthreshold laser Diode laser (40 eyes;	Standard threshold laser	• VA (considering a 2-line change of Snellen's). • Secondary outcome:

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		each eye Exclusion criteria: • Severe NPDR or PDR in either of the eyes • Significant media opacities • Previous laser photocoagulation	20 focal and 20 grid)	Argon green (40 eyes; 20 focal and 20 grid)	complications such as submacular haemorrhage
Venkatesh 2011	12 Months FU	Inclusion criteria: • Focal and diffuse • NPDR Exclusion criteria: • PR • Significant media opacities • Prior medical treatment (intravitreal/peribulbar steroids or antiangiogenic drugs), or prior laser treatment	Subthreshold laser Subthreshold micropause diode laser (n = 23)	Standard threshold laser Double-frequency neodymium YAG (Nd:YAG) laser (n = 23)	• Change in the Central Macular Thickness as measured by OCT • change in macular retinal sensitivity • measured using multifocal electroretinography • change in BCVA and contrast sensitivity
Vujosevic 2010	12-months FU	Inclusion criteria: • CSMO • Type II diabetes Exclusion criteria: • Significant media opacities • Any type of previous macular treatment (macular laser photocoagulation, vitrectomy, intravitreal steroids, antiangiogenic drugs)	Subthreshold laser Micropulse diode laser (32 eyes)	Standard threshold laser (30 eyes) m-ETDRS with green laser	• Retinal sensitivity • FAF changes. • OCT changes and BCVA.
Xie 2013	12-months FU	Inclusion criteria: • Type 2 or type 1 diabetes. • DMO by ophthalmologist combined FFA, OCT • no significant refractive media	Argon ion laser group	subthreshold micropulse diode laser (SDM, 810nm)	• mean best corrected visual acuity (BCVA) • mean Central macular thickness

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		turbidity. • no other ocular disease history include glaucoma or anti - glaucoma surgery history, congenital retinal disease history or acquired retinal surgery, retinal laser treatment history.			

BCVA: best-corrected visual acuity; CMT: central macular thickness; CRT: central retinal thickness; CSMO: clinically significant macular oedema; CSRT: central subfield retinal thickness; DME: diabetic macular oedema; DMO: diabetic macular oedema; DR: diabetic retinopathy; ETDRS: Early Treatment Diabetic Retinopathy Study; FAZ: foveal avascular zone; IVS: intravitreal steroid; logMAR: log of the Minimum Angle of Resolution; mETDRS: modified Early Treatment of Diabetic Retinopathy Study; MMG: mild macular grid; MO: macular oedema; NPDR: non-proliferative diabetic retinopathy; NR: not reported; OCT: optical coherence tomography; PDR: proliferative diabetic retinopathy; PR: proliferative retinopathy; PRN: pro-re-nata (i.e. as needed); PRP: panretinal photocoagulation; SDM: subthreshold micropulse diode; VA: visual acuity; VEGF: vascular endothelial growth factor

Table 6: Randomised controlled trials (for full study details, see Mehta et al. 2018)

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
Randomised controlled trials (from Mehta et al. 2018 Cochrane systematic review)					
DRCRnet U 2018 (Maturi 2018)	6 Months FU	Inclusion criteria: • Persistent DMO (previously received at least 3 injections of anti-VEGF within prior 20 weeks) • Retinal thickening involving the centre of the macular • CMT thickness greater than 300 µm • VA letter score in study eye ≤ 78 and ≥ 24 logMAR letters (approximate Snellen equivalent 20/32 to 20/320) Type I or type II diabetes	Intravitreal ranibizumab (0.3 mg) and dexamethasone implant (0.7g)	Intravitreal ranibizumab (0.3 mg) and sham injection	• mean change in visual acuity letter score Secondary outcome measures: • percentage of eyes with at least 10 and at least 15 ETDRS letter gain (increase) or loss (decrease) in visual acuity. • visual acuity area under the curve (AUC) • mean change in OCT central macular thickness • percentage of eyes with worsening or improvement of diabetic retinopathy on clinical exam • adverse events

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
Lim 2012	12 Months FU	Inclusion criteria: • CSMO • CMT of at least 300 µm Exclusion criteria: • Previous treatment for DMO • PDR with active neovascularisation Previous panretinal photocoagulation	Intravitreal bevacizumab (1.25mg/0.05ml) and intravitreal triamcinolone acetonide (2mg/0.05ml)	• Intravitreal bevacizumab (1.25mg/0.05ml) Intravitreal triamcinolone acetonide (2mg/0.05ml)	Change in BCVA at 1 year (LogMAR chart) Change in CMT at 1 year
Maturi 2015	12 Months FU	Inclusion criteria: • BCVA scores between 24 and 78, ETDRS letters (20/32–20/320 Snellen equivalent) • DMO because of type I or type II diabetes CMT of greater than 250 µm	Intravitreal bevacizumab (1.25mg) and dexamethasone implant (0.7mg)	Intravitreal bevacizumab (1.25mg)	• Visual acuity (ETDRS letters) at 12 months • Central subfield thickness (OCT) at 12 months • Speed of visual improvement: time until gain 15 letters • Number of injections required • Adverse events
Neto 2017	6 Months FU	Inclusion criteria: • CRT ≥ 275 µm • BCVA score between 20 letters (20/400 ETDRS) and 70 letters (20/40 ETDRS) • Type I or type II diabetes Without prior foveal treatment with laser therapy	Intravitreal bevacizumab (1.25mg/0.05ml) and intravitreal triamcinolone acetate (4mg/0.1ml)	• Intravitreal bevacizumab (1.25mg/0.05ml) • Intravitreal triamcinolone acetate (4mg/0.1ml)	• BCVA (ETDRS) • IOP • Retinal thickness • Adverse events
Riazi-Esfahani 2017	6 Months FU	Inclusion criteria: • Bilateral clinically significant DMO based on ETDRS criteria • CMT of > 320 µm Exclusion criteria: • PDR • Significant media opacities • A history of any treatment for DMO (panretinal or focal laser photocoagulation and	Intravitreal bevacizumab (1.25mg/0.05ml) and intravitreal triamcinolone acetonide (1mg/0.025ml)	Intravitreal bevacizumab (1.25mg/0.05ml)	• Mean change in BCVA at 24 weeks: Snellen chart • CMT change at weeks 2, 4, 6, 12 and 24: SD-OCT • Injection - related complications • Number of injections • Adverse events

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		anti-VEGF or IVS) • VA ≤ 20/320			
Shoeibi 2013	6 Months FU	Inclusion criteria: • DMO refractory to laser treatment • Participants had refractory DMO that had not responded to macular laser treatment Exclusion criteria: • Significant media opacities	Intravitreal bevacizumab (1.25mg/0.05ml) and triamcinolone acetonide (2mg/0.05ml)	Intravitreal bevacizumab (1.25mg/0.05ml) and sham injection	• Change in CMT: OCT (Stratus OCT 3; Carl Zeiss Meditec) • BCVA: Snellen chart converted into LogMAR • Adverse event
Soheilian 2012	12 Months FU 24 months FU	Inclusion criteria: • CSMO based on ETDRS criteria Exclusion criteria: • High-risk PDR • Significant media opacities Panretinal or focal laser photocoagulation	Intravitreal bevacizumab (1.25mg/0.05ml) and triamcinolone acetonide (2mg/ 0.05ml) n = 50 eyes	Intravitreal bevacizumab (1.25mg/0.05ml) Standard threshold laser (Focal or modified grid laser) n = 50 eyes	• BCVA • CMT • Injection related complications • Adverse events
Synek 2011	6 Months FU	Inclusion criteria: • CSMO unresponsive to previous macular photocoagulation Exclusion criteria: • History of cataract surgery within past 6 months • PDR with high-risk characteristics • Significant media opacities • Prior intraocular injection or vitrectomy	Intravitreal bevacizumab (1.25mg/0.05ml) and triamcinolone acetonide (2mg/0.05ml)	Intravitreal bevacizumab (1.25mg/0.05ml)	• Change in CMT at 6 months: OCT • Change in BCVA at 6 months: Snellen chart converted to LogMAR • Ocular adverse events: IOP rise, cataract progression, intraocular inflammation

Study	Follow-up time	Population	Intervention	Comparator	Outcomes

BCVA: best-corrected visual acuity; CMT: central macular thickness; CRT: central retinal thickness; CSMO: clinically significant macular oedema; CSRT: central subfield retinal thickness; DME: diabetic macular oedema; DMO: diabetic macular oedema; DR: diabetic retinopathy; ETDRS: Early Treatment Diabetic Retinopathy Study; FAZ: foveal avascular zone; IVS: intravitreal steroid; logMAR: log of the Minimum Angle of Resolution; mETDRS: modified Early Treatment of Diabetic Retinopathy Study; MMG: mild macular grid; MO: macular oedema; NPDR: non-proliferative diabetic retinopathy; NR: not reported; OCT: optical coherence tomography; PDR: proliferative diabetic retinopathy; PR: proliferative retinopathy; PRN: pro-re-nata (i.e. as needed); PRP: panretinal photocoagulation; SDM: subthreshold micropulse diode; VA: visual acuity; VEGF: vascular endothelial growth factor

Table 7: Randomised controlled trials (for full study details, see Rittiphairoj et al. 2020)

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
Randomised controlled trials (from Rittiphairoj et al. 2020 Cochrane systematic review)					
BEVORDEX 2014 (Gillies 2014)	12 Months FU	Inclusion criteria: • DME for whom the investigator believed that laser treatment would be unhelpful • BCVA 20/400 to 20/40	Intravitreal dexamethasone implant (Ozurdex 0.7 mg) every 16 weeks (PRN)	Intravitreal bevacizumab (1.25 mg) every 4 weeks (PRN)	• change in mean BCVA • mean change in CMT • mean number of treatments • incidence of cataracts • adverse events • Patient-reported outcome: Impact of Vision Impairment questionnaire
Callanan 2017	12 Months FU	Inclusion criteria: • CRT by SD-OCT ≥ 300 µm with Spectralis (Heidelberg) or ≥ 275 µm with Cirrus (Zeiss) • BCVA > 34 and < 70	Intravitreal treatment with dexamethasone implant 0.7 mg	Ranibizumab 0.5 mg	• CRT • BCVA • Mean number of treatments • Incidence of cataracts • Adverse events
DRCR.net 2008	24 Months FU	Inclusion criteria: • Definite retinal thickening resulting from DME involving the centre of the macular • CRT of ≥ 250 µm in the central subfield • Best-corrected electronic ETDRS VA letter score	• Intravitreal triamcinolone (1 mg) Intravitreal triamcinolone (4 mg)	Standard threshold laser (Focal/grid laser)	• BCVA • retinal thickness • adverse events

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		between 73 (approximately 20/40) and 24 (approximately 20/320) • Type I or type II diabetes Exclusion criteria: Prior treatment with intravitreal corticosteroids			
FAME 2011 (Campochiaro 2011)	24 Months FU	Inclusion criteria: • Mean foveal thickness of at least 250 µm in the study eye • BCVA of ≥ 19 and ≤ 68 letters (20/50 or worse but at least 20/ 400) in the study eye by an ETDRS chart. • BCVA of the non-study eye must be no worse than 20/400. • Type I or type II diabetes • At least 1 macular laser treatment more than 12 weeks prior to the screening visit	• 0.2 µg/day fluocinolone (low dose insert) 0.5 µg/day fluocinolone (high dose insert)	Sham injection	• improvement from baseline BCVA • adverse events
Kriechbaum 2014	12 Months FU	Inclusion criteria: • CSRT of at least 300 µm • BCVA of 20/25 to 20/400 Snellen equivalent in the study eye Exclusion criteria: • Active proliferative DR with necessity of panretinal laser treatment Previous macular laser photocoagulation or intravitreal injection therapy	3 injections of 2.5 mg bevacizumab, 2 sham injections after 4 and 8 weeks, then PRN regimen	1 initial injection of 8 mg triamcinolone, 2 sham injections after 4 and 8 weeks, then PRN regimen	• correlation BCVA • central subfield retinal thickness

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
Lim 2012	12 Months FU	• eyes with clinically significant DME based on ETDRS criteria • macular oedema with central macular thickness of at least 300 µm by OCT Exclusion criteria: • unstable medical status, including glycaemic control and blood pressure any previous treatment for DME, including intravitreal, sub-Tenon injection or macular photocoagulation • history of vitreoretinal surgery • uncontrolled glaucoma • proliferative diabetic retinopathy with active neovascularization • previous panretinal photocoagulation • presence of vitreomacular traction	Treatment intervention 1: intravitreal injection of bevacizumab alone Treatment intervention 2: intravitreal injection of bevacizumab 1.25 mg with triamcinolone 2 mg	Treatment intervention 3: intravitreal injection of triamcinolone 2 mg	• logMAR BCVA. • central macular thickness. • Adverse events
MEAD 2014 (Boyer 2014)	12 Months FU	Inclusion criteria: • Fovea-involved macular oedema that was associated with DR • CRT of 300 µm • BCVA between 34 and 68 letters (20/200 to 20/50) • Type I or type II diabetes • Previously treated with medical or laser therapy Naïve patients who had refused laser treatment or would not benefit from laser	• Intravitreal dexamethasone implant 0.7 mg Intravitreal dexamethasone implant 0.37 mg	Sham procedure	• change in BCVA from baseline • time to 15-letter improvement in BCVA • from baseline, • percentage of participants with BCVA of 20/40 at each study visit, • change in CRT from baseline • adverse events

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		therapy			
Ockrim 2008	12 Months FU	Inclusion criteria: • CSMO persisting 4 months or more • BCVA between 6/12 and 3/60 • At least 1 prior laser treatment	Intravitreal triamcinolone 4 mg	Standard threshold laser	• proportion of participants who improved by 15 or more ETDRS letters at 12 months • mean ETDRS letter score at 12 months • mean CRT measured with OCT • adverse events
Sutter 2004	12 Months FU	Inclusion criteria: • Persistent DME, diffuse or focal, involving the central fovea persisting 3 months or more after adequate laser treatment. BCVA in the affected eye(s) of 6/9 or worse	Intravitreal triamcinolone (4 mg)	Sham treatment (subconjunctival saline injection)	• best corrected logMAR visual acuity • adverse events • change in macular thickness

BCVA: best-corrected visual acuity; CMT: central macular thickness; CRT: central retinal thickness; CSMO: clinically significant macular oedema; CSRT: central subfield retinal thickness; DME: diabetic macular oedema; DMO: diabetic macular oedema; DR: diabetic retinopathy; ETDRS: Early Treatment Diabetic Retinopathy Study; FAZ: foveal avascular zone; IVS: intravitreal steroid; logMAR: log of the Minimum Angle of Resolution; mETDRS: modified Early Treatment of Diabetic Retinopathy Study; MMG: mild macular grid; MO: macular oedema; NPDR: non-proliferative diabetic retinopathy; NR: not reported; OCT: optical coherence tomography; PDR: proliferative diabetic retinopathy; PR: proliferative retinopathy; PRN: pro-re-nata (i.e. as needed); PRP: panretinal photocoagulation; SDM: subthreshold micropulse diode; VA: visual acuity; VEGF: vascular endothelial growth factor

1.1.6 Summary of the effectiveness evidence

Network meta-analysis

People with centre-involving macular oedema

Visual acuity

Whole population

Table 8: Visual acuity at 12 months relative to Standard threshold laser

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Sub-threshold laser	0.00 (-0.05, 0.06)	Moderate	Could not differentiate
Bevacizumab	-0.12 (-0.16, -0.08)		Favours Bevacizumab
Ranibizumab	-0.13 (-0.16, -0.10)		Favours Ranibizumab
Aflibercept	-0.18 (-0.22, -0.15)		Favours Aflibercept
Pegaptanib	0.01 (-0.11, 0.13)		Could not differentiate
Dexamethasone	-0.10 (-0.15, -0.05)		Favours Dexamethasone
Triamcinolone	-0.03 (-0.08, 0.02)		Could not differentiate
Ranibizumab + standard threshold laser	-0.11 (-0.15, -0.08)		Favours Ranibizumab + standard threshold laser
Triamcinolone + standard threshold laser	-0.02 (-0.07, 0.03)		Could not differentiate
Bevacizumab + standard threshold laser	-0.16 (-0.31, -0.02)		Favours Bevacizumab + standard threshold laser
Bevacizumab + triamcinolone	-0.08 (-0.15, -0.01)		Favours Bevacizumab + triamcinolone

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Treatment	MD (95% CrI)	Quality	Interpretation of effect
Sham	0.10 (-0.01, 0.21)		Could not differentiate
Dexamethasone + ranibizumab	-0.12 (-0.21, -0.04)		Favours Dexamethasone + Ranibizumab
Dexamethasone + bevacizumab	-0.13 (-0.30, 0.04)		Could not differentiate
Conbercept	-0.17 (-0.25, -0.09)		Favours Conbercept
Faricimab	-0.20 (-0.26, -0.14)		Favours Faricimab
Brolucizumab	-0.20 (-0.29, -0.12)		Favours brolucizumab

Table 9: Visual acuity at 24 months relative to Standard threshold laser

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Bevacizumab	-0.12 (-0.36, 0.11)	Moderate	Could not differentiate
Ranibizumab	-0.13 (-0.46, 0.20)		Could not differentiate
Aflibercept	-0.11 (-0.29, 0.07)		Could not differentiate
Dexamethasone	-0.06 (-0.38, 0.25)		Could not differentiate
Triamcinolone	0.08 (-0.25, 0.41)		Could not differentiate
Ranibizumab + standard threshold laser	-0.12 (-0.45, 0.21)		Could not differentiate
Fluocinolone	-0.08 (-0.51, 0.34)		Could not differentiate
Sham	-0.03 (-0.30, 0.24)		Could not differentiate
Triamcinolone + standard threshold laser	-0.02 (-0.35, 0.31)		Could not differentiate

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

Subgroup analysis: People with baseline central retinal thickness >400 micrometres

Table 10: Visual acuity at 12 months relative to Standard threshold laser

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Bevacizumab	-0.13 (-0.18, -0.09)	High	Favours Bevacizumab
Ranibizumab	-0.15 (-0.18, -0.11)		Favours Ranibizumab
Aflibercept	-0.20 (-0.25, -0.15)		Favours Aflibercept
Pegaptanib	0.00 (-0.13, 0.14)		Could not differentiate
Dexamethasone	-0.12 (-0.18, -0.05)		Favours Dexamethasone
Triamcinolone	-0.04 (-0.09, 0.02)		Could not differentiate
Ranibizumab + standard threshold laser	-0.13 (-0.18, -0.09)		Favours Ranibizumab + standard threshold laser
Triamcinolone + standard threshold laser	-0.04 (-0.12, 0.04)		Could not differentiate
Bevacizumab + triamcinolone	-0.08 (-0.16, 0.00)		Could not differentiate
Sham	0.09 (-0.03, 0.20)		Could not differentiate
Conbercept	-0.17 (-0.26, -0.08)		Favours Conbercept
Faricimab	-0.22 (-0.29, -0.15)		Favours Faricimab
Brolucizumab	-0.20 (-0.27, -0.13)		Favours Brolucizumab

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Table 11: Visual acuity at 24 months relative to Standard threshold laser

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Bevacizumab	-0.18 (-0.21, -0.15)	Moderate	Favours Bevacizumab
Ranibizumab	-0.23 (-0.27, -0.18)		Favours Ranibizumab
Aflibercept	-0.24 (-0.27, -0.20)		Favours Aflibercept
Dexamethasone	-0.10 (-0.22, 0.02)		Could not differentiate
Triamcinolone	0.00 (-0.26, 0.26)		Could not differentiate
Ranibizumab + standard threshold laser	-0.12 (-0.17, -0.07)		Favours Ranibizumab + standard threshold laser
Fluocinolone	-0.11 (-0.24, 0.02)		Could not differentiate
Sham	-0.05 (-0.18, 0.07)		Could not differentiate
Triamcinolone + standard threshold laser	-0.02 (-0.07, 0.03)		Could not differentiate

Central retinal thickness

Whole population

Table 12: Central retinal thickness at 12 months relative to Standard threshold laser

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Sub-threshold laser	-2.07 (-42.09, 38.77)	Moderate	Could not differentiate
Bevacizumab	-22.76 (-59.94, 16.37)		Could not differentiate
Ranibizumab	-62.10 (-86.42, -33.97)		Favours ranibizumab
Aflibercept	-81.73 (-112.00, -48.48)		Favours aflibercept
Dexamethasone	-106.40 (-149.60, -59.93)		Favours dexamethasone
Triamcinolone	2.04 (-47.06, 50.60)		Could not differentiate
Ranibizumab + standard threshold laser	-78.56 (-112.70, -40.65)		Favours ranibizumab + standard threshold laser
Bevacizumab + triamcinolone	-21.56 (-83.84, 42.79)		Could not differentiate
Dexamethasone + ranibizumab	-98.95 (-162.10, -28.33)		Favours dexamethasone + ranibizumab
Fluocinolone	-4.27 (-88.96, 80.39)		Could not differentiate
Conbercept	-54.85 (-125.30, 17.72)		Could not differentiate
Sham	70.93 (1.24, 140.30)		Favours standard threshold laser
Dexamethasone + bevacizumab	-28.84 (-115.10, 58.85)		Could not differentiate
Bevacizumab + standard threshold laser	-21.35 (-91.20, 51.43)		Could not differentiate

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Brolucizumab	-98.53 (-149.70, -41.49)		Could not differentiate

Table 13: Central retinal thickness at 24 months relative to Standard threshold laser

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Bevacizumab	-65.47 (-96.59, -34.19)	Moderate	Favours bevacizumab
Ranibizumab	-92.13 (-123.70, -60.70)		Favours ranibizumab
Aflibercept	-109.70 (-132.90, -86.52)		Favours aflibercept
Dexamethasone	-44.67 (-87.87, -2.08)		Favours dexamethasone
Triamcinolone	66.54 (42.15, 91.00)		Could not differentiate
Ranibizumab + standard threshold laser	24.93 (-24.70, 73.77)		Could not differentiate
Fluocinolone	-23.15 (-66.75, 20.09)		Could not differentiate
Sham	35.27 (-4.62, 74.69)		Could not differentiate
Sub-threshold laser	-0.59 (-13.95, 12.78)		Could not differentiate

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

Subgroup analysis: People with baseline central retinal thickness >400 micrometres

Table 14: Central retinal thickness at 12 months relative to Standard threshold laser

Treatment	MD (95% CrI)	Quality	Interpretation of effect
Bevacizumab	-22.28 (-62.30, 21.66)	Moderate	Could not differentiate
Ranibizumab	-63.56 (-93.06, -30.04)		Favours ranibizumab
Aflibercept	-83.62 (-118.70, -43.30)		Favours aflibercept
Dexamethasone	-107.70 (-156.90, -53.21)		Favours dexamethasone
Triamcinolone	-36.21 (-109.40, 41.46)		Could not differentiate
Ranibizumab + standard threshold laser	-74.24 (-112.40, -31.67)		Favours ranibizumab + standard threshold laser
Triamcinolone + standard threshold laser	-70.28 (-135.70, -0.94)		Favours triamcinolone + standard threshold laser
Bevacizumab + triamcinolone	-31.47 (-104.10, 45.91)		Could not differentiate
Fluocinolone	-6.49 (-98.95, 87.64)		Favours fluocinolone
Conbercept	-52.80 (-130.00, 26.19)		Favours conbercept
Sham	68.40 (-6.94, 144.40)		Could not differentiate
Sub-threshold laser	40.46 (-56.57, 137.60)		Could not differentiate
Bevacizumab + standard threshold laser	-20.43 (-97.03, 60.93)		Could not differentiate
Dexamethasone + bevacizumab	-27.83 (-119.40, 66.07)		Could not differentiate
Brolucizumab	-98.68 (-156.60, -32.01)		Favours brolucizumab

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Pairwise Meta-analysis

People with centre-involving macular oedema (whole population)

Anti-VEGFs vs standard threshold laser

Table 15: Anti-VEGF vs standard threshold laser: Visual Acuity: three or more lines improvement from baseline up to 12M

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement from baseline up to 12M (RR greater than 1 favours anti-VEGF)					
Overall					
11	Parallel RCTs	2410	RR: 2.30 [1.54, 3.45]	Very Low	Favours Anti-VEGF
Subgroup: Conbercept (RR greater than 1 favours anti-VEGF)					
1	Parallel RCTs	199	RR: 1.67 [0.92, 3.03]	High	Could not differentiate
Subgroup aflibercept (RR greater than 1 favours anti-VEGF)					
4	Parallel RCT	1098	RR: 3.36 [2.15, 5.23]	Moderate	Favours aflibercept
Subgroup bevacizumab (RR greater than 1 favours anti-VEGF)					
1	Parallel RCT	50	RR: 2.26 [0.47, 10.98]	High	Could not differentiate
Subgroup ranibizumab (RR greater than 1 favours anti-VEGF)					
5	Parallel RCT	1033	RR: 1.92 [0.87, 4.24]	Very Low	Could not differentiate

Table 16: Anti-VEGF vs standard threshold laser: The mean number of treatments at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Subgroup aflibercept (MD lower than 0 favours anti-VEGF)					
4	Parallel RCT	905	MD: 9.49 [8.76, 10.23]	Low	Favours standard threshold laser
Subgroup bevacizumab (MD lower than 0 favours anti-VEGF)					
2	Parallel RCT	164	MD: 2.10 [1.62, 2.58]	Moderate	Favours standard threshold laser
Subgroup ranibizumab (MD lower than 0 favours anti-VEGF)					
4	Parallel RCT	903	MD: 1.98 [-2.34, 6.29]	Very Low	Favours standard threshold laser
Subgroup: Conbercept (MD lower than 0 favours anti-VEGF)					

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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1	Parallel RCT	157	MD: -0.10 [-1.18, 0.98]	High	Could not differentiate

Table 17:Anti-VEGF vs standard threshold laser: The mean number of treatments at 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept (MD lower than 0 favours anti-vegf)					
2	Parallel RCT	578	MD: 19.00 [16.64, 21.35]	Moderate	Favours standard threshold laser

Table 18:Anti-VEGF vs standard threshold laser: Adverse Events at 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adverse Event: Cataract progression Subgroup aflibercept (RR lower than 1 favours anti-VEGF)					
3	Parallel RCTs	1132	RR: 0.92 [0.36, 2.35]	High	Favours standard threshold laser
Subgroup: ranibizumab (RR lower than 1 favours anti-VEGF)					
1	Parallel RCTs	227	RR: 0.32 [0.01, 7.75]	High	Favours standard threshold laser
Adverse Event: IOP increase					
Subgroup aflibercept (RR lower than 1 favours anti-VEGF)					
2	Parallel RCT	554	RR: 1.75 [0.94, 3.26]	Moderate	Favours standard threshold laser
Subgroup bevacizumab (RR lower than 1 favours anti-VEGF)					
1	Parallel RCT	80	RR: 2.72 [0.11, 64.85]	High	Favours standard threshold laser
Subgroup ranibizumab (RR lower than 1 favours anti-VEGF)					

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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1	Parallel RCT	80	RR: 8.14 [0.49, 134.21]	High	Favours standard threshold laser
Adverse Event: Vitreous haemorrhage					
Subgroup aflibercept (RR lower than 1 favours anti-VEGF)					
3	Parallel RCTs	1132	RR: 0.73 [0.35, 1.50]	Low	Favours standard threshold laser
Subgroup: Conbercept (RR lower than 1 favours anti-VEGF)					
1	Parallel RCTs	156	RR: 1.05 [0.27, 4.06]	High	Favours standard threshold laser
Subgroup bevacizumab (RR lower than 1 favours anti-VEGF)					
1	Parallel RCT	80	RR: 0.30 [0.01, 7.21]	High	Favours standard threshold laser
Subgroup ranibizumab (RR lower than 1 favours anti-VEGF)					
1	Parallel RCT	382	RR: 0.31 [0.08, 1.11]	High	Favours standard threshold laser

Anti-VEGF

vs Anti-VEGF

Table 19: Bevacizumab VS Ranibizumab

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement from baseline up to 12M (RR lower than 1 favours bevacizumab)					
2	Parallel RCTs	636	RR: 0.88 [0.68, 1.14]	High	Could not differentiate
The mean number of treatments at 12 months (MD lower than 0 favours bevacizumab)					
2	Parallel RCT	226	MD: 1.06 [-1.09, 3.22]	High	Favours bevacizumab

Table 20: Aflibercept vs Ranibizumab

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
The mean number of treatments at 12 months (MD lower than 0 favours aflibercept)					
2	Parallel RCT	182	MD: -0.95 [-2.11, 0.21]	Low	Could not differentiate

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Table 21 Brolucizumab vs Aflibercept

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement from baseline up to 12M (RR greater than 1 favours anti-VEGF)					
2	Parallel RCTs	736	RR: 1.14 [0.96, 1.37]	High	Could not differentiate
The mean number of treatments at 12 months (MD lower than 0 favours brolucizumab)					
2	Parallel RCT	736	MD: -1.60 [-1.80, -1.39]	High	Favours brolucizumab

Table 22: Faricimab vs Aflibercept

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement from baseline up to 12M (RR greater than 1 favours anti-VEGF)					
2	Parallel RCTs	1094	RR: 1.01 [0.85, 1.21]	High	Could not differentiate

Anti-VEGF plus standard threshold laser vs Anti-VEGFTable 23: Ranibizumab vs Ranibizumab + standard threshold laser

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement from baseline up to 12M (RR greater than 1 favour anti-VEGF plus laser)					

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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
3	Parallel RCTs	636	RR: 1.05 [0.78, 1.42]	Moderate	Could not distinguish

Table 24**: Bevacizumab vs Bevacizumab + standard threshold laser**

No. of studies	Study design	Sample	Effect size (95% CI)	Quality	Interpretation of effect
The mean number of treatments at 12 months (MD lower than 0 favours bevacizumab+ laser)					
1	Parallel RCT	736	MD: 0.26 [-0.25, 0.77]	High	Could not differentiate

Anti-VEGF vs sham

Table 25**: Ranibizumab vs sham**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement from baseline up to 12M (RR greater than 1 favours anti-VEGF)					
2	Parallel RCTs	509	2.66 [1.94, 3.65]	High	Favours ranibizumab

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Anti-VEGFs + steroids vs Anti-VEGF

Table 26: Anti-VEGF and steroid versus anti-VEGF alone

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Significant intraocular inflammation (RR less than 1 favour Anti-VEGF and steroid)					
2	Parallel RCTs	189	RR 0.99 [0.14, 6.95]	High	Could not differentiate
Development of cataract (RR less than 1 favour Anti-VEGF and steroid)					
3	Parallel RCTs	268	RR: 9.30 [2.21, 39.02]	High	Favours anti- VEGF alone
Raised intraocular pressure (RR less than 1 favour Anti-VEGF and steroid)					
7	Parallel RCT	557	RR: 12.07 [4.67, 31.25]	Moderate	Favours anti- VEGF alone

Steroids vs sham

Table 27. Intravitreal dexamethasone versus sham

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement from baseline up to 12M (RR greater than 1 favours intravitreal dexamethasone)					
1	Parallel RCTs	701	RR: 1.39 [0.91, 2.12]	Moderate	Could not differentiate
Visual Acuity: three or more lines improvement from baseline up to 24 M (RR greater than 1 favours intravitreal dexamethasone)					
1	Parallel RCTs	701	RR: 1.54 [1.04, 2.26]	Moderate	Favours intravitreal dexamethasone
Adverse events Cataract progression at 36 months (RR less than 1 favours intravitreal dexamethasone)					
1	Parallel RCT	697	RR 3.89 [2.75, 5.50]	Moderate	Favours sham
Adverse events IOP increase at 36 months (RR less than 1 favours intravitreal dexamethasone)					

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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1	Parallel RCT	697	RR: 8.99 [5.05, 16.03]	Moderate	Favours sham

Table 28. Intravitreal fluocinolone acetonide implant versus sham

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement from baseline up to 12M (RR greater than 1 favour Intravitreal fluocinolone acetonide implant)					
1	Parallel RCTs	560	RR: 1.79 [1.16, 2.78]	High	Favours Intravitreal fluocinolone acetonide
Visual Acuity: three or more lines improvement from baseline up to 24 M (RR greater than 1 favour Intravitreal fluocinolone acetonide implant)					
1	Parallel RCTs	560	RR: 1.76 [1.22, 2.53]	High	Favours Intravitreal fluocinolone acetonide
Adverse events Cataract progression at 24 M (RR less than 1 favours Intravitreal fluocinolone acetonide implant)					
1	Parallel RCT	351	RR: 1.63 [1.35, 1.97]	High	Favours sham
Adverse events IOP increase at 24 M (RR less than 1 favours Intravitreal fluocinolone acetonide implant)					
1	Parallel RCT	531	RR: 3.35 [2.22, 5.06]	High	Favours sham

Table 29. Intravitreal triamcinolone acetonide injection versus sham

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect

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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement (RR greater than 1 favour Intravitreal triamcinolone acetonide					
1	Parallel RCTs	69	RR: 4.12 [0.48, 34.99]	Moderate	Favours Intravitreal triamcinolone acetonide injection
Adverse events Cataract progression at 24 M (RR less than 1 favours Intravitreal triamcinolone acetonide					
1	Parallel RCT	69	RR: 3.00 [0.97, 9.30]	Moderate	Favours Intravitreal triamcinolone acetonide injection
Adverse events IOP increase at 24 M (RR less than 1 favours Intravitreal triamcinolone acetonide					
1	Parallel RCT	69	RR: 10.29 [1.39, 76.12]	Moderate	Favours sham

Steroids vs Anti-VEGFs

Table 30: Intravitreal dexamethasone versus intravitreal anti-VEGF

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement from baseline up to 12M (RR greater than 1 favours: Intravitreal dexamethasone Subgroup bevacizumab					
1	Parallel RCT	88	RR: 0.99 [0.70, 1.40]	Moderate	Could not differentiate
Subgroup ranibizumab (RR greater than 1 favour: Intravitreal dexamethasone					
1	Parallel RCT	363	RR: 0.50 [0.32, 0.79]	Moderate	Favours ranibizumab

Table 31: Intravitreal dexamethasone versus intravitreal anti-VEGF: The mean number of treatments at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Subgroup aflibercept					
1	Parallel RCT	98	MD: Not estimable	High	Could not differentiate
Subgroup bevacizumab					
1	Parallel RCT	88	MD:Not estimable	High	Could not differentiate
Subgroup ranibizumab					
1	Parallel RCT	363	MD: Not estimable	High	Could not differentiate

Table 32: Intravitreal dexamethasone versus intravitreal anti-VEGF: Adverse Events at 12 and 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adverse Event: Cataract progression at 12 to 24 months					
Subgroup bevacizumab (RR less than 1 favours: Intravitreal dexamethasone					
1	Parallel RCTs	88	RR: 2.74 [0.58, 12.84]	High	Could not differentiate
Subgroup: Ranibizumab (RR less than 1 favours: Intravitreal dexamethasone					
1	Parallel RCTs	247	RR: 4.54 [2.41, 8.55]	High	Favours Ranibizumab
Adverse Event: IOP increase at 24 months					
Subgroup aflibercept (RR less than 1 favours: Intravitreal dexamethasone					
1	Parallel RCT	98	RR: 11.45 [0.65, 201.60]	High	Could not differentiate
Subgroup bevacizumab (RR less than 1 favours: Intravitreal dexamethasone					
1	Parallel RCT	88	RR: 2.40 [1.19, 4.82]	High	Favours bevacizumab
Subgroup ranibizumab (RR less than 1 favours					
1	Parallel RCT	363	RR: 5.03 [1.12, 22.63]	High	Favours Ranibizumab

Steroids vs Macular Laser

Table 33: Intravitreal triamcinolone acetonide versus macular laser

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Visual Acuity: three or more lines improvement from baseline up to 12M					
1	Parallel RCTs	584	RR: 0.85[0.55,1.35]	High	Could not differentiate
Visual Acuity: three or more lines improvement from baseline up to 24 M					
1	Parallel RCTs	584	RR: 0.95 [0.66, 1.35]	High	Could not differentiate
Adverse events Cataract progression at 24 M					
1	Parallel RCT	459	RR: 2.68 [2.21, 3.24]	High	Favours standard threshold laser
Adverse events IOP increase at 24 M					
1	Parallel RCT	584	RR: 9.20 [5.14, 16.47]	High	Favours standard threshold laser

Subthreshold laser vs standard threshold laser

Table 34: Mean change in BCVA in the study eye from baseline to month 24 (ETDRS letters), mean (SD)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Mean change in BCVA in the study eye from baseline to month 24 (ETDRS letters), mean (SD) (MD lower than 0 favours Subthreshold laser)					
Lois 2023	Pragmatic RCT	230	MD 0.32 [-0.98, 1.62]	High	Could not differentiate

Table 35: Mean change in CRT in the study eye, as determined by SD-OCT from baseline to month 24, mean (SD)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Mean change in CRT in the study eye, as determined by SD-OCT from baseline to month 24, mean (SD) (MD lower than 0 favours Subthreshold laser)					
Lois 2023	Pragmatic RCT	230	MD: -0.64 [-14.06, 12.78]	High	Could not differentiate

Table 36: Number of patients meeting driving standards at month 24, n (%)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Number of patients meeting driving standards at month 24, n (%)					
Lois 2023	Pragmatic RCT	217	OR: 0.74 [0.16, 3.37]	High	Favours standard threshold laser

Table 37: Number of laser treatments used from baseline to month 24 in study eye, mean (SD)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Number of laser treatments used from baseline to month 24 in study eye, mean (SD)					
Lois 2023	Pragmatic RCT	231	-1.96 [-3.89, -0.03]	High	Favours standard threshold laser

People with non-centre-involving macular oedema

Comparisons vs standard threshold laser

Table 38: Comparisons vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Sub-threshold laser MD less than 0 favours comparison					

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 Figueira 2009	Parallel RCTs	84	MD -0.04 [-018,0.08]	High	Could not differentiate
Bevacizumab MD less than 0 favours comparison					
1 Soheilian 2007	Parallel RCTs	85	MD -0.19 [-0.32.-0.08]	Moderate	Favours Bevacizumab
Ranibizumab MD less than 0 favours comparison					
1 Turkoglu 2015	Parallel RCT	70	MD -0.10 [-0.19.-0.02]	High	Favours ranibizumab
Triamcinolone MD less than 0 favours comparison					
1 Ockrim 2008	Parallel RCT	83	MD 0.04 [-0.57.0.64]	Low	Could not differentiate
Ranibizumab + conventional laser MD less than 0 favours comparison					
1 RELATION 2012	Parallel RCT	128	MD -0.10 [-0.16.-0.04]	Low	Favours Triamcinolone

Table 39: Change in central retinal thickness from baseline (mean difference) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Sub-threshold laser MD less than 0 favours comparison					
1 Figueira 2009	Parallel RCTs	84	MD 13.20 [-31.58 , 57.98]	High	Could not differentiate
Bevacizumab MD less than 0 favours comparison					
1 Soheilian 2007	Parallel RCTs	85	MD -42.00 [-95.60, -11.60]	Moderate	Could not differentiate
Ranibizumab MD less than 0 favours comparison					

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 Turkoglu 2015	Parallel RCT	70	MD -66.00 [-78.59, --55.41]	High	Favours ranibizumab

Table 40: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Bevacizumab MD less than 0 favours comparison					
1 Soheilian 2012	**Parallel RCTs**	**78**	**MD -0.07 [-0.23,0.09]**	**High**	**Could not differentiate**
Bevacizumab + triamcinolone MD less than 0 favours comparison					
1 Soheilian 2012	**Parallel RCTs**	**75**	**MD -0.06 [-0.21,0.09]**	**High**	**Could not differentiate**

Table 41:Change in central retinal thickness at 24 months (mean difference)

Table 42:Change in central retinal thickness at 24 months (mean difference) No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Bevacizumab MD less than 0 favours comparison					
1 Soheilian 2012	Parallel RCTs	75	MD -4.00 [-66.81,58.81]	High	Could not differentiate
Bevacizumab + triamcinolone MD less than 0 favours comparison					
1 Soheilian 2012	Parallel RCTs	78	MD -26.00 [-81.03, 29.03]	High	Could not differentiate

Anti-VEGFs vs sham

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Bevacizumab (MD less than 0 favours anti-vegf)					
1 Ahmadieh 2008	Parallel RCTs	78	MD -0.15 [-0.26, -0.04]	High	Favours Bevacizumab

Table 43: Anti-VEGF vs sham: Change in visual acuity from baseline (logMAR) at 12 months

Subgroup analysis: People with centre-involving diabetic macular oedema with a baseline central retinal thickness of less than 400 micrometres

Sub-threshold vs standard threshold laser

Table 44: Sub-threshold vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Sub-threshold laser vs standard threshold laser (MD less than 0 favours subthreshold laser)					
4	Parallel RCT	213	MD -0.01 [-0.12, 0.09]	Low	Could not differentiate

Anti-VEGFs vs Anti-VEGFs with standard threshold laser

Table 45: bevacizumab vs bevacizumab + standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Bevacizumab vs bevacizumab + standard threshold laser (MD less than 0 favours vs bevacizumab + standard threshold laser)					
1 (Faghihi,2010)	Parallel RCT	80	MD: -0.04 [-0.17, 0.08]	High	Could not differentiate

Anti-VEGFs vs standard threshold laser

Table 46: Anti-VEGF vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Bevacizumab Vs Standard threshold laser (MD less than 0 favours anti-VEGF)					
2	Parallel RCT		MD -0.17 [-0.21, -0.13]	Moderate	Favours bevacizumab
Aflibercept Vs Standard threshold laser (MD less than 0 favours anti-VEGF)					
3	Parallel RCT		MD -0.09 [-0.19, 0.02]	Low	Could not differentiate

Steroids vs sham

Table 47: Steroids vs sham: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Fluocinolone Vs Sham (MD less than 0 favours steroid)					
1 FAME 2011 (Campochiaro 2011)	Parallel RCT	560	MD -0.06 [-0.08, -0.03]	High	Favours Fluocinolone
Dexamethasone Vs Sham (MD less than 0 favours steroid)					
1 MEAD 2014 (Boyer 2014)	Parallel RCT	701	MD -0.05 [-0.09, 0.00]	High	Favour Dexamethasone

Anti-VEGF vs Anti-VEGF

Table 48: Brolucizumab vs aflibercept: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Brolucizumab Vs Aflibercept (MD less than 0 favours Brolucizumab)					
1 (Brown 2022)	Parallel RCT	360	MD 0.02 [-0.02, 0.07]	High	Could not differentiate

Table 49: Anti VEGF vs Anti VEGF: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs. Bevacizumab (MD less than 0 favours Aflibercept)					
1 DRCRnet 2015	Parallel RCT	386	MD-0.06 [-0.10, -0.01]	High	Favour Aflibercept
Aflibercept vs Ranibizumab (MD less than 0 favours Aflibercept)					
1 DRCRnet 2015	Parallel RCT	392	MD -0.01 [-0.06, 0.04]	High	Could not differentiate
Ranibizumab vs Bevacizumab (MD less than 0 favours Ranibizumab)					
1 DRCRnet 2015	Parallel RCT	376	MD -0.05 [-0.09, -0.00]	High	Favour Ranibizumab

Steroids vs Anti-VEGFs

Table 50:Dexamethasone vs bevacizumab: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Dexamethasone Vs Bevacizumab (MD less than 0 favours Dexamethasone)					
1 BEVORDEX 2014 (Gillies 2014)	Parallel RCT	88	MD 0.08 [-0.03, 0.19]	High	Could not differentiate

Steroids vs standard threshold laser

Table 51:Triamcinolone vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Triamcinolone Vs Standard 70hreshold laser (MD less than 0 favours Triamcinolone)					
1 DRCRnet 2008	Parallel RCT	584	MD 0.08 [0.01, 0.15]	High	Favours Standard threshold laser

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

Combination treatments vs standard threshold laser

Table 52:Combination treatment vs sham + standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
ranibizumab + standard threshold laser (MD less than 0 favours ranibizumab + standard threshold laser					
1 DRCRnet 2010	Parallel RCT	480	MD -0.12 [-0.17, -0.07]	High	Favours ranibizumab + standard threshold laser
triamcinolone + standard threshold laser (MD less than 0 favours triamcinolone + conventional laser)					
1 DRCRnet 2010	Parallel RCT	479	MD -0.02 [-0.07, 0.03]	High	Could not differentiate

Combination treatments vs Anti-VEGFs

Table 53: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Bevacizumab Vs Triamcinolone + Bevacizumab (MD less than 0 favours Triamcinolone + Bevacizumab)					
1 Soheilian 2012	Parallel RCT	75	MD 0.01 [-0.15, 0.17]	High	Could not differentiate

Table 54: Change in visual acuity from baseline (logMAR) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Ranibizumab + standard threshold laser vs standard threshold laser: (MD less than 0 favours Ranibizumab + standard threshold laser)					

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 DRCRnet 2010	Parallel RCT	253	MD -0.08 [-0.13, -0.03]	High	Favours Ranibizumab + standard threshold laser
Triamcinolone + standard threshold laser vs standard threshold laser: (MD less than 0 favours triamcinolone + standard threshold laser)					
1 DRCRnet 2010	Parallel RCT	256	MD 0.00 [-0.06, 0.06]	High	Favours triamcinolone + standard threshold laser

Anti-VEGFs vs standard threshold laser

Table 55:Aflibercept vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs standard threshold Laser (MD less than 0 favours Aflibercept)					
1 VISTA & VIVID (Korobelnik 2014)	Parallel RCT	168	MD -0.15 [-0.15, -0.14]	High	Favours Aflibercept

Table 56: Aflibercept vs standard threshold laser: Change in visual acuity (logMAR) at 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs standard threshold laser: (MD less than 0 favours Aflibercept)					
1 VISTA & VIVID (Korobelnik 2014)	Parallel RCT	168	MD -0.15 [-0.16, -0.14]	High	Favours Aflibercept

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

Table 57:Aflibercept vs standard threshold laser: Change in central retinal thickness at 12 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs standard threshold laser: (MD less than 0 favours Aflibercept)					
1 VISTA & VIVID (Midena 2018)	Parallel RCT	168	MD -69.30 [-73.28, -65.32]	High	Favours Aflibercept

Table 58: Aflibercept vs standard threshold laser: Change in central retinal thickness at 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Laser vs aflibercept: change in central retinal thickness at 24 months. (MD less than 0 favours aflibercept)					
1 VISTA & VIVID (Midena 2018	Parallel RCT	168	MD 67.80 [63.42, 72.18]	High	Favours standard threshold laser

Steroids vs standard threshold laser

Table 59: Triamcinolone vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	
Triamcinolone vs standard threshold laser: (MD less than 0 favours Triamcinolone)					
1 DRCRnet 2008	Parallel RCT	296	MD 0.08 [0.01, 0.15]	High	Favours standard threshold laser

Combination treatments vs standard threshold laser

Table 60: Combination treatment vs standard threshold laser: Change in central retinal thickness from baseline (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Ranibizumab + standard threshold laser (MD less than 0 favours Ranibizumab + standard threshold laser)					
1 DRCRnet 2010	Parallel RCT	227	MD -44.00 [-65.63, -22.37	High	Favours Ranibizumab + standard threshold laser
triamcinolone + standard threshold laser (MD less than 0 favours triamcinolone + standard threshold laser					
1 DRCRnet 2010	Parallel RCT	231	MD -32.00 [-54.39, -9.61]	High	Favours triamcinolone + standard threshold laser

Subgroup analysis: People with centre-involving diabetic macular oedema with a baseline central retinal thickness of 400 micrometres or more

Table 61: Aflibercept vs standard threshold laser

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Aflibercept vs standard threshold laser: Change in central retinal thickness from baseline to 24 months (MD less than 0 favours aflibercept)					
1 VISTA & VIVID (Midena 2018)	Parallel RCT	168	MD -151.70 [-154.35, -149.05]	High	Favours standard threshold laser

Subgroup analysis: People with non-centre-involving diabetic macular oedema and baseline central retinal thickness of less than 400 micrometres

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

Table 62 Comparisons vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Subthreshold laser vs standard threshold laser (MD less than 0 favours Subthreshold laser)					
1 Figueira 2009	Parallel RCT	84	MD -0.04 [-0.16, 0.08]	High	Could not differentiate
Bevacizumab vs standard threshold laser (MD less than 0 favours Bevacizumab)					
1 Soheilian 2007	Parallel RCT	85	MD -0.19 [-0.32, -0.06]	High	Favours Bevacizumab

Table 63 Comparisons vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Subthreshold laser vs standard threshold laser (MD less than 0 favours Subthreshold laser)					
1 Figueira 2009	Parallel RCT	84	MD 13.20 [-31.58, 57.98]	High	Could not differentiate
Bevacizumab vs standard threshold laser (MD less than 0 favours Bevacizumab					
1 Soheilian 2007	Parallel RCT	85	MD -42.00 [-95.60, 11.60]	High	Could not differentiate

Subgroup analysis: People with non-centre-involving diabetic macular oedema and baseline central retinal thickness of 400 micrometres or more

Table 64:Comparisons vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months.

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Ranibizumab vs standard threshold laser					
Turkoglu 2015	Parallel RCT	70	MD -0.10 [-0.19, -0.02]	High	Favours Ranibizumab
Triamcinolone vs standard threshold laser					
Ockrim 2008	Parallel RCT	83	MD 0.04 [-0.57, 0.64]	High	Could not differentiate

Table 65:Ranibizumab vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Ranibizumab + standard threshold laser vs standard threshold laser					
RELATION 2012	Parallel RCT	128	MD -0.10 [-0.16, -0.04]	High	Favours Ranibizumab + standard threshold laser

Table 66:Bevacizumab vs sham

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Bevacizumab vs sham					

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Ahmadieh 2008	Parallel RCT	78	MD -0.15 [-0.26, -0.04]	High	Favours Bevacizumab

Table 67:Ranibizumab vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Ranibizumab vs standard threshold laser					
Turkoglu 2015	Parallel RCT	70	MD -66.00 [-76.59, -55.41]	High	Favours Ranibizumab

Table 68:Comparisons vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
VA (logMAR) at 24M bevacizumab					
Soheilian 2012	Parallel RCT	77	MD -0.07 [-0.23, 0.09]	High	Could not differentiate
bevacizumab + triamcinolone					

1 Effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Soheilian 2012	Parallel RCT	74	MD -0.06 [-0.21, 0.09]	High	Could not differentiate

Table 69:Comparisons vs standard threshold laser: Change in central retinal thickness from baseline to 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Bevacizumab					
Soheilian 2012	Parallel RCT	77	MD -4.00 [-66.81, 58.81]	High	Could not differentiate
Bevacizumab + triamcinolone					
Soheilian 2012	Parallel RCT	74	MD -26.00 [-81.03, 29.03]	High	Could not differentiate

See Appendix G for full GRADE tables.

1.1.7 Economic evidence

A literature search was conducted to identify published economic evaluations to answer this question. Additionally any relevant economic analyses conducted for published technology appraisals were reviewed for use in discussion around model conceptualisation and validation for the de novo economic model developed for this review question. The following technology appraisals in treatments for DMO were reviewed: TA824, TA820, TA799, TA346, TA301, TA274.

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 672 studies. Based on title and abstract screening, 638 studies could confidently be excluded for this review question and a further 24 studies excluded following the full-text review. Thus, 10 studies were included in the review (see Appendix G).

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

1.1.7.2 Excluded studies

Twenty-four studies were excluded at full text review. Some studies were selectively excluded based on limitations of the study, given there were similar studies with fewer limitations already included in the review.

See Appendix J for excluded studies and reasons for exclusion.

1.1.8 Summary of included economic evidence

Table 70: Economic evidence profile

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
Regnier et al (2015) Cost-effectiveness of ranibizumab versus aflibercept in the treatment of visual impairment due to diabetic macular edema: a UK healthcare perspective	Directly applicable; NHS perspective	Minor limitations, assumes treatment limited to 3 years	Markov cohort model with 8 health states based on visual acuity plus death health state Aflibercept compared with ranibizumab treat and extend (T&E) vs. ranibizumab treatment as needed (PRN) Population included patients with any central retinal thickness	Aflibercept compared with ranibizumab PRN: £5,841 and ranibizumab T&E: £2,930	Aflibercept compared with ranibizumab PRN: 0.05 and ranibizumab T&E: 0.05	ICER Aflibercept compared with ranibizumab PRN: £116,820 and ranibizumab T&E: £58,600 NMB at £20K Ranibizumab PRN: £6,768 Ranibizumab T&E: £3,934	Deterministic: The results were most sensitive to changes in the odds ratio of ranibizumab PRN compared with aflibercept, followed by the price discount assumed to apply to aflibercept (20%) and assumptions made for the number of injections and monitoring assumptions for ranibizumab and aflibercept. The net monetary benefit (NMB) for ranibizumab PRN remained positive in all scenarios explored. Probabilistic: Ranibizumab PRN had a 79% probability and ranibizumab (T&E) had a 67% probability of being cost effective

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
							compared with aflibercept assuming QALYs are valued at £20,000 each.
Mitchell et al (2012) Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial	Directly applicable; NHS perspective	Minor limitations, EQ-5D used as utility source in the base-case which is not sensitive to changes in eye conditions	Based on RESTORE and RETAIN clinical trials The study did not mention whether the population was separated by central retinal thickness	Ranibizumab monotherapy compared with laser mono: £4,191 Ranibizumab combo compared with laser mono: £4,695	Ranibizumab mono compared with laser: 0.17 Ranibizumab combo compared with laser mono: 0.13	Ranibizumab mono compared with laser mono: £24,028 Ranibizumab combo compared with laser mono: £36,106	Deterministic: Model most sensitive to changes in the number of injections and reducing the time horizon to 10 years. Changing the source of utilities increased the QALY gains and reduced the ICER. Probabilistic: 64% probability ranibizumab monotherapy would be cost effective compared to laser and 42% probability combination therapy would be cost effective compared to laser therapy based on a willingness to pay threshold of £30,000 per QALY.
Pochopien et al (2019) Cost-	Directly applicable; NHS	Minor limitations, disutility applied to	The text refers to the use of	Pseudophakic lens at baseline:	Pseudophakic lens at baseline:	Pseudophakic lens at baseline:	Deterministic: Main drivers of the ICER for

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
effectiveness of fluocinolone acetonide implant (ILUVIEN R) in UK patients with chronic diabetic macular oedema considered insufficiently responsive to available therapies	perspective	anti-VEGF injections only and not for insertion of implants	dexamethasone in the Pseudophakic population however the table reports the results for dexamethasone under the phakic lens population Analysis was not separated by central retinal thickness Disutility applied to injections for anti-VEGFs however not applied to the implant	Fluocinolone acetonide implant (FAc) compared with usual care: £3,066 FAc compared with dexamethasone: £1,777 Phakic lens at baseline: FAc compared with usual care: £3,170	FAc compared with usual care: 0.185 FAc compared with dexamethasone 0.126 Phakic lens at baseline: FAc compared with usual care: 0.11	FAc compared with usual care: £16,609 FAc compared with dexamethasone: £14,070 Phakic lens at baseline: FAc compared with usual care: £28,751 Incremental costs and QALYs are rounded so calculating the ICER from above gives a different result	FAc compared with usual care were utility decrements per health state, distribution of treatment within usual care, transition probabilities for sham baseline for the pseudo phakic population. Main drivers of the ICER for FAc compared with dexamethasone were the cost of dexamethasone and the number of outpatient visits for patients treated with FAc in the pseudo phakic population. Phakic population: Main driver of the ICER for FAc compared with usual care in the phakic population was the transition probabilities. Probabilistic: Pseudophakic population

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
							The FAc implant was found to have a 73.4% probability of being cost effective compared to usual care based on a willingness to pay threshold of £30,000. No probabilistic results presented for dexamethasone. Phakic population: The FAc implant was found to have a 59.2% probability of being cost effective compared to usual care based on a willingness to pay threshold of £30,000.
Haig et al (2016) Cost-effectiveness of ranibizumab in the treatment of visual impairment due to diabetic macular edema	Partially applicable; Canada study setting with 5% discount rate	Minor limitations, due to a lack of data, clinical expertise was used to populate resource use for treatment monitoring	Analysis for both societal and health care system were presented in the analysis, only results for the healthcare	Ranibizumab mono compared with laser mono: CA$9,849 (£5,555) Ranibizumab combo	Ranibizumab mono compared with laser mono: 0.4 Ranibizumab combo	Ranibizumab mono compared with laser mono: CA$24,494 (£13,815) Ranibizumab combo	Deterministic: Ranibizumab monotherapy and combination remained cost effective compared with laser monotherapy. Model most sensitive to removing the assumption patients

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
			perspective are presented to align with NICE reference case The analysis was not separated by central retinal thickness	compared with laser mono: CA$ 11,471 (£6,470)	compared with laser mono: 0.32	compared with laser mono: CA$ 36,414 (£20,538)	stopped treatment if BCVA above 75 letters this increased the ICER to CA$72,989 (£41,167) for ranibizumab monotherapy. Probabilistic: Ranibizumab monotherapy and ranibizumab combination therapy had a 74% and 60% probability of being cost effective at the ICER threshold of CA$50,000 (£28,201)
Holekamp et al (2020) Cost-effectiveness of ranibizumab and aflibercept to treat diabetic macular edema from a US perspective: analysis of 2-year Protocol T data	Partially applicable; US study; 3% discount rate from 2 years onwards	Potentially serious limitations, base-case only 2 years based on trial data, natural history source is unclear	Based on the Protocol T clinical trial, uses ranibizumab 0.3mg rather than 0.5mg Accounted for treatment in one or two eyes, assumptions made for starting treatment for the	Aflibercept compared with ranibizumab: 2 years: Full cohort: $9,894 (£6,896) VA 20/40 or better at baseline: $8,597 (£5,992)	Aflibercept compared with ranibizumab (2 years): Full cohort: 0.010 VA 20/40 or better at baseline: -0.002	Aflibercept compared with ranibizumab (2 years): Full cohort: $986,159 (£687,353) VA 20/40 or better at baseline: ranibizumab dominates	Deterministic: Model most sensitive to drug costs and the number of injections. Aflibercept only became cost effective for the full cohort based on an ICER of $19,930 (£13,891) when the number of injections for aflibercept over 2 years reduced from 15 to 11 whilst ranibizumab

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
			second eye to be mid study if not at baseline The analysis was not separated by central retinal thickness	VA 20/50 or worse: $10,967 (£7,644) Aflibercept compared with ranibizumab: 10 years: Full cohort: $20,608 (£14,364) VA 20/40 or better at baseline: $19,721 (£13,746) VA 20/50 or worse: $21,633 (£15,078)	VA 20/50 or worse: 0.021 Aflibercept compared with ranibizumab (10 years): Full cohort: 0.029 VA 20/40 or better at baseline: -0.032 VA 20/50 or worse: 0.088	VA 20/50 or worse: $523,377 (£364,794) Aflibercept compared with ranibizumab (10 years): Full cohort: $711,301 (£495,777) VA 20/40 or better at baseline: Ranibizumab dominates VA 20/50 or worse: $246,978 (£172,144)	remained the same. Ranibizumab remained dominant in all scenarios in the 20/40 or better VA subgroup. Probabilistic: Assuming QALYs were valued at $150,000 ((£104,550) aflibercept had a 0.1% probability of being cost effective for the full cohort and 2.5% probability for the 20/50 or worse VA subgroup.
Brown et al (2015) The Cost-effectiveness of ranibizumab for the treatment of	Partially applicable; US study (includes societal costs); 3% discount rate	Potentially serious limitations, assumes last observation from 24 months is	RIDE and RISE clinical trials with vision loss from 20/40 to 20/320 from DMO. Laser	Ranibizumab compared with sham (all direct medical costs considering both	Ranibizumab compared with sham 0.9981	Ranibizumab compared with sham considering both	No full deterministic or probabilistic sensitivity analysis was presented, only scenarios around the frequency of

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
diabetic macular edema		carried forward for the remainder of the model which may overestimate benefits, no deterministic or probabilistic sensitivity analysis	treatment could be given in addition to all treatment arms. 0.3mg ranibizumab cohort received average 0.8 laser treatments and the sham arm received 1.8 laser treatments over 24 months. Societal perspective was used in the base-case only the payer perspective results are presented here Assumes vision similar in both eyes, treatment in both eyes considered in the base-case, adverse events were included	eyes): $4,578 (£3,186)		eyes $4,587 (£3,193)/QALY	injections over 3 years. ICERS range from $37,693 (£26,234) /QALY for first eye to $107,784 (£75,018) when four annual injections administered bilaterally through 36 months. Assuming monthly injections for ranibizumab up to 36 months the ICER is $33,029 (£22,988) /QALY

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
			The analysis was not separated by central retinal thickness				
Stein et al (2013) Cost-effectiveness of various interventions for newly diagnosed diabetic macular edema	Partially applicable; US study; 3% discount rates	Minor limitations, time horizon may not cover all patients lifetime and equal efficacy assumed between bevacizumab and ranibizumab and no data available for the rates of cerebrovascular accident (CVA) for bevacizumab	Includes focal laser plus triamcinolone as a comparator which is not an included comparator within this guideline as the intraocular formulation is not available in the UK The analysis was not separated by central retinal thickness	Laser compared with: Laser plus ranibizumab $58,257 (£40,663) Delayed laser plus ranibizumab $61,424 (£42,874) Laser plus bevacizumab $27,200 (£18,986) Delayed laser plus bevacizumab $26,485 (£18,487)	Laser compared with: Laser plus ranibizumab: 10.83 Delayed laser plus ranibizumab: 10.99 Laser plus bevacizumab: 10.83 Delayed laser plus bevacizumab: 10.99	Laser compared with: Laser plus ranibizumab: $89,903 (£62,752) Delayed laser plus ranibizumab: $71,271 (£49,747) Laser plus bevacizumab Dominated by delayed laser plus bevacizumab Delayed laser plus bevacizumab:	Scenarios including the side effects of adverse events were included, which increased costs and reduced HRQOL for laser which had high rates of 6%. Due to the uncertainty around the rates of CVA for bevacizumab scenarios were run to identify if bevacizumab would not be considered cost effective based on a QALY valued at $50,000 if the probability of CVA is more than 4%. Probabilistic: In the analysis with ranibizumab based on a willingness to pay threshold of $50,000 per QALY there is a 70% probability laser would

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
						$11,138 (£7,774)	be the preferred treatment, when the threshold is increased to $100,000/QALY there is a 90% probability that ranibizumab with laser (either immediate or delayed) would be the preferred treatment. In the scenario with bevacizumab, at a value of $14,000 (£9,772) /QALY bevacizumab is very likely to be the preferred treatment compared with laser with over 90% probability.
Sharma et al (2000) The cost-effectiveness of grid laser photocoagulation for the treatment of diabetic macular edema: results of a patient-based cost-utility analysis	Partially applicable; US study; 0 or 5% discount rate used	Potentially serious limitations, not all costs considered only direct treatment costs, no probabilistic sensitivity analysis	Data based on ETDRS clinical trial. Utility valuations for adverse events based on physician opinion The analysis was not separated by central retinal	Laser photocoagulation compared with no treatment $733 (£509)	Laser photocoagulation compared with no treatment: 0.236	Laser photocoagulation compared with no treatment: No discounting $3,101 (£2,152) 5% discount rate based on an additional 40-	Deterministic: Efficacy values were varied within the 95% confidence limits, the results remained robust with laser photocoagulation remained the preferred treatment. No probabilistic

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
			thickness			year life expected $3,655 (£2,537)	sensitivity analysis was undertaken.
Lois et al (2022) Standard threshold laser versus subthreshold micro pulse laser for adults with diabetic macular oedema: the DIAMONDS non-inferiority RCT	Directly applicable; NHS and PSS perspective	Minor limitations, short 2-year time horizon	Data based on the DIAMOND clinical trial The population was people with central retinal thickness <400µm	Subthreshold micro pulse laser compared with standard threshold laser: -£365	Subthreshold micro pulse laser compared with standard threshold laser: 0.008	Subthreshold micro pulse laser compared with standard threshold laser: Subthreshold micro pulse laser dominates	Large confidence intervals for the cost difference of subthreshold micro pulse laser compared with standard threshold laser 95% confidence interval (-£822 to £93). Subthreshold micro pulse laser had 80% probability of being cost effective at a threshold of £15,000 per QALY and 76% probability of being cost effective at £20,000 per QALY.
Hutton et al (2023) Cost-effectiveness of aflibercept monotherapy vs bevacizumab first followed by aflibercept if needed for	Partially applicable; US healthcare setting	Minor limitations, 3% discount rate, short 2-year time horizon	Data based on the DRCR retina network protocol AC clinical trial The mean retinal thickness of the population was 504µm, with a	Aflibercept monotherapy compared with bevacizumab first followed by aflibercept if needed: $12,575 (£8,740)	Aflibercept monotherapy compared with bevacizumab first followed by aflibercept if needed: 0.015	Aflibercept monotherapy compared with bevacizumab first followed by aflibercept if needed: $837,077 (£581,769)	Deterministic: Changing utility source from Brown et al 1999 to RESTORE clinical trial and assumptions around costs will likely change the results, however the ICER would remain above

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
diabetic macular edema			95% CI of 487 to 521µm				$100,000 (£69,500). Probabilistic sensitivity analysis: 0% probability aflibercept monotherapy would be considered cost effective at a willingness to pay below $200,000 (£139,000) per QALY gained.

Abbreviations: BCVA: Best corrected visual acuity; BSE: Best seeing eye; CI-DME, centre involving diabetic macular oedema; Combo: combination therapy; CVA: cerebrovascular accident; CRT: central retinal thickness; FAc: Fluocinolone acetonide implant; Mono: Monotherapy; NMB: Net monetary benefit; PRN: Pro re nata – treatment as needed; PRP, pan retinal photocoagulation; PSS: Personal social services; T & E: treat and extend dosage schedule; WSE: Worst seeing eye.

**Costs have been converted from dollars to pounds using EPPI-Centre Cost Converter https://eppi.ioe.ac.uk/costconversion/default.aspx*

1.1.9 Economic model

A de novo Markov economic model was conducted from the perspective of UK NHS and personal social services (PSS) for this review question.

Due to the heterogeneity of the population and associated treatments for diabetic macular oedema (DMO), the model results have been separated by the following populations:

- All centre involving DMO
- Centre involving DMO with a central retinal thickness (CRT) ≥400μm

Due to a lack of data to be able to form an NMA, it was not possible to generate model results for the subpopulations of "centre involving DMO with a CRT<400μm" and "non-centre involving DMO".

The model was a lifetime cost-utility analysis comparing eleven treatments along with no treatment for DMO: standard threshold laser; subthreshold laser; aflibercept; ranibizumab (Lucentis); ranibizumab plus standard threshold laser; bevacizumab; bevacizumab plus standard threshold laser; brolucizumab; faricimab; fluocinolone acetonide; and dexamethasone. In addition, ranibizumab biosimilar (Ongavia) was considered as a scenario assuming the same efficacy, safety and resource use as ranibizumab.

Clinical inputs in the model were based on the literature, while the results of an NMA informed the mean difference in visual acuity. Main outputs were costs, health outcomes (in quality-adjusted life-years; QALYs), incremental cost-effectiveness ratios (ICERs) and net monetary benefits (NMBs).

All centre involving diabetic macular oedema

In the base-case probabilistic analysis using list prices for the anti-VEGF therapies, dexamethasone and fluocinolone acetonide, subthreshold had the lowest ICER of £1,248 compared with no treatment. The probabilistic base-case fully incremental results are presented in Table 71. Macular laser treatments are not suitable for all people with centre involving macular oedema, for example people with thicker retinas, and for this reason the probabilistic base-case results compared with no treatment are also presented in Table 72. Whilst subthreshold laser treatment still had the lowest ICER compared with no treatment (and standard threshold laser had the second lowest ICER), bevacizumab monotherapy also had an ICER below £20,000 which is the opportunity cost used by NICE for decision making.

It should be noted that these results were not used by the committee when drafting recommendations for this review question, as they do not take into account the confidential discounts associated with each of the anti-VEGF treatments, dexamethasone and fluocinolone acetonide.

The committee was also presented with the results of the probabilistic base-case and scenario analyses when the confidential Patient Access Scheme (PAS) discounts were applied in the model and these results were used as the basis for their recommendations. These results cannot be presented here because they are commercially sensitive. When these discounts were applied, subthreshold laser remained the treatment with the lowest ICER, and standard threshold laser had the second lowest ICER. Subthreshold laser was the treatment with the lowest ICER in most scenario analyses, but the difference was very small between the two macular laser types. Both bevacizumab and brolucizumab had ICERs below £20,000 per QALY in people for whom laser treatments are not suitable. In the scenario where the confidential prices and the ranibizumab biosimilar (Ongavia) were considered, ranibizumab biosimilar (Ongavia) as both monotherapy and in combination with standard threshold laser had an ICER below £20,000 per QALY. Dexamethasone, aflibercept, ranibizumab (Lucentis) and faricimab had ICERs between £20,000 and £25,000 per QALY, whilst fluocinolone still had an ICER above £30,000 per QALY. It should be noted that the NICE reference case uses an opportunity cost of £20,000 per QALY gained, but consideration can be given to therapies with an ICER between £20,000 and £30,000, for example when there are few other treatments available for a population or if the strategy is likely to reduce health inequalities.

Table 71: Economic model results (list price) fully incremental analysis

Strategy	Absolute costs	Absolute QALYs	Inc. costs	Inc. QALYs	ICER	NMB at £20K/QALY (95% CI)
No treatment	£3,843	8.485	-	-	-	£165,850 (£152,520 to £179,419)
Subthreshold laser	£4,431	8.956	£588	0.471	£1,248	£174,682 (£160,969 to £188,956)
Standard threshold laser	£4,823	8.976	£392	0.020	£19,272	£174,697 (£161,500 to £188,126)
Bevacizumab	£9,385	9.201	£4,562	0.225	£20,318	£174,625

Strategy	Absolute costs	Absolute QALYs	Inc. costs	Inc. QALYs	ICER	NMB at £20K/QALY (95% CI)
						(£161,698 to £188,032)
Bevacizumab plus standard laser	£11,408	9.216	£2,023	0.015	£133,549	£172,905 (£159,025 to £186,478)
Dexamethasone	£17,780	9.177	£6,372	-0.038	Dominated	£165,767 (£152,852 to £178,340)
Ranibizumab	£23,920	9.220	£12,511	0.004	Extendedly dominated	£160,471 (£147,567 to £173,477)
Brolucizumab	£24,360	9.266	£12,952	0.051	£256,445	£160,963 (£147,392 to £174,636)
Ranibizumab plus standard laser	£24,693	9.199	£333	-0.067	Dominated	£159,295 (£146,028 to £173,040)
Faricimab	£33,947	9.266	£9,587	0.000	Dominated	£151,368 (£137,455 to £166,067)
Aflibercept	£34,388	9.258	£10,028	-0.008	Dominated	£150,771 (£136,228 to £165,577)
Fluocinolone acetonide	£51,400	9.186	£27,040	-0.080	Dominated	£132,319 (£114,734 to £148,611)

1 **Table 72: Economic model results (list price) compared with no treatment**

Strategy	Absolute costs	Absolute QALYs	Inc. costs	Inc. QALYs	ICER
No treatment	£3,843	8.485	-	-	-
Subthreshold laser	£4,431	8.956	£588	0.471	£1,248
Standard threshold laser	£4,823	8.976	£980	0.491	£1,994
Bevacizumab	£9,385	9.201	£5,542	0.716	£7,741
Bevacizumab plus standard laser	£11,408	9.216	£7,565	0.731	£10,349

Strategy	Absolute costs	Absolute QALYs	Inc. costs	Inc. QALYs	ICER
Dexamethasone	£17,780	9.177	£13,937	0.693	£20,121
Ranibizumab	£23,920	9.220	£20,076	0.735	£27,319
Brolucizumab	£24,360	9.266	£20,517	0.781	£26,253
Ranibizumab plus standard laser	£24,693	9.199	£20,849	0.715	£29,172
Faricimab	£33,947	9.266	£30,104	0.781	£38,541
Aflibercept	£34,388	9.258	£30,545	0.773	£39,500
Fluocinolone acetonide	£51,400	9.186	£47,557	0.701	£67,813

Centre involving diabetic macular oedema with a CRT≥400µm

In the base-case probabilistic analysis using list prices for the anti-VEGF therapies, dexamethasone and fluocinolone acetonide, subthreshold laser had the lowest ICER of £1,442 compared with no treatment. The probabilistic base-case fully incremental results are presented in Table 73 and the results compared with no treatment are presented in Table 74. Whilst subthreshold laser treatment still had the lowest ICER compared with no treatment (and standard threshold laser had the second lowest ICER), for people in whom laser therapy is not suitable bevacizumab monotherapy also had an ICER below £20,000 which is the opportunity cost used by NICE for decision making. It should be noted that these results were not used by the committee when drafting recommendations for this review question, as they do not take into account the confidential discounts associated with each of the anti-VEGF treatments, dexamethasone and fluocinolone acetonide.

The committee was also presented with the results of the probabilistic base-case and scenario analyses when the confidential PAS discounts were applied in the model and these results were used as the basis for their recommendations. These results cannot be presented here because they are commercially sensitive. When these discounts were applied, subthreshold laser remained treatment with the lowest ICER, while standard threshold laser remained the treatment with the second lowest ICER. The difference was very small between the two macular laser types and it should be noted that the efficacy for subthreshold laser was assumed equivalent to standard threshold laser due to a lack of data for this population which would explain the very small differences. When the confidential prices were considered both macular lasers, bevacizumab and brolucizumab had ICERs below £20,000 per QALY gained, compared with no treatment. When the confidential price of ranibizumab biosimilar (Ongavia) was also considered it had an ICER below £20,000 per

QALY, as both monotherapy and in combination with standard threshold laser. Dexamethasone, aflibercept, ranibizumab (Lucentis) and faricimab could be had ICERs between £20,000 and £25,000 per QALY, whilst fluocinolone acetonide remained unlikely to be considered cost-effective with an ICER above £30,000 per QALY.

Table 73: Economic model results (list price) fully incremental analysis

Strategy	Absolute costs	Absolute QALYs	Inc. costs	Inc. QALYs	ICER	NMB at £20K/QALY (95% CI)
No treatment	£3,822	8.503	£0	0.000	£0	£166,238 (£152,957 to £180,234)
Subthreshold laser	£4,458	8.944	£635	0.441	£1,442	£174,414 (£160,952 to £187,227)
Standard threshold laser	£4,919	8.928	£462	-0.015	Dominated	£173,646 (£159,605 to £187,244)
Bevacizumab	£9,308	9.211	£4,850	0.268	£18,125	£174,916 (£161,429 to £187,533)
Bevacizumab plus standard laser	£11,325	9.211	£2,017	0.000	Extendedly dominated	£172,899 (£159,168 to £186,269)
Dexamethasone	£17,867	9.180	£8,559	-0.031	Dominated	£165,730 (£152,352 to £178,782)
Ranibizumab	£24,039	9.224	£14,731	0.012	Extendedly dominated	£160,434 (£146,828 to £174,059)
Brolucizumab	£24,348	9.268	£15,040	0.057	£263,607	£161,016 (£147,669 to £173,755)
Ranibizumab plus standard laser	£24,904	9.209	£556	-0.060	Dominated	£159,268 (£145,571 to £172,882)
Faricimab	£33,979	9.271	£9,630	0.003	£3,116,792	£151,448 (£137,073 to £164,968)
Aflibercept	£34,522	9.267	£544	-0.005	Dominated	£150,813 (£136,809 to £164,845)
Fluocinolone acetonide	£51,480	9.193	£17,502	-0.078	Dominated	£132,389 (£115,368 to £148,012)

Table 74: Economic model results (list price) compared with no treatment

Strategy	Absolute costs	Absolute QALYs	Inc. costs	Inc. QALYs	ICER
No treatment	£3,822	8.503	-	-	-
Subthreshold laser	£4,458	8.944	£635	0.441	£1,442
Standard threshold laser	£4,919	8.928	£1,097	0.425	£2,579
Bevacizumab	£9,308	9.211	£5,485	0.708	£7,746
Bevacizumab plus standard laser	£11,325	9.211	£7,502	0.708	£10,593
Dexamethasone	£17,867	9.180	£14,044	0.677	£20,751
Ranibizumab	£24,039	9.224	£20,216	0.721	£28,054
Brolucizumab	£24,348	9.268	£20,526	0.765	£26,824
Ranibizumab plus standard laser	£24,904	9.209	£21,081	0.706	£29,878
Faricimab	£33,979	9.271	£30,156	0.768	£39,250
Aflibercept	£34,522	9.267	£30,700	0.764	£40,196
Fluocinolone acetonide	£51,480	9.193	£47,658	0.690	£69,025

Non-centre involving diabetic macular oedema

As described above there was insufficient evidence to form an NMA. However, a pairwise comparison was available for the treatment of non-centre involving DMO with bevacizumab compared with sham treatment. After exploring the impact this mean difference would have on results, no change in conclusion was found compared to the centre involving population. Bevacizumab could still be considered a cost-effective treatment compared with no treatment in people for whom laser treatment is unsuitable.

1.1.10 Unit costs

The list prices of the drugs for this review question are presented in Table 75. It should be noted that aflibercept, ranibizumab, brolucizumab, faricimab, bevacizumab, fluocinolone acetonide and dexamethasone are recommended by NICE only if the manufacturer provides them with the agreed confidential patient access scheme discount.

Table 75: List prices for treatments included in the recommendations

Resource	Unit costs	Source
Aflibercept 4.0mg/0.1ml	£816.00	BNF (accessed 13/02/2023)
Ranibizumab (Lucentis) 2.3mg/0.23ml	£551.00	BNF (accessed 13/02/2023)
Ranibizumab biosimilar (Ongavia) 2.3mg/0.23ml	£523.45	BNF (accessed 28/04/2023)
Bevacizumab* 1.25mg	£50.00	Poku et al (2012) cited in NICE TA824
Brolucizumab	£816.00	BNF (accessed 13/02/2023)

Resource	Unit costs	Source
19.8mg/0.165ml		
Faricimab 28.8mg/0.24ml	£857.00	BNF (accessed 13/02/2023)
Fluocinolone acetonide 190 microgram	£5,550.00	BNF (accessed 13/02/2023)
Dexamethasone 700 microgram	£870.00	BNF (accessed 13/02/2023)
Standard threshold laser	£41.16	Lois et al (2022)
Subthreshold laser	£47.11	Lois et al (2022)

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

1.1.11 Economic evidence statements

Ten published cost-utility analyses were identified:

- Regnier et al (2015) compared intravitreal ranibizumab treatment (as needed and treat and extend regimens) with intravitreal aflibercept for the treatment of DMO. This study found that over a lifetime horizon both of the intravitreal ranibizumab treatment regimens were more effective and less costly compared with aflibercept. This analysis was from an NHS perspective and was informed by the RESTORE clinical trial.

- Mitchell et al (2012) compared intravitreal ranibizumab monotherapy, intravitreal ranibizumab in combination with laser therapy and laser monotherapy for the treatment of DMO from an NHS perspective. This study found over a 15-year time horizon ranibizumab monotherapy could be considered cost effective assuming a willingness-to-pay threshold of £30,000 per QALY.

- Pochopien et al (2019) compared the cost effectiveness of fluocinolone acetonide (FAc) implant with dexamethasone and usual care (mixture of laser treatment and anti-VEGF treatments ranibizumab, bevacizumab and aflibercept) for the treatment of vision impairment in people with DMO which has not responded to previous treatment and who have Pseudophakic lens. The authors also compared the cost effectiveness of FAc compared with usual care for eyes with phakic lens. This study found that over 15 years FAc could be considered cost effective for the population with Pseudophakic lens based on an ICER of £14,070 for FAc compared with dexamethasone and an ICER of £16,609 for FAc compared with usual care.

- Haig et al (2016) compared the cost effectiveness of intravitreal ranibizumab monotherapy and intravitreal ranibizumab in combination with laser therapy with laser monotherapy for the treatment of DMO from a Canadian healthcare system perspective. The authors considered both ranibizumab monotherapy and ranibizumab in combination with laser to be cost effective over a period of 36 months compared with laser monotherapy for the treatment of visual impairment in people with DMO assuming QALYs are valued at CA$50,000. However, this study was only considered partially applicable due to the Canadian study setting and the different ICER thresholds.

- Holekamp et al (2020) compared the cost effectiveness of intravitreal ranibizumab and intravitreal aflibercept for the treatment of DMO. This study found over 10 years aflibercept could not be considered cost effective compared to ranibizumab for the

treatment of DMO. However, this study was only partially applicable due to the US study setting which is very different to the NHS, and the study had serious limitations with how the analysis was conducted and reported.

- Brown et al (2015) compared the cost effectiveness of intravitreal ranibizumab compared with the sham arm from RIDE and RISE clinical trials for the treatment of DMO. This study found over 14 years that the ICER incorporating all direct costs from a third-party insurer perspective was $4,587 (£3,186) per QALY. However, this study was only partially applicable due to the US study setting, which is very different to the NHS and the study had serious limitations with how the analysis was conducted and reported.

- Stein et al (2013) compared the cost-effectiveness of immediate laser treatment plus ranibizumab, delayed laser treatment plus ranibizumab, immediate laser treatment plus bevacizumab, and delayed laser treatment plus bevacizumab with laser monotherapy for the treatment of DMO. This study found that over 25 years delayed laser treatment was considered cost effective compared to laser treatment with an ICER of $11,138 (£7,774) per QALY and dominated immediate laser plus bevacizumab because deferred laser plus bevacizumab both increased QALYs and had lower costs. Neither immediate laser plus ranibizumab or delayed laser plus ranibizumab would not be considered cost effective with an ICER of $89,903 (£62,752) and $71,271 (£49,747) respectively per QALY. However, this study was only partially applicable due to the US study setting, which is very different to the NHS.

- Sharma et al (2000) compared the cost-effectiveness of laser photocoagulation with no treatment in people with DMO. The study estimated over a 40-year life expectancy laser treatment could be considered cost effective compared to no treatment for improving vision in DMO based on a QALY being valued at $20,000. However, this study was only partially applicable due to the US study setting, which is very different to the NHS and the study had serious limitations with how the analysis was conducted and reported.

- Lois et al (2022) compared the cost-effectiveness of subthreshold micro pulse laser compared with standard threshold laser treatment in adults with centre involving DMO with either a CRT between 300µm and 400µm or CRT<300µm and subretinal fluid was present in the central subfield. Over the two-year DIAMOND clinical trial duration, the study estimated that subthreshold laser could be considered equivalent to standard threshold laser in terms of both costs and clinical benefits and considered both treatments to be cost-effective treatments in people for whom laser treatment is suitable and have a CRT<400µm.

- Hutton et al (2023) compared the cost-effectiveness of aflibercept monotherapy with bevacizumab as first line treatment followed by aflibercept if needed. The study estimated bevacizumab as first line treatment followed by aflibercept if needed to be a cost saving treatment without any changes in visual acuity gains across the two-year clinical trial duration. Aflibercept monotherapy was not considered to be cost effective compared with bevacizumab as first line treatment.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1The outcomes that matter most

The committee agreed that change in visual acuity as well as change in central (subfield) retinal thickness are very important outcomes in decision-making. These are the outcomes that determine how a person's diabetic macular oedema can be treated and managed, and improvements in vision are a crucial outcome for people who have diabetic macular oedema.

The committee were also interested in other outcomes, such as visual acuity gain of three lines or more and the complications associated with treatment (adverse events). While improving or maintaining vision is a crucial aim of treatments for people with diabetic macular oedema, some of the adverse events associated with some treatments can have a considerable impact on a person's quality of life. As such the committee thought it was important to consider these when deciding on recommendations.

1.1.12.2 The quality of the evidence

People with centre-involving diabetic macular oedema

There was sufficient evidence to combine the data into a network meta-analysis (NMA) for the outcomes of change of best corrected visual acuity and central retinal thickness.at 12 months and 24 months for people with centre-involving diabetic macular oedema. NMA outcomes were moderate- to high-quality and directly applicable to the review.

The evidence in the NMAs were considered to be from similar population groups and sufficiently representative of current practice in the NHS. The evidence for various anti-VEGFs, particularly aflibercept, used a range of doses, time between doses and treatment durations. However, the committee stated that these were all within an acceptable range for clinical practice and so the data was grouped for analysis. Studies reported visual acuity using a range of outcomes, as either logMAR, the number of ETDRS letters or using the Snellen ratio. To ensure these could be compared, all visual acuity results were converted into logMAR which the committee agreed was a suitable way to interpret the results.

There was considerably more data for the NMAs at 12 months than at 24 months. Fewer studies for the 24-month analysis, and therefore wider credible intervals, made it difficult to be confident in the longer-term effects of different treatment options on visual acuity. The effects for change in central retinal thickness were more apparent, but there were fewer treatments in the evidence base, making it difficult to determine whether treatments that were most effective at 12 months were also most effective longer-term. However, the committee thought that the results from the 12-month analysis were of high enough quality on which to base decision making, agreeing that at 12 months, any improvements in visual acuity are important to people who have diabetic macular oedema.

Data for outcomes other than visual acuity and central retinal thickness were much less widely reported and ranged from high- to very low-quality. For this reason, most of the decisions on recommendations were based on the visual acuity and central retinal thickness data, with the committee using their clinical knowledge and experience of other outcomes, such as adverse events.

A number of subgroups were listed in the protocol. However, data was only available for one of these subgroups (central retinal thickness of 400 micrometres or more, and central retinal thickness of less than 400 micrometres at baseline). Where studies reported data separated

into these categories, the relevant data was included in each subgroup. However, many of the studies only reported pooled results for all people in the trial and did not separate the results by subgroups based on central retinal thickness. In this instance, studies were assigned to a subgroup based on whether the mean central retinal thickness at baseline was above or below 400 micrometres. A limitation to this subgroup analysis is that some people who had central retinal thickness of below 400 micrometres will have been included in the over 400 micrometres subgroup if the mean central retinal thickness for the whole study was above 400 micrometres (and vice versa). However, limited reporting in the studies meant that it was not possible to differentiate these populations further. Most of the studies had a mean baseline central retinal thickness of 400 micrometres or more and so there was limited information to determine whether the effects of treatment were different for these groups. While there was enough data to compare the effectiveness of different treatments using an NMA for the subgroup of 400 micrometres or more, the limited number of studies in the less than 400 micrometres subgroup meant that pairwise meta-analysis had to be used. As the studies reported on a range of different interventions and comparators, some of the outcomes were based on the result of a single study. Quality of the evidence for the outcomes for people in the less than 400 micrometres subgroup ranged from high- to low-quality, with most being high-quality.

The committee also discussed the use of rescue treatments in the studies. Rescue treatments may make the treatment used in the study arms appear more effective. However, this was not clearly reported in many of the studies, making it difficult to be sure whether the effect was purely a result of the treatment used in the intervention arm, or whether the results also represented the effect of any rescue treatments.

People with non-centre-involving diabetic macular oedema

There were very few studies for people with non-centre-involving diabetic macular oedema, and evidence for each of the outcomes was fully applicable to the review and ranged from low- to high-quality. Most of the studies had small sample sizes, and each reported on different interventions. This meant that the evidence was based on results from single studies, rather than pooled pairwise meta-analysis. Neither of the primary outcomes (change in visual acuity and change in central retinal thickness from baseline) were widely reported in these studies. There was very limited evidence for other outcomes, for example ocular adverse events were rare and poorly reported, which limited the comparisons that the committee could make between different treatments.

1.1.12.3 Imprecision and clinical importance of effects.

People with centre-involving diabetic macular oedema

At 12 months in the overall NMA analysis and in the NMA analysis for the subgroup with central retinal thickness of 400 micrometres or more, most anti-VEGFs (Bevacizumab, Ranibizumab, Aflibercept, Faricimab and Brolucizumab) as well as intravitreal dexamethasone implant were more effective at improving visual acuity than standard threshold laser for people with centre-involving macular oedema. The credible intervals did not cross the line of no effect and the committee were satisfied that this reflected a genuine effect that was large enough to be clinically meaningful. Most anti-VEGFs were also more effective at reducing central retinal thickness at 12 months than standard threshold laser, although results for bevacizumab crossed the line of no effect.

Combination treatments such as Ranibizumab with Dexamethasone, Ranibizumab with standard threshold laser, Triamcinolone with Bevacizumab and Bevacizumab with standard threshold laser were also more effective at improving visual acuity at 12 months than

standard threshold laser alone. Some combination treatments (Ranibizumab with Dexamethasone, Ranibizumab with standard threshold laser) were more effective than standard threshold laser at reducing central retinal thickness at 12 months. This indicates that where anti-VEGF treatment alone is not effective, the addition of macular laser may be beneficial.

Results varied for the subgroup of people with central retinal thickness less than 400 micrometres. Many of the outcomes were based on single study analysis and some had wide confidence intervals, making it more difficult to be certain of the effects of different treatments for those outcomes. The evidence indicated there were some benefits in improving visual acuity and reducing central retinal thickness with anti-VEGFs compared to standard threshold laser. However, the limited number of studies and the range of different comparisons made it more difficult for the committee to be certain of the effectiveness of different treatments than it was for the subgroup with central retinal thickness of 400 micrometres or more.

There was considerably less data available to assess longer-term effectiveness of each treatment for the overall analysis and the subgroups. For change in visual acuity, the NMA effect estimates at 24 months favoured anti-VEGF treatments and anti-VEGF combined with standard threshold laser in comparison to standard threshold laser alone. However, the limited data meant there were wide credible intervals making it difficult to be sure of the longer-term effects of each treatment. Results for change in central retinal thickness at 24 months were more precise, and the committee thought that these indicated a clinically meaningful effect. The committee were confident that, while there was less evidence and fewer treatments for the 24 month analysis, the short-term results were enough to make recommendations on the most effective treatments for people with centre-involving macular oedema.

People with non-central-involving diabetic macular oedema

The limited number of studies, small sample sizes and reliance on outcomes from single studies meant that it was difficult to be certain of the effects of different treatments. These limitations also meant that many of the outcomes had wide confidence intervals, which made decision making about the most effective treatment options for this group more difficult. Therefore, the committee relied on their clinical knowledge and experience as well as information from the treatment thresholds review when discussing recommendations (see evidence review B).

1.1.12.4 Benefits and harms

People with centre-involving and non-centre-involving diabetic macular oedema.

The committee highlighted the importance of all people who have clinically significant diabetic macular oedema being offered treatment, whether this is centre-involving or non-centre-involving oedema. Without treatment all people with clinically significant diabetic macular oedema are at risk of vision loss and of needing further treatments. They also discussed the importance of ensuring that people with diabetic macular oedema are aware of their diagnosis, including whether they have centre-involving or non-centre-involving macular oedema. They should also be made aware of the benefits and side-effects of each treatment option. It was highlighted that many people with macular oedema are offered treatment without being provided with a clear explanation of what the treatment involves and why it is being offered to them. This can be very stressful, particularly at a time when people are already concerned about further loss of vision. People are unlikely to be familiar with macular laser and anti-VEGF treatments and are therefore often concerned about what the

treatments may involve. Shared decision making is therefore an important part of the treatment pathway for macular oedema and will help patients to understand why a particular treatment may be best for them. It will also ensure that treatment fits their personal needs and circumstances.

People with non-centre-involving diabetic macular oedema.

Given the limited evidence for people with non-centre-involving diabetic macular oedema, the committee used their clinical knowledge and experience, as well as evidence from the thresholds for starting treatment review (see evidence review B) to decide on the recommendations for this group.

The committee highlighted the importance of the use of macular laser for people with non-centre-involving macular oedema, as this can delay the need for anti-VEGF treatment that is more commonly needed once a person's macular oedema progresses to the point where it is centre-involving. Although there was limited evidence to compare the effectiveness of macular laser to other treatments for people with non-centre involving macular oedema, the committee were confident that this is an effective treatment for this group, and something that already happens in clinical practice. They thought a recommendation was important for this group because, without treatment, these people will progress to centre-involving macular oedema and be at higher risk of its associated complications, such as vision loss. They also noted that the review on treatment thresholds (see Tables 12 and 13 and section 1.1.11.4 in evidence review B) included high- to moderate-quality evidence from a large study that indicated that when macular laser is provided when someone is at an early stage of diabetic macular oedema, it can slow the worsening of visual acuity compared to when it is provided later. Slowing the worsening of visual acuity is an important outcome for people who have diabetic retinopathy, and so it was recommended that macular laser should be offered to all people who have non-centre-involving diabetic macular oedema as this is an early stage of diabetic macular oedema.

People with centre-involving diabetic macular oedema.

The NMAs showed that compared to standard threshold laser treatment, many of the anti-VEGFs, either alone or combined with standard threshold laser, are more effective at improving visual acuity and reducing central retinal thickness at 12 months than standard threshold laser alone. Pairwise meta-analysis indicated that anti-VEGF treatments resulted in more people achieving a gain in visual acuity of three lines or more than standard threshold laser, although it did have a higher mean number of treatments. The number of adverse events reported for both treatments were very small and could not differentiate between treatments. The committee noted that, in their experience, anti-VEGFs are not commonly associated with a high number of ocular adverse events and are generally well tolerated.

Steroids were also included in the NMAs. In comparison to standard threshold laser, visual acuity was improved with the use of dexamethasone alone or in combination with ranibizumab at 12 months. However, pairwise meta-analysis results showed a higher number of ocular adverse events (development of cataract, increased intraocular pressure and vitreous haemorrhage) associated with intravitreal steroids. The committee also emphasised that there is no way to predict who is more likely develop adverse events which makes decision making difficult, particularly as some of the adverse events could have a big impact on someone's quality of life. The pairwise meta-analysis also showed greater improvements in visual acuity (three or more lines improvement) for anti-VEGFs than steroids at 12 months.

Based on the evidence of effectiveness from the NMA and adverse events from pairwise meta-analysis, the committee decided to recommend that anti-VEGFs should be offered as first line treatment for people with centre-involving diabetic macular oedema and central

retinal thickness of 400 micrometres or more. The benefits of greater improvements in vision compared to other treatment options was considered important, as this will have a considerable impact on the lives of people who have diabetic macular oedema. Macular laser is often less effective for this group of people and therefore the committee thought that, although anti-VEGFs can require a greater number of treatments than macular laser, this is outweighed by the benefits of improvements in vision and the relatively small risks of adverse events. The committee added an extra criteria that these recommendations are for people with visual impairment, as they were aware that the most effective treatment varies between those who have good and poor vision. The criteria to distinguish between people who are considered to have good or poor vision was based on the inclusion criteria that are reported in many of the studies. The recommendations for the use of anti-VEGFs included reference to the NICE technology appraisals for the use of ranibizumab, aflibercept, faricimab and brolucizumab. Each of these anti-VEGFs was shown to be effective in the NMA and so the committee were satisfied that there were no contradictions in the evidence base.

While the overall NMA in this review indicated that anti-VEGFs are both clinically and cost-effective for the full diabetic macular oedema population, they are only considered to be cost-effective for people with central retinal thickness of 400 micrometres or more in the technology appraisals. The committee discussed how some people, such as women and people of South Asian or Afro-Caribbean descent tend to have thinner retinas. This means that even if they have retinal thickening, they may not reach, or will take longer to reach, the 400 micrometre threshold, and may therefore miss out on important treatment, which could lead to greater loss of vision. Given that the NMAs in this review showed anti-VEGFs to be clinically and cost-effective for a wider population, and the meta-analysis indicated that there may be some benefits to the use of anti-VEGFs in this group, the committee decided to recommend that anti-VEGFs are considered for people with central retinal thickness of less than 400 micrometres. With more limited evidence for people with thinner retinas, and an awareness that macular laser can have benefits, they did not think they could make as strong a recommendation in favour of anti-VEGFs as for those in the subgroup with greater central retinal thickness. Macular laser was recommended as the alternative option for this group. Although the analysis suggests that some anti-VEGFs may be most effective, macular laser can also be effective and is current practice for many people in this group because of the 400 micrometre threshold in the NICE technology appraisal guidance. It also has the benefit of delaying the need for anti-VEGF treatment for some people.

The committee were aware that some people who have anti-VEGF treatments will not respond as well as others and may need additional treatment. For this reason, they recommended that clinicians should consider macular laser as rescue treatment, or an alternative anti-VEGF treatment, if a person's vision does not improve or stabilise after the anti-VEGF loading dose. They also thought it was important to highlight that a further review should take place after 12 months, and another class of drug should be considered if someone has a suboptimal response to treatment.

When discussing a change in treatment following a suboptimal response, the committee decided to recommend the use of intravitreal steroids, particularly the intravitreal dexamethasone implant. The NMA showed that an intravitreal dexamethasone implant is an effective treatment option, even if associated with a higher number of adverse events. This was therefore recommended for people where anti-VEGFs have not been effective. The committee noted that there are also some people who may not be able to regularly attend a clinic to have anti-VEGF injections, or who may not want to continue with regular injections. They therefore recommended that intravitreal dexamethasone is also considered for these people to ensure that they don't miss out on the benefits of treatment. Finally, the committee highlighted how some people may not be able to have non-corticosteroid therapy, such as people who are pregnant, and so this was also included in the recommendation. The

recommendation to consider the use of dexamethasone is in line with the NICE technology appraisal guidance on dexamethasone intravitreal implant for treating diabetic macular oedema. Reference was also included to the NICE technology appraisal guidance on fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy, for people who may need steroid therapy but who have an intraocular (pseudophakic) lens. The fluocinolone implant was less effective in the NMAs and less cost-effective and so the recommendations for steroids primarily focused on the use of dexamethasone. However, the technology appraisal identified that people who have an intraocular lens may benefit from this treatment and so it was included in the recommendations for this group.

Most of the recommendations are based on people who have central-involving diabetic macular oedema and poor vision, as this is the group who will benefit most from treatment and reflects most of the evidence base. However, some people with diabetic macular oedema will have good vision. These people may gain fewer benefits from the use of anti-VEGFs, steroids or macular laser, but could still be considered for treatment. In the review on thresholds for starting treatment (see evidence review B), one study with high quality outcomes (ETDRS 1985) reported that early laser can reduce the worsening of visual acuity and the incidence of clinically significant macular oedema compared to delayed macular laser treatment. The committee thought this was important to consider because, in their clinical experience, macular laser can be useful for people with diabetic macular oedema and good vision as a way to delay the need for anti-VEGF treatment, which will be needed once their vision becomes worse. However, given that this evidence was based on a single study, the committee decided to recommend that either observation or macular laser should be considered for this group of people. The decision over which to use should be based on a discussion with the patient about the benefits and risks of each option. The committee were aware that while the two types of macular laser (standard threshold and subthreshold) show similar levels of effectiveness, subthreshold laser is associated with fewer adverse events, and so may be a more beneficial option for this group of people. However, there are currently no studies that compare the effectiveness of subthreshold laser to observation, and so the committee thought that the decision over macular laser or observation should be a choice between a patient and their clinician and should involve careful consideration of the best option to reduce the patients' chance of progression.

1.1.12.5 Cost-effectiveness and resource use

The committee considered the ten cost-effectiveness studies identified in the literature for the treatment of diabetic macular oedema (DMO). Although some studies were directly applicable the committee felt that not all relevant comparators were included in the studies to suitably aid the decision making. The de novo economic model allowed all treatment options to be considered together using inputs and assumptions relevant to NHS clinical practice based on both the literature and committee expertise.

The committee considered the de novo economic model results alongside the clinical evidence for centre involving DMO. The economic model results for all people with centre involving DMO found subthreshold laser treatment had the lowest ICER and was considered to be the most cost-effective therapy compared with no treatment. At list price bevacizumab was the only anti-VEGF to have an ICER below £20,000 per QALY. When PAS prices were considered, brolucizumab and ranibizumab biosimilar (Ongavia) also had ICERs below £20,000 per QALY compared with no treatment. However, brolucizumab would not be considered cost-effective compared with bevacizumab. The committee considered these results to be reasonable given anti-VEGFs are only reimbursed by NICE for the population of people with centre-involving DMO with a CRT≥400µm. The committee did discuss that in

general subthreshold laser would be expected to be used predominantly in those with a CRT<400µm and laser-based therapies may not be suitable for those with a CRT≥400µm. The results were found to be sensitive to changes in assumptions around the source of utility mapping from visual acuity to evaluate quality of life and the number of treatment and monitoring visits anticipated over time. In the base-case analysis, the committee felt the utility values from Czoski-Murray et al (2009) were most appropriate as it has been widely accepted within the technology appraisals in DMO despite the limitation of this being a simulated study. The use of other utility sources were explored in scenario analyses. The economic model results for people with centre involving DMO and a CRT≥400µm found subthreshold laser treatment to be the most cost-effective therapy compared to no treatment. At list price bevacizumab was the only anti-VEGF to be considered cost effective below an ICER threshold of £20,000 per QALY. When PAS prices were considered, brolucizumab and ranibizumab biosimilar (Ongavia) could also be considered cost effective compared with no treatment. However, brolucizumab would not be considered cost effective compared with bevacizumab. The committee highlighted that the restriction to treatment using anti-VEGFs for those with a CRT≥400µm could increase health inequalities. The committee explained that some populations such as some ethnic minority populations and females commonly have thinner retinas, meaning they may miss out on treatment options for the anti-VEGFs restricted to the treatment of people with a CRT≥400µm.

The committee discussed that given the potential health inequalities associated with limiting recommending anti-VEGFs based on central retinal thickness threshold they should be at least considered as treatment for everyone with centre involving DMO with reduced visual acuity. This recommendation is supported by the economic evidence given the similarity in the results across both the all centre involving DMO population and the subgroup of those with a CRT≥400µm.

The committee discussed the key differences in the assumptions and data used within the technology appraisal guidance and of the de novo cost-effectiveness analysis presented to the committee. The clinical data used to inform the economic model was different to that used in the technology appraisals, in that this model utilised outcomes of NMAs on mean difference in BCVA with aggregate data from many RCTs, whereas technology appraisals generally use patient level data from RCTs that include the technology being appraised. The NMA results found anti-VEGFs to be clinically effective compared with macular laser therapy or no treatment; however, it is possible this effect may be different than in the individual technology appraisals because of the wider population and evidence base considered. Although anti-VEGFs were more clinically effective than either type of laser, both lasers came out as most cost-effective options since they were very cheap even when the confidential prices for anti-VEGFs were used. This may explain any differences in conclusions of cost-effectiveness of treatments, where the anti-VEGFs are recommended currently by NICE for those with a CRT≥400µm.

The results were sensitive to changes in the utility source, the proportion of patients remaining on treatment after five years and the number of monitoring and treatment visits. Many of the previous technology appraisals restricted treatment duration to five years, which the committee discussed is not realistic in current clinical practice. When this scenario was explored most anti-VEGFs became cost effective below an ICER threshold of £20,000 per QALY. However, people can remain on anti-VEGFs for much longer than this which is why this assumption was not used within the base-case analysis.

After accounting for patient costs, other anti-VEGFs could also be considered cost effective; however, it should be noted that these are only community related costs outside of the NHS and PSS perspective for people with low vision, which refers to BCVA of less than 35 letters. The committee discussed the substantial burden of transport related costs for attending the

frequent appointments associated with anti-VEGFs. It is possible the results of this scenario could be different should data on transport costs for patients become available.

The committee recommended the use of anti-VEGFs as a first line treatment for those with centre-involving DMO. However, the committee discussed the difficulties around recommending bevacizumab as an off-label treatment. The committee discussed biosimilars available for anti-VEGFs offer a cost-effective alternative to bevacizumab where they are available. The committee discussed anti-VEGFs can be resource intensive in terms of clinical time as patients may be required to attend appointments as regularly as every four weeks, which can have pressure on demand for services. Likewise, attending clinics can be burdensome for the patient particularly for those of working age. The committee discussed that the benefits of treatment with anti-VEGF outweighs the costs in terms of preventing sight loss which can reduce the high long-term costs associated with support for people with low vision and has a greater impact on quality of life. Overall, the committee did not anticipate this would have a resource impact as this is currently in line with current clinical practice. However, it should be noted that the long-term usage of an anti-VEGF can represent a large cost burden to both the NHS and the patient in terms of transport costs for frequent clinic visits. The expected introduction of biosimilars is anticipated to reduce some of this financial burden to the NHS.

The committee thought fluocinolone acetonide was very unlikely to be a cost-effective use of resources in any of the DMO subgroups given the economic analysis found that the ICER associated with fluocinolone acetonide was well above the £20,000 per QALY gained threshold used for decision making at NICE. The recommendations on steroids were therefore focused on the use of dexamethasone, with a recommendation included for fluocinolone acetonide only in people with an intraocular lens, aligning with the technology appraisal on this therapy (TA301).

No economic analyses were presented alongside the clinical evidence for non-centre involving DMO. The committee discussed that by offering a macular laser this can delay regression of disease and reduce the need and quantity of costly anti-VEGF treatments. Overall, the committee anticipated that by treating people with non-centre involving DMO with a macular laser treatment, this would have a positive resource impact by delaying the need for more resource intensive treatment.

1.1.13 Recommendations supported by this evidence review.

This evidence review supports recommendations 1.5.1 to 1.5.14.

1.1.14 References – included studies

1.1.14.1 Effectiveness

Included studies from NICE search

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Appendices

Appendix A – Review protocols

Review protocol for the effectiveness of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema.

ID	Field	Content
0.	PROSPERO registration number	CRD42022361588
1.	Review title	The effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema
2.	Review question	Q7: What is the effectiveness and acceptability of intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema
3.	Objective	To determine the clinical, cost effectiveness and acceptability of different therapies intravitreal steroids, macular laser and anti-vascular endothelial growth factor agents for treating diabetic macular oedema
4.	Searches	Studies included in the following Cochrane review will be considered for inclusion in this review: Intravitreal steroids for macular edema in diabetes Anti-vascular endothelial growth factor (anti-VEGF) drugs for diabetic macular oedema Single therapy laser photocoagulation for diabetic macular oedema Anti-vascular endothelial growth factor (anti-VEGF) plus intravitreal steroids for diabetic macular oedema The following databases will be searched for the clinical

		review: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • HTA (legacy records) • INAHTA • MEDLINE • Medline in Process • Medline EPub Ahead of Print For the economics review the following databases will be searched on population only: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA Searches will be restricted by: • Studies reported in English • Study design RCT filters will be applied and the Cochrane RCT classifier will be used. • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • No date limit: combination treatments are not included in the Cochrane reviews, therefore no date limit can be applied. • 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
6.	Population	Inclusion: People diagnosed with diabetic macular oedema Exclusion: People who are about to undergo or have undergone cataract surgery. Interventions for people who are about to undergo or have undergone cataract surgery are considered separately as part of another evidence review.

7.	Intervention	• Intravitreal steroid therapy (intravitreal injection or surgical implantation).
		• Macular laser, subclassified as:
		  o Standard threshold threshold laser
		  o Subthreshold laser
		• Anti-vascular endothelial growth factor agents
		• Anti-vascular endothelial growth factor agents plus intravitreal steroid therapy
		• Anti-vascular endothelial growth factor agents plus macular laser
		• Intravitreal steroid therapy plus macular laser

8.	Comparator	• Another intervention listed in section 7 • Placebo, sham treatment or no treatment - Trials comparing standard threshold and subthreshold laser will be included. Trials comparing types of standard threshold laser or types of subthreshold laser will not be included. - Trials comparing different Anti-VEGF agents or different intravitreal steroids will be included.
9.	Types of study to be included	• Randomised controlled trials • Qualitative studies running alongside included randomised trials (sibling studies) reporting qualitative data on acceptability will also be

		included.
10.	Other exclusion criteria	Studies evaluating 'retisert' (a fluocinolone acetonide intravitreal implant developed for use in non-infectious uveitis, that is not approved for use to treat diabetic macular oedema in the UK) Trials that were not reported in English, unless the study was already included as part of one of the Cochrane reviews Studies solely comparing doses of treatments Studies with less than 6 months follow up
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
		  ○ (1) the change from baseline of best-corrected visual acuity (BCVA) as continuous data (converted into logMAR); and
		  ○ (2) three or more lines improvement from baseline (ETDRS, Snellen, or logMAR equivalent; one line improvement analysed if three lines not available).
		
		Outcomes will be assessed at 12 months (plus or minus 6 months) and at the longest timepoint available in the study if 24 months or greater

13.	Secondary outcomes (important outcomes)	• Mean change in retinal thickness from baseline • Quality of life (assessed using a validated tool) • Adverse events (development of cataract, Intraocular inflammation, raised intraocular pressure, need for glaucoma drainage surgery) • Acceptability (additional outcome not assessed in Cochrane reviews). Qualitative or quantitative data on acceptability collected alongside included randomised controlled trials will be included • Driving vision (dichotomous outcome, number of

		participants with vision sufficient to allow driving). • Number of treatments Outcomes will be assessed at 12 months (plus or minus 3 months) and at the longest timepoint available in the study if 24 months.or greater .
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. Where evidence tables are available from the Cochrane reviews described in section 4, these will be used without modification.

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. Where risk of bias judgements have been made by Cochrane reviews, these judgments will be used without modification.
16.	Strategy for data synthesis	A network meta-analysis will be carried out for all outcomes where the network is connected, assumptions for network meta-analysis are met and the results of the network meta-analysis are considered useful for decision making. Network meta-analysis will be carried out using winbugs. In cases where the assumptions for network meta-analysis are not met, pairwise meta-analysis will be conducted. Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as I2≥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 will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered. If multiple qualitative studies are identified, information from

		the studies will be combined using a thematic synthesis. The thematic synthesis will based partly on a priori categories describing phenomena the committee was interested in (for this review: • Factors that increase acceptability of interventions • Factors that reduce acceptability of interventions) and partly on themes that emerge from the coding of the included studies. Papers will be uploaded to NVivo 11 software where the relevant data from the papers will be coded. The resulting sets of codes will be aggregated into themes and sub-themes. The aggregated themes will be used to develop interpretive 'review findings'. CERQual will be used to assess the confidence we have in the summary findings of each of the identified themes.
17.	Analysis of sub-groups	Data will be presented separately for the following groups: • Pregnant women • Centre involving vs non centre involving diabetic macular oedema If data is available a subgroup analysis will be conducted by: • Ethnicity • People with a learning disability • Age: (People under the age of 18, people aged 18 to 80, people aged greater than 80) • Socioeconomic status • First line treatment vs treatment when previous treatment has been unsuccessful. • Central retinal thickness (under 400 microns, above 400 microns) For acceptability aspect only: • Gender
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 macular oedema, anti-VEGF, laser, intravitreal steriods
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published

		☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Search design and peer review

NICE information specialists conducted the literature searches for the evidence review. The searches were run in October 2022. Update searches were run in Feb 2023. This search report is compliant with the requirements of PRISMA-S.

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

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

Review Management

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

Limits and restrictions

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

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

Search filters

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

RCTs

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

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

Qualitative studies

The terms used for qualitative 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)	19/10/2022	Wiley	19/10/2022 10:20:55
Cochrane Database of Systematic Reviews (CDSR)	19/10/2022	Wiley	19/10/2022 10:20:55
Embase	19/10/2022	Ovid	1974 to 2022 October 17
Epistemonikos	Not searched	n/a	n/a
HTA	19/10/2022	CRD	19/10/2022
INAHTA	19/10/2022	Ovid	19/10/2022
MEDLINE	19/10/2022	Ovid	1946 to October 18, 2022
MEDLINE-in-Process	19/10/2022	Ovid	<1946 to October 18, 2022>
MEDLINE ePub Ahead-of-Print	19/10/2022	Ovid	October 18, 2022

Database: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Diabetic Retinopathy] this term only 1580
#2 MeSH descriptor: [Macular Edema] this term only 1281
#3 (diabet* near/6 (retin* or eye* or macular* or maculopath*)):ti,ab,kw 5642
#4 {or #1-#3} 6086
#5 MeSH descriptor: [Light Coagulation] explode all trees 767
#6 (photocoagulat* or thermocoagulat* or argon or diode or micropulse):ti,ab,kw 5012
#7 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) near/4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)):ti,ab,kw 20960
#8 ((focal or grid) near/3 laser*):ti,ab,kw 344
#9 PRP:ti,ab,kw 2909
#10 {or #5-#9} 25248
#11 MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees 1490
#12 MeSH descriptor: [Receptors, Vascular Endothelial Growth Factor] explode all trees 451
#13 (anti near/2 VEGF*):ti,ab,kw 1519
#14 (anti-VEGF* or antiVEGF*):ti,ab,kw 1496

#15 ((anti-vascular or antivascular) near/2 endothelial growth factor*):ti,ab,kw 653
#16 (((vascular endothelial near/2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) near/2 (trap* or inhibit* or antagonist*)):ti,ab,kw 6631
#17 (vascular proliferation near/4 inhibit*):ti,ab,kw 94
#18 (endothelial near/2 growth near/2 factor*):ti,ab,kw 4608
#19 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees 1381
#20 MeSH descriptor: [Angiogenesis Inducing Agents] this term only 51
#21 Aflibercept*:ti,ab,kw 1017
#22 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005):ti,ab,kw 246
#23 MeSH descriptor: [Bevacizumab] this term only 2254
#24 Bevacizumab*:ti,ab,kw 7038
#25 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865):ti,ab,kw 928
#26 (IVB near/2 inject*):ti,ab,kw 84
#27 MeSH descriptor: [Ranibizumab] this term only 967
#28 Ranibizumab*:ti,ab,kw 2184
#29 (Lucentis or rhuFab):ti,ab,kw 446
#30 (IVR near/2 inject*):ti,ab,kw 30
#31 (Faricimab or Vabysmo):ti,ab,kw 36
#32 (Pegaptanib* or macugen*):ti,ab,kw 181
#33 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838):ti,ab,kw 82
#34 MeSH descriptor: [Sunitinib] this term only 353
#35 (Sunitinib or Sutent):ti,ab,kw 1338
#36 MeSH descriptor: [Sorafenib] this term only 540
#37 (Sorafenib or Nexavar):ti,ab,kw 2023
#38 MeSH descriptor: [Axitinib] this term only 111
#39 (Axitinib or Inlyta):ti,ab,kw 371
#40 (Pazopanib or Votrient):ti,ab,kw 610
#41 {or #11-#40} 21081
#42 MeSH descriptor: [Intravitreal Injections] this term only 982
#43 (Intravitreal* near/2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)):ti,ab,kw 3166
#44 MeSH descriptor: [Dexamethasone] this term only 5090
#45 MeSH descriptor: [Fluocinolone Acetonide] this term only 351
#46 MeSH descriptor: [Triamcinolone Acetonide] this term only 1200
#47 (Dexamethasone* or kenalog or kenacort or retisert*):ti,ab,kw 14132
#48 ((fluocinolone* or triamcinolone*) near/2 acetonide*):ti,ab,kw 2897
#49 Iluvien*:ti,ab,kw 15
#50 (Adcortyl* or Kenalog*):ti,ab,kw 112
#51 {or #42-#50} 19426
#52 #10 or #41 or #51 61265
#53 #4 and #52 3264
#54 "conference":pt or (clinicaltrials or trialsearch):so 642991
#55 #53 not #54 1900

Database: Embase

1 diabetic retinopathy/ 47724
2 macular edema/ 6415
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 52880
4 or/1-3 71779
5 exp laser coagulation/ 23420
6 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 60175
7 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 141216
8 ((focal or grid) adj3 laser*).tw. 1456
9 PRP.tw. 24648
10 or/5-9 219315
11 exp vasculotropin/ 153716
12 exp vasculotropin receptor/ 12728
13 (anti adj2 VEGF*).tw. 14667
14 (anti-VEGF* or antiVEGF*).tw. 14299
15 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 6700
16 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 16550
17 (vascular proliferation adj4 inhibit*).tw. 45
18 (endothelial adj2 growth adj2 factor*).tw. 88154
19 angiogenesis/ or angiogenesis inhibitor/ or angiogenic factor/ or endothelial cell growth factor/ 163911
20 aflibercept/ 8147
21 Aflibercept*.tw. 4499
22 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 1628
23 bevacizumab/ 69007
24 Bevacizumab*.tw. 34254
25 (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. 10683
26 (IVB adj2 inject*).tw. 385
27 ranibizumab/ 11754
28 Ranibizumab*.tw. 6983
29 (Lucentis or rhuFab).tw. 3068
30 (IVR adj2 inject*).tw. 190
31 faricimab/ 161
32 (Faricimab or Vabysmo).tw. 84
33 pegaptanib/ 2412
34 (Pegaptanib* or macugen*).tw. 1573
35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 1245
36 sunitinib/ 26084
37 (Sunitinib or Sutent).tw. 13964
38 sorafenib/ 35065
39 (Sorafenib or Nexavar).tw. 20490
40 axitinib/ 6463
41 (Axitinib or Inlyta).tw. 2653
42 pazopanib/ 9865
43 (Pazopanib or Votrient).tw. 4456

44 or/11-43 381761
45 intravitreal drug administration/ 6354
46 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 18844
47 dexamethasone/ or fluocinolone acetonide/ or triamcinolone acetonide/ 191574
48 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 91477
49 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 6999
50 Iluvien*.tw. 384
51 (Adcortyl* or Kenalog*).tw. 1803
52 or/45-51 222259
53 10 or 44 or 52 793360
54 4 and 53 20999
55 random:.tw. 1846273
56 placebo:.mp. 503155
57 double-blind:.tw. 234639
58 or/55-57 2116884
59 Qualitative Research/ 105658
60 exp Interview/ 342641
61 exp Questionnaire/ 860262
62 exp Observational Method/ 7250
63 Narrative/ 19282
64 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw. 2397893
65 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj4 analys$) or theoretical sampl$ or purposive sampl$).tw. 157891
66 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw. 15458
67 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or metathem$ or meta-them$).tw. 2467
68 "critical interpretive synthes*".tw. 173
69 (realist adj (review* or synthes*)).tw. 836
70 (noblit and hare).tw. 103
71 (meta adj (method or triangulation)).tw. 47
72 (CERQUAL or CONQUAL).tw. 366
73 ((thematic or framework) adj synthes*).tw. 1773
74 (trial adj3 sibling*).tw. 61
75 (sibling adj2 (qualitative* or stud*)).tw. 1020
76 or/59-75 2666341
77 58 or 76 4511324
78 54 and 77 3290
79 limit 78 to english language 2988
80 Nonhuman/ not Human/ 5072852
81 79 not 80 2870
82 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5346653
83 81 not 82 2051
84 83 and 58 1704
85 83 and 76 428

Database: Health Technology Assessment (HTA)

Line	Search	Hits
1	MeSH DESCRIPTOR Diabetic Retinopathy IN HTA	29
2	MeSH DESCRIPTOR Macular Edema IN HTA	25
3	(((diabet* adj6 (retin* or eye* or macular* or maculopath*))))) IN HTA	60
4	#1 OR #2 OR #3	67
5	MeSH DESCRIPTOR Light Coagulation EXPLODE ALL TREES IN HTA	18
6	((photocoagulat* or thermocoagulat* or argon or diode or micropulse)) IN HTA	40
7	(((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*))) IN HTA	360
8	(((focal or grid) adj3 laser*)) IN HTA	1
9	(PRP) IN HTA	9
10	#5 OR #6 OR #7 OR #8 OR #9	383
11	MeSH DESCRIPTOR Vascular Endothelial Growth Factors EXPLODE ALL TREES IN HTA	26
12	MeSH DESCRIPTOR Receptors, Vascular Endothelial Growth Factor EXPLODE ALL TREES IN HTA	20
13	((anti adj2 VEGF*)) IN HTA	9
14	((anti-VEGF* or antiVEGF*)) IN HTA	9
15	(((anti-vascular or antivascular) adj2 endothelial growth factor*)) IN HTA	6
16	((((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*))) IN HTA	16
17	((vascular proliferation adj4 inhibit*)) IN HTA	0
18		61

	(endothelial adj2 growth adj2 factor*) IN HTA	
19	MeSH DESCRIPTOR Angiogenesis Inducing Agents EXPLODE ALL TREES	2
20	(Aflibercept*) IN HTA	22
21	(Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005) IN HTA	10
22	MeSH DESCRIPTOR Bevacizumab IN HTA	11
23	(Bevacizumab*) IN HTA	79
24	(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) IN HTA	41
25	(IVB adj2 inject*) IN HTA	0
26	MeSH DESCRIPTOR Ranibizumab IN HTA	1
27	(Ranibizumab*) IN HTA	29
28	(Lucentis or rhuFab) IN HTA	7
29	(IVR adj2 inject*) IN HTA	0
30	(Faricimab or Vabysmo) IN HTA	0
31	(Pegaptanib* or macugen*) IN HTA	12
32	("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838) IN HTA	4
33	MeSH DESCRIPTOR Sunitinib IN HTA	1
34	(Sunitinib or Sutent) IN HTA	29
35	MeSH DESCRIPTOR Sorafenib IN HTA	0
36	(Sorafenib or Nexavar) IN HTA	18
37	MeSH DESCRIPTOR Axitinib IN HTA	2

38	MeSH DESCRIPTOR Axitinib IN HTA	2
39	(Axitinib or Inlyta) IN HTA	8
40	(Pazopanib or Votrient) IN HTA	9
41	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	186
42	MeSH DESCRIPTOR Intravitreal Injections IN HTA	9
43	((Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*))) IN HTA	18
44	MeSH DESCRIPTOR Dexamethasone IN HTA	20
45	MeSH DESCRIPTOR Fluocinolone Acetonide IN HTA	2
46	MeSH DESCRIPTOR Triamcinolone Acetonide IN HTA	0
47	(Dexamethasone* or kenalog or kenacort or retisert*) IN HTA	40
48	(((fluocinolone* or triamcinolone*) adj2 acetonide*)) IN HTA	8
49	(Iluvien*) IN HTA	4
50	(Adcortyl* or Kenalog*) IN HTA	0
51	#42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50	60
52	#10 OR #41 OR #51	604
53	#4 AND #52	39

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

(((Iluvien* or Adcortyl* or Kenalog*) OR (((fluocinolone* or triamcinolone*) AND acetonide*)) OR (Dexamethasone* or kenalog or kenacort or retisert*) OR ("Fluocinolone Acetonide"[mh]) OR ("Triamcinolone Acetonide"[mh]) OR ("Dexamethasone"[mh]) OR ((Intravitreal* AND (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*))) OR

("Intravitreal Injections"[mh])) OR ((Axitinib or Inlyta or Pazopanib or Votrient) OR ("Axitinib"[mh]) OR (Sorafenib or Nexavar) OR (Sunitinib or Sutent) OR ("Sunitinib"[mh]) OR (Faricimab or Vabysmo or Pegaptanib* or macugen* or "EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838) OR (IVR AND inject*) OR (Ranibizumab* or Lucentis or rhuFab) OR ("Ranibizumab"[mh]) OR (IVB AND inject*) OR (Bevacizumab* or Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865) OR ("Bevacizumab"[mh]) OR (Aflibercept or Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005) OR ("Endothelial Cells"[mh]) OR ("Angiogenesis Inhibitors"[mhe]) OR (endothelial AND growth AND factor*) OR ((vascular proliferation AND inhibit*)) OR ((((vascular endothelial AND growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) AND (trap* or inhibit* or antagonist*))) OR (((anti-vascular or antivascular) AND endothelial growth factor*)) OR (anti-VEGF* or antiVEGF*) OR (anti AND VEGF*) OR ("Vascular Endothelial Growth Factors"[mhe]) OR ("Receptors, Vasoactive Intestinal Peptide"[mhe])) OR (((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) AND (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cautery*)) OR (PRP) OR ((focal or grid) AND laser*) OR (photocoagulat* or thermocoagulat* or argon or diode or micropulse) OR ("Light Coagulation"[mhe]))) AND ((Diabetic Retinopathy)[mh] OR (Macular Edema)[mh] OR ((diabet* AND (retin* or eye* or macular* or maculopath*))))

Database: Ovid MEDLINE(R)

1 Diabetic Retinopathy/ 28933
2 Macular Edema/ 8758
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 33564
4 or/1-3 43919
5 exp Light Coagulation/ 13179
6 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 36873
7 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 98558
8 ((focal or grid) adj3 laser*).tw. 870
9 PRP.tw. 15772
10 or/5-9 145238
11 exp Vascular Endothelial Growth Factors/ 63299
12 exp Receptors, Vascular Endothelial Growth Factor/ 18011
13 (anti adj2 VEGF*).tw. 7299
14 (anti-VEGF* or antiVEGF*).tw. 7055
15 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 4407
16 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 9550
17 (vascular proliferation adj4 inhibit*).tw. 30
18 (endothelial adj2 growth adj2 factor*).tw. 62370
19 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 115202
20 Aflibercept*.tw. 2145
21 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 233

22 Bevacizumab/ 13906
23 Bevacizumab*.tw. 15685
24 (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. 1383
25 (IVB adj2 inject*).tw. 236
26 Ranibizumab/ 4612
27 Ranibizumab*.tw. 3834
28 (Lucentis or rhuFab).tw. 361
29 (IVR adj2 inject*).tw. 108
30 (Faricimab or Vabysmo).tw. 39
31 (Pegaptanib* or macugen*).tw. 458
32 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 118
33 Sunitinib/ 4093
34 (Sunitinib or Sutent).tw. 5462
35 Sorafenib/ 6136
36 (Sorafenib or Nexavar).tw. 8202
37 Axitinib/ 703
38 (Axitinib or Inlyta).tw. 1005
39 (Pazopanib or Votrient).tw. 1625
40 or/11-39 152868
41 Intravitreal Injections/ 9580
42 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 11666
43 Dexamethasone/ or Fluocinolone Acetonide/ or Triamcinolone Acetonide/ 62162
44 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 57991
45 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 5005
46 Iluvien*.tw. 56
47 (Adcortyl* or Kenalog*).tw. 217
48 or/41-47 95264
49 randomized controlled trial.pt. 586759
50 randomi?ed.mp. 950876
51 placebo.mp. 222603
52 or/49-51 1007776
53 Qualitative Research/ 79475
54 Nursing Methodology Research/ 16407
55 Interview.pt. 29706
56 exp Interviews as Topic/ 66807
57 "Questionnaires"/ 554280
58 Narration/ 9975
59 Health Care Surveys/ 33992
60 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw. 1613438
61 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj4 analys$) or theoretical sampl$ or purposive sampl$).tw. 111488
62 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw. 11300
63 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or metathem$ or meta-them$).tw. 1952
64 "critical interpretive synthes*".tw. 147

65 (realist adj (review* or synthes*)).tw. 690
66 (noblit and hare).tw. 85
67 (meta adj (method or triangulation)).tw. 35
68 (CERQUAL or CONQUAL).tw. 319
69 ((thematic or framework) adj synthes*).tw. 1356
70 (trial adj3 sibling*).tw. 28
71 (sibling adj2 (qualitative* or stud*)).tw. 636
72 or/53-71 1835429
73 52 or 72 2735226
74 10 or 40 or 48 376278
75 4 and 74 11843
76 73 and 75 1865
77 animals/ not humans/ 5060889
78 76 not 77 1842
79 limit 78 to english language 1732
80 52 and 79 1514
81 72 and 79 313

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. 11
4 or/1-3 11
5 exp Light Coagulation/ 0
6 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 1
7 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 27
8 ((focal or grid) adj3 laser*).tw. 0
9 PRP.tw. 2
10 or/5-9 29
11 exp Vascular Endothelial Growth Factors/ 0
12 exp Receptors, Vascular Endothelial Growth Factor/ 0
13 (anti adj2 VEGF*).tw. 2
14 (anti-VEGF* or antiVEGF*).tw. 2
15 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 3
16 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 2
17 (vascular proliferation adj4 inhibit*).tw. 0
18 (endothelial adj2 growth adj2 factor*).tw. 10
19 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 0
20 Aflibercept*.tw. 0
21 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 0
22 Bevacizumab/ 0

23 Bevacizumab*.tw. 4
24 (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
25 (IVB adj2 inject*).tw. 0
26 Ranibizumab/ 0
27 Ranibizumab*.tw. 2
28 (Lucentis or rhuFab).tw. 1
29 (IVR adj2 inject*).tw. 0
30 (Faricimab or Vabysmo).tw. 0
31 (Pegaptanib* or macugen*).tw. 0
32 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 0
33 Sunitinib/ 0
34 (Sunitinib or Sutent).tw. 3
35 Sorafenib/ 0
36 (Sorafenib or Nexavar).tw. 6
37 Axitinib/ 0
38 (Axitinib or Inlyta).tw. 1
39 (Pazopanib or Votrient).tw. 2
40 or/11-39 22
41 Intravitreal Injections/ 0
42 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 7
43 Dexamethasone/ or Fluocinolone Acetonide/ or Triamcinolone Acetonide/ 0
44 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 8
45 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 2
46 Iluvien*.tw. 0
47 (Adcortyl* or Kenalog*).tw. 0
48 or/41-47 16
49 randomized controlled trial.pt. 0
50 randomi?ed.mp. 203
51 placebo.mp. 46
52 or/49-51 216
53 Qualitative Research/ 0
54 Nursing Methodology Research/ 0
55 Interview.pt. 0
56 exp Interviews as Topic/ 0
57 "Questionnaires"/ 0
58 Narration/ 0
59 Health Care Surveys/ 0
60 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw. 528
61 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj4 analys$) or theoretical sampl$ or purposive sampl$).tw. 52
62 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw. 3
63 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or metathem$ or meta-them$).tw. 1
64 "critical interpretive synthes*".tw. 0
65 (realist adj (review* or synthes*)).tw. 0

66 (noblit and hare).tw. 0
67 (meta adj (method or triangulation)).tw. 0
68 (CERQUAL or CONQUAL).tw. 0
69 ((thematic or framework) adj synthes*).tw. 1
70 (trial adj3 sibling*).tw. 0
71 (sibling adj2 (qualitative* or stud*)).tw. 0
72 or/53-71 536
73 52 or 72 717
74 10 or 40 or 48 64
75 4 and 74 0
76 73 and 75 0
77 animals/ not humans/ 0
78 76 not 77 0
79 limit 78 to english language 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. 519
4 or/1-3 519
5 exp Light Coagulation/ 0
6 (photocoagulat* or thermocoagulat* or argon or diode or micropulse).tw. 669
7 ((Laser* or light* or panretinal* or pan-retinal* or photo* or light*) adj4 (coagulat* or co-agulat* or surg* or treat* or procedure* or therap* or cauteri*)).tw. 1464
8 ((focal or grid) adj3 laser*).tw. 12
9 PRP.tw. 180
10 or/5-9 2181
11 exp Vascular Endothelial Growth Factors/ 0
12 exp Receptors, Vascular Endothelial Growth Factor/ 0
13 (anti adj2 VEGF*).tw. 177
14 (anti-VEGF* or antiVEGF*).tw. 174
15 ((anti-vascular or antivascular) adj2 endothelial growth factor*).tw. 127
16 (((vascular endothelial adj2 growth factor*) or vasculotropin or VEGF* or vascular permeability factor* or VPF) adj2 (trap* or inhibit* or antagonist*)).tw. 123
17 (vascular proliferation adj4 inhibit*).tw. 0
18 (endothelial adj2 growth adj2 factor*).tw. 634
19 angiogenesis/ or exp angiogenesis inhibitors/ or angiogenic factor/ or endothelial cell growth factor/ or exp vasculotropin/ 0
20 Aflibercept*.tw. 82
21 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).tw. 6
22 Bevacizumab/ 0
23 Bevacizumab*.tw. 289

24 (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. 11
25 (IVB adj2 inject*).tw. 3
26 Ranibizumab/ 0
27 Ranibizumab*.tw. 87
28 (Lucentis or rhuFab).tw. 5
29 (IVR adj2 inject*).tw. 0
30 (Faricimab or Vabysmo).tw. 2
31 (Pegaptanib* or macugen*).tw. 10
32 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).tw. 1
33 Sunitinib/ 0
34 (Sunitinib or Sutent).tw. 76
35 Sorafenib/ 0
36 (Sorafenib or Nexavar).tw. 124
37 Axitinib/ 0
38 (Axitinib or Inlyta).tw. 34
39 (Pazopanib or Votrient).tw. 36
40 or/11-39 1182
41 Intravitreal Injections/ 0
42 (Intravitreal* adj2 (injection* or steroid* or treat* or therap* or techni* or medic* or prescript* or drug* or agent*)).tw. 236
43 Dexamethasone/ or Fluocinolone Acetonide/ or Triamcinolone Acetonide/ 0
44 (Dexamethasone* or kenalog or kenacort or retisert*).tw. 513
45 ((fluocinolone* or triamcinolone*) adj2 acetonide*).tw. 61
46 Iluvien*.tw. 9
47 (Adcortyl* or Kenalog*).tw. 0
48 or/41-47 774
49 randomized controlled trial.pt. 1
50 randomi?ed.mp. 11957
51 placebo.mp. 2399
52 or/49-51 12718
53 Qualitative Research/ 0
54 Nursing Methodology Research/ 0
55 Interview.pt. 3
56 exp Interviews as Topic/ 0
57 "Questionnaires"/ 0
58 Narration/ 0
59 Health Care Surveys/ 0
60 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw. 34569
61 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj4 analys$) or theoretical sampl$ or purposive sampl$).tw. 3947
62 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw. 210
63 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or metathem$ or meta-them$).tw. 95
64 "critical interpretive synthes*".tw. 8
65 (realist adj (review* or synthes*)).tw. 58
66 (noblit and hare).tw. 1

67	(meta adj (method or triangulation)).tw.	0
68	(CERQUAL or CONQUAL).tw.	26
69	((thematic or framework) adj synthes*).tw.	93
70	(trial adj3 sibling*).tw.	0
71	(sibling adj2 (qualitative* or stud*)).tw.	11
72	or/53-71	35565
73	52 or 72	46357
74	10 or 40 or 48	3894
75	4 and 74	138
76	73 and 75	24
77	animals/ not humans/	0
78	76 not 77	24
79	limit 78 to english language	23
80	52 and 79	22
81	72 and 79	4

Cost effectiveness searches

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

Limits and restrictions

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

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

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

Search filters

Cost utility

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

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

Cohort studies

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

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

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

Cost effectiveness search strategies

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

Database: EconLit

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

4 1 or 2 or 3 14

Database: Embase

Cost utility search:

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

Cohort studies:

1 diabetic Retinopathy/ 45440
2 macular Edema/ 5828
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47762
4 or/1-3 66388
5 cohort analysis/ 811098
6 Retrospective study/ 1206857
7 Prospective study/ 748103
8 (Cohort adj (study or studies)).tw. 380594
9 (cohort adj (analy* or regist*)).tw. 16437
10 (follow up adj (study or studies)).tw. 68508
11 longitudinal.tw. 384899
12 prospective.tw. 981024
13 retrospective.tw. 1068301
14 or/5-13 3358085
15 4 and 14 13743
16 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or

grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ 1511773
17 exp "organisation for economic co-operation and development"/ 1933
18 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ 3545238
19 european union/ 29144
20 developed country/ 34415
21 or/17-20 3576072
22 16 not 21 1373176
23 15 not 22 12938
24 limit 23 to english language 12133
25 nonhuman/ not human/ 4938000
26 24 not 25 12067
27 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 7072757
28 26 not 27 8733

29 limit 28 to dc=20120101-20220228 6467

Database: HTA

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118
2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82
3 ((diabet* adj4 (retin* or eye* or macular*))) 216
4 #1 OR #2 OR #3 245
5 * IN HTA FROM 2012 TO 2022 5598
6 #4 AND #5 26

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

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

Database: Ovid Medline (R)

Cost utility search:

1 Diabetic Retinopathy/ 27250
2 Macular Edema/ 8126
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 29608
4 1 or 2 or 3 40314
5 Cost-Benefit Analysis/ 88398
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 13197
7 ((incremental* adj2 cost*) or ICER).tw. 13599
8 (cost adj2 utilit*).tw. 5176
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 1698
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 17986
11 (cost and (effect* or utilit*)).ti. 30223
12 or/5-11 100083
13 4 and 12 287
14 animals/ not humans/ 4924997
15 13 not 14 287

Cohort studies:

1 Diabetic Retinopathy/ 27317
2 Macular Edema/ 8133
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 29694
4 or/1-3 40407
5 exp Cohort Studies/ 2302163
6 (cohort adj (study or studies)).tw. 225137
7 (cohort adj (analy* or regist*)).tw. 8773
8 (follow up adj (study or studies)).tw. 48799
9 longitudinal.tw. 243228
10 prospective.tw. 570236
11 retrospective.tw. 546033
12 or/5-11 2652900
13 4 and 12 10289
14 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ 1201994
15 "organisation for economic co-operation and development"/ 417
16 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/

or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ 3386234
17 european union/ 17116
18 developed countries/ 21089
19 or/15-18 3401513
20 14 not 19 1115138
21 13 not 20 9710
22 limit 21 to english language 8875
23 Animals/ not Humans/ 4930479
24 22 not 23 8825
25 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 2225022
26 24 not 25 8658
27 limit 26 to ed=20120101-20220228 4813

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

Cost utility search:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 335
4 1 or 2 or 3 335
5 Cost-Benefit Analysis/ 0
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 196
7 ((incremental* adj2 cost*) or ICER).tw. 177
8 (cost adj2 utilit*).tw. 74
9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 29
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 242
11 (cost and (effect* or utilit*)).ti. 286
12 or/5-11 450
13 4 and 12 2
14 animals/ not humans/ 0
15 13 not 14 2

Cohort studies:

1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 336

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

Database: Ovid MEDLINE(R) Epub Ahead of Print

Cost utility search:

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

Cohort studies:

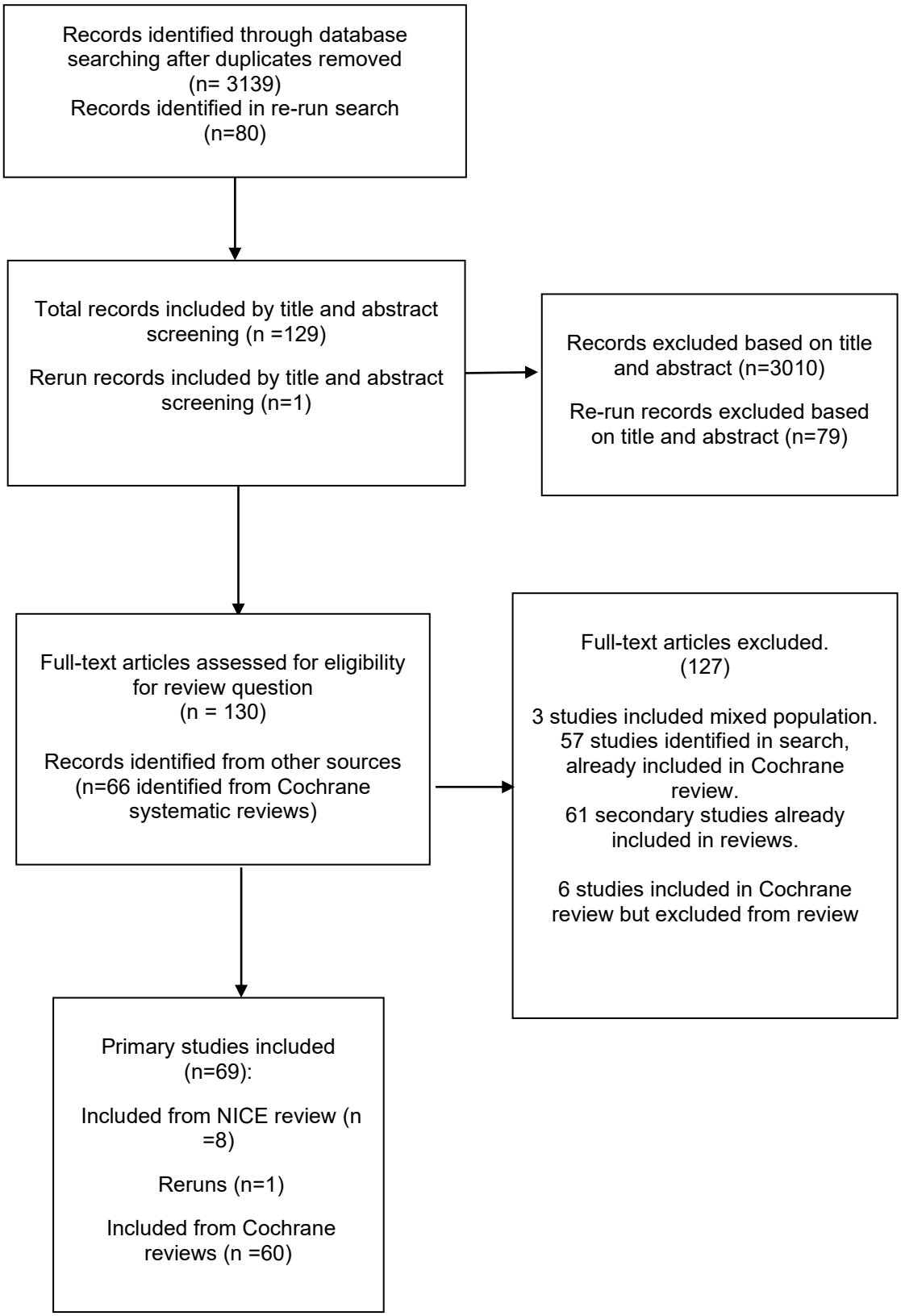
1 Diabetic Retinopathy/ 0
2 Macular Edema/ 0
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 563
4 or/1-3 563
5 exp Cohort Studies/ 0
6 (cohort adj (study or studies)).tw. 9207
7 (cohort adj (analy* or regist*)).tw. 349
8 (follow up adj (study or studies)).tw. 607
9 longitudinal.tw. 6722

10	prospective.tw.	12241
11	retrospective.tw.	18324
12	or/5-11	37987
13	4 and 12	147
14	limit 13 to english language	147

Database: NHS Economic Evaluation Database

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

Appendix C – Effectiveness evidence study selection



Appendix D – Effectiveness evidence

D.1 NICE additional studies

Callanan, 2013

Bibliographic Reference

Callanan, David G; Gupta, Sunil; Boyer, David S; Ciulla, Thomas A; Singer, Michael A; Kuppermann, Baruch D; Liu, Ching-Chi; Li, Xiao-Yan; Hollander, David A; Schiffman, Rhett M; Whitcup, Scott M; Ozurdex PLACID Study, Group; Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema.; Ophthalmology; 2013; vol. 120 (no. 9); 1843-51

Study details

Study dates	Enrolment commenced in May 2007 and the study was completed in February 2010.
Sources of funding	Sponsored by Allergan, Inc., Irvine, California. The sponsor participated in design of the study, data management, data analysis, interpretation of the data, and the preparation, review, and approval of the manuscript.
Inclusion criteria	At least 18 years of age Diagnosis of type 1 or type 2 diabetes mellitus Mean retinal thickness 275 mm by OCT in the 1-mm central macular subfield due to diffuse DME not amenable to laser at stand-alone treatment (at screening) Diffuse macular capillary bed leakage evident on FA BCVA >34 and <70 letters (approximately 20/200 and 20/40Snellen) using the ETDRS method at screening and baseline)
Exclusion criteria	Uncontrolled systemic disease Use of systemic corticosteroid within 12 weeks prior to baseline or anticipated use during the study Active ocular infection (either eye) Glaucoma (either eye) History of an IOP increase 10 mm Hg or to 25 mm Hg in response to corticosteroid treatment that required multiple IOP-lowering medications or laser or surgical treatment (either eye)

	History or presence of venous occlusive disease, uveitis, Irvine-Gass syndrome, or any condition other than diabetic retinopathy that could contribute to macular oedema Epiretinal membrane or vitreomacular traction macular oedema History of pars plana vitrectomy Active optic disc or retinal neovascularization History of intravitreal corticosteroid use except dexamethasone 4 mg triamcinolone dosed at least 13 weeks prior to baseline
Intervention(s)	Dexamethasone Intravitreal Implant Plus Laser
Comparator	Laser Alone
Outcome measures	Mean of best corrected visual acuity in logMAR Mean of central macular thickness, Mean number of treatments
Number of participants	253
Duration of follow-up	12-months
Loss to follow-up	5 people dropped out at 12-months
Baseline characteristics	
Age (yrs.) Mean (SD):	Dexamethasone Intravitreal Implant Plus Laser: 61.8 (11.1) Laser Alone: 61.3 (9.3)
Gender, n females (%)	Dexamethasone Intravitreal Implant Plus Laser: 64 (50.8) Laser Alone: 61 (48.0)

Study arms

DEX implant plus laser (N = 126)

sham implant and laser (N = 127)

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

Chen, 2020

Bibliographic Reference	Chen, Y.-X.; Li, X.-X.; Yoon, Y.H.; Sun, X.; Astakhov, Y.; Xu, G.; Wang, H.; Ren, X.; Asmus, F.; Intravitreal aflibercept versus laser photocoagulation in asian patients with diabetic macular edema: The VIVID-east study; Clinical Ophthalmology; 2020; vol. 14; 741-750

Study details

Study location	25 centres across China, Hong Kong, Republic of Korea, and Russia
Study setting	
Sources of funding	The VIVID-East study was sponsored by Bayer AG, Berlin, Germany. The sponsor participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript.
Inclusion criteria	Adult patients (aged ≥18 years) type 1 or 2 diabetes mellitus who presented with clinically significant DME involving the center of the macula (defined as the area of the center subfield of optical coherence tomography [OCT]) in the study eye Eligible patients had central retinal thickness (CRT), as assessed by OCT, ≥300µm the best corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score between 73 and 24 (20/40 to 20/320 Snellen equivalent) in the study eye. Only 1 eye per patient was enrolled in the study.
Exclusion criteria	Patients with an ocular condition with a poorer prognosis in the fellow eye than in the study eye any surgical interventions or laser photocoagulation in the study eye within 120 and 90 days of day 1 any treatments with corticosteroids or anti-angiogenic drugs in either eye within 90 days of day 1 active proliferative diabetic retinopathy in the study eye a history of idiopathic or autoimmune uveitis in the study eye

Intervention(s)	Eyes were randomized 1:1:1 to receive either: 2 mg IVT-AFL every 4 weeks (2q4; a maximum of 13 injections) with sham laser; 2 mg IVT-AFL every 8 weeks (after 5 initial monthly doses from baseline to week 16; a maximum of 9 injections)
Comparator	macular laser at baseline and sham injections at every visit (laser control group;
Outcome measures	mean change in BCVA in ETDRS letter score from baseline. eyes that gained ≥10 ETDRS letters from baseline proportion of eyes that gained ≥15 ETDRS letters from baseline proportion of eyes with a ≥2-step improvement from baseline in the Diabetic Retinopathy Severity Scale (DRSS) change in CRT from baseline mean number of treatments
Number of participants	381
Duration of follow-up	52 weeks
Loss to follow-up	Group A Discontinued (n=5) • Adverse event (n=4) • Withdrawal of consent (n=1) Group B Discontinued (n=11) • Adverse event (n=5) • Withdrawal of consent (n=3) • Lost to follow-up (n=3) Group C Discontinued (n=7) • Adverse event (n=4) • Withdrawal of consent (n=3)
Baseline characteristics	
Age (yrs.) Mean (SD):	IVT-AFL 2q4: 59.3 (10.3) Laser: 58.8 (10.5)
Gender, n females (%)	IVT-AFL 2q4: 68 (53.5) Laser: 60 (48.4)

Study arms

IVT-AFL every 4 weeks (N = 127)

IVT-AFL every 8 weeks (N = 127)

2 mg IVT-AFL every 8 weeks

macular laser (N = 127)

sham injections on nontreatment visits or macular laser

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

Faghihi, 2010

Bibliographic Reference	Faghihi, H; Esfahani, MR; Harandi, ZA; Madani, S; Intravitreal bevacizumab vs. combination of intravitreal bevacizumab plus macular photocoagulation in clinically significant diabetic macular edema: 6 months results of a randomized clinical trial; Iranian journal of ophthalmology; 2010; vol. 22 (no. 1); 21-26

Study details

Study location	Iran
Study setting	Eye Research Center, Farabi Eye Hospital,
Study dates	between October 2007 and September 2008.
Sources of funding	not reported
Inclusion criteria	Bilateral non-tractional CSME 10/10> V.A < 1/10 Controlled blood pressure.
Exclusion criteria	HRC PDR Advanced or advanced active PDR Significant cataract Glaucoma History of recent vascular accident (e.g, MI, CVA,) Previous treatment of CSME or PDR, or pharmacotherapy for CSME. Macular ischemia

	Uncontrolled hypertension
Intervention(s)	One eye of each patient was selected randomly for MPC. All the MPCs were done by one retinal specialist in the morning, and in the same afternoon the IVB injections were done Under aseptic condition, 1.25 mg of bevacizumab (Avastin) was injected intravitreally from supertemporal pars plana in both eyes of each patient
Comparator	only 1.25 mg of bevacizumab (Avastin) was injected intravitreally
Outcome measures	Mean of best corrected visual acuity in logMAR Mean of central macular thickness Mean number of treatments
Number of participants	40
Duration of follow-up	6 months
Loss to follow-up	
Baseline characteristics Age (yrs.) Mean (SD): Gender, n females (%)	 57.7±8 years 11 (27.5%) females

Study arms

IVB (N = 40)

IVB plus MPC (N = 40)

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

Fouda, 2017

Bibliographic Reference	Fouda, S.M.; Bahgat, A.M.; Intravitreal aflibercept versus intravitreal ranibizumab for the treatment of diabetic macular edema; Clinical Ophthalmology; 2017; vol. 11; 567-571

Study details

Study location	Egypt
Study setting	Department of Ophthalmology, Faculty of Medicine, Zagazig University, Zagazig
Sources of funding	not reported
Inclusion criteria	Patients with type I or II diabetes, DME in eyes as diagnosed clinically and with OCT patients with best corrected visual acuity (BCVA) ranged from 0.1 to 0.25 (moderate visual loss) oedema affecting the central 1 mm of the macula (detected with optical coherence tomography)
Exclusion criteria	Eyes with vascular retinal disorders other than diabetic retinopathy (eg, choroidal neovascularization), eyes that received previous intravitreal injection of any agents, eyes
Intervention(s)	All eyes in group I received an injection of 2 mg/0.05 mL aflibercept (Eylea; Regeneron Pharmaceuticals, NY, USA) and those in
Comparator	group II received an injection of 0.5 mg/0.1 mL ranibizumab (Lucentis; Genentech, USA, Inc., San Francisco, CA, USA)
Outcome measures	Best corrected visual acuity Central macular thickness Mean number of treatments
Number of participants	A total of 70 eyes of 42 diabetic patients
Duration of follow-up	All eyes were examined monthly for 12 months after the last injection of the loading dose.
Baseline characteristics	group I: 55.05±4.7 years

Age (yrs.) Mean (SD):	group II: 56.64±5.8 years
Gender, n females (%)	NR

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

Gillies, 2009

Bibliographic Reference	Gillies, Mark C; Simpson, Judy M; Gaston, Christine; Hunt, Grace; Ali, Haipha; Zhu, Meidong; Sutter, Florian; Five-year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema.; Ophthalmology; 2009; vol. 116 (no. 11); 2182-7

Study details

Intervention(s)	Intravitreal injection of 0.1 ml of 40 mg/ml triamcinolone acetonide with adjunctive laser therapy
Comparator	Placebo
Outcomes	Best corrected visual acuity in logMAR
Number of participants	A total of 69 eyes (41 patients)
Duration of follow-up	5 years
Baseline characteristics	
Age (yrs.) Mean (SD):	NR
Gender, n	NR

females (%)	

Study arms

Initial Triamcinolone (N = 23)

Initial Placebo (N = 21)

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

Lam, 2007

Bibliographic Reference	Lam, Dennis S C; Chan, Carmen K M; Mohamed, Shaheeda; Lai, Timothy Y Y; Lee, Vincent Y W; Liu, David T L; Li, Kenneth K W; Li, Patrick S H; Shanmugam, Mahesh P; Intravitreal triamcinolone plus sequential grid laser versus triamcinolone or laser alone for treating diabetic macular edema: six-month outcomes.; Ophthalmology; 2007; vol. 114 (no. 12); 2162-7

Study details

Inclusion criteria	Patients 18 years or older with type I or II diabetes mellitus Eyes had DME involving the fovea, as defined by clinically significant macular oedema according to ETDRS guidelines central foveal thickness (CFT) >250 um, as measured (OCT)
Exclusion criteria	macular oedema secondary to causes other than diabetic maculopathy signs of vitreomacular traction proliferative diabetic retinopathy Patients who had phakia history of glaucoma or ocular hypertension macular ischemia (1 disc diameters of capillary closure at the macula on fluorescein angiography). Patients who had any laser procedure within 3 months Patients who had ocular surgery within 6 months, or significant media opacities
Intervention(s)	Patients were randomized to, 4 mg of intravitreal TA (38 eyes), or 4 mg of

	intravitreal TA combined with sequential grid laser about 1 month later (36 eyes).
Comparator	grid laser (37 eyes)
Outcome measures	Central foveal thickness (logMAR) best-corrected visual acuity
Number of participants	One hundred eleven eyes of 111 patients with DME involving the fovea
Duration of follow-up	The 6-month results are reported
Baseline characteristics Age (yrs.) Mean (SD):	Laser: 66.2 (8.2) IVTA: 67.2 (9.8) Combined: 64.7 (10.3)
Gender, n males (%)	Laser: 15 (41%) IVTA: 18 (47%) Combined: 21 (58%)

Study arms

grid laser (N = 37)

4 mg of intravitreal TA (N = 38)

4 mg of intravitreal TA + grid laser (N = 36)

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

Ozsaygili, 2020

Bibliographic Ozsaygili, Cemal; Duru, Necati; COMPARISON OF INTRAVITREAL

Reference	DEXAMETHASONE IMPLANT AND AFLIBERCEPT IN PATIENTS WITH TREATMENT-NAIVE DIABETIC MACULAR EDEMA WITH SEROUS RETINAL DETACHMENT.; Retina (Philadelphia, Pa.); 2020; vol. 40 (no. 6); 1044-1052

Study details

Study location	
Study setting	Medical Retina clinic
Study dates	from January 2017 to June 2018
Inclusion criteria	1) Patients older than 18 years of age diagnosed with Type 1 or Type 2 DM. 2) Treatment-naïve DMO with SRD and hyperreflective foci 3) BCVA letter score between 73 and 34 (Snellen equivalent 20/40–20/200); 4) The CRT obtained from the 1-mm central macular subfield greater than 450 mm by SD-OCT.
Exclusion criteria	1) Previous history of intraocular anti-VEGF or steroid injection 2) evidence of macular ischemia defined by fundus fluorescein angiogram 3) any other ocular pathologies causing visual impairment (neovascular age-related macular degeneration, choroidal neovascularization, retinal venous occlusion, uveitis, and recent intraocular surgery) 4) recent (within 3 months) serious cardiovascular or cerebrovascular events 5) IOP over 23mmHg without treatment or IOP over 21 mmHg with one antiglaucoma medication 6) presence of vitreomacular interface abnormalities 7) aphakia or ananterior chamber intraocular lens 8) active proliferative diabetic retinopathy.
Intervention(s)	3 monthly injections of 2 mg of aflibercept as a loading phase in the anti–vascular endothelial growth factor group
Comparator	0.7 mg of DEX implant in the DEX group and then pro re nata treatment.
Outcome measures	Mean best corrected visual acuity Mean number of treatments Adverse events
Number of participants	Ninety-eight eyes of 62 consecutive treatment-naive patients with DME

Duration of follow-up	12-month follow-ups
Baseline characteristics Age (yrs.) Mean (SD):	DEX group: 64.8 ± 7.9 Aflibercept Group: 66.4 ± 2.0
Gender, n males (%)	DEX group: 15 (51.7) Aflibercept Group: 20 (60.6)

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

Vader, 2020

Bibliographic Reference	Vader, Maartje J C; Schauwvlieghe, Ann-Sofie M E; Verbraak, Frank D; Dijkman, Greetje; Hooymans, Johanna M M; Los, Leonoor I; Zwinderman, Aeilko H; Peto, Tunde; Hoyng, Carel B; van Leeuwen, Redmer; Vingerling, Johannes R; Moll, Annette C; van Lith-Verhoeven, Janneke J C; Dijkgraaf, Marcel G W; Schlingemann, Reinier O; Bevacizumab and Ranibizumab in Diabetic Macular Edema Study, Group; Comparing the Efficacy of Bevacizumab and Ranibizumab in Patients with Diabetic Macular Edema (BRDME): The BRDME Study, a Randomized Trial.; Ophthalmology. Retina; 2020; vol. 4 (no. 8); 777-788

Study details

Study dates	From June 2012 through February 2018
Inclusion criteria	patients were older than 18 years, diagnosed with type 1 or type 2 diabetes mellitus and with a glycosylated haemoglobin of less than 12%, central area thickness on (OCT) of more than 325 mm visual impairment resulting from DME. best-corrected visual acuity (BCVA) outcome of at least 24 letters and less than 79 letters on standardized ETDRS

Exclusion criteria	Untreated PDR was defined as leakage on. fluorescein angiogram resulting from a neovascularization. the presence of preretinal haemorrhages vitreous haemorrhages, Structural damage included the presence of laser scars, retinal pigment epithelium atrophy organized hard exudate plaques close to the macula
Intervention(s)	randomized to receive bevacizumab
Comparator	randomized to receive ranibizumab
Outcome measures	Mean of best corrected visual acuity in logMAR Mean of central macular thickness Mean number of treatments
Number of participants	170
Duration of follow-up	6 months
Baseline characteristics Age (yrs.) Mean (SD): Gender, n females (%)	 Bevacizumab Group: 63.9 (11.6) Ranibizumab group: 64.9 (11.6) Bevacizumab Group: 40 (47.6) Ranibizumab group: 25 (30.5)

Study arms

1.25 mg bevacizumab (N = 86)

0.5 mg ranibizumab (N = 84)

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

Section	Question	Answer

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Lois, 2022

Bibliographic Reference Lois, Noemi; Campbell, Christina; Waugh, Norman; Azuara-Blanco, Augusto; Maredza, Mandy; Mistry, Hema; McAuley, Danny; Acharya, Nachiketa; Aslam, Tariq M; Bailey, Clare; Chong, Victor; Downey, Louise; Eleftheriadis, Haralabos; Fatum, Samia; George, Sheena; Ghanchi, Faruque; Groppe, Markus; Hamilton, Robin; Menon, Geeta; Saad, Ahmed; Sivaprasad, Sobha; Shiew, Marianne; Steel, David H; Talks, James Stephen; Doherty, Paul; McDowell, Cliona; Clarke, Mike; Standard threshold laser versus subthreshold micropulse laser for adults with diabetic macular oedema: the DIAMONDS non-inferiority RCT.; Health technology assessment (Winchester, England); 2022; vol. 26 (no. 50); 1-86

Study details

Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	specialist hospital eye services (HES) (n = 16) in the UK.
Study dates	18 January 2017 and 20 November 2018.
Sources of funding	The Belfast Health and Social Care Trust (BHSCT) was the sponsor for the DIAMONDS trial.
Inclusion criteria	centre-involving DMO, as determined by slit-lamp biomicroscopy and SD-OCT in one or both eyes, with either: a CRT of > 300 µm but < 400 µm in the central subfield (central 1 mm) owing to DMO as determined by SD-OCT a CRT of < 300 µm provided that intra-retinal and/or subretinal fluid was present in the central subfield (central 1 mm) owing to DMO. The following conditions also had to be met:

	visual acuity of > 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent > 20/320) amenable to laser treatment, as judged by the treating ophthalmologist aged ≥ 18 years.
Exclusion criteria	A patient's eyes were not eligible for the study if their macular oedema was owing to causes other than DMO o ineligible for macular laser, as judged by the treating ophthalmologist DMO with a CRT of ≥ 400 µm active PDR requiring treatment received intravitreal anti-VEGF therapy within the previous 2 months received macular laser treatment within the previous 12 months received intravitreal injection of steroids cataract surgery within the previous 6 weeks panretinal photocoagulation (PRP) within the previous 3 months.
Intervention(s)	subthreshold micropulse laser 577 nm SML
Comparator	Standard threshold laser [e.g. argon, frequency doubled neodymium-doped yttrium aluminium garnet (Nd:YAG) 532 nm laser].
Outcomes	Mean change in BCVA Mean change in CRT Number meeting driving standards Number of laser treatments used
Number of participants	(intervention, n = 133; control, n = 133)
Duration of follow-up	12 Months and 24 Months
Loss to follow-up	SML (n=17) (Lost to follow-up, n=7,Withdrawal of patient consent, n=5,Deaths, n=3,Other, n=2) SL (n=17) (Lost to follow-up, n=5,AE, n=1,SAE, n=1, Withdrawal of patient consent, n=6, Deaths, n=4)
Methods of analysis	ITT
Baseline	Subthreshold Total Micropulse Laser: 61.9 (10.1)

characteristics	
Age (yrs.) Mean (SD):	Standard threshold laser: 62.6 (10.4)
Gender, n females (%)	Subthreshold Total Micropulse Laser: 42 (31.6%) Standard threshold laser: 37 (28.0%)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(pragmatic, multicentre, allocation-concealed, non-inferiority, randomised, double-masked (participants and outcome assessors), prospective clinical trial)*
Overall bias and Directness	Overall Directness	Directly applicable

D.2 Cochrane Systematic Reviews

For full evidence tables for primary studies from the Cochrane systematic reviews, see Jorge et al. 2018, Mehta et al. 2018, Rittiphairoj et al. 2020, and Virgili et al. 2022.

Jorge et al-2018

Bibliographic Reference	Jorge EC, Jorge EN, Botelho M, Farat JG, Virgili G, El Dib R. Monotherapy laser photocoagulation for diabetic macular oedema.Cochrane Database of Systematic Reviews 2018, Issue 10. Art.

Study Characteristics

Study design	Systematic review
Study details	Dates searched Up to 24 July 2018.
Inclusion criteria	Randomised controlled trials (RCTs) comparing any type of focal/grid macular laser versus another type or technique of laser treatment and no intervention.
Exclusion criteria	Excluded studies comparing laser with other interventions
Intervention(s)	Different macular laser as monotherapy in the treatment of diabetic macular oedema.
Outcome(s)	• Gain or loss of 3 lines (0.3 logMAR or 15 ETDRS letters) of best-corrected visual acuity (BCVA) at one year of follow-up (plus or minus six months) after treatment initiation. • Mean change in BCVA. • Resolution of macular oedema • Central retinal thickness • Quality of life • Adverse events, all at one year
Number of studies included in the systematic review	24 studies

Studies from the systematic review that are relevant for use in the current review	• Bandello 2005 • Blankenship 1979 • Casson 2012 • DRCNET 2007 • ETDRS 1985 • Figueira 2009 • Ladas 1993 • Laursen 2004 • Lavinsky 2011 • Olk 1986 • Pei-Pei 2015 • Tewari 1998 • Venkatesh 2011 • Vujosevic 2010 • Xie 2013
Additional comments	Summary details of included RCTs available in summary Table 5 and full evidence tables and risk of bias assessments can be found in Jorge et al. 2018

Critical appraisal - GDT Crit App - ROBIS checklist

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

Mehta et al-2018

Bibliographic Reference	Mehta H, Hennings C, Gillies MC, Nguyen V, Campain A, Fraser-Bell S. Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema. Cochrane Database of Systematic Reviews 2018, Issue 4.

Study Characteristics

Study design	Systematic review
Study details	Dates searched Up to 21 February 2018.
Inclusion criteria	Randomised controlled trials (RCTs) comparing intravitreal anti-VEGF combined with intravitreal steroids versus intravitreal anti-VEGF alone, intravitreal steroids alone or macular laser alone for managing DMO

Exclusion criteria	NR
Intervention(s)	intravitreal anti-VEGF combined with intravitreal steroids versus intravitreal anti-VEGF alone, intravitreal steroids alone or macular laser alone
Outcome(s)	• Change in best corrected visual acuity (BCVA) between baseline and one year • Change in central macular thickness (CMT) • Quality of life. • Adverse events including intraocular inflammation, raised intraocular pressure (IOP) and development of cataract
Number of studies included in the systematic review	8 studies
Studies from the systematic review that are relevant for use in the current review	• DRCRnet U 2018 (Maturi 2018) • Lim 2012 • Maturi 2015 • Neto 2017 • Riazi-Esfahani 2017 • Shoeibi 2013 • Soheilian 2012 • Synek 2011
Additional comments	Summary details of included RCTs available in summary Table 6and full evidence tables and risk of bias assessments can be found in Mehta et al. 2018

Critical appraisal - GDT Crit App - ROBIS checklist

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

Rittiphairoj et al-2020

Bibliographic Reference	Rittiphairoj T, Mir TA, Li T, Virgili G. Intravitreal steroids for macular edema in diabetes. Cochrane Database of Systematic Reviews 2020, Issue 11. Art. No.: CD005656

Study Characteristics

Study design	Systematic review
Study details	Dates searched Up to 21 October 2020
Inclusion criteria	Randomised controlled trials (RCTs) comparing intravitreal steroid therapies versus other treatments, including intravitreal anti-VEGF therapy, laser photocoagulation, and sham injection
Exclusion criteria	NR
Intervention(s)	any type of intravitreal steroids as monotherapy against any other intervention (e.g., observation, laser, anti-vascular endothelial growth factor (anti-VEGF) for DME.
Outcome(s)	• Change in best corrected visual acuity (BCVA) between baseline and one year • improvement of three or more lines of visual acuity • Change in central macular thickness (CMT) • Adverse events including intraocular inflammation, raised intraocular pressure (IOP) and development of cataract
Number of studies included in the systematic review	10 studies
Studies from the systematic review that are relevant for use in the current review	BEVORDEX 2014 (Gillies 2014) Callanan 2017 DRCR.net 2008 FAME 2011 (Campochiaro 2011)

	Kriechbaum 2014 Lim 2012 MEAD 2014 (Boyer 2014) Ockrim 2008 Sutter 2004
Additional comments	Summary details of included RCTs available in summary Table 7and full evidence tables and risk of bias assessments can be found in, Rittiphairoj et al. 2020

Critical appraisal - GDT Crit App - ROBIS checklist

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

Virgili et al-2022

Bibliographic Reference	Virgili G, Curran K, Lucenteforte E, Peto T, Parravano M. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database of Systematic Reviews 2018, Issue 10. Art

Study Characteristics

Study design	Systematic review
Study details	Dates searched Up to 15 October 2021.
Inclusion criteria	Randomised controlled trials (RCTs) comparing any anti-angiogenic drug with an anti-VEGF mechanism of action versus another anti-VEGF drug, another treatment, sham or no treatment in people with DMO
Exclusion criteria	People with normal best corrected visual acuity (BCVA) were not included
Intervention(s)	any anti-angiogenic drug with an anti-VEGF mechanism of action versus another anti-VEGF drug, another treatment, sham, or no treatment
Outcome(s)	• Change in best corrected visual acuity (BCVA) between baseline and one year • Change of BCVA at 24 months. • Improvement of three or more lines of visual acuity

	• Change in central macular thickness (CMT)
Number of studies included in the systematic review	24 studies
Studies from the systematic review that are relevant for use in the current review	• Azad 2012 • Baker 2019 • BOLT 2010 (Michaelides 2010) • Brown 2015 • Brown 2020 • Chatzirallis 2020 • DA VINCI 2011 (Do 2012) • DRCRnet 2010 • DRCRnet 2015 • Ekinci 2014 • Ishibashi 2014 • Korobelnik 2014 (1) • Li 2019 • Liu 2022 • Prunte 2016 • LUCIDATE 2014 (Comyn 2014) • Macugen 2005 • Macugen 2011 (Sultan 2011) • Nepomuceno 2013 • READ2 2009 (Nguyen 2009) • RELATION 2012 • RESOLVE 2010 (Massin 2010) • RESPOND 2013 • RESTORE 2011 (Mitchell 2011) • REVEAL 2015 (Ishibashi 2015) • RISE-RIDE (Nguyen 2012) • Soheilian 2007 • Turkoglu 2015 • Wykoff 2022
Additional comments	Summary details of included RCTs available in summary Table 4 and full evidence tables and risk of bias assessments can be found in Virgili et al. 2022)

Critical appraisal - GDT Crit App - ROBIS checklist

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

Section	Question	Answer
Overall study ratings	Applicability as a source of data	Directly applicable

Appendix E – Forest plots

E.1 People with centre-involving macular oedema (whole population)

Anti-VEGF vs standard threshold laser

Figure 1: Visual Acuity: three or more lines improvement from baseline up to 12M

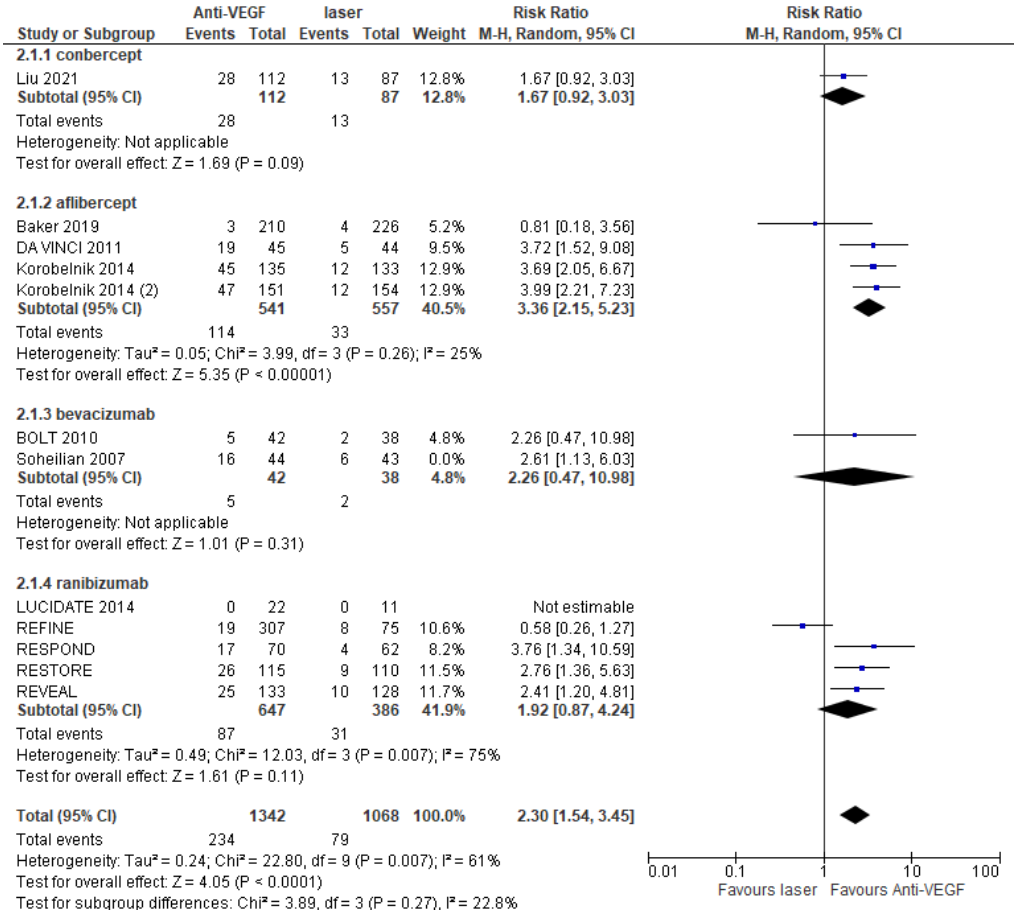
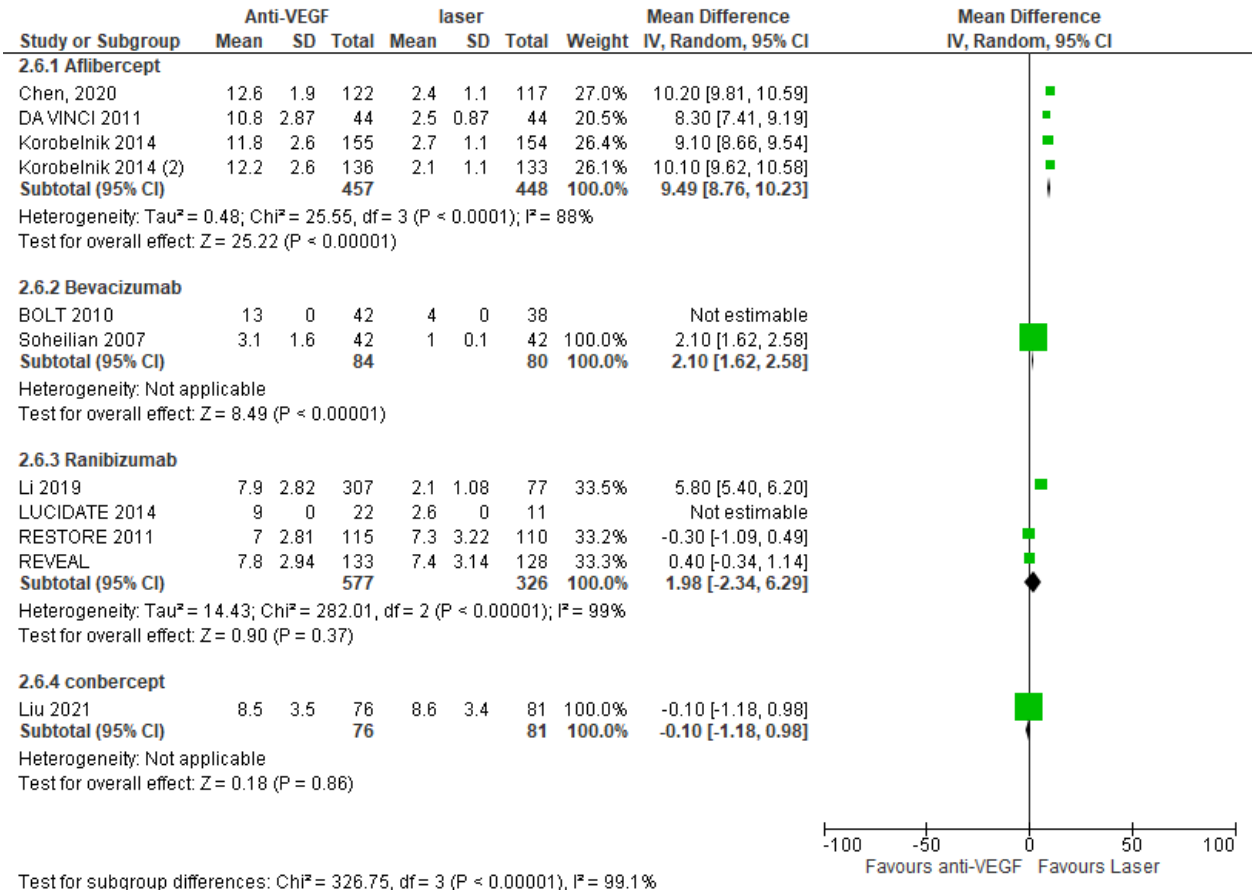


Figure 2: The mean number of treatments at 12 months

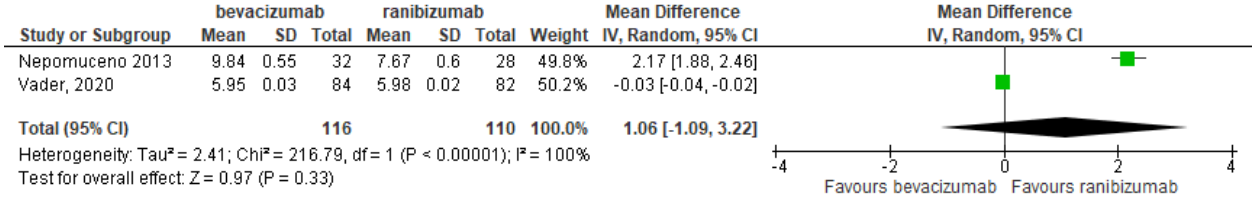


Anti-VEGF vs anti-VEGFs

Bevacizumab versus ranibizumab

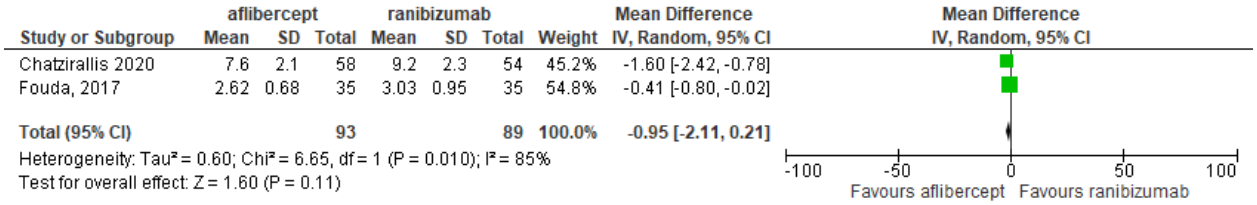
Figure 3: Visual Acuity: three or more lines improvement from baseline up to 12M

Figure 4: Mean number of treatments at 12 months



Aflibercept versus ranibizumab

Figure 5: the mean number of treatments at 12 months



Brolucizumab vs aflibercept

Figure 6: Visual Acuity: three or more lines improvement from baseline to 2 years

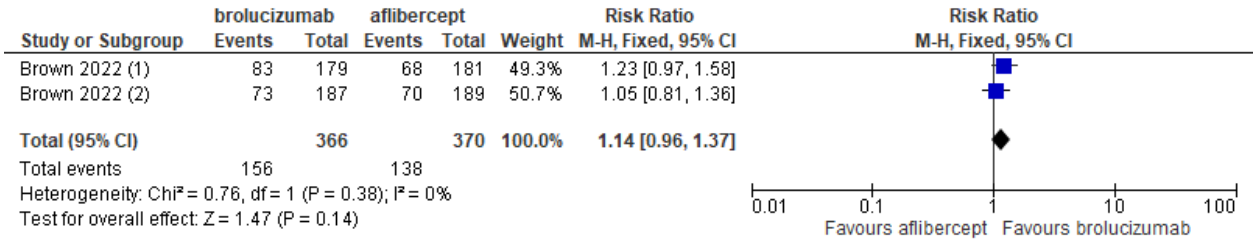
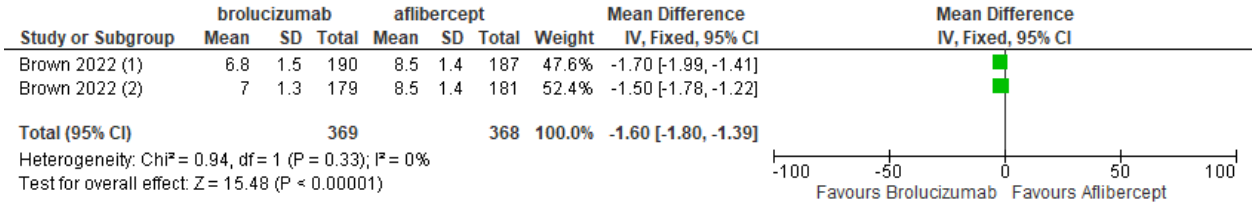
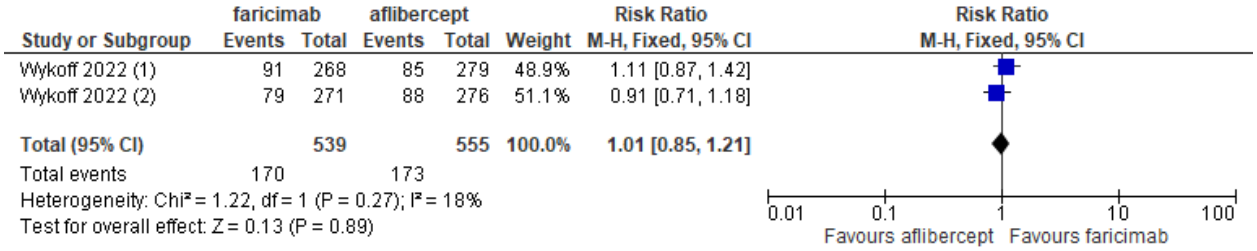


Figure 7: The mean number of treatments at 24 months



Faricimab vs aflibercept

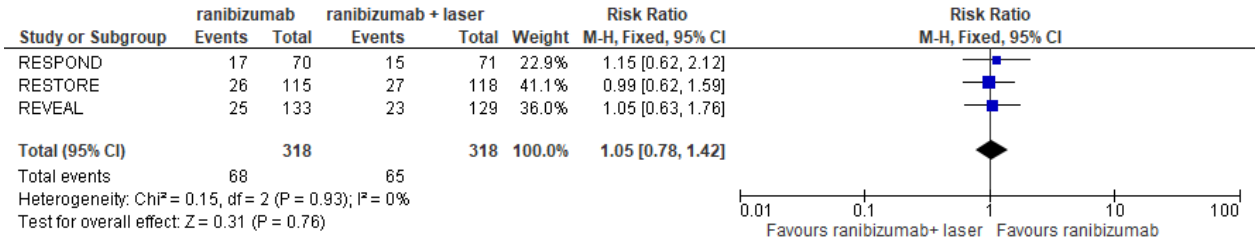
Figure 8: Visual Acuity: three or more lines improvement from baseline to 1 year



Anti-VEGF plus standard threshold laser vs anti-VEGF

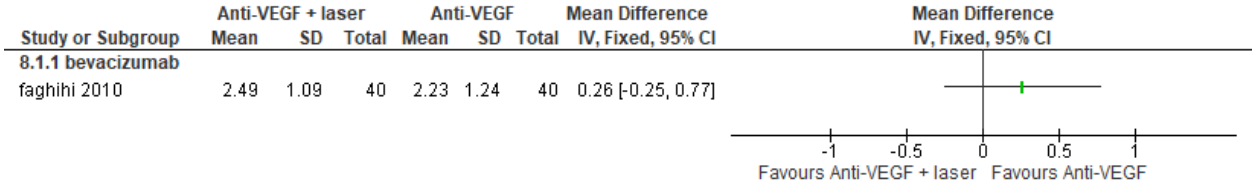
Ranibizumab plus standard threshold laser vs ranibizumab

Figure 9: Visual Acuity: three or more lines improvement from baseline up to 12M



Bevacizumab plus standard threshold laser vs Bevacizumab

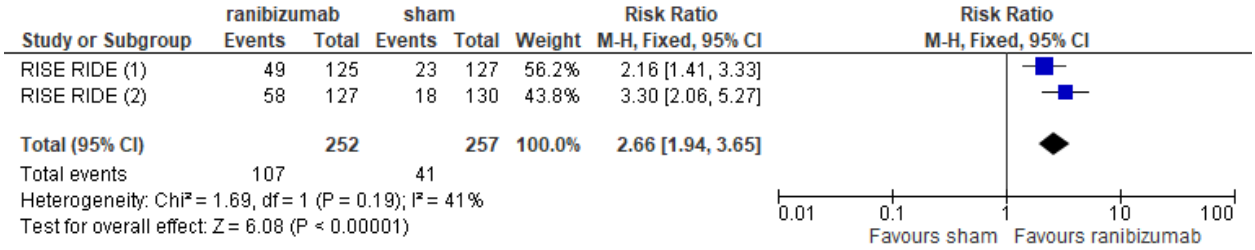
Figure 10: mean number of treatments



Anti-VEGF vs sham

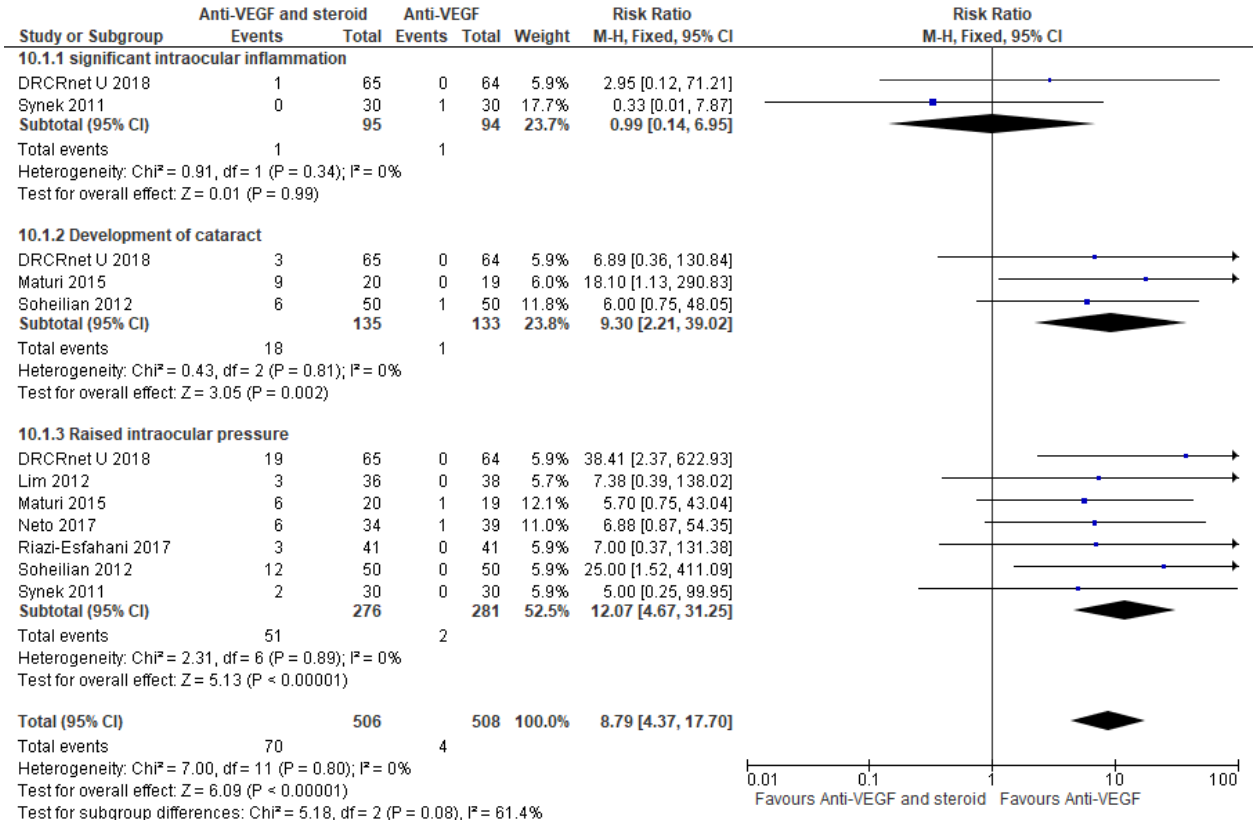
Ranibizumab vs sham

Figure 11: Visual Acuity: three or more lines improvement from baseline to 2 years



Anti-VEGF and steroid versus anti-VEGF alone

Figure 12: Adverse events at 12 months



Steroids versus sham

Intravitreal dexamethasone versus sham:

Figure 13: Gain of three or more lines visual acuity at 12 months

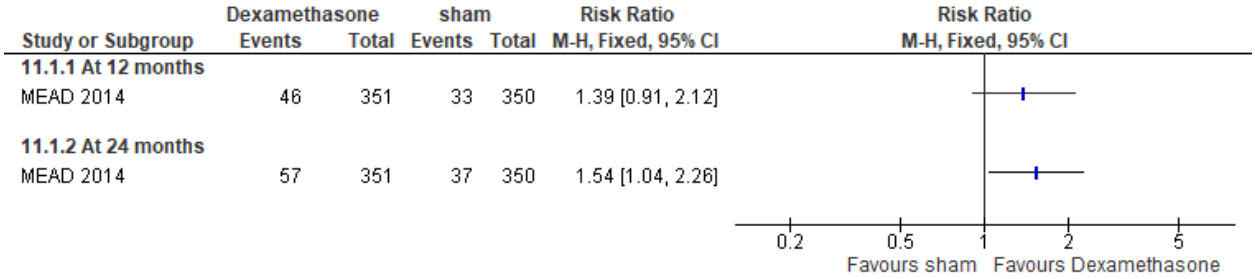
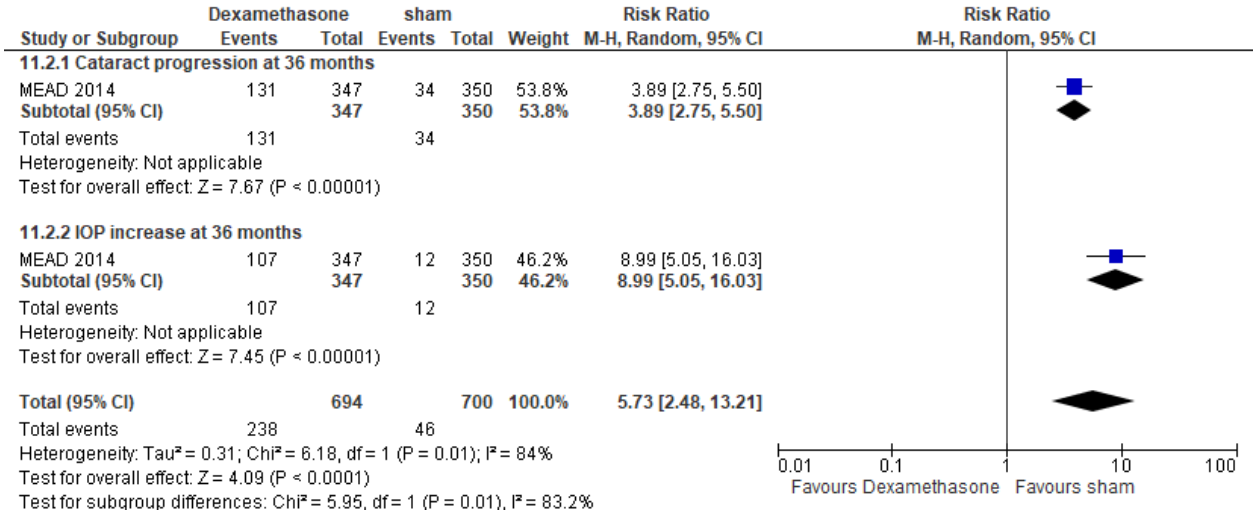


Figure 14: Adverse events at 36 months



Intravitreal fluocinolone acetonide implant versus sham

Figure 15: Gain of three or more lines visual acuity at 12 and 24 months

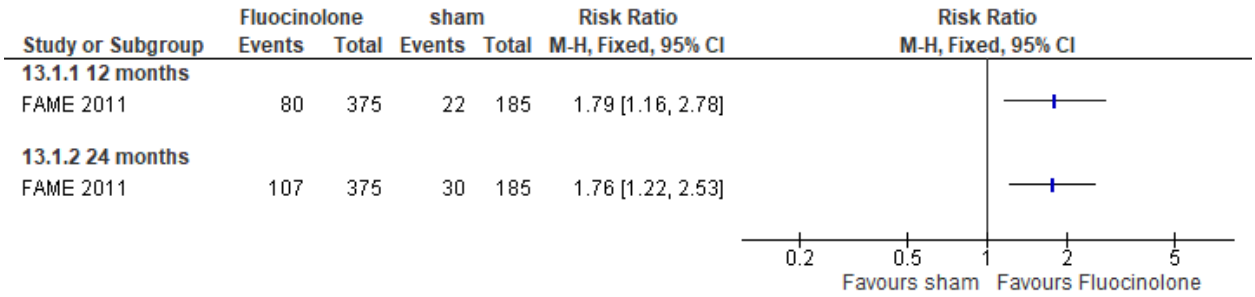
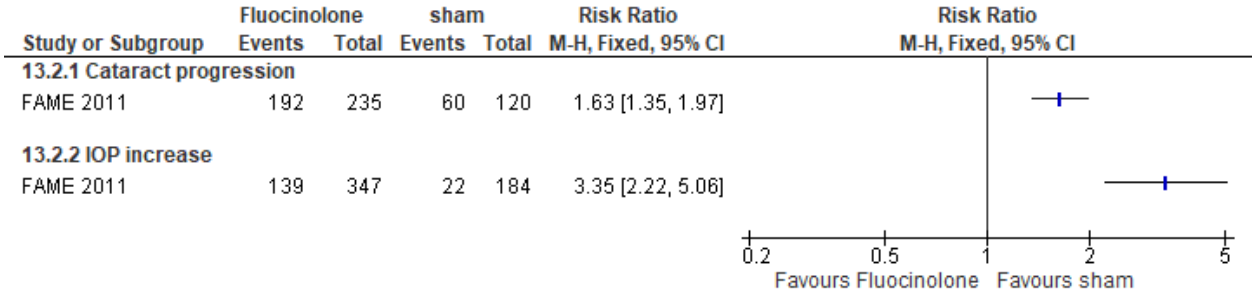


Figure 16: Adverse Event at 24 months.



Intravitreal triamcinolone acetonide injection versus sham

Figure 17: Gain of three or more lines visual acuity at 12 months

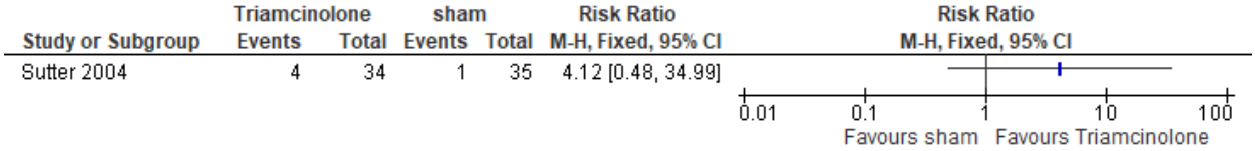
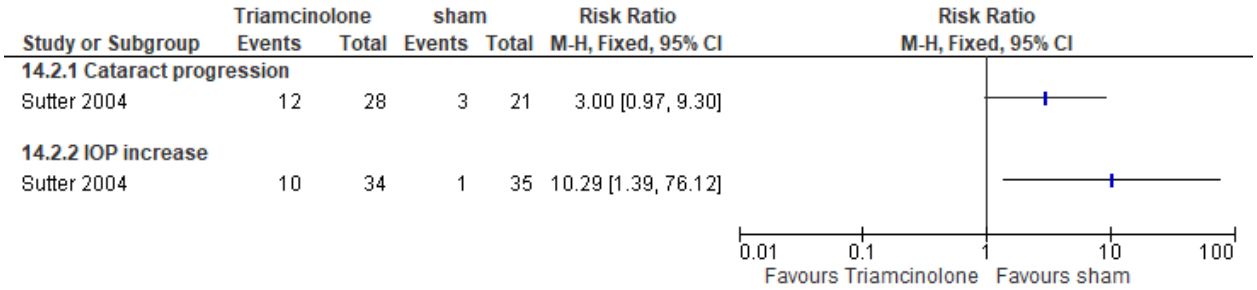


Figure 18: Adverse Event at 24 months



Steroids versus anti-VEGFs

Intravitreal dexamethasone versus intravitreal anti-VEGF

Figure 19: Gain of three or more lines visual acuity at 12 months

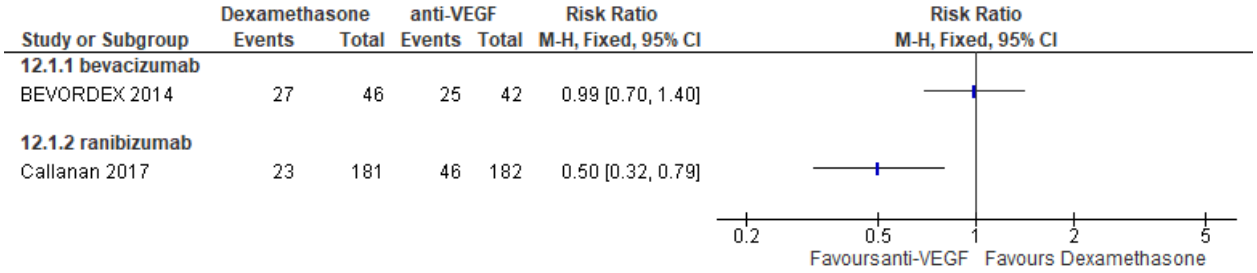


Figure 20: The mean number of treatments at 12 months

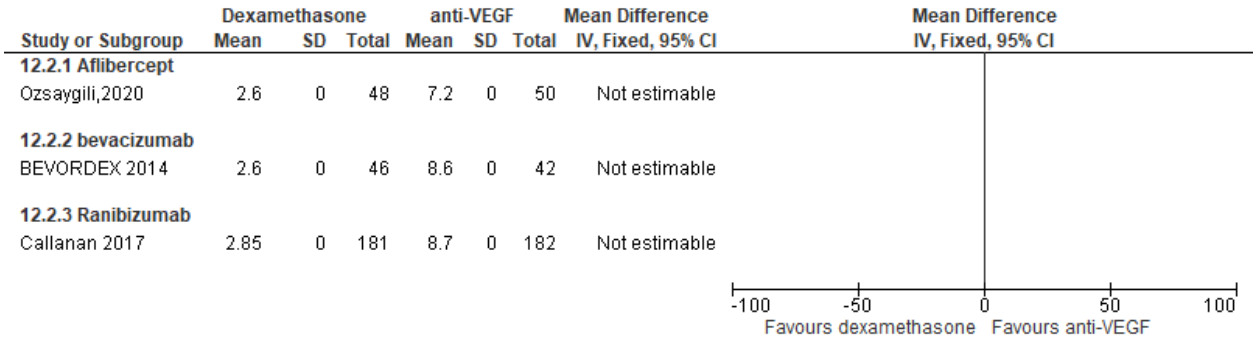


Figure 21: Cataract progression at 12 to 24 months

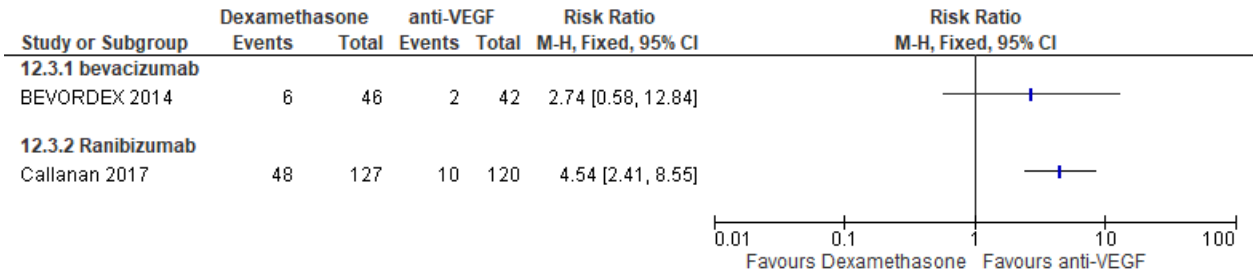
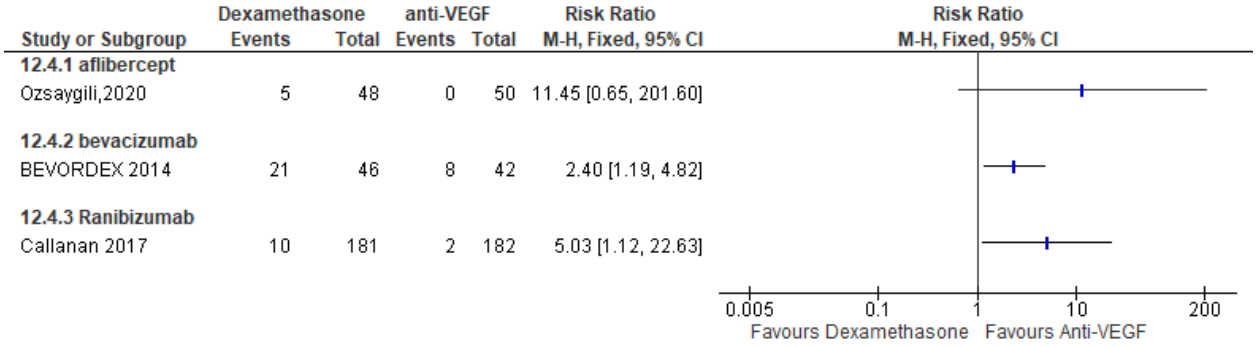


Figure 22: Adverse Event: IOP increase at 24 months.



Steroids versus standard threshold laser

Intravitreal triamcinolone acetonide versus vs standard threshold laser:

Figure 23: Gain of three or more lines visual acuity at 12 and 24 months

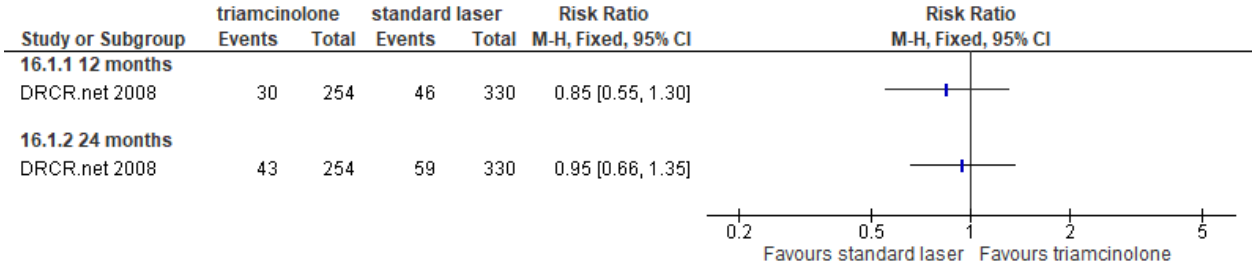
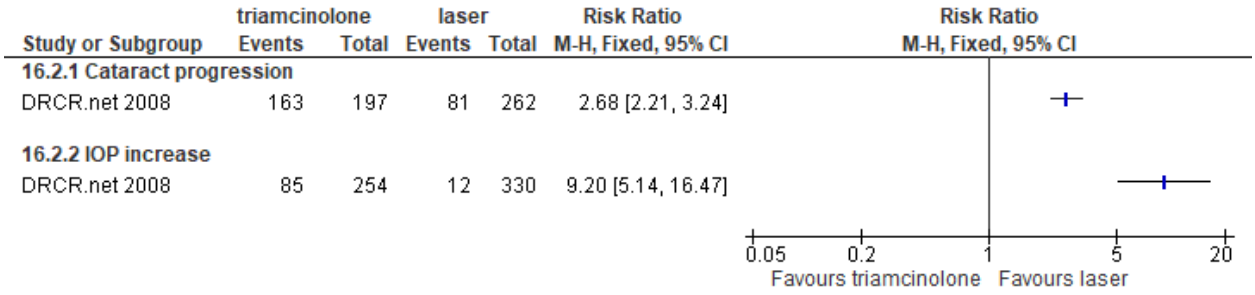


Figure 24 :Adverse Event: cataract progression and IOP increase at 24 months.



Subthreshold laser versus standard threshold laser

Figure 25: Mean change in BCVA in the study eye from baseline to month 24 (ETDRS letters), mean (SD)

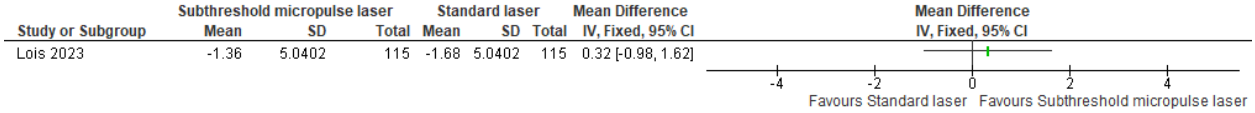


Figure 26: Mean change in CRT in the study eye, as determined by SD-OCT from baseline to month 24, mean

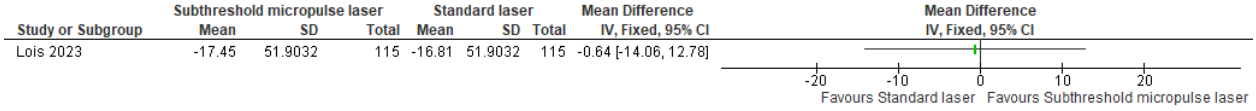


Figure 27: Number of patients meeting driving standards at month 24, n (%)

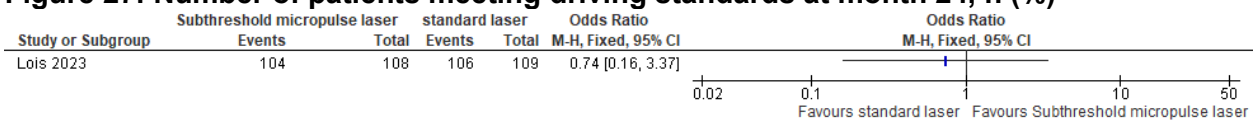
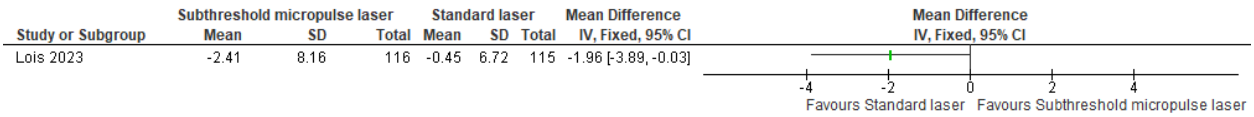


Figure 28: Number of laser treatments used from baseline to month 24 in study eye, mean



E.2 People with non-centre-involving macular oedema

Comparisons with vs standard threshold laser

Figure 29: Change in visual acuity from baseline (logMAR) at 12 months.

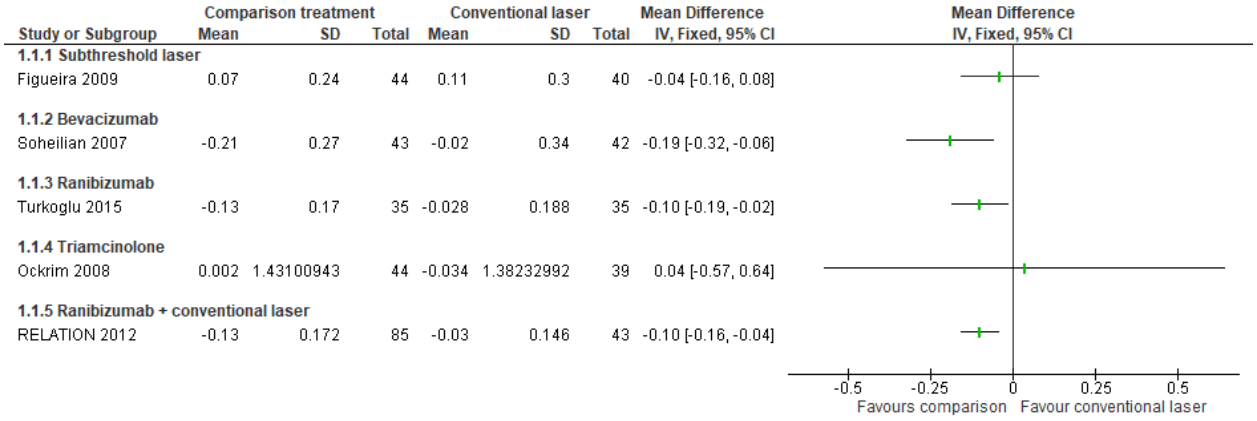


Figure 30:Change in central retinal thickness from baseline (mean difference) at 12 months

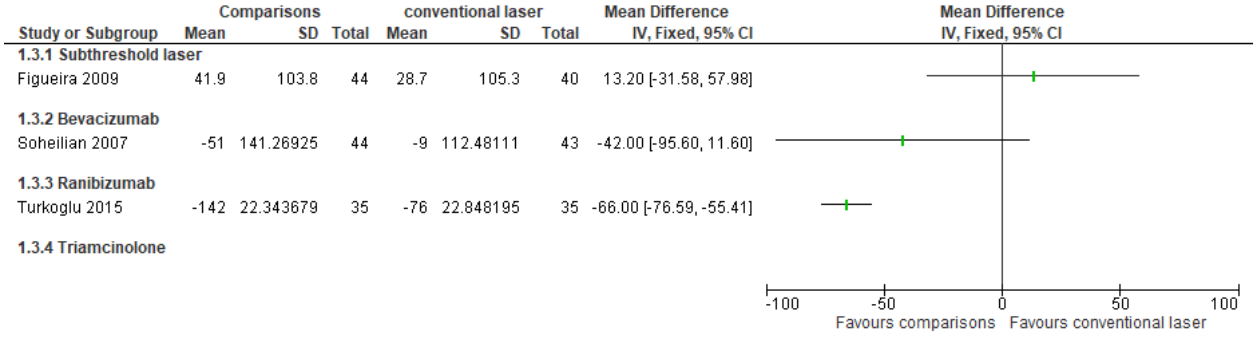


Figure 31: Change in visual acuity LogMAR at 24 months (mean difference)

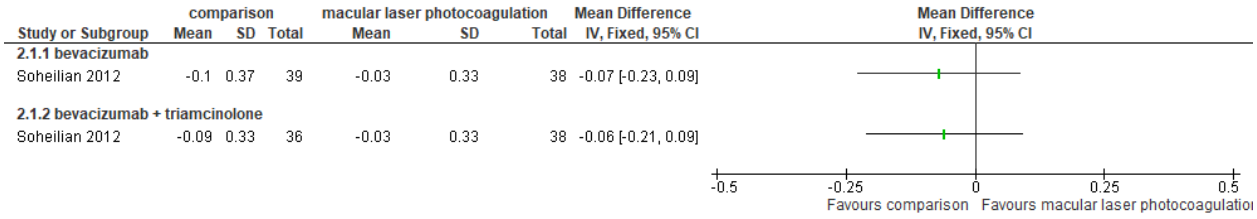
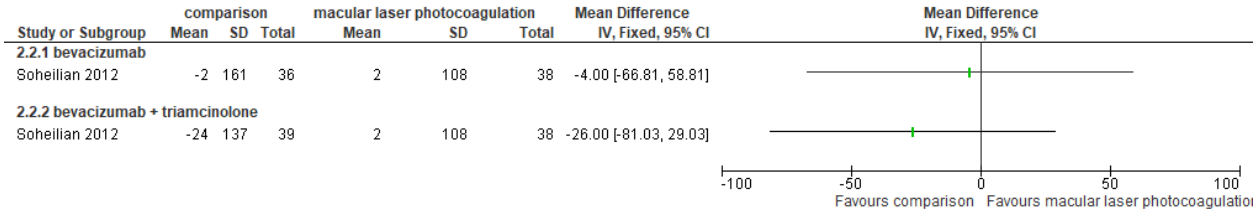


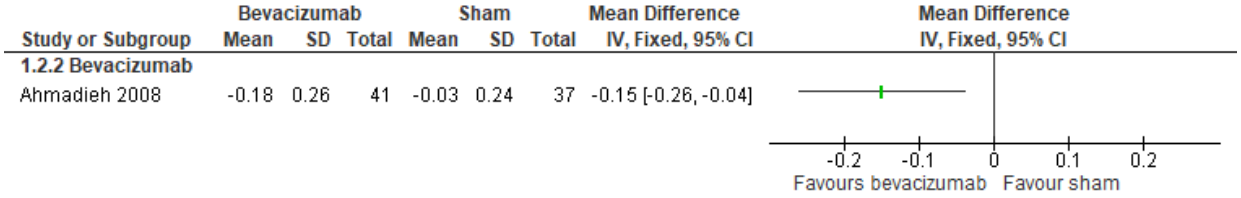
Figure 32: Change in central retinal thickness at 24 months (mean difference)

.



Anti-VEGF vs sham

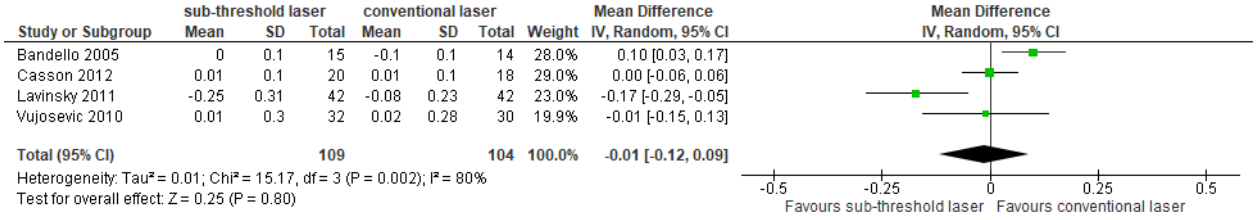
Figure 33: Change in visual acuity from baseline (logMAR) at 12 months.



E.3 Subgroup analysis: People with centre-involving diabetic macular oedema with a baseline central retinal thickness of less than 400 micrometres

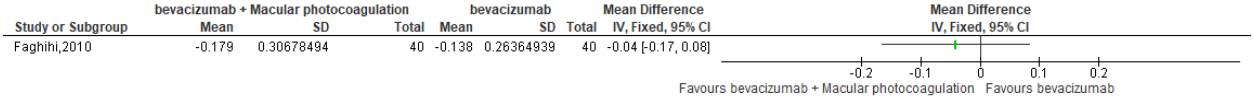
Sub-threshold vs standard threshold laser

Figure 34: Sub-threshold vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months.



Anti-VEGFs vs Anti-VEGFs with standard threshold laser

Figure 35: bevacizumab vs bevacizumab + standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months.



Anti-VEGFs vs standard threshold laser

Figure 36: Bevacizumab vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

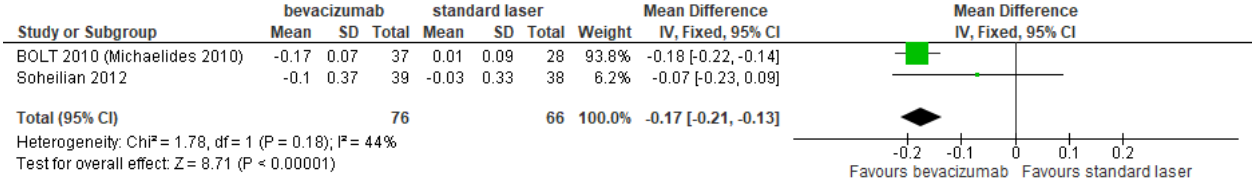


Figure 37: Aflibercept vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

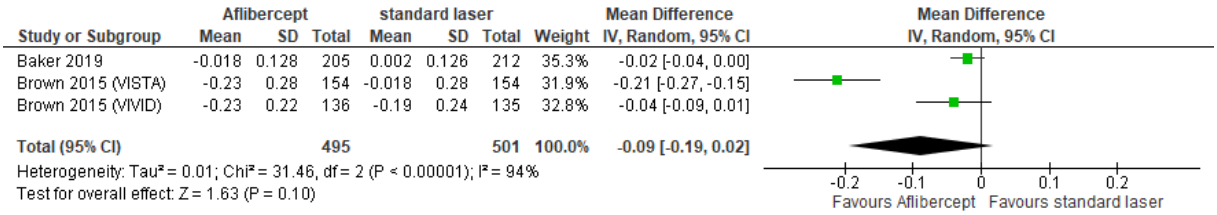


Figure 38: Steroids vs sham: Change in visual acuity LogMAR at 24 months (mean difference)

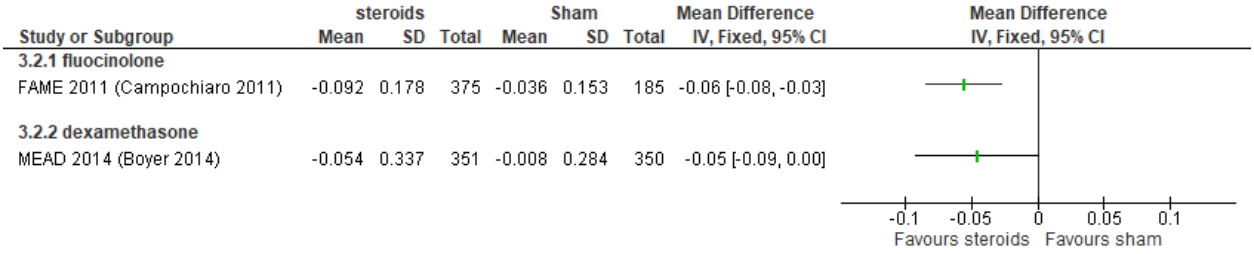


Figure 39: Brolucizumab vs aflibercept: Change in visual acuity LogMAR at 24 months (mean difference)

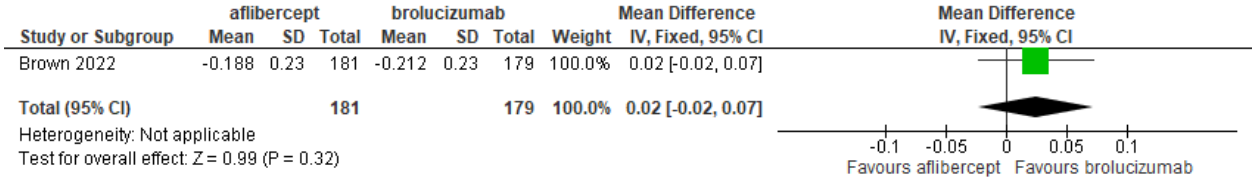
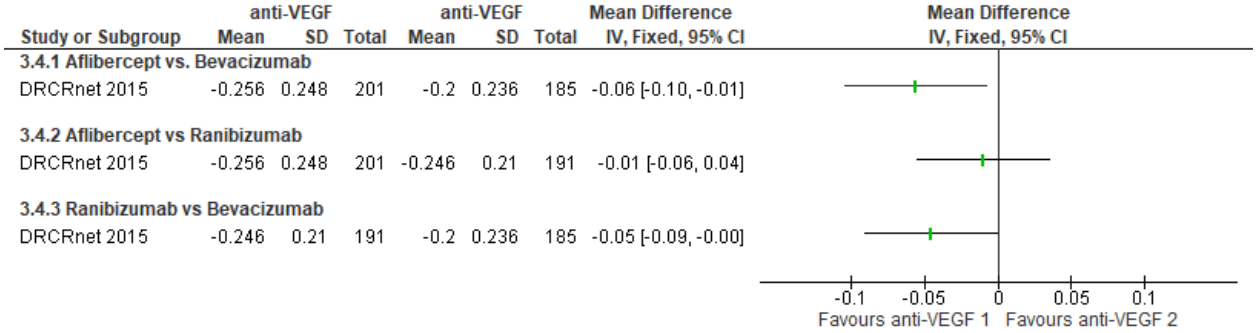
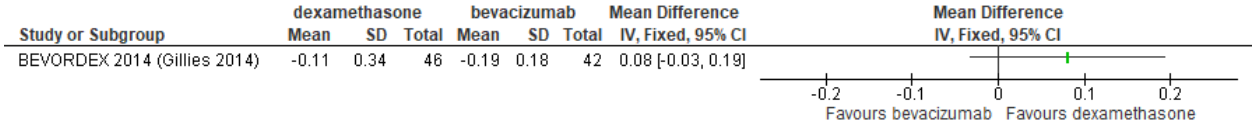


Figure 40: Anti VEGF vs Anti VEGF: Change in visual acuity LogMAR at 24 months (mean difference)



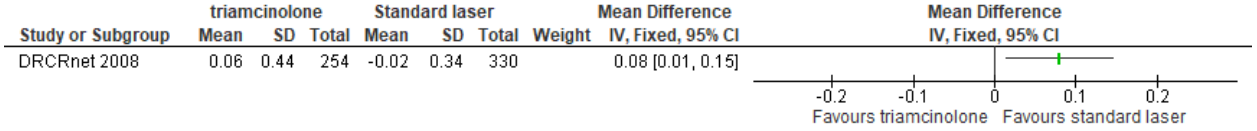
Steroids vs anti-VEGFs

Figure 41: Dexamethasone vs bevacizumab: Change in visual acuity LogMAR at 24 months (mean difference)



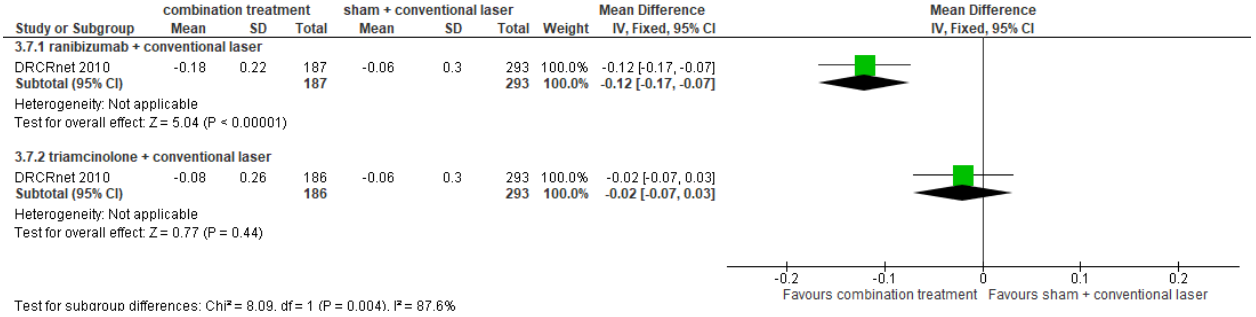
Steroids vs standard threshold laser

Figure 42: Triamcinolone vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)



Combination treatments vs standard threshold laser

Figure 43: Combination treatment vs sham + standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)



Combination treatments vs anti-VEGFs

Figure 44: Triamcinolone + Bevacizumab vs Bevacizumab: Change in visual acuity LogMAR at 24 months (mean difference)

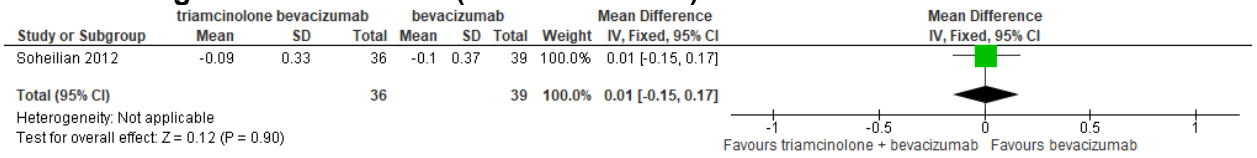
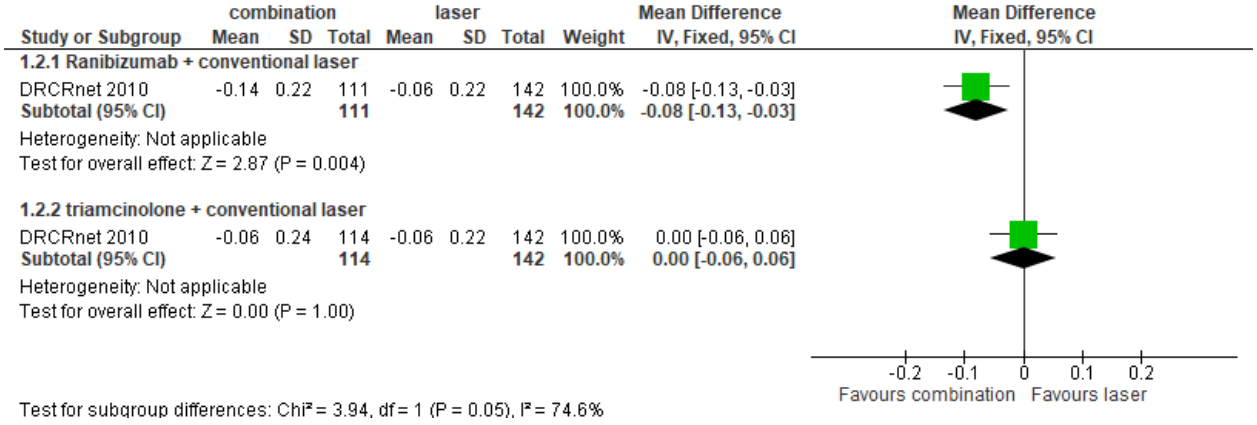


Figure 45: Combination treatment vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months



Anti-VEGFs vs standard threshold laser

Figure 46: Aflibercept every 4 weeks (2q4) vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months

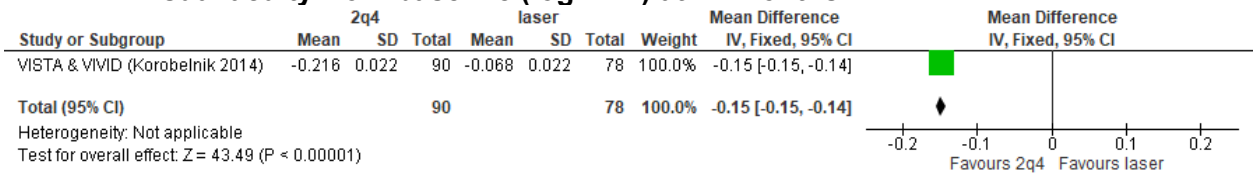


Figure 47: Aflibercept every 4 weeks (2q4) vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

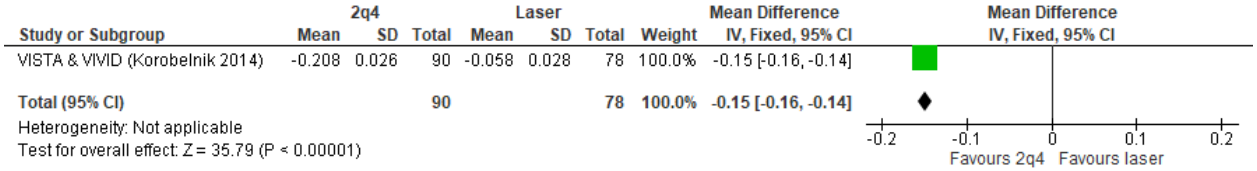


Figure 48: Aflibercept every 4 weeks (2q4) vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months.

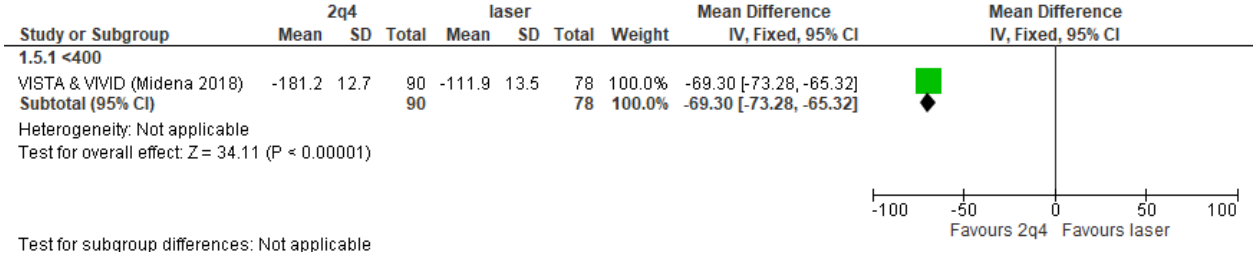
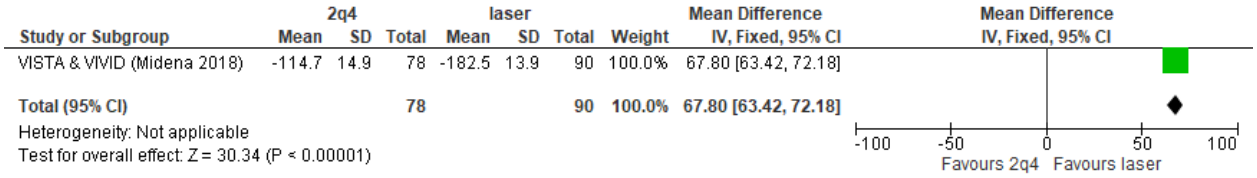
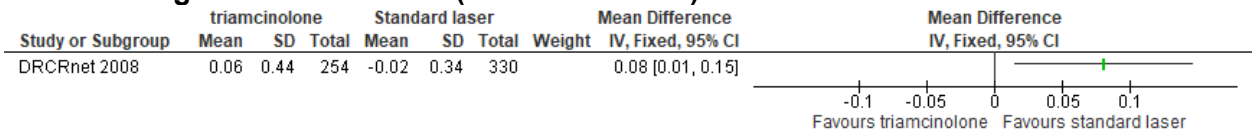


Figure 49: Aflibercept every 4 weeks (2q4) vs standard threshold laser: Change in central retinal thickness from baseline to 24 months



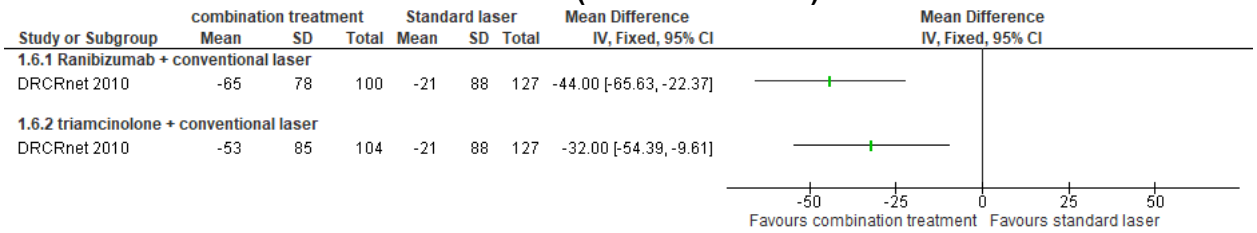
Steroids vs standard threshold laser

Figure 50: Triamcinolone vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)



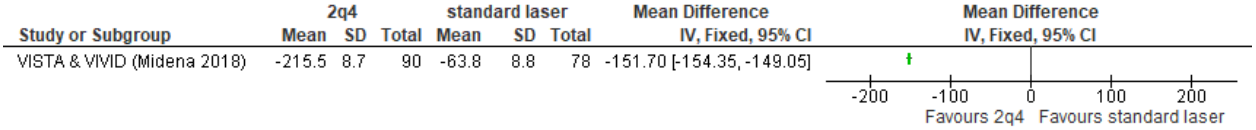
Combination treatments vs standard threshold laser

Figure 51: Combination treatment vs standard threshold laser: Change in central retinal thickness from baseline (mean difference)



E.4 Subgroup analysis: People with centre-involving diabetic macular oedema with a baseline central retinal thickness of 400 micrometres or more

Figure 52: Aflibercept vs standard threshold laser: Change in central retinal thickness from baseline to 24 months



E.5 Subgroup analysis: People with non-centre-involving diabetic macular oedema and baseline central retinal thickness of less than 400 micrometres

Figure 53: Comparisons vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months

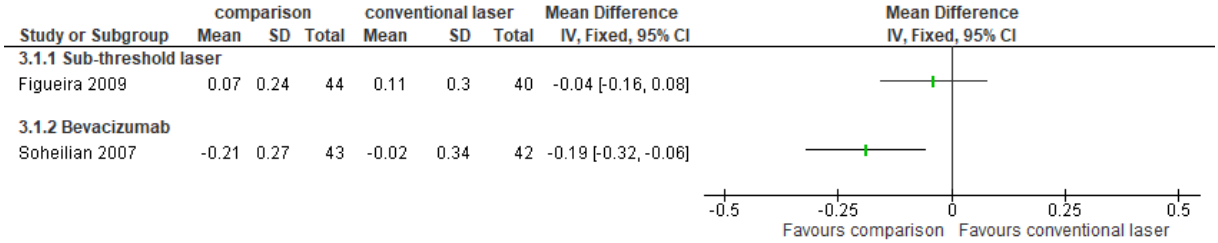
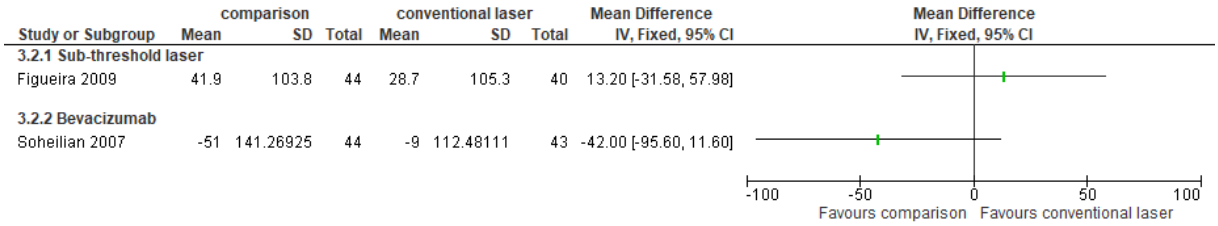


Figure 54:Comparisons vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months



Subgroup analysis: People with non-centre-involving diabetic macular oedema and baseline central retinal thickness of 400 micrometres or more

Figure 55:Comparisons vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months.

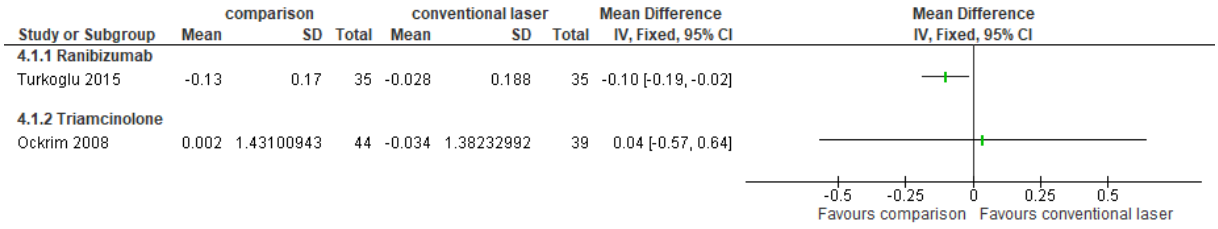


Figure 56: Ranibizumab vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months.

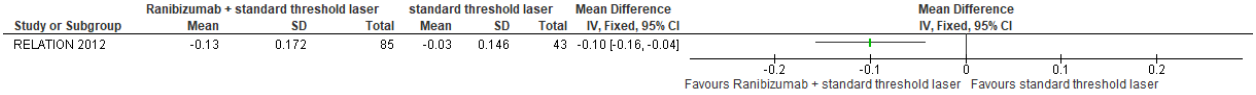


Figure 57:Bevacizumab vs sham

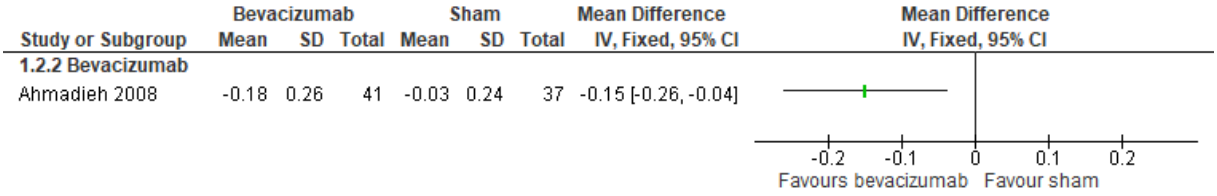


Figure 58:Ranibizumab vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months.>400

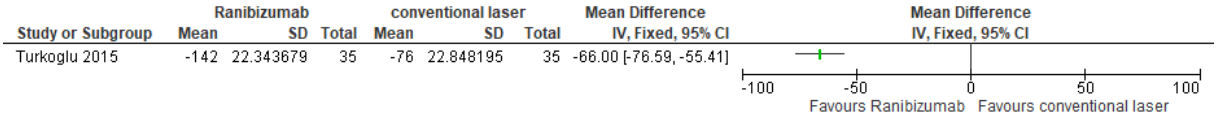


Figure 59:Comparisons vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

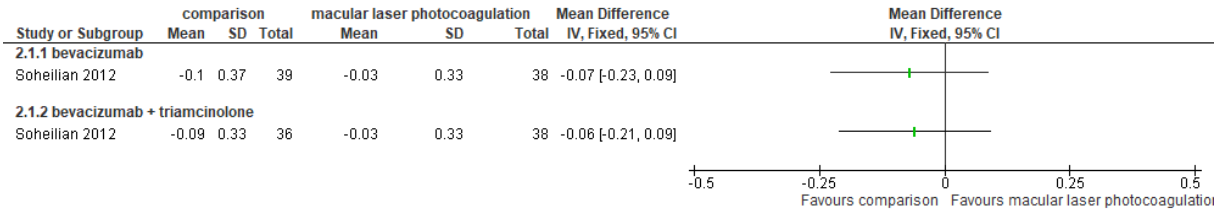
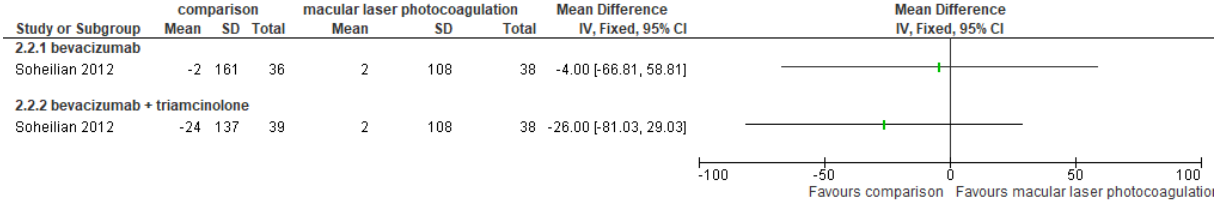


Figure 60:Comparisons vs standard threshold laser: Change in central retinal thickness from baseline to 24 months.



Appendix F – GRADE Tables

F.1 Network meta-analyses

People with centre-involving macular oedema

Visual acuity

Table 76. Change in visual acuity

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Quality
Change in visual acuity at 12 months (people with centre-involving macular oedema)							
41	RCT	8,469	See appendix K	No serious	No serious	Serious[1]	Moderate
Change in visual acuity at 24 months (people with centre-involving macular oedema)							
11	RCT	4,786	See appendix K	Serious[2]	No serious	No Serious	Moderate
Change in visual acuity at 12 months (people with centre-involving macular oedema and central retinal thickness >400 µm at baseline)							
30	RCT	6.936	See appendix K	No serious	No serious	No Serious	High
Change in visual acuity at 24 months (people with centre-involving macular oedema and central retinal thickness >400 µm at baseline)							
9	RCT	3,769	See appendix K	Serious[2]	No serious	No Serious	Moderate

1. Between study SD indicates some between trial heterogeneity.
2. >33.3% of studies in the NMA at moderate or high risk of bias. Quality downgraded 1 level

Central retinal thickness

Table 77. Change in central retinal thickness

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Quality
Change in central retinal thickness at 12 months (people with centre-involving macular oedema)							
32	RCT	5,285	See appendix K	Serious[1]	No serious	No serious	Moderate
Change in central retinal thickness at 24 months (people with centre-involving macular oedema)							
11	RCT	4,786	See appendix K	Serious[2]	No serious	No Serious	Moderate
Change in visual acuity at 12 months (people with centre-involving macular oedema and central retinal thickness >400 µm at baseline)							
24	RCT	4.530	See appendix K	Serious[1]	No serious	No serious	Moderate

1. >33.3% of studies in the NMA at moderate or high risk of bias. Quality downgraded 1 level

F.2 Pairwise meta-analysis

People with centre-involving macular oedema (whole population)

Anti-VEGFs vs standard threshold laser

Table 78:Visual Acuity: three or more lines improvement from baseline up to 12M

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 12M									
Overall									
11	Parallel RCTs	2410	RR: 2.30 [1.54, 3.45]	7 per 100	17 per 100 (11 lower,26 higher)	Serious[1]	Very serious[2]	No serious	Very low
Subgroup: Conbercept									
1	Parallel RCTs	199	RR: 1.67 [0.92, 3.03]	15 per 100	25 per 100 (14 lower,45 higher)	No serious	n/a[3]	No serious	High
Subgroup aflibercept									
4	Parallel RCT	1098	RR: 3.36 [2.15, 5.23]	6 per 100	20 per 100 (13 lower,31 higher)	No serious	serious [4]	No serious	Moderate
Subgroup bevacizumab									
1	Parallel RCT	50	RR: 2.26 [0.47, 10.98]	5 per 100	12 per 100 (2 lower,58 higher)	No serious	n/a[3]	No serious	High
Subgroup ranibizumab									
5	Parallel RCT	1033	RR: 1.92 [0.87, 4.24]	8 per 100	15 per 100 (7 lower,34 higher)	serious[1]	Very serious[2]	No serious	Very Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality

1. greater than 33.3% of the weight in the meta-analysis came from studies at moderate or high risk of bias
2. Studies with I^2 value >66%
3. Data from a single study
4. Studies with a I_2 value >33%

Table 79: Anti-VEGF vs standard threshold laser: the mean number of treatments at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Subgroup aflibercept									
4	Parallel RCT	905	MD: 9.49 [8.76, 10.23]	-	-	No serious	Very Serious[4]	No serious	Low
Subgroup bevacizumab									
2	Parallel RCT	164	MD: 2.10 [1.62, 2.58]	-	-	serious[2]	n/a[3]	No serious	Moderate
Subgroup ranibizumab									
4	Parallel RCT	903	MD: 1.98 [-2.34, 6.29]	-	-	serious[2]	Very serious[4]	No serious	Very Low
Subgroup: Conbercept									
1	Parallel RCT	157	MD: -0.10 [-1.18, 0.98]	-	-	No serious	N/A[3]	No serious	High

1. Studies with a I_2 value >33%
2. Study high risk of bias
3. Data from a single study
4. Studies with I2 value >66%

Table 80:Anti-VEGF vs standard threshold laser the mean number of treatments at 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Aflibercept									
2	Parallel RCT	578	MD: 19.00 [16.64, 21.35]	-	-	No serious	Serious[1]	No serious	Moderate

Table 81:Anti-VEGF vs standard threshold laser Adverse Events at 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Adverse Event: Cataract progression									
Subgroup aflibercept									
3	Parallel RCTs	1132	RR: 0.92 [0.36, 2.35]	2 per 100	1 per 100 (1 lower 4 higher)	No serious	No serious	No serious	High
Subgroup: ranibizumab									
1	Parallel RCTs	227	RR: 0.32 [0.01, 7.75]	1 per 100	0 per 100 (0 lower 7 higher)	No serious	n/a[3]	No serious	High
Adverse Event: Intraocular Pressure increase									
Subgroup aflibercept									
2	Parallel RCT	554	RR: 1.75 [0.94, 3.26]	5 per 100	9 per 100 (5 lower, 17 higher)	No serious	serious [1]	No serious	Moderate
Subgroup bevacizumab									
1	Parallel RCT	80	RR: 2.72 [0.11, 64.85]	0 per 100	0 per 100 (0 lower,0 higher)	No serious	n/a[3]	No serious	High
Subgroup ranibizumab									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1	Parallel RCT	382	RR: 8.14 [0.49, 134.21]	0 per 100	0 per 100 (0 lower,0 higher)	No serious	n/a[3]	No serious	High
Adverse Event: Vitreous haemorrhage									
Subgroup aflibercept									
3	Parallel RCTs	1132	RR: 0.73 [0.35, 1.50]	3 per 100	2 per 100 (1 lower, 4 higher)	No serious	Not serious	No serious	High
Subgroup: Conbercept									
1	Parallel RCTs	156	RR: 1.05 [0.27, 4.06]	5 per 100	5 per 100 (1 lower 20 higher)	No serious	n/a[3]	No serious	High
Subgroup bevacizumab									
1	Parallel RCT	80	RR: 0.30 [0.01, 7.21]	3 per 100	1 per 100 (0 lower,19 higher)	No serious	n/a[3]	No serious	High
Subgroup ranibizumab									
1	Parallel RCT	382	RR: 0.31 [0.08, 1.11]	5 per 100	2 per 100 9 (0 lower ,6 higher)	No serious	n/a[3]	No serious	High

1. Studies with a I_2 value >33%
2. Studies with I^2 value >66%
3. Data from a single study

Anti-VEGF vs Anti-VEGF

Table 82: Bevacizumab VS Ranibizumab

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 12M									
2	Parallel RCTs	636	RR: 0.88 [0.68, 1.14]	34 per 100	30 per 100 (23 lower 38 higher)	No serious	No serious	No serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
The mean number of treatments at 12 months									
2	Parallel RCT	226	MD 1.06 [-1.09, 3.22]	-	-	No serious	No serious	No serious	High

Table 83:Aflibercept vs Ranibizumab

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
The mean number of treatments at 12 months									
2	Parallel RCT	182	MD: -0.95 [-2.11, 0.21]	-	-	Serious[1]	Very serious[2]	No serious	Low

1. greater than 33.3% of the weight in the meta-analysis came from studies at moderate or high risk of bias
2. I^2 >66%

Table 84:**Brolucizumab vs Aflibercept**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 12M									
2	Parallel RCTs	736	RR: 1.14 [0.96, 1.37]	37 per 100	43 per 100 (36 lower 51 higher)	No serious	No serious	No serious	High
The mean number of treatments at 12 months									
2	Parallel RCT	736	MD: -1.60 [-1.80, -1.39]	-	-	No serious	No serious	No serious	High

Table 85: Faricimab vs Aflibercept

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 12M									
2	Parallel RCTs	1094	RR: 1.01 [0.85, 1.21]	31 per 100	31 per 100 (26 lower,38 higher)	No serious	No serious	No serious	High

Anti-VEGF plus standard threshold laser vs Anti-VEGF

Table 86: Ranibizumab vs Ranibizumab + standard threshold laser

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 12M									
3	Parallel RCTs	636	RR: 1.05 [0.78, 1.42]	20 per 100	21 per 100 (16 lower, 29 higher)	Serious[1]	No serious	No serious	Moderate
1. greater than 33.3% of the weight in the meta-analysis came from studies at moderate or high risk of bias									

Table 87: Bevacizumab vs Bevacizumab + standard threshold laser

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
The mean number of treatments at 12 months									
1	Parallel RCT	736	MD: 0.26 [-0.25, 0.77]	-	-	No serious	N/A[1]	No serious	High
1. Data from a single study									

Anti-VEGF vs sham

Table 88: Ranibizumab vs sham

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 24M									
1	Parallel RCT	509	RR: 2.66 [1.94, 3.65]	16 per 100	42 per 100 (31 lower,58 higher)	No serious	N/A[1]	No serious	High
Data from a single study									

Anti-VEGFs + steroids vs Anti-VEGF

Table 89: Anti-VEGF and steroid versus anti-VEGF alone: adverse events at 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
significant intraocular inflammation									
2	Parallel RCTs	189	RR: 0.99 [0.14, 6.95]	1 per 100	1 per 100 (0 lower 7 higher)	No serious	No serious	No serious	High
Cataract progression									
3	Parallel RCTs	268	RR: 9.30 [2.21, 39.02] 8.38 [1.97, 35.70]	1 per 100	7 per 100 (2 lower, 29 higher)	No serious	No serious	No serious	High
Raised intraocular pressure									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
7	Parallel RCT	557	RR: 12.07 [4.67, 31.25]	1 per 100	9 per 100 (3 lower, 22 higher)	Serious	No serious	No serious	Moderate

Steroids vs sham

Table 90:Intravitreal dexamethasone versus sham

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 12M									
1	Parallel RCTs	701	RR: 1.39 [0.91, 2.12]	9 per 100	13 per 100 (9 lower, 20 higher)	Serious[1]	N/A[2]	No serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 24 M									
1	Parallel RCTs	701	RR: 1.54 [1.04, 2.26]	11 per 100	16 per 100 (11 lower, 24 higher)	Serious[1]	N/A[2]	No serious	Moderate
Adverse events Cataract progression at 36 months									
1	Parallel RCT	697	RR: 3.89 [2.75, 5.50]	10 per 100	38 per 100 (27 lower, 53 higher)	Serious[1]	N/A[2]	No serious	Moderate
Adverse events IOP increase at 36 months									
1	Parallel RCT	697	RR: 8.99 [5.05, 16.03]	3 per 100	31 per 100 (17 lower, 55 higher)	Serious[1]	N/A[2]	No serious	Moderate

1. greater than 33.3% of the weight in the meta-analysis came from studies at moderate or high risk of bias
2. Data from a single study

Table 91:Intravitreal fluocinolone acetonide implant versus sham

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 12M									
1	Parallel RCTs	560	RR: 1.79 [1.16, 2.78]	12 per 100	21 per 100 (14 lower 33 higher)	No serious	N/A[1]	No serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 24 M									
1	Parallel RCTs	560	RR: 1.76 [1.22, 2.53]	16 per 100	29 per 100 (20 lower, 41 higher)	No serious	N/A[1]	No serious	High
Adverse events Cataract progression at 24 M									
1	Parallel RCT	351	RR: 1.63 [1.35, 1.97]	50 per 100	82 per 100 (68 lower,99 higher)	No serious	N/A[1]	No serious	High
Adverse events IOP increase at 24 M									
1	Parallel RCT	531	RR: 3.35 [2.22, 5.06]	12 per 100	40 per 100 (27 lower, higher 61)	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 92: Intravitreal triamcinolone acetonide injection versus sham

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement									
1	Parallel RCTs	69	RR: 4.12 [0.48, 34.99]	3 per 100	12 per 100 (1 lower,100 higher)	serious[1]	N/A[2]	No serious	Moderate
Adverse events Cataract progression at 24 M									
1	Parallel RCT	69	RR: 3.00 [0.97, 9.30]	14 per 100	43 per 100 (14 lower 133 higher)	serious[1]	N/A[2]	No serious	Moderate
Adverse events IOP increase at 24 M									
1	Parallel RCT	69	RR: 10.29 [1.39, 76.12]	3 per 100	29 per 100 (4 lower, 217 higher)	serious[1]	N/A[2]	No serious	Moderate

1. Greater than 33.3% of the weight in the meta-analysis came from studies at moderate or high risk of bias
2. Data from a single study

Steroids vs anti-VEGF

Table 93:Intravitreal dexamethasone versus intravitreal anti-VEGF Visual Acuity: three or more lines improvement from baseline up to 12M

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 12M									
Subgroup bevacizumab									
1	Parallel RCT	88	RR: 0.99 [0.70, 1.40]	60 per 100	59 per 100 (42 lower, 83 higher)	No serious	N/A[1]	No serious	Moderate
Subgroup ranibizumab									
1	Parallel RCT	363	RR: 0.50 [0.32, 0.79]	25 per 100	13 per 100 (8 lower,20 higher)	No serious	N/A[1]	No serious	Moderate

1. Data from a single study

Table 94:Intravitreal dexamethasone versus intravitreal anti-VEGF The mean number of treatments at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Subgroup aflibercept									
1	Parallel RCT	98	MD:] Not estimable[2]	-	-	No serious	N/A[1]	No serious	High
Subgroup bevacizumab									
1	Parallel RCT	88	MD:] Not estimable[2]	-	-	No serious	N/A[1]	No serious	High
Subgroup ranibizumab									
1	Parallel RCT	363	MD: Not estimable[2]	-	-	No serious	N/A[1]	No serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality

1. Data from a single study
2. Not estimatable study did not report SD values

Table 95:Intravitreal dexamethasone versus intravitreal anti-VEGF Adverse Events at 12 to 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Adverse Event: Cataract progression at 24 months									
Subgroup bevacizumab									
1	Parallel RCTs	88	RR: 2.74 [0.58, 12.84]	5 per 100	13 per 100 (3 lower, 61 higher)	No serious	N/A[1]	No serious	High
Subgroup: Ranibizumab									
1	Parallel RCTs	247	RR: 4.54 [2.41, 8.55]	8 per 100	38 per 100 (20 lower, 71 higher)	No serious	N/A[1]	No serious	High
Adverse Event: IOP increase at 24 months									
Subgroup aflibercept									
1	Parallel RCT	98	RR: 11.45 [0.65, 201.60]	0 per 100	0 per 100 (0 lower 0 higher)	No serious	N/A[1]	No serious	High
Subgroup bevacizumab									
1	Parallel RCT	88	RR: 2.40 [1.19, 4.82]	19 per 100	46 per 100 (23 lower,92 higher)	No serious	N/A[1]	No serious	High
Subgroup ranibizumab									
1	Parallel RCT	363	RR: 5.03 [1.12, 22.63]	1 per 100	6 per 100, (1 lower 25 higher)	No serious	N/A[1]	No serious	High
1. Data from a single study									

Steroids vs macular laser

Table 96:Intravitreal triamcinolone acetonide versus macular laser

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Visual Acuity: three or more lines improvement from baseline up to 12M									
1	Parallel RCTs	584	RR: 0.85 [0.55, 1.30]	14 per 100	12 per 100 (8 lower,18 higher)	No serious	N/A[1]	No serious	High
Visual Acuity: three or more lines improvement from baseline up to 24 M									
1	Parallel RCTs	584	RR: 0.95 [0.66, 1.35]	per 100	per 100	No serious	N/A[1]	No serious	High
Adverse events Cataract progression at 24 M									
1	Parallel RCT	459	RR: 2.68 [2.21, 3.24]	31 per 100	83 per 100 (68 lower 100 higher)	No serious	N/A[1]	No serious	High
Adverse events IOP increase at 24 M									
1	Parallel RCT	584	RR: 9.20 [5.14, 16.47]	4 per 100	33 per 100 (19 lower,60 higher)	No serious	N/A[1]	No serious	High

1. Data from a single study

Subthreshold laser versus standard threshold laser

Table 97:Mean change in BCVA in the study eye from baseline to month 24 (ETDRS letters), mean (SD)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Mean change in BCVA in the study eye from baseline to month 24 (ETDRS letters), mean (SD)									
Lois 2023	Pragmatic RCT	230	MD: 0.32 [-0.98, 1.62]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 98:Mean change in CRT in the study eye, as determined by SD-OCT from baseline to month 24, mean (SD)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Mean change in CRT in the study eye, as determined by SD-OCT from baseline to month 24, mean (SD)									
Lois 2023	Pragmatic RCT	230	MD -0.64 [-14.06, 12.78]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 99:Number of patients meeting driving standards at month 24, n (%)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Number of patients meeting driving standards at month 24, n (%)									
Lois 2023	Pragmatic RCT	217	OR: 0.74 [0.16, 3.37]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 100:Number of laser treatments used from baseline to month 24 in study eye, mean (SD)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Number of laser treatments used from baseline to month 24 in study eye, mean (SD)									
Lois 2023	Pragmatic RCT	231	MD -1.96 [-3.89, -0.03]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

People with non-centre-involving macular oedema

Comparisons vs standard threshold laser

Table 101:Comparisons vs standard threshold laser Change in visual acuity from baseline (logMAR) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Sub-threshold laser									
1 Figueira 2009	Parallel RCTs	84	MD -0.04 [-0.16,0.08]	-	-	No serious	N/A[1]	No serious	High
Bevacizumab									
1 Soheilian 2007	Parallel RCTs	85	MD -0.19 [-0.32, -0.06]	-	-	Serious [2]	N/A[1]	No serious	Moderate
Ranibizumab									
1 Turkoglu 2015	Parallel RCT	70	MD -0.10 [-0.19, -0.02]	-	-	No serious	N/A[1]	No serious	High
Triamcinolone									
1 Ockrim 2008	Parallel RCT	83	MD 0.04 [-0.57.-0.64]	-	-	Very serious[3]	N/A[1]	No serious	Low
Triamcinolone									
1 RELATION 2012	Parallel RCT	128	MD -0.10 [-0.16.-0.04]	-	-	Very serious[3]	N/A[1]	No serious	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality

1. Data from a single study
2. Study at moderate risk of bias
3. Study at high risk of bias

Table 102:Comparisons vs standard threshold laser change in CRT at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Sub-threshold laser									
1 Figueira 2009	Parallel RCTs	84	MD: 13.20 [-31.58 , 57.98]	-	-	No serious	N/A[1]	No serious	High
Bevacizumab									
1 Soheilian 2007	Parallel RCTs	85	MD: -42.00 [-95.60.-, -11.60]	-	-	Serious[2]	N/A[1]	No serious	Moderate
Ranibizumab									
1 Turkoglu 2015	Parallel RCT	70	MD: -66.00 [-78.59, --55.41	-	-	No serious	N/A[1]	No serious	High
Triamcinolone									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality

1. Data from a single study
2. Study at moderate risk of bias
3. Study at high risk of bias

Anti-VEGFs vs sham

Table 103:Anti-VEGF vs sham: Change in visual acuity from baseline (logMAR) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Bevacizumab									
1 Ahmadieh 2008	Parallel RCTs	78	MD -0.15 [-0.26.-0.04]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Subgroup analysis: People with centre-involving diabetic macular oedema with a baseline central retinal thickness of less than 400 micrometres

Sub-threshold vs standard threshold laser

Table 104:Sub-threshold vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Sub-threshold laser vs standard threshold laser									
4	Parallel RCT	213	MD -0.01 [-0.12, 0.09]	-	-	No serious	Very Serious[1]	No serious	Low

1. Study with a I^2 value >66%

Anti-VEGFs vs Anti-VEGFs with standard threshold laser

Table 105:bevacizumab vs bevacizumab + Macular laser: Change in visual acuity from baseline (logMAR) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Bevacizumab vs bevacizumab + Macular laser									
1 (Faghihi,2010)	Parallel RCT	80	MD: -0.04 [-0.17, 0.08]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Anti-VEGFs vs standard threshold laser

Table 106:Anti-VEGF vs standard threshold laser : Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Bevacizumab Vs standard threshold laser									
2	Parallel RCT		MD -0.17 [-0.21, -0.13]	-	-	No serious	serious[1]	No serious	Moderate
Aflibercept Vs standard threshold laser									
3	Parallel RCT		MD -0.09 [-0.19, 0.02]	-	-	No serious	Very Serious[2]	No serious	Low

1. Study with a I2 value >33%
2. Study with a I^2 value >66%

Steroids vs sham

Table 107:Steroids vs sham: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Fluocinolone Vs Sham (MD less than 0 favours steroid)									
1 FAME 2011 (Campochiaro 2011)	Parallel RCT	560	MD: -0.06 [-0.08, -0.03]	-	-	No serious	N/A[1]	No serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Dexamethasone Vs Sham (MD less than 0 favours steroid)									
1 MEAD 2014 (Boyer 2014)	Parallel RCT	701	MD: -0.05 [-0.09, 0.00]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Anti-VEGF vs Anti-VEGF

Table 108: Brolucizumab vs aflibercept: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Brolucizumab Vs Aflibercept									
1 (Brown 2022)	Parallel RCT	360	0.02 [-0.02, 0.07]	-	-	No serious	N/A[1]	No serious	High

1. Study with a I^2 value >66%

Table 109:Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Aflibercept vs. Bevacizumab									
DRCRnet 2015	Parallel RCT	386	MD -0.06 [-0.10, -0.01]	-	-	No serious	N/A[1]	No serious	High
Aflibercept vs Ranibizumab									
DRCRnet	Parallel RCT	392	MD -0.01 [-	-	-	No	N/A[1]	No serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
2015			0.06, 0.04]			serious			
Ranibizumab vs Bevacizumab									
DRCRnet 2015	Parallel RCT	376	MD -0.05 [-0.09, -0.00]	-	-	No serious	N/A[1]	No serious	High
2. Data from a single study									

Steroids vs Anti-VEGFs

Table 110:Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Dexamethasone Vs Bevacizumab									
BEVORDEX 2014 (Gillies 2014)	Parallel RCT	88	MD 0.08 [-0.03, 0.19]	-	-	No serious	N/A[1]	No serious	High
1. Data from a single study									

Steroids vs standard threshold laser

Table 111:Triamcinolone vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Triamcinolone Vs standard threshold laser									
DRCRnet 2008	Parallel RCT	584	MD 0.08 [0.01, 0.15]	-	-	No serious	N/A[1]	No serious	High
1. Data from a single study									

Combination treatments vs standard threshold laser

Table 112:Combination treatment vs sham + standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
ranibizumab + standard threshold laser									
DRCRnet 2010	Parallel RCT	480	MD -0.12 [-0.17, -0.07]	-	-	No serious	N/A[1]	No serious	High
triamcinolone + standard threshold laser									
DRCRnet 2010	Parallel RCT	479	MD -0.02 [-0.07, 0.03]	-	-	No serious	N/A[1]	No serious	High
1. Data from a single study									

Combination treatments vs Anti-VEGFs

Table 113:bevacizumab vs triamcinolone + bevacizumab: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Bevacizumab Vs Triamcinolone + Bevacizumab									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Soheilian 2012	Parallel RCT	75	MD 0.01 [-0.15, 0.17]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 114: Change in visual acuity from baseline (logMAR) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Ranibizumab + standard threshold laser vs standard threshold laser									
DRCRnet 2010	Parallel RCT	253	MD -0.08 [-0.03, -0.13]	-	-	No serious	N/A[1]	No serious	High
triamcinolone + standard threshold laser vs standard threshold laser:									
DRCRnet 2010	Parallel RCT	256	MD 0.00 [--0.06, 0.06]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Anti-VEGFs vs standard threshold laser

Table 115:Aflibercept vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Aflibercept vs standard threshold laser									
VISTA & VIVID (Korobelnik 2014)	Parallel RCT	168	MD -0.15 [-0.15, -0.14]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 116:Aflibercept vs standard threshold laser: Change in visual acuity (logMAR) at 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Aflibercept vs standard threshold laser: Visual acuity at 24 months									
VISTA & VIVID (Korobelnik 2014)	Parallel RCT	168	MD -0.15 [-0.16, -0.14]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 117: Aflibercept vs standard threshold laser: Change in central retinal thickness from baseline to 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
standard threshold laser vs 2q4: mean central retinal thickness at 12 months.									
VISTA & VIVID (Midena 2018)	Parallel RCT	168	MD -69.30 [-73.28, -65.32]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 118:Aflibercept vs standard threshold laser: Change in central retinal thickness from baseline to 24 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
standard threshold laser vs 2q4: mean central retinal thickness at 24 months.									
VISTA & VIVID (Midena 2018)	Parallel RCT	168	MD 67.80 [63.42, 72.18]	-	-	No serious	N/A[1]	No serious	High

2. Data from a single study

Steroids vs standard threshold laser

Table 119:Triamcinolone vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Triamcinolone 4 mg vs standard threshold laser									
DRCRnet 2008	Parallel RCT	296	MD 0.08 [0.01, 0.15]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Combination treatments vs standard threshold laser

Table 120:Combination treatment vs standard threshold laser: Change in central retinal thickness from baseline (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Ranibizumab + standard threshold laser									
DRCRnet 2010	Parallel RCT	227	MD -44.00 [-22.37, -65.63]	-	-	No serious	N/A[1]	No serious	High
triamcinolone + standard threshold laser									
DRCRnet 2010	Parallel RCT	231	MD -32.00 [-9.61, -54.39]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Subgroup analysis: People with centre-involving diabetic macular oedema with a baseline central retinal thickness of 400 micrometres or more

Table 121:Aflibercept vs standard threshold laser: Change in central retinal thickness from baseline to 24 months. and >400.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
>400									
VISTA & VIVID (Midena 2018)	Parallel RCT	168	MD -151.70 [-149.05, -154.35]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Subgroup analysis: People with non-centre-involving diabetic macular oedema and baseline central retinal thickness of less than 400 micrometres

Table 122:Comparisons vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Subthreshold laser vs standard threshold laser									
Figueira 2009	Parallel RCT	84	MD -0.04 [-0.16, 0.08]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 123:Comparisons vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Bevacizumab vs standard threshold laser									
Soheilian 2007	Parallel RCT	85	MD -0.19 [-0.32, -0.06]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 124:Comparisons vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Subthreshold laser vs standard threshold laser									
Figueira 2009	Parallel RCT	84	MD 13.20 [-31.58, 57.98]	-	-	No serious	N/A[1]	No serious	High
Bevacizumab vs standard threshold laser									
Soheilian 2007	Parallel RCT	85	MD -42.00 [-95.60, 11.60]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Subgroup analysis: People with non-centre-involving diabetic macular oedema and baseline central retinal thickness of 400 micrometres or more

Table 125:Comparisons vs standard threshold laser: Change in visual acuity from baseline (logMAR) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Ranibizumab vs standard threshold laser									
Turkoglu 2015	Parallel RCT	70	MD -0.10 [-	-	-	No	N/A[1]	No serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
			0.19, -0.02]			serious			
Triamcinolone vs standard threshold laser									
Ockrim 2008	Parallel RCT	83	MD 0.04 [-0.57, 0.64]	-	-	No serious	N/A[1]	No serious	High
1. Data from a single study									

Table 126:Ranibizumab vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Ranibizumab + standard threshold laser vs standard threshold laser									
RELATION 2012	Parallel RCT	128	MD -0.10 [-0.16, -0.04]	-	-	No serious	N/A[1]	No serious	High
1. Data from a single study									

Table 127:Bevacizumab vs sham

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Bevacizumab vs sham									
Ahmadieh 2008	Parallel RCT	78	MD -0.15 [-0.26, -0.04]	-	-	No serious	N/A[1]	No serious	High
1. Data from a single study									

Table 128:Ranibizumab vs standard threshold laser: Change in central retinal thickness from baseline (mean difference) at 12 months

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Ranibizumab vs standard threshold laser									
Turkoglu 2015	Parallel RCT	70	MD -66.00 [-76.59, -55.41]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Table 129:Comparisons vs standard threshold laser: Change in visual acuity LogMAR at 24 months (mean difference)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
VA (logMAR) at 24M bevacizumab									
Soheilian 2012	Parallel RCT	77	MD 0.07 [-0.23, 0.09]	-	-	No serious	N/A[1]	No serious	High
bevacizumab + triamcinolone									
Soheilian 2012	Parallel RCT	74	MD -0.06 [-0.21, 0.09]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

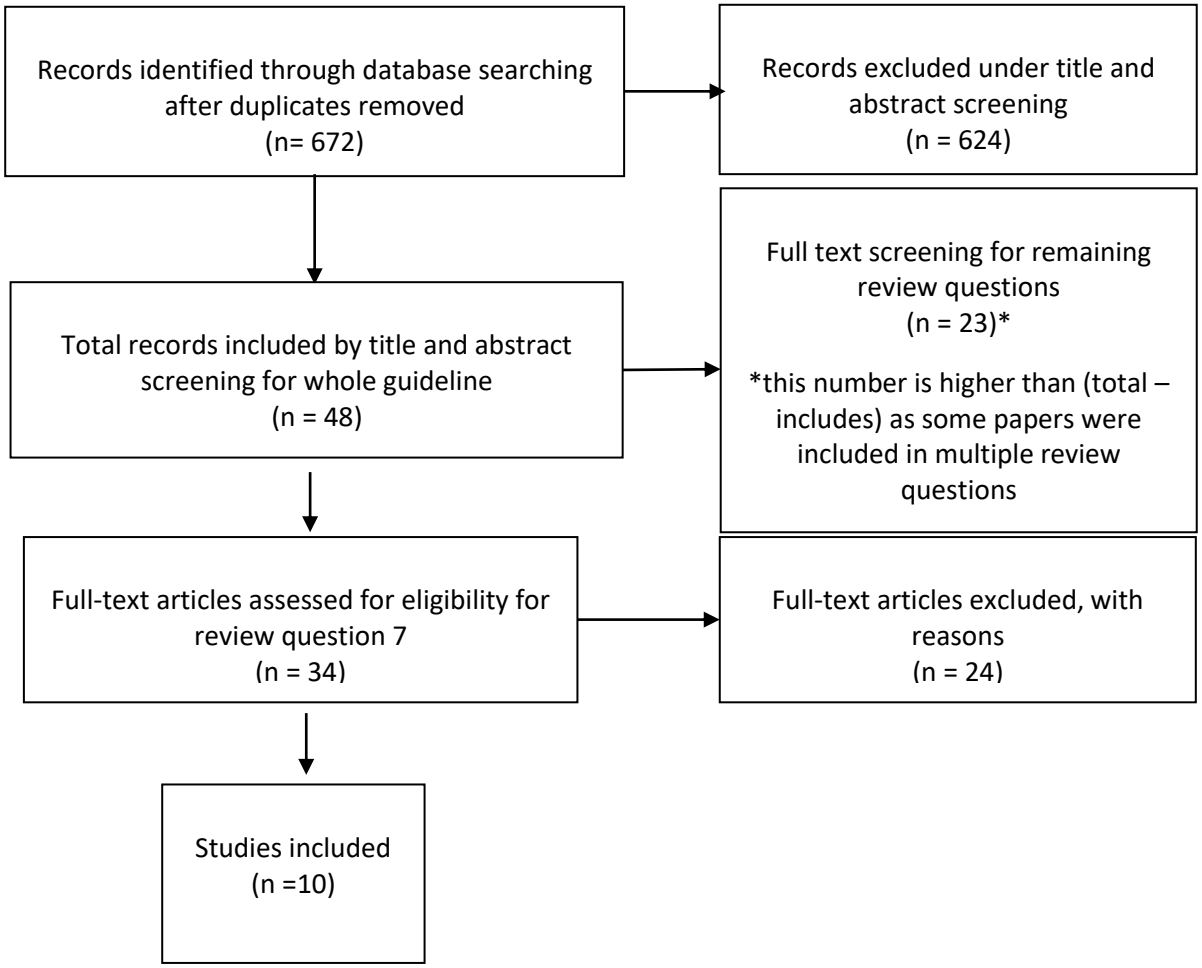
Table 130:Comparisons vs standard threshold laser: Change in central retinal thickness from baseline to 24 months.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
bevacizumab									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Soheilian 2012	Parallel RCT	77	MD -4.00 [-66.81, 58.81]	-	-	No serious	N/A[1]	No serious	High
bevacizumab + triamcinolone									
Soheilian 2012	Parallel RCT	74	MD -26.00 [-81.03, 29.03]	-	-	No serious	N/A[1]	No serious	High

1. Data from a single study

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Table 131: Economic evidence table

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
Regnier et al (2015)	Economic analysis: Cost-utility analysis Study design: Markov cohort model Time horizon: 3 years and lifetime	Setting: UK Perspective: NHS and PSS	Ranibizumab 0.5mg pro re nata (PRN) (as needed) Ranibizumab 0.5mg treat and extend (T&E) Aflibercept 2mg, 5 initial monthly doses followed by every 8 weeks	Patients with diabetic macular oedema, based on the RESTORE clinical trial Baseline age of 65 assumed, 60% of patients were treated in their WSE, 18% treated in BSE and 22% treated in both eyes as reported in RESTORE study Baseline BCVA (letters): 86-100: 0% patients 76-85: 11% patients 66-75: 39% patients 56-65: 27% patients 46-55: 15% patients 36-45: 8% patients 26-35: 0% ≤ 25: 0%	Discount rates: 3.5% Cycle length: 3 months Patients could gain or lose a maximum of 2 health states per cycle. Half cycle correction applied. Baseline BCVA and ranibizumab 0.5mg PRN: RESTORE study. Transition probabilities: Years 1-3: ranibizumab 0.5mg calculated using the RESTORE study 3-year data. Year 4 onwards: WESDR study (assuming no treatment) Aflibercept Year 1: Published NMA, Year 2 onwards: same TPs assumed as ranibizumab due to a lack of published data. Ranibizumab (T&E): RETAIN study, ranibizumab 0.5mg (mono therapy or in combination with laser), Patients assessed monthly for stabilisation, if stabilisation is confirmed patients receive no treatment, patients were assessed	Ranibizumab was dominant over aflibercept with net monetary benefit of £6,768 for ranibizumab PRN and £3,934 for ranibizumab (T&E) at a willingness to pay threshold of £20,000.	Deterministic: Main driver of the results was changes in the odds ratio of ranibizumab PRN compared with aflibercept, number of injections and higher costs of aflibercept Probabilistic: Ranibizumab PRN had a 79% probability and ranibizumab (T&E) had a 67% probability of being cost effective compared with aflibercept assuming a willingness to pay threshold of £20,000 per QALY.	Source of funding: Novartis Not a full incremental analysis Adverse events were not included in the analysis as they were assumed equivalent. Authors conclusions: Ranibizumab both as needed or (T&E) regimens were dominant over aflibercept for the treatment of visual impairment due to DME. Ranibizumab lead to both higher QALY gains and lower costs compared with aflibercept.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					monthly, if no loss of BCVA patients would not be treated again for a maximum of 3 months without treatment, same transition probabilities as ranibizumab PRN assumed after year 1. Baseline/natural history: WSDR study used for transition probabilities from year 4 onwards. Utilities: Assigned by whether the treated eye was BSE or WSE and by BCVA. Czoski-Murray et al were used for the BSE (0.86–0.368* LogMar –0.001*age), a utility decrement of 0.1 was assumed between best and worst states in WSE. Resource use: Ranibizumab PRN: Treatment frequencies years 1-3 and monitoring year 1 – RESTORE Monitoring frequencies years 2 to 3 were from DRCR.net study since monthly monitoring is no longer required. Aflibercept treatment frequencies: year 1 mean from trials VIVID-DME and VISTA-DME			

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					year 2 mean frequency from VIVID-DME, year 3 assumed to be the same as year 2. Ranibizumab T & E: RETAIN trial, frequency for year 3 assumed to be the same as year 2 Cost of blindness applied to those with BCVA less than 35 letters.			
Mitchell et al (2012)	Economic analysis: Cost-utility analysis Study design: Markov cohort model 15 year time horizon based on 12 months of RESTORE trial data	Setting: UK NHS and PSS perspective	Ranibizumab monotherapy Combination therapy laser and ranibizumab Laser monotherapy	Patients with diabetic macular oedema, based on the RESTORE clinical trial Age 63 years, 40.2% treated in their better seeing eye (BSE)	Markov cohort model with 3-month cycle with 8 mutually exclusive health states defined by BCVA intervals (86-100, 76-85, 66-75, 56-65, 46-55, 36-45, 26-35 and ≤ 25 letters) in addition to a 9th absorbing death health state. Patients could gain or lose a maximum of 2 health states per cycle. Half cycle correction applied. Discount rates: 3.5% Treatment frequency based on RESTORE for year 1, In year 2 proportionately fewer injections assumed based on DRCR.net. After year 2 laser therapy only was assumed for all arms.	Incremental costs: Ranibizumab mono compared with laser mono: £4,191 Ranibizumab combo compared with laser mono: £4,695 Incremental QALYs: Ranibizumab mono compared with laser mono: 0.17 Ranibizumab combo compared with laser mono: 0.13 ICER:	Deterministic: Model most sensitive to changes in the number of injections and reducing the time horizon to 10 years. Changing the source of utilities increased the QALY gains and reduced the ICER. Probabilistic: 64% probability ranibizumab monotherapy would be cost effective compared to laser and 42% probability combination therapy would be cost effective compared to laser therapy based on a willingness to pay threshold of £30,000 per QALY.	Source of funding: Novartis Authors conclusions: Ranibizumab monotherapy is considered cost effective assuming QALYs are values at £30,000 each. Limitations: Only the cost effectiveness of treating one eye was considered, not both eyes. EQ-5D values were used in the base-case which are known to be insensitive to changes in eye conditions. Absolute results are not presented, only the incremental results.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					BCVA achieved in year 1 assumed to be maintained during year 2 based on observations from protocol I. Year 3 onwards all treatment arms transition probabilities based on natural history from WESDR reports. Treatment discontinuation applied in year one only, no adverse events included. Mortality: Hazard ratios associated with both type 2 diabetes (Mulnier et al 2006) and DME (Hirai et al 2008) were applied to general UK population mortality. Utility: EQ-5D from restore was used in the base-case analysis, mapping from VA by Lloyd et al 2008 and Brown et al 1999 were used as scenarios.	Ranibizumab mono compared with laser mono: £24,028 Ranibizumab combo compared with laser mono: £36,106		
Pochopien et al (2019)	Economic analysis: Cost-utility analysis Study design: Markov cohort model Time horizon: 15 years	Setting: UK NHS and PSS perspective	Fluocinolone acetonide Intravitreal implant (FAc) 190 mcg every 36 months Dexamethasone 700mcg Intravitreal implant every 6	Adults with chronic DMO in at least one eye which was unresponsive to usual care Separated into two sub	Data on baseline characteristics, and treatment efficacy for FAc was sourced from the FAME clinical trial and NMA. Sham arm from FAME was assumed representative of usual care given the target	Incremental costs: Pseudophakic lens at baseline: Fluocinolone acetonide implant (FAc) compared with usual care:	Deterministic: Main drivers of the ICER for FAc compared with usual care were utility decrements per health state, distribution of treatment within usual care, transition probabilities for sham	Limitations: Treatment duration assumed to be limited to 6 years. Probabilistic results only presented for the comparison with usual care and not dexamethasone. Sham arm of the FAME trial used for the efficacy inputs for usual care

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
			months Usual care based on ILUVIEN clinical evaluation-UK study mixture of laser photocoagulation, ranibizumab 0.5mg, bevacizumab 1.25mg and aflibercept 2mg	populations: Patients with pseudo phakic lens (after cataract surgery); Patients with phakic lens	population is for people with insufficient response to usual care (anti-VEGFs) in the study eye. Treatment efficacy modelled over 3 phases: response (3 months, one cycle) where active treatment can improve BCVA, Maintenance phase, slower improvements in BCVA up to year 6 and from year 6 onwards constant decline of vision over time assumed. Utilities: Estimated using the Czoski-Murray et al (2009) mapping from VA. Utility decrements for adverse events sourced from the literature. Cost data sourced from the BNF, NHS dictionary of medicines and devices, NHS reference costs (adverse events and monitoring costs). Cost of blindness estimated using Meads et al (2003) applied to those with BCVA less than 35 letters.	£3,066 Fluocinolone acetonide implant (FAc) compared with dexamethasone: £1,777 Phakic lens at baseline: Fluocinolone acetonide implant (FAc) compared with usual care: £3,170 Incremental QALY's: Pseudophakic lens at baseline: Fluocinolone acetonide implant (FAc) compared with usual care: 0.185 Fluocinolone acetonide implant (FAc) compared with dexamethasone 0.126 Phakic lens at baseline: Fluocinolone	baseline for the pseudo phakic population. Main drivers of the ICER for FAc compared with dexamethasone were the cost of dexamethasone and the number of outpatient visits for patients treated with FAc in the pseudo phakic population. Phakic population: Main driver of the ICER for FAc compared with usual care in the phakic population was the transition probabilities. Probabilistic: Pseudophakic population The FAc implant was found to have a 73.4% probability of being cost effective compared to usual care based on a willingness to pay threshold of £30,000. No probabilistic results presented for dexamethasone.	based on the assumption this population is for people with insufficient response to anti-VEGFs. The populations in the studies between dexamethasone and FAc had different patient characteristics. Authors conclusions: FAc was estimated to be cost effective compared to dexamethasone for people with diabetic macular oedema who have had insufficient response to anti-VEGFs.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
						acetonide implant (FAc) compared with usual care: 0.11 ICER: Pseudophakic lens at baseline: Fluocinolone acetonide implant (FAc) compared with usual care: £16,609 Fluocinolone acetonide implant (FAc) compared with dexamethasone £14,070 Phakic lens at baseline: Fluocinolone acetonide implant (FAc) compared with usual care: £28,751	Phakic population: The FAc implant was found to have a 59.2% probability of being cost effective compared to usual care based on a willingness to pay threshold of £30,000.	
Haig et al (2016)	Economic analysis: Cost-utility analysis Study design: Markov cohort model	Canada healthcare system perspective	Ranibizumab monotherapy 0.5mg Combination	Patients with DME due to type 1 or type 2 diabetes mellitus, baseline characteristics	Markov cohort model with 3-month cycle with 8 mutually exclusive health states defined by BCVA intervals (86-100, 76-85, 66-75, 56-65, 46-55, 36-	Total costs: Ranibizumab mono: CA$25,233 (£14,232)	DSA: Model sensitive to changes in the assumption of discontinuing treatment if BCVA goes above 75 letters	Source of funding: Novartis Authors conclusion: Both ranibizumab monotherapy and in combination with laser

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
	Time horizon: Lifetime		therapy laser and ranibizumab 0.5mg Laser monotherapy	based on the RESTORE clinical trial Mean (standard deviation [SD]) BCVAs for ranibizumab monotherapy, combination therapy and laser were 64.8 (10.1), 63.4 (10.0) and 62.4 (11.1) letters respectively Age 63.3 years, 40.2% treated in their better seeing eye (BSE)	45, 26-35 and ≤ 25 letters) in addition to a 9th absorbing death health state to compare the long term costs and benefits associated with ranibizumab monotherapy, ranibizumab in combination with laser therapy and laser monotherapy. Lifetime time horizon. Withdrawal rates, based on treatment group within RESTORE trial between 11.7-12.7%, patients withdrawing assumed to have the same transition probabilities but only incur costs associated with laser monotherapy. Relative risk of death due to diabetes and DMO were sourced from Canadian and US sources and applied to all cause mortality data for Canada. Adverse events were not included due to similarities across arms. Utilities for BSE sourced from Czoski-Murray 2009 in the base-case, Brown 1999 and Sharma 2000 used as scenarios, and	Ranibizumab combo: CA$26,854 (£15,146) Laser: CA$15,383 (£8,876) Total QALY's: Ranibizumab mono: 8.17 Ranibizumab combo: 8.09 Laser: 7.77 ICER: Ranibizumab mono compared with laser mono: CA$24,494 (£13,815) Ranibizumab combo compared with laser mono: CA$ 36,414 (£20,538)	and reducing the time horizon to 10 years. PSA: Ranibizumab monotherapy and ranibizumab combination therapy had a 74% and 60% probability of being cost effective at the ICER threshold of CA$50,000	treatment were considered cost effective over 36 months compared with laser monotherapy and is associated with increased time without legal blindness (less than 35 letters). Limitations noted by the authors: Not all relevant comparators were considered and the lack of utility values specific to DME, meaning the utility source was based on studies using utilities associated with AMD rather than DME.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					Canadian HUI study used for WSE. Resource use for frequency of treatment sourced from RESTORE study for all arms in the first year, ranibizumab monotherapy and combination therapy frequencies sourced from RESTORE for years 2 and 3, frequency of laser sessions sourced from RCR.net trial data, treatment costs sourced from Quebec sources (2013), treatment costs only applied for the first 3 years. Monitoring frequency: Ranibizumab – monthly per label, laser and those not receiving treatment with BCVA less than 46 letters would have 3 monitoring visits per year, whilst those with BCVA of at least 46 letters would have 5 monitoring visits as per clinical advisor input. Cost of visual impairment based on Canadian observation study. Natural history from Mitchell et al 2012 based on the WESDR study adjusted to account for			

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					DMO using data from restore.			
Holekamp et al (2020)	Economic analysis: Cost-utility analysis Study design: Markov cohort model. Time horizon: 10 years	Setting: US payer perspective	Aflibercept 2.0 mg Ranibizumab 0.3mg	Adults with diabetes and centre involved DMO, and BCVA score of 78-24 letters. Who had no anti-VEGF treatment in the previous 12 months Mean age 61 years	Model with eight VA health states and an additional absorbing death health state. Resource use and efficacy from Protocol T. Natural history source unclear. Utility source: Czoski-Murray et al 2009. Disutility associated with adverse events sourced from the literature. US cost sources (2016) based on Medicare and the literature used for treatment costs and adverse events. Accounting for treatment in both eyes: Assume weighted benefit of 75% and 25% for BSE and WSE, these proportions were varied in sensitivity analyses. Mortality: US lifetables adjusted for higher mortality in people with diabetes.	Incremental costs: Aflibercept compared with ranibizumab: 2 years: Full cohort: $9,894 (£6,896) VA 20/40 or better at baseline: $8,597 (£5,992) VA 20/50 or worse: $10,967 (£7,644) Aflibercept compared with ranibizumab: 10 years: Full cohort: $20,608 (£14,364) VA 20/40 or better at baseline: $19,721 (£13,746) VA 20/50 or worse: $21,633	Deterministic: Model most sensitive to drug costs and the number of injections. Additionally alternative utility values and assumptions around the number of injections administered to the fellow eye also had an impact on results. Aflibercept only became cost effective for the full cohort based on an ICER $19,930 (£13,891) when the number of injections for aflibercept over 2 years reduced from 15 to 11 whilst ranibizumab remained the same. Ranibizumab remained dominant in all scenarios in the 20/40 or better VA subgroup. Probabilistic: Assuming QALYs were valued at $150,000 (£104,550) aflibercept had a 0.1% probability of being cost effective for the	Authors conclusions: Aflibercept is not cost effective compared to ranibizumab for the treatment of vision loss in DMO. Limitations: Patients were not randomised to sub-group by VA in protocol T

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
						(£15,078) Incremental QALYS: Aflibercept compared with ranibizumab: 2 years: Full cohort: 0.010 VA 20/40 or better at baseline: -0.002 VA 20/50 or worse: 0.021 Aflibercept compared with ranibizumab: 10 years: Full cohort: 0.029 VA 20/40 or better at baseline: -0.032 VA 20/50 or worse: 0.088 ICER: Aflibercept	full cohort and 2.5% probability for the 20/50 or worse VA subgroup	

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
						compared with ranibizumab: 2 years: Full cohort: $986,159 (£687,353) VA 20/40 or better at baseline: Ranibizumab dominates VA 20/50 or worse: $523,377 (£364,794) Aflibercept compared with ranibizumab: 10 years: Full cohort: $711,301 (£495,777) VA 20/40 or better at baseline: Ranibizumab dominates VA 20/50 or worse: $246,978 (£172,144)		
Brown et al (2015)	Economic analysis: Cost-utility analysis	US third party payer	Ranibizumab 0.3mg	Patients enrolled with a single eye	Effectiveness: RIDE and RISE 24	Ranibizumab compared with	No full deterministic or probabilistic sensitivity	Author conclusions: Ranibizumab is cost effective

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
	Time horizon 14 years		Sham	from RIDE and RISE clinical trials with vision loss from 20/40 to 20/320 from DMO. Mean age of 63 years old	months observations, assume the last observation for the remainder of the model. Treatment of both eyes assumed in the base-case. Utilities: Estimated using Brown 2005 using time-trade off utilities from patients with ocular diseases using VF-14 scores. Costs sourced from US sources (2012) using Medicare fee schedules. Disutility associated with adverse event were included by subtracting from total utilities. No significant difference was identified between the two arms.	sham for treatment of both eyes Incremental costs: $4,578 (£3,186) Incremental QALYs 0.9981 ICER $4,587 (£3,193) /QALY	analysis was presented, only scenarios around the frequency of injections over 3 years. ICERS range from $37,693 (£26,234) /QALY for first eye to $107,784 (£75,018) when four annual injections administered bilaterally through 36 months. Assuming monthly injections for ranibizumab up to 36 months the ICER is $33,029 (£22,988) /QALY	compared to sham. Author limitations: RIDE and RISE outcomes modelled from months 25 through 168 using last observation could cause bias. Analysis methods unclear. 14 years was considered sufficient time horizon because it gave the average life expectancy for people with diabetes.
Stein et al (2013)	Economic analysis: Cost-utility analysis Study design: Markov cohort model,	US payer	Laser Laser plus ranibizumab Delayed laser plus ranibizumab Laser plus	People with clinically significant diabetic macular oedema based on DRCR.net trial using a hypothetical cohort of 57-year-olds	Markov model structure with 9 health states, 6 based on visual acuity ranges and 2 additional health states specific to adverse events acute myocardial infarction (AMI) and cerebrovascular accident (CVA) and an absorbing death health state.	Incremental costs: Laser compared with: Laser plus ranibizumab $58,257 (£40,663)	Scenarios including the side effects of AEs were included, which increased costs and reduced HRQOL for laser which had high rates of 6%. Due to the uncertainty around the rates of CVA for bevacizumab scenarios were run to	Ranibizumab and bevacizumab were modelled separately, unclear what dosages were used. Laser plus triamcinolone was included as an additional intervention within both analyses however has not been included as it is not a relevant comparator for this review question.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
			bevacizumab Delayed laser plus bevacizumab		Time horizon: 25 years Efficacy: Observed BCVAs from DRCRnet trial for years 1 and 2. Years 3 onwards, base-case assume the distribution of BCVA did not change after 2 years. Scenario allow for BCVA to decline each year. Bevacizumab assumed to have same efficacy as ranibizumab except in sensitivity analyses. Mortality: US life tables adjusted to capture the increased risk of mortality for people with diabetic retinopathy. Costs: Direct medical costs based on CMS allowable 2011 and included costs of provider visits, intervention costs, monitoring costs and adverse event treatment and costs of blindness when BCVA less than or equal to 20/200. Utilities: Mapping based on Brown	Delayed laser plus ranibizumab $61,424 (£42,874) Laser plus bevacizumab $27,200 (£18,986) Delayed laser plus bevacizumab $26,485 (£18,487) Incremental QALYs: Laser compared with: Laser plus ranibizumab 10.83 Delayed laser plus ranibizumab 10.99 Laser plus bevacizumab 10.83 Delayed laser plus	identify if bevacizumab would not be considered cost effective based on a QALY valued at $50,000 if the probability of CVA is more than 4%. Probabilistic: In the analysis with ranibizumab based on a willingness to pay threshold of $50,000 per QALY there is a 70% probability laser would be the preferred treatment, when the threshold is increased to $100,000/QALY there is a 90% probability that ranibizumab with laser (either immediate or delayed) would be the preferred treatment. In the scenario with bevacizumab, at a value of $14,000/QALY bevacizumab is very likely to be the preferred treatment compared with laser with over 90% probability.	Authors conclusions: Laser plus bevacizumab is the most cost effectiveness treatment when a QALY is valued at $10,000 or more. The annual risk of CVA would need to be over 1.5% higher for laser plus bevacizumab compared to laser plus ranibizumab for laser plus ranibizumab to no longer be considered the most cost-effective treatment.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					et al 1999	bevacizumab 10.99 ICER: Laser compared with: Laser plus ranibizumab $89,903 (£62,752) Delayed laser plus ranibizumab $71,271 (£49,747) Laser plus bevacizumab Dominated by delayed laser plus bevacizumab Delayed laser plus bevacizumab $11,138 (£7,774)		
Sharma et al (2000)	Economic analysis: Cost-utility analysis Study design: econometric model	US payer	Laser photocoagulation No treatment	Adults with vision loss due to diabetic macular oedema using data from the ETDRS study	Decision tree model combined with econometric modelling where patients began in one of 5 visual acuity states, either gained or did not gain 2 or more lines of	Laser photocoagulation compared with no treatment Incremental costs: $733 (£509)	Deterministic: Efficacy values were varied within the 95% confidence limits, the results remained robust with laser photocoagulation	Authors conclusions: Laser treatment can be considered highly cost effective compared to no treatment based on QALYs valued at $20,000.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					visual loss. Utility was then determined based on treatment benefits with utilities associated with complications subtracted. Costs based on 1999 Medicare costs.	Incremental QALYs: 0.236 ICER No discounting $3,101 (£2,152) 5% discount rate based on an additional 40-year life expected $3,655 (£2,537)	remained the preferred treatment No probabilistic sensitivity analysis was undertaken	Treatment was only assumed to be for one eye. Outcome was assessed by whether patients experienced doubling of visual angle.
Lois et al (2022)	Economic analysis: Cost-utility analysis Study design: Regression model based on DIAMOND clinical trial 2 year duration	NHS and PSS	Subthreshold micro pulse laser Standard threshold laser	Adults with centre involving DMO either a central retinal thickness (CRT) >300 µm and <400 µm or CRT <300 µm and subretinal fluid was present in the central subfield	Regression model calculating the difference in costs and QALYs between subthreshold laser and standard threshold laser across the duration of the 2 year DIAMOND clinical trial adjusted for baseline utilities, BMI, BCVA, previous patient reported use of anti-VEGFs and macular laser. Resource use and efficacy data from DIAMOND clinical trial. Utility: EQ-5D-5L mapped onto EQ-5D-3L additionally vision specific measures	Subthreshold micro pulse laser compared with standard threshold laser: Incremental costs: -£365 95% CI (–£822 to £93) Incremental QALYs: 0.008 95% CI (–0.059 to 0.075) Subthreshold micro pulse laser dominates compared to standard	Subthreshold laser had 80% probability of being cost effective at a threshold of £15,000 per QALY and 76% probability of being cost effective at £20,000 per QALY	Authors highlight that whilst subthreshold laser appear both less expensive and more effective, the difference in QALYs as measured by EQ-5D-5L scores were not statistically significantly different. The higher total costs in the standard threshold laser arm were because of a small number of patients needing a large number of rescue anti-VEGF injections. Authors conclude subthreshold micro pulse laser was found to be equivalent to standard threshold laser in terms of both costs and clinical benefits and consider both laser types to be suitable

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					of NEI-VFQ-25 and VisQoL were collected within the DIAMOND clinical trial. Cost data: Cost of staff time based on PSSRU 2020 and anti-VEGF costs based on NHS reference costs 2019-2020, Laser equipment costs based on quotations for each laser type used.	threshold laser		treatment in people who are able to have macular laser treatment with CRT<400 µm
Hutton et al (2023)	Economic analysis: Cost-utility analysis Study design: Within trial analysis based on protocol AC clinical trial 2 year duration	US health system perspective	Aflibercept monotherapy Bevacizumab first followed by aflibercept if needed	Adults with centre involved DMO and BCVA between 20/50 to 20/320	Cost effectiveness analysis based on the 2 year protocol AC clinical trial. Efficacy: Protocol AC clinical trial Utility: Mapping from visual acuity by Brown et al 2003 (age related macular degeneration population), scenario using EQ-5D values from RESTORE Mitchell 2012 Costs based on 2022 Medicare costs.	Aflibercept monotherapy compared with bevacizumab first followed by aflibercept if needed Incremental costs: $12,575 (£8,740) Incremental QALYs: 0.015 ICER: $837,077 (£581,769)	Deterministic: Changing utility source from Brown et al 2003 to RESTORE clinical trial and assumptions around costs will likely change the results, however the ICER would remain above $100,000 (£69,500) Probabilistic sensitivity analysis: 0% probability aflibercept monotherapy would be considered cost effective at a willingness to pay below $200,000 (£139,000) per QALY gained	Authors conclusions: Bevacizumab first followed by aflibercept if needed may offer substantial cost savings without any changes in visual acuity gains over two years compared with aflibercept monotherapy

Abbreviations: AMD: Age related macular degeneration; AMI: acute myocardial infarction; BCVA: Best corrected visual acuity; BSE: Best seeing eye; CI-DME, centre involving diabetic macular oedema; Combo: combination therapy; CRT: Central retinal thickness; CVA: cerebrovascular accident; DME/DMO: Diabetic macular oedema; FAc: Fluocinolone acetonide implant; Mono: Monotherapy; NMB: Net monetary benefit; PRN: Pro re nata – treatment as needed; PRP, pan retinal photocoagulation; PSS: Personal social services; Ran, ranibizumab; T & E: treat and extend dosage schedule; WSE: Worst seeing eye.

**Costs have been converted from dollars to pounds using EPPI-Centre Cost Converter https://eppi.ioe.ac.uk/costconversion/default.aspx*

Table 132: Economic evaluation checklist

Study identification **Regnier et al 2015 Cost-effectiveness of ranibizumab versus aflibercept in the treatment of visual impairment due to diabetic macular edema: a UK healthcare perspective**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	Ranibizumab 0.5mg pro re nata, ranibizumab 0.5mg treat and extend (no treatment for up to 3 months after stabilization is confirmed, aflibercept 2mg every 8 weeks after 5 initial monthly doses
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	Yes EQ-5D based on mapping from BCVA using Czoski-Murray et al, if the treated eye was BSE (defined by Bressler et al, for the WSE a utility decrement of 0.1 was assumed between the best and worst possible states
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov cohort model, eight linear health states defined by increments of 10 letters in BCVA in the treated eye with a 3-month cycle length. Patients could gain or lose a maximum of 2 health states between

Study identification **Regnier et al 2015 Cost-effectiveness of ranibizumab versus aflibercept in the treatment of visual impairment due to diabetic macular edema: a UK healthcare perspective**		
Category	**Rating**	**Comments**
		cycles
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Both a 3 year and life-time time horizon were used
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	RESTORE and RETAIN clinical trials, natural history sources from WESDR study
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	NMA using VIVID-DME and VISTA-DME clinical trials
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	Ranibizumab PRN treatment frequencies in years 1-3 and monitoring in year 1 taken from RESTORE, monitoring frequencies for years 2 and 3 were from DRCR.net study
2.8 Are the unit costs of resources from the best available source?	Yes	Cost of being blind applied if BCVA<35 letters
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	No	Project funded by Novartis
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

2.

3.

Study identification **Mitchell et al 2012 Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial.**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	Ranibizumab monotherapy, laser mono therapy, ranibizumab and laser combination
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	Yes, EQ-5D collected within Restore trial, however EQ-5D is not very sensitive to changes in visual acuity measure by BCVA
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov cohort model, eight linear health states by BCVA in the treated eye with a 3-month cycle length
2.2 Is the time horizon sufficiently long to reflect all	Partly	15 years from a baseline age of 63

Study identification **Mitchell et al 2012 Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial.**		
Category	**Rating**	**Comments**
important differences in costs and outcomes?		
2.3 Are all important and relevant outcomes included?	Partly	Other outcomes such as retinal detachment and floaters are not included which may have an impact on quality of life
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Restore clinical trial, assumed to be the same in year 2 as observed in year 1 as found in protocol I study. After year 2 natural history is informed by the 4-year health state transition outcomes from Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reports
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	RESTORE clinical trial
2.6 Are all important and relevant costs included?	Yes	Cost of blindness by Meads et al also included
2.7 Are the estimates of resource use from the best available source?	Yes	Restore clinical trial and adjusted based on the protocol I clinical trial findings for the second year
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	No	Novartis
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

4.

Study identification **Pochopien et al 2019 Cost-effectiveness of fluocinolone acetonide implant (ILUVIEN R) in UK patients with chronic diabetic macular oedema considered insufficiently responsive to available therapies.**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	Patients insufficiently responsive to available treatments
1.2 Are the interventions appropriate for the review question?	Yes	Fluocinolone acetonide implant 0.2 micrograms/day, dexamethasone (pseudo phakic patients) 700 micro grams or usual care (mixture of laser photocoagulation and anti-VEGFs (phakic and pseudo phakic patients) ranibizumab 0.5mg, bevacizumab 1.25 mg and aflibercept 2 mg, based on the ILUVIEN Clinical Evaluation-UK (ICE-UK) study
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK
1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS and PSS
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	Czoski-Murray 2009, uses approach from Fielding et al2014 and Regnier et al 2015
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	32 state Markov model, 3-month cycle length, 8 score levels by BCVA separated by lens status (either eye could be

Study identification **Pochopien et al 2019 Cost-effectiveness of fluocinolone acetonide implant (ILUVIEN R) in UK patients with chronic diabetic macular oedema considered insufficiently responsive to available therapies.**		
Category	**Rating**	**Comments**
		phakic without cataract, phakic with cataract, phakic with cataract undergoing a cataract surgery, or pseudo phakic)
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	15 years rather than lifetime
2.3 Are all important and relevant outcomes included?	Yes	ILUVIEN Clinical Evaluation-UK
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	FAME clinical trial, outcomes for usual care based on the SHAM arm although authors note anti-VEGF use less in the FAME trial than usual care
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	ILUVIEN Clinical Evaluation-UK, FAME clinical trial, outcomes for usual care based on the Sham arm, NMA used for dexamethasone Mastropasqua et al., 2015
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	No	Funded by Alimera sciences
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Study identification **Haig et al 2016 Cost-effectiveness of ranibizumab in the treatment of visual impairment due to diabetic macular edema**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	Ranibizumab monotherapy Ranibizumab and laser combination therapy Laser monotherapy
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Canada
1.4 Is the perspective for costs appropriate for the review question?	Yes	Scenarios for healthcare system and societal perspective were separate
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Discounted at 5% rather than 3.5%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	Yes EQ-5D based on mapping from BCVA using Czoski-Murray et al. Utility values associated with each BCVA health state were determined separately for patients in their BSE and those treated in their worse-seeing eye. When both eyes were treated utilities of BSE were used.
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Markov 8 state by BCVA, 3-month cycle length
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime
2.3 Are all important and relevant outcomes	Yes	Adverse events were not included due to no significant difference

Study identification Haig et al 2016 Cost-effectiveness of ranibizumab in the treatment of visual impairment due to diabetic macular edema		
Category	**Rating**	**Comments**
included?		between the treatment arms
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	RESTORE clinical trial
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	RESTORE clinical trial for ranibizumab and DRCR.net trial for laser photocoagulation
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Partly	RESTORE clinical trial for ranibizumab and DRCR.net trial for laser photocoagulation and assumptions based on clinical expertise was used for monitoring
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	No	Authors employed by pharmaceutical companies Novartis and Optum
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Study identification Holekamp et al (2020) Cost-effectiveness of ranibizumab and aflibercept to treat diabetic macular edema from a US perspective: analysis of 2-year Protocol T data		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the	Yes	Adults with diabetes, centre-involved

Study identification **Holekamp et al (2020) Cost-effectiveness of ranibizumab and aflibercept to treat diabetic macular edema from a US perspective: analysis of 2-year Protocol T data**		
Category	**Rating**	**Comments**
review question?		DME, and best-corrected VA (BCVA) letter score of 78–24 (Approximate Snellen equivalent, 20/32–20/320)
1.2 Are the interventions appropriate for the review question?	Yes	Aflibercept 2.0mg, ranibizumab 0.3mg, bevacizumab 1.25mg
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US system has substantial differences to the UK
1.4 Is the perspective for costs appropriate for the review question?	Yes	Payer perspective (direct medical costs), sensitivity analysis included societal perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	Payer perspective (direct medical costs), sensitivity analysis included societal perspective
1.6 Are all future costs and outcomes discounted appropriately?	Partly	From years 2 onwards using 3% discount rate, rather than 3.5%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	Czoski-Murray et al. 2009 (note these estimates may not fully represent those experience by patients as it does not account for adaption)
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	8 health states defined by VA for treated and fellow eyes separately
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	Base-case: no (only 2 years using RCT data, extrapolated to 10 years which is still shorter than NICE base-case of lifetime)
2.3 Are all important and relevant outcomes included?	Yes	

Study identification Holekamp et al (2020) Cost-effectiveness of ranibizumab and aflibercept to treat diabetic macular edema from a US perspective: analysis of 2-year Protocol T data		
Category	**Rating**	**Comments**
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Based on the protocol T RCT and natural history, unclear where this natural history is sourced from.
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	Best available source for the US, however these are not applicable to the UK
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	PSA and scenarios were conducted
2.11 Has no potential financial conflict of interest been declared?	Partly	Employees of pharmaceutical companies
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Study identification Brown et al. (2015) The Cost-Effectiveness of Ranibizumab for the Treatment of Diabetic Macular Edema.		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	

Study identification **Brown et al. (2015) The Cost-Effectiveness of Ranibizumab for the Treatment of Diabetic Macular Edema.**		
Category	**Rating**	**Comments**
1.2 Are the interventions appropriate for the review question?	Yes	0.3-mg or 0.5mg intravitreal ranibizumab injection therapy compared with sham therapy
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US system has substantial differences to the UK
1.4 Is the perspective for costs appropriate for the review question?	Partly	Includes societal costs and third-party insurer may not be fully applicable
1.5 Is the perspective for outcomes appropriate for the review question?	Partly	Includes societal costs and third-party insurer may not be fully applicable
1.6 Are all future costs and outcomes discounted appropriately?	Partly	3%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	TTO from patients with ocular diseases rather than general population. Vision and adverse event data was converted into utilities using the pharmaceutical utility database.
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Partly	Months 25 through 168 were modelled using a last observation carried forward, may overestimate benefit of treatment
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	14 years as the average life expectancy for the mean baseline 63 year old with diabetes
2.3 Are all important and relevant outcomes included?	Partly	Assumes vision in each eye was similar, assumes bilateral ranibizumab therapy as the base-case
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	RTC's RIDE and RISE
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Note compared to SHAM rather than other interventions

Study identification **Brown et al. (2015) The Cost-Effectiveness of Ranibizumab for the Treatment of Diabetic Macular Edema.**		
Category	**Rating**	**Comments**
2.6 Are all important and relevant costs included?	Partly	All included however costs associated with time off work are also included which is not part of the NICE reference case
2.7 Are the estimates of resource use from the best available source?	Unclear	
2.8 Are the unit costs of resources from the best available source?	Yes	Yes, however US costs which are not applicable to England
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	Only scenario analysis has been conducted, no deterministic or probabilistic sensitivity analysis has been reported.
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Study identification **Stein et al 2013 Cost-Effectiveness of Various Interventions for Newly Diagnosed Diabetic Macular Edema**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	Newly diagnosed diabetic macular edema
1.2 Are the interventions appropriate for the review question?	Partly	Focal laser photocoagulation, focal laser photocoagulation plus ranibizumab, focal laser photocoagulation plus bevacizumab, focal

Study identification Stein et al 2013 Cost-Effectiveness of Various Interventions for Newly Diagnosed Diabetic Macular Edema		
Category	**Rating**	**Comments**
		laser photocoagulation plus triamcinolone. Triamcinolone is not included as part of the review.
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	USA
1.4 Is the perspective for costs appropriate for the review question?	Yes	Direct medical costs
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	3% rather than 3.5%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	BCVA converted to utilities using Brown et al, utility scores for complications were obtained from the literature
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	Hypothetical cohort of 57 years of age with a 25-year time horizon
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	DRCRnet trial, scenarios used to explore after 2 years
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	DRCRnet trial

Study identification Stein et al 2013 Cost-Effectiveness of Various Interventions for Newly Diagnosed Diabetic Macular Edema		
Category	**Rating**	**Comments**
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	DRCRnet trial
2.8 Are the unit costs of resources from the best available source?	Yes	US Medicare costs
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Study identification Sharma et al 2000 The cost-effectiveness of grid laser photocoagulation for the treatment of diabetic macular edema: results of a patient-based cost-utility analysis.		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	Grid laser photocoagulation, no treatment
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	USA

Study identification **Sharma et al 2000 The cost-effectiveness of grid laser photocoagulation for the treatment of diabetic macular edema: results of a patient-based cost-utility analysis.**		
Category	**Rating**	**Comments**
1.4 Is the perspective for costs appropriate for the review question?	Yes	Third party insurer, includes all healthcare related costs
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Two scenarios of no discounting and a discount rate of 5% were used
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	Survey of 100 patients with diabetic retinopathy using the time-trade-off technique
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Partly	Decision tree based on whether a patient received photocoagulation or no treatment, which whilst a very simplified model structure, the costs and QALYs were determined through the use of econometric modelling for each treatment pathway
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	40 years, would be equivalent to a lifetime, time horizon
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	ETDRS study
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	Administration costs, or any others assumed to be equivalent for both

Study identification **Sharma et al 2000 The cost-effectiveness of grid laser photocoagulation for the treatment of diabetic macular edema: results of a patient-based cost-utility analysis.**		
Category	**Rating**	**Comments**
		treatment arms were not included.
2.7 Are the estimates of resource use from the best available source?	unclear	Resource use estimates are not included, assumed to be the same between treatment arms
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Partly	Only the ICER
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Only deterministic sensitivity analysis was undertaken using the 95% confidence interval
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Lois et al 2022 Standard threshold laser versus subthreshold micropulse laser for adults with diabetic macular oedema: the DIAMONDS non-inferiority RCT.		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	Sub population: centre involving DMO with CRT <400µm and VA>24 letters (ETDRS) in at least one eye
1.2 Are the interventions appropriate for the review question?	Yes	Subthreshold laser and standard threshold laser
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK

Lois et al 2022 Standard threshold laser versus subthreshold micropulse laser for adults with diabetic macular oedema: the DIAMONDS non-inferiority RCT.		
Category	**Rating**	**Comments**
1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS and PSS
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	NHS and PSS
1.6 Are all future costs and outcomes discounted appropriately?	Yes	After 1 year 3.5%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	EQ-5D-5L mapped onto EQ-5D-3L and NEI-VFQ-25 and VisQoL
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE/**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Regression model calculating the difference in costs and QALYs between subthreshold laser and standard threshold laser adjusted for baseline utilities, BMI, BCVA, previous patient reported use of anti-VEGFs and macular laser
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	partly	2 years, duration of the clinical trial
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Diamond clinical trial
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Diamond clinical trial
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best	Partly	Clinical trial

Lois et al 2022 Standard threshold laser versus subthreshold micropulse laser for adults with diabetic macular oedema: the DIAMONDS non-inferiority RCT.		
Category	**Rating**	**Comments**
available source?		
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Hutton et al 2023 Cost-effectiveness of Aflibercept Monotherapy vs Bevacizumab First Followed by Aflibercept If Needed for Diabetic Macular Edema		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	Aflibercept monotherapy versus bevacizumab followed by aflibercept in eyes with suboptimal response
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	No	USA
1.4 Is the perspective for costs appropriate for the review question?	Yes	Health system perspective: Medical costs included, only those medical costs expected to vary between treatments, adverse events were excluded as they were not

Hutton et al 2023 Cost-effectiveness of Aflibercept Monotherapy vs Bevacizumab First Followed by Aflibercept If Needed for Diabetic Macular Edema		
Category	**Rating**	**Comments**
		expected to differ between treatment arms
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	3%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	Visual acuity mapped to Brown et al 2003, scenario using RESTORE Mitchell 2012
1.8 OVERALL JUDGEMENT	**PARTIALY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Analysis of the differences in costs and outcomes across the 2 year time horizon
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	2 years time horizon
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Clinical trial
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Clinical trial
2.6 Are all important and relevant costs included?	Yes	Only the costs associated with treatment which they would anticipate changes between the arms are included.
2.7 Are the estimates of resource use from the best available source?	Partly	Clinical trial
2.8 Are the unit costs of resources from the best	Yes	

Hutton et al 2023 Cost-effectiveness of Aflibercept Monotherapy vs Bevacizumab First Followed by Aflibercept If Needed for Diabetic Macular Edema		
Category	**Rating**	**Comments**
available source?		
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Appendix I – Health economic model

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

Appendix J – Excluded studies

Clinical evidence

Study	Reason for exclusion
Ahmadieh, H, Shoeibi, N, Entezari, S et al. (2008) Intravitreal Bevacizumab With or Without Triamcinolone for Refractory Diabetic Macular Edema: long-term Results of a Clinical Trial. American academy of ophthalmology: 262	- people with Refractory Diabetic Macular Edema
Ahmadieh, Hamid, Ramezani, Alireza, Shoeibi, Nasser et al. (2008) Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 246(4): 483-9	- study included in cochrane review
Anonymous. (2018) Erratum: Persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: A secondary analysis of a randomized clinical trial (JAMA Ophthalmology (2018) 136:3 (257-269) DOI: 10.1001/jamaophthalmol.2017.6565). JAMA Ophthalmology 136(5): 601	- Secondary publication of an included study that does not provide any additional relevant information
Arevalo, J Fernando, Fromow-Guerra, Jans, Quiroz-Mercado, Hugo et al. (2007) Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. Ophthalmology 114(4): 743-50	- study included in cochrane review
Aroney, Christine, Fraser-Bell, Samantha, Lamoureux, Ecosse L et al. (2016) Vision-Related Quality of Life Outcomes in the BEVORDEX Study: A Clinical Trial Comparing Ozurdex Sustained Release Dexamethasone Intravitreal Implant and Bevacizumab Treatment for Diabetic Macular Edema. Investigative ophthalmology & visual science 57(13): 5541-5546	- study included in cochrane review
Augustin, Albert J, Kuppermann, Baruch D, Lanzetta, Paolo et al. (2015) Dexamethasone intravitreal implant in previously treated patients with diabetic macular edema: subgroup analysis of the MEAD study. BMC ophthalmology 15: 150	- Secondary publication of an included study that does not provide any additional relevant information

Bahrami, Bobak, Hong, Thomas, Zhu, Meidong et al. (2017) Switching therapy from bevacizumab to aflibercept for the management of persistent diabetic macular edema. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 255(6): 1133-1140	- Comparator in study does not match that specified in protocol
Baker, Carl W, Glassman, Adam R, Beaulieu, Wesley 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 321(19): 1880-1894	- study included in cochrane review
Bandello, F, Polito, A, Dimastrogiovanni, A et al. (2005) Intravitreal Triamcinolone Associated with Grid Laser Photocoagulation for Diffuse Diabetic Macular Edema. The macula society: 196	- study included in cochrane review
Bertelmann, Thomas, Feltgen, Nicolas, Scheffler, Martin et al. (2016) Vision-related quality of life in patients receiving intravitreal ranibizumab injections in routine clinical practice: baseline data from the German OCEAN study. Health and quality of life outcomes 14(1): 132	- Secondary publication of an included study that does not provide any additional relevant information
Bodla, A.A. and Bodla, M.A. (2017) A prospective, randomized, interventional study comparing treatment modalities for diffuse diabetic macular oedema: Bevacizumab and bevacizumab combined with macular grid - A prospective single centre study. Medical Forum Monthly 28(2): 103-107	- people with Refractory Diabetic Macular Edema
Bordon, AF, Kuczmainski, JF, Gelmini, A et al. (2006) Photocoagulation versus 8 mg Intravitreous Trimcinolone Acetate (TAAC) for Diabetic Clinical Significant Macular Edema (CSME): a Prospective Study. IOVS 47: ARVO E-abstract 3844	- Comparator in study does not match that specified in protocol
Bressler, Neil M, Beaulieu, Wesley T, Glassman, Adam R et al. (2018) Persistent Macular Thickening Following Intravitreous Aflibercept, Bevacizumab, or Ranibizumab for Central-Involved Diabetic Macular Edema With Vision Impairment: A Secondary Analysis of a Randomized Clinical Trial. JAMA ophthalmology 136(3): 257-269	- study included in cochrane review
Brown, David M, Boyer, David S, Csaky, Karl et al. (2022) INTRAVITREAL NESVACUMAB (ANTIANGIOPOIETIN 2) PLUS AFLIBERCEPT IN DIABETIC MACULAR EDEMA: Phase 2 RUBY Randomized Trial. Retina (Philadelphia, Pa.) 42(6): 1111-1120	- study included in cochrane review
Brown, David M, Emanuelli, Andres, Bandello, Francesco et al. (2022) KESTREL and KITE: 52-Week Results From Two Phase III Pivotal Trials of Brolucizumab for Diabetic Macular Edema. American journal of ophthalmology 238: 157-172	- Secondary publication of an included study that does not provide any additional relevant information

Brown, David M, Nguyen, Quan Dong, Marcus, Dennis M et al. (2013) Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 120(10): 2013-22	- Secondary publication of an included study that does not provide any additional relevant information
Brown, David M, Schmidt-Erfurth, Ursula, Do, Diana V et al. (2015) Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology 122(10): 2044-52	- study included in cochrane review
Callanan, David G, Loewenstein, Anat, Patel, Sunil S et al. (2017) A multicenter, 12-month randomized study comparing dexamethasone intravitreal implant with ranibizumab in patients with diabetic macular edema. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 255(3): 463-473	- study included in cochrane review
Chakrabarti, M, Chakrabarti, A, Stephen, V et al. (2008) Intravitreal Monotherapy With Bevacizumab and Triamcinolone Acetonide vs. Combination Therapy for Recalcitrant Diabetic Macular Edema. American academy of ophthalmology: 263	- Secondary publication of an included study that does not provide any additional relevant information
Chatzirallis, Alexandros, Theodossiadis, Panagiotis, Droutsas, Konstantinos et al. (2020) Ranibizumab versus aflibercept for diabetic macular edema: 18-month results of a comparative, prospective, randomized study and multivariate analysis of visual outcome predictors. Cutaneous and ocular toxicology 39(4): 317-322	- Secondary publication of an included study that does not provide any additional relevant information
Chen, Guohai, Li, Wensheng, Tzekov, Radouil et al. (2014) Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema: a meta-analysis of randomized controlled trials. PloS one 9(12): e115797	- Secondary publication of an included study that does not provide any additional relevant information
Cheung, Ning; Wong, Ian Y; Wong, Tien Y (2014) Ocular anti-VEGF therapy for diabetic retinopathy: overview of clinical efficacy and evolving applications. Diabetes care 37(4): 900-5	- population with age-related macular degeneration
Cho, Hee Yoon, Kang, Se Woong, Kim, Yun Taek et al. (2012) A three-year follow-up of intravitreal triamcinolone acetonide injection and macular laser photocoagulation for diffuse diabetic macular edema. Korean journal of ophthalmology : KJO 26(5): 362-8	- Comparator in study does not match that specified in protocol
CRFB002DCA05 (2014) A Canadian 12-month, prospective, randomized, open-label, multicenter, phase IIIb study assessing the efficacy, safety and cost of ranibizumab as combination and monotherapy in patients with visual impairment due to diabetic macular edema. Novartis clinical trial results database www.novctrd.com/ctrdwebapp/clinicaltrialrepository/public/login.jsp	- Secondary publication of an included study that does not provide any additional relevant information

CRFB002DD13 (2014) A 12-month, two-armed, randomized, double-masked, multicenter, phase IIIb study assessing the efficacy and safety of laser photocoagulation as adjunctive to ranibizumab intravitreal injections vs. laser photocoagulation monotherapy in patients with visual impairment due to diabetic macular edema followed by a 12 month follow up period. Novartis clinical trial results database www.novctrd.com/ctrdwebapp/clinicaltrialrepository/public/login.jsp	- study included in cochrane review
Cunningham, Emmett T Jr, Adamis, Anthony P, Altaweel, Michael et al. (2005) A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 112(10): 1747-57	- Secondary publication of an included study that does not provide any additional relevant information
Dehghan, Mohammad H, Ahmadieh, Hamid, Ramezani, Alireza et al. (2008) A randomized, placebo-controlled clinical trial of intravitreal triamcinolone for refractory diabetic macular edema. International ophthalmology 28(1): 7-17	- Secondary publication of an included study that does not provide any additional relevant information
Diabetic Retinopathy Clinical Research Network, (DRCR.net), Beck, Roy W, Edwards, Allison R et al. (2009) Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. Archives of ophthalmology (Chicago, Ill. : 1960) 127(3): 245-51	- study included in cochrane review
Diabetic Retinopathy Clinical Research, Network (2008) A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 115(9): 1447-10	- study included in cochrane review
Diabetic Retinopathy Clinical Research, Network, Googe, Joseph, Brucker, Alexander J et al. (2011) Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. Retina (Philadelphia, Pa.) 31(6): 1009-27	- study included in cochrane review
Diabetic Retinopathy Clinical Research, Network, Scott, Ingrid U, Edwards, Allison R et al. (2007) A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. Ophthalmology 114(10): 1860-7	- Secondary publication of an included study that does not provide any additional relevant information
Diabetic Retinopathy Clinical Research, Network, Wells, John A, Glassman, Adam R et al. (2015) Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. The New England journal of medicine 372(13): 1193-203	- study included in cochrane review
Do, Diana V, Nguyen, Quan Dong, Vitti, Robert et al. (2016) Intravitreal Aflibercept Injection in Diabetic Macular Edema Patients with and without Prior Anti-Vascular Endothelial Growth	- Secondary publication of an included study that does not provide

Factor Treatment: Outcomes from the Phase 3 Program. Ophthalmology 123(4): 850-7	any additional relevant information
Dugel, P.U., Hillenkamp, J., Sivaprasad, S. et al. (2016) Baseline visual acuity strongly predicts visual acuity gain in patients with diabetic macular edema following anti-vascular endothelial growth factor treatment across trials. Clinical Ophthalmology 10: 1103-1110	- Retrospective cohort
Ehlers, J.P., Wang, K., Singh, R.P. et al. (2018) A Prospective Randomized Comparative Dosing Trial of Ranibizumab in Bevacizumab-Resistant Diabetic Macular Edema: The REACT Study. Ophthalmology Retina 2(3): 217-224	- Comparator in study does not match that specified in protocol
Ertan, Elif; Duman, Rahmi; Duman, Resat (2020) Comparison of pain during intravitreal dexamethasone, ranibizumab and aflibercept injection. Clinical & experimental optometry 103(5): 630-633	- study included in cochrane review
Escobar-Barranco, JJ; Pina-Marin, B; Fernandez-Bonet, M (2015) Dexamethasone implants in patients with naive or refractory diffuse diabetic macular edema. Ophthalmologica. Journal international d'ophtalmologie [International journal of ophthalmology] 233: 176-185	- people with Refractory Diabetic Macular Edema
Faghihi, H, Roohipoor, R, Mohammadi, S-F et al. (2008) Intravitreal bevacizumab versus combined bevacizumab-triamcinolone versus macular laser photocoagulation in diabetic macular edema. European journal of ophthalmology 18(6): 941-8	- study included in cochrane review
Fazel, F., Oliya, B., Mirmohammadkhani, M. et al. (2020) Intravitreal injections of bevacizumab plus methotrexate versus bevacizumab alone for the treatment of diabetic macular edema: A randomized, sham-controlled trial. Journal of Current Ophthalmology 32(2): 164-169	- Secondary publication of an included study that does not provide any additional relevant information
Fortin P, Mintzes B, Innes M (2012) A systematic review of intravitreal bevacizumab for the treatment of diabetic macular edema. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH)	- Secondary publication of an included study that does not provide any additional relevant information
Gardner, TW (2011) The restore study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Evidence-based ophthalmology 12(4): 206-207	- Secondary publication of an included study that does not provide any additional relevant information
Garweg, Justus G, Stefanickova, Jana, Hoyng, Carel et al. (2019) Vision-Related Quality of Life in Patients with Diabetic Macular Edema Treated with Intravitreal Aflibercept: The AQUA Study. Ophthalmology. Retina 3(7): 567-575	- Secondary publication of an included study that does not provide any additional relevant information

Gillies, Mark C, McAllister, Ian L, Zhu, Meidong et al. (2011) Intravitreal triamcinolone prior to laser treatment of diabetic macular edema: 24-month results of a randomized controlled trial. Ophthalmology 118(5): 866-72	- study included in cochrane review
Gillies, Mark C, Sutter, Florian K P, Simpson, Judy M et al. (2006) Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. Ophthalmology 113(9): 1533-8	- Secondary publication of an included study that does not provide any additional relevant information
Gillies, MC (2008) Intravitreal Triamcinolone for Refractory Diabetic Macular Oedema: 5-Year Results of a Double-Masked, Placebo-Controlled, Randomised Clinical Trial With Open Label Extension. IOVS: ARVO E- abstract 1565	- Does not contain a population of people with XXX
Giocanti-Auregan, A., Hrarat, L., Qu, L.M. et al. (2017) Functional and anatomical outcomes in patients with serous retinal detachment in diabetic macular edema treated with ranibizumab. Investigative Ophthalmology and Visual Science 58(2): 797-800	- Retrospective cohort
Glassman, Adam R, Wells, John A 3rd, Josic, Kristin et al. (2020) Five-Year Outcomes after Initial Aflibercept, Bevacizumab, or Ranibizumab Treatment for Diabetic Macular Edema (Protocol T Extension Study). Ophthalmology 127(9): 1201-1210	- study included in cochrane review
Goodart, RA, Faber, DW, Mehr, DS et al. (2007) Lucentis in the Treatment of Macular Edema (LIME): a Phase II Study Evaluating the Safety and Efficacy of Ranibizumab versus Focal Laser Treatment in Patients With Diabetic Macular Edema. IOVS 48: ARVO E-Abstract 1431	- More recent systematic review included that covers the same topic
Granstam, Elisabet, Rosenblad, Andreas, Modher Raghib, Aseel et al. (2020) Long-term follow-up of antivascular endothelial growth factor treatment for diabetic macular oedema: a four-year real-world study. Acta ophthalmologica 98(4): 360-367	- Retrospective cohort
Granstrom, Therese, Forsman, Henrietta, Lindholm Olinder, Anna et al. (2016) Patient-reported outcomes and visual acuity after 12months of anti-VEGF-treatment for sight-threatening diabetic macular edema in a real world setting. Diabetes research and clinical practice 121: 157-165	- Retrospective cohort
Greigorian, R A, Zarbin, M A, Brimacombe, M et al. (2004) Comparison of subthreshold micropulse diode laser photocoagulation with conventional laser photocoagulation for clinically significant macular edema in diabetic patients. IOVS 45: ARVO E-abstract 4067	- Comparator in study does not match that specified in protocol
Habib, Ahmed E, Abdel-Kader, Ahmed A, Eissa, Iman M et al. (2019) Adherence to Intravitreal Anti-Vascular Endothelial Growth Factor (Anti-VEGF) Drugs in Diabetic Macular Edema in an	- Retrospective cohort

Egyptian Population: A Health Belief Model. Current eye research 44(3): 303-310	
Heier, Jeffrey S, Bressler, Neil M, Avery, Robert L et al. (2016) Comparison of Aflibercept, Bevacizumab, and Ranibizumab for Treatment of Diabetic Macular Edema: Extrapolation of Data to Clinical Practice. JAMA ophthalmology 134(1): 95-9	- study included in cochrane review
Heier, Jeffrey S, Korobelnik, Jean-Francois, Brown, David M et al. (2016) Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies. Ophthalmology 123(11): 2376-2385	- Secondary publication of an included study that does not provide any additional relevant information
Hernandez-Bel, Laura, Cervera-Taulet, Enrique, Navarro-Palop, Catalina et al. (2019) Sequential Dexamethasone and Aflibercept Treatment in Patients with Diabetic Macular Edema: Structural and Functional Outcomes at 52 Weeks. Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde 241(2): 98-104	- Retrospective cohort
Hu, X.-Y., Cao, L., Gao, Y. et al. (2023) Comparative Efficacy of Subthreshold Micropulse Laser Photocoagulation vs. Conventional Laser Photocoagulation for Diabetic Macular Edema: A Meta-analysis. Ophthalmic research	- Systematic review used as source of primary studies
Hykin, P, Ockrim, Z, Falk, S et al. (2006) A Randomized Trial of Intravitreal Triamcinolone vs. Macular Laser Therapy for Persistent Clinically Significant Diabetic Macular Edema. The macula society: 174	- study included in cochrane review
Ip, Michael S, Bressler, Susan B, Antoszyk, Andrew N et al. (2008) A randomized trial comparing intravitreal triamcinolone and focal/grid photocoagulation for diabetic macular edema: baseline features. Retina (Philadelphia, Pa.) 28(7): 919-30	- study included in cochrane review
Jampol, Lee M, Glassman, Adam R, Bressler, Neil M et al. (2016) Anti-Vascular Endothelial Growth Factor Comparative Effectiveness Trial for Diabetic Macular Edema: Additional Efficacy Post Hoc Analyses of a Randomized Clinical Trial. JAMA ophthalmology 134(12)	- study included in cochrane review
Javanovic, Sandra, Canadanovic, Vladimir, Sabo, Ana et al. (2015) Intravitreal bevacizumab injection alone or combined with macular photocoagulation compared to macular photocoagulation as primary treatment of diabetic macular edema. Vojnosanitetski pregled 72(10): 876-82	- study included in cochrane review
Kaldirim, Havva, Yazgan, Serpil, Kirgiz, Ahmet et al. (2019) A Comparison Study of Ranibizumab and Aflibercept in Patients with Naive Diabetic Macular Edema in Presence of Serous Retinal Detachment. Current eye research 44(9): 987-993	- Comparator in study does not match that specified in protocol

Kaya, M., Atas, F., Kocak, N. et al. (2023) Intravitreal Ranibizumab and Dexamethasone Implant Injections as Primary Treatment of Diabetic Macular Edema: The Month 24 Results from Simultaneously Double Protocol. Current Eye Research	- Study does not contain a relevant intervention
Kim, HD, Kang, KD, Choi, KS et al. (2014) Combined therapy with intravitreal bevacizumab and posterior subtenon triamcinolone acetonide injection in diabetic macular oedema. Acta ophthalmologica 92(7): e589-e590	- study included in cochrane review
Kim, Judy E, Pollack, John S, Miller, David G et al. (2008) ISIS-DME: a prospective, randomized, dose-escalation intravitreal steroid injection study for refractory diabetic macular edema. Retina (Philadelphia, Pa.) 28(5): 735-40	- study included in cochrane review
Kriechbaum, K, Prager, S, Mylonas, G et al. (2014) Intravitreal bevacizumab (Avastin) versus triamcinolone (Volon A) for treatment of diabetic macular edema: one-year results. Eye (London, England) 28(1): 9-16	- study included in cochrane review
Lee, C M and Olk, R J (1991) Modified grid laser photocoagulation for diffuse diabetic macular edema. Long-term visual results. Ophthalmology 98(10): 1594-602	- study included in cochrane review
Lee, Ho Young; Lee, Seung Yong; Park, Jong Seok (2009) Comparison of photocoagulation with combined intravitreal triamcinolone for diabetic macular edema. Korean journal of ophthalmology : KJO 23(3): 153-8	- study included in cochrane review
Li, Xiaoxin, Dai, Hong, Li, Xiaorong et al. (2019) Efficacy and safety of ranibizumab 0.5 mg in Chinese patients with visual impairment due to diabetic macular edema: results from the 12-month REFINE study. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 257(3): 529-541	- Secondary publication of an included study that does not provide any additional relevant information
Limon, U (2021) Early effect of simultaneous intravitreal dexamethasone and bevacizumab combination treatment in patients with persistent diabetic macular edema. Journal francais d'ophtalmologie 44(6): 849-854	- study included in cochrane review
Liu, Kun, Wang, Hanying, He, Wei et al. (2022) Intravitreal conbercept for diabetic macular oedema: 2-year results from a randomised controlled trial and open-label extension study. The British journal of ophthalmology 106(10): 1436-1443	- Secondary publication of an included study that does not provide any additional relevant information
Liu, Xiangdong, Zhou, Xiaodong, Wang, Zhi et al. (2014) Intravitreal bevacizumab with or without triamcinolone acetonide for diabetic macular edema: a meta-analysis of randomized controlled trials. Chinese medical journal 127(19): 3471-6	- study included in cochrane review

Marey, HM and Ellakwa, AF (2011) Intravitreal bevacizumab alone or combined with triamcinolone acetonide as the primary treatment for diabetic macular edema. Clinical ophthalmology (Auckland, N.Z.) 5(1): 1011-1016	- study included in cochrane review
Martel, A, Nahon-Esteve, S, Martini, K et al. (2020) Feelings, preoperative anxiety, and need for information in patients undergoing intravitreal injections. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 258(7): 1395-1403	- study included in cochrane review
Massin, Pascale, Bandello, Francesco, Garweg, Justus G et al. (2010) Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes care 33(11): 2399-405	- study included in cochrane review
Massin, PG (2008) Phase 2 RESOLVE Trial: twelve-Month Analysis of Ranibizumab in Diabetic Macular Edema. American academy of ophthalmology: 180	- study included in cochrane review
Maturi, Raj K, Glassman, Adam R, Liu, Danni et al. (2018) Effect of Adding Dexamethasone to Continued Ranibizumab Treatment in Patients With Persistent Diabetic Macular Edema: A DRCR Network Phase 2 Randomized Clinical Trial. JAMA ophthalmology 136(1): 29-38	- study included in cochrane review
Michaelides, Michel, Kaines, Andrew, Hamilton, Robin D et al. (2010) A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology 117(6): 1078-1086e2	- study included in cochrane review
Mitchell, Paul, Sheidow, Tom G, Farah, Michel E et al. (2020) Effectiveness and safety of ranibizumab 0.5 mg in treatment-naive patients with diabetic macular edema: Results from the real-world global LUMINOUS study. PloS one 15(6): e0233595	- study included in cochrane review
Nepomuceno, Antonio Brunno, Takaki, Erika, Paes de Almeida, Felipe Piacentini et al. (2013) A prospective randomized trial of intravitreal bevacizumab versus ranibizumab for the management of diabetic macular edema. American journal of ophthalmology 156(3): 502-510e2	- study included in cochrane review
Neto, Hermelino O, Regatieri, Caio V, Nobrega, Mario J et al. (2017) Multicenter, Randomized Clinical Trial to Assess the Effectiveness of Intravitreal Injections of Bevacizumab, Triamcinolone, or Their Combination in the Treatment of Diabetic Macular Edema. Ophthalmic surgery, lasers & imaging retina 48(9): 734-740	- Secondary publication of an included study that does not provide any additional relevant information
Nguyen, QD (2012) Randomized, Multi-center, Phase 2 Study of	- Secondary publication

the Safety, Tolerability and Bioactivity of Repeated Intravitreal Injections of iCo-007 as Monotherapy or in Combination with Ranibizumab or Laser Photocoagulation in the Treatment of Diabetic Macular Edema with Involvement of the FoveAL Center (the iDEAL Study). Ocular surgery news 30(6): 9-8	of an included study that does not provide any additional relevant information
Ockrim, ZK, Senswathi, S, Falk, S et al. (2006) A Randomised Trial of Intravitreal Triamcinolone verses Macular Laser Therapy for Persistent Clinically Significant Diabetic Macular Oedema. IOVS 47: ARVO E-abstract 5438	- study included in cochrane review
Pappas, GD, Adam, CI, Papageorgioy, E et al. (2008) Triamcinolone and Grid Laser versus Bevacizumab Alone for the Treatment of Diabetic Macular Edema. IOVS: ARVO E- abstract 3483	- Comparator in study does not match that specified in protocol
Patil, N.S., Mihalache, A., Hatamnejad, A. et al. (2022) Intravitreal Steroids Compared with Anti-VEGF Treatment for Diabetic Macular Edema: A Meta-Analysis. Ophthalmology Retina	- Data not reported in an extractable format
Pearson, P.A., Comstock, T.L., Ip, M. et al. (2011) Fluocinolone acetonide intravitreal implant for diabetic macular edema: A 3-year multicenter, randomized, controlled clinical trial. Ophthalmology 118(8): 1580-1587	- Secondary publication of an included study that does not provide any additional relevant information
Pearson, P, Baker, C, Eliott, D et al. (2004) Fluocinolone Acetonide Intravitreal Implant for Diabetic Macular Edema: 2 Year Results. IOVS 45: ARVO E-abstract 1111	- study included in cochrane review
Pearson, P, Baker, CW, Eliott, D et al. (2003) Fluocinolone Acetonide Intravitreal Implant in Patients with Diabetic Macular Edema: 12 Month Results. IOVS: ARVO E-abstract 4288	- Secondary publication of an included study that does not provide any additional relevant information
Pearson, P; Levy, B; Cornstock, T (2006) Fluocinolone Acetonide Intravitreal Implant to Treat Diabetic Macular Edema: 3-Year Results of a Multi-Center Clinical Trial. IOVS 47: ARVO E-abstract 5442	- study included in cochrane review
Pei-Pei, W, Shi-Zhou, H, Zhen, T et al. (2015) Randomised clinical trial evaluating best-corrected visual acuity and central macular thickness after 532-nm subthreshold laser grid photocoagulation treatment in diabetic macular oedema. Eye (London, England) 29(3): 313-322	- study included in cochrane review
Pennington, Becky M, Hernandez-Alava, Monica, Hykin, Philip et al. (2020) Mapping From Visual Acuity to EQ-5D, EQ-5D With Vision Bolt-On, and VFQ-UI in Patients With Macular Edema in the LEAVO Trial. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 23(7): 928-935	- study included in cochrane review

Prunte, Christian, Fajnkuchen, Franck, Mahmood, Sajjad et al. (2016) Ranibizumab 0.5 mg treat-and-extend regimen for diabetic macular oedema: the RETAIN study. The British journal of ophthalmology 100(6): 787-95	- study included in cochrane review
Rajendram, Ranjan, Fraser-Bell, Samantha, Kaines, Andrew et al. (2012) A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. Archives of ophthalmology (Chicago, Ill. : 1960) 130(8): 972-9	- Secondary publication of an included study that does not provide any additional relevant information
Rodrigues, Murilo W, Cardillo, Jose A, Messias, Andre et al. (2020) Bevacizumab versus triamcinolone for persistent diabetic macular edema: a randomized clinical trial. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 258(3): 479-490	- Secondary publication of an included study that does not provide any additional relevant information
Schmidt-Erfurth, Ursula, Lang, Gabriele E, Holz, Frank G et al. (2014) Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. Ophthalmology 121(5): 1045-53	- Secondary publication of an included study that does not provide any additional relevant information
Scott, Ingrid U, Danis, Ronald P, Bressler, Susan B et al. (2009) Effect of focal/grid photocoagulation on visual acuity and retinal thickening in eyes with non-center-involved diabetic macular edema. Retina (Philadelphia, Pa.) 29(5): 613-7	- study included in cochrane review
Shah, Chirag P and Heier, Jeffrey S (2016) Aflibercept for Diabetic Macular Edema in Eyes Previously Treated With Ranibizumab and/or Bevacizumab May Further Improve Macular Thickness. Ophthalmic surgery, lasers & imaging retina 47(9): 836-9	- Retrospective cohort
Shah, SM, Nguyen, QD, Sy, JP et al. (2008) The RIDE and RISE Studies of the Efficacy and Safety of Intravitreal Ranibizumab (LUCENTIS®) in Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus. IOVS: ARVO E-abstract 1562	- population with age-related macular degeneration
Sharma, Ashish, Bellala, Keerthi, Dongre, Pankaj et al. (2020) Anti-VEGF versus dexamethasone implant (Ozurdex) for the management of Centre involved Diabetic Macular Edema (CiDME): a randomized study. International ophthalmology 40(1): 67-72	- study included in cochrane review
Singer, Michael A; Wykoff, Charles C; Grewal, Dilraj S (2020) Effects of Long-Term DME Control With 0.2 microg/Day Fluocinolone Acetonide Implant on Quality of Life: An Exploratory Analysis From the FAME Trial. Ophthalmic surgery, lasers & imaging retina 51(11): 658-667	- study included in cochrane review

Soheilian, Masoud, Garfami, Kiumars Heidari, Ramezani, Alireza et al. (2012) Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. Retina (Philadelphia, Pa.) 32(2): 314-21	- study included in cochrane review
Soheilian, Masoud, Ramezani, Alireza, Bijanzadeh, Bijan et al. (2007) Intravitreal bevacizumab (avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of diabetic macular edema. Retina (Philadelphia, Pa.) 27(9): 1187-95	- study included in cochrane review
Soheilian, Masoud, Ramezani, Alireza, Obudi, Arash et al. (2009) Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. Ophthalmology 116(6): 1142-50	- study included in cochrane review
Solaiman, Kamal A M; Diab, Mohammad M; Abo-Elenin, Mostafa (2010) Intravitreal bevacizumab and/or macular photocoagulation as a primary treatment for diffuse diabetic macular edema. Retina (Philadelphia, Pa.) 30(10): 1638-45	- study included in cochrane review
Sutter, FK; Simpson, JM; Gillies, MC (2004) Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. Ophthalmology 111(11): 2044-2049	- study included in cochrane review
Tornambe, Paul (2017) Re: Wells et al.: Aflibercept, Bevacizumab, or Ranibizumab for diabetic macular edema: Two-year results from a comparative effectiveness randomized clinical trial (Ophthalmology 2016;123:1351-1358). Ophthalmology 124(3): e25-e26	- Secondary publication of an included study that does not provide any additional relevant information
Tranos, P G, Topouzis, F, Stangos, N T et al. (2004) Effect of laser photocoagulation treatment for diabetic macular oedema on patient's vision-related quality of life. Current eye research 29(1): 41-9	- study included in cochrane review
Turkoglu, Elif Betul, Celik, Erkan, Aksoy, Nilgun et al. (2015) Changes in vision related quality of life in patients with diabetic macular edema: ranibizumab or laser treatment?. Journal of diabetes and its complications 29(4): 540-3	- study included in cochrane review
Virgili, G, Parravano, M, Evans, JR et al. (2018) Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database of Systematic Reviews	- Secondary publication of an included study that does not provide any additional relevant information
Wang, Jia-Kang, Huang, Tzu-Lun, Su, Pei-Yuan et al. (2015) An updated review of long-term outcomes from randomized controlled trials in approved pharmaceuticals for diabetic macular edema	- study included in cochrane review

Eye science 30(4): 176-83	
Wang, X-X, Zhang, P-C, Xie, J et al. (2021) Efficacy of Aflibercept versus Ranibizumab in the treatment of diabetic macular edema. International eye science 21(12): 2183-2186	- study included in cochrane review
Wang, Yu-Sheng, Li, Xiao, Wang, Hai-Yan et al. (2011) Intravitreal bevacizumab combined with/without triamcinolone acetonide in single injection for treatment of diabetic macular edema. Chinese medical journal 124(3): 352-8	- study included in cochrane review
Weingessel, B, Mihăltz, K, Gleiss, A et al. (2018) Treatment of Diabetic Macular Edema with Intravitreal Antivascular Endothelial Growth Factor and Prompt versus Deferred Focal Laser during Long-Term Follow-Up and Identification of Prognostic Retinal Markers. Journal of ophthalmology: 1-11	- Study does not contain a relevant intervention - Full text paper not available
Wells, John A, Glassman, Adam R, Ayala, Allison R et al. (2016) Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology 123(6): 1351-9	- study included in cochrane review
Wells, John A, Glassman, Adam R, Jampol, Lee M et al. (2016) Association of Baseline Visual Acuity and Retinal Thickness With 1-Year Efficacy of Aflibercept, Bevacizumab, and Ranibizumab for Diabetic Macular Edema. JAMA ophthalmology 134(2): 127-34	- study included in cochrane review
Wykoff, C.C., Marcus, D.M., Midena, E. et al. (2017) Intravitreal aflibercept injection in eyes with substantial vision loss after laser photocoagulation for diabetic macular edema subanalysis of the vista and vivid randomized clinical trials. JAMA Ophthalmology 135(2): 107-114	- Secondary publication of an included study that does not provide any additional relevant information
Wykoff, Charles C, Abreu, Francis, Adamis, Anthony P et al. (2022) Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet (London, England) 399(10326): 741-755	- study included in cochrane review
Yahia, SB, Attia, S, Hmidi, K et al. (2008) Intravitreal Bevacizumab vs. Intravitreal Triamcinolone for Diabetic Macular Edema With Severe Hard Exudates. American academy of ophthalmology: 181	- study included in cochrane review
Yaseri, M, Zeraati, H, Mohammad, K et al. (2014) Intravitreal bevacizumab injection alone or combined with triamcinolone versus macular photocoagulation in bilateral diabetic macular edema; application of bivariate generalized linear mixed model with asymmetric random effects in a subgroup of a clinical trial. Journal of ophthalmic and vision research 9(4): 453-460	- Secondary publication of an included study that does not provide any additional relevant information

Ziemssen, F., Cruess, A., Dunger-Baldauf, C. et al. (2017) Ranibizumab in diabetic macular oedema - A benefit-risk analysis of ranibizumab 0.5 mg PRN versus laser treatment. European Endocrinology 13(2): 91-98	- study included in cochrane review
Ziemssen, Focke and Agostini, Hansjurgen (2015) Re: Boyer et al.: Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema (Ophthalmology 2014;121:1904-14). Ophthalmology 122(3): e20-1	- Secondary publication of an included study that does not provide any additional relevant information

Economic evidence

Study	Reason for exclusion
Anonymous (2018) Pharmacoeconomic Review Report: Dexamethasone (Ozurdex): (Allergan Inc.): Indication: For the treatment of adult patients with diabetic macular edema who are pseudophakic.	• Pharmacoeconomic review report
Anonymous (2019) Pharmacoeconomic Review Report: Fluocinolone acetonide intravitreal implant (Iluvien): (Knight Therapeutics Inc.): Indication: For the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.	• Pharmacoeconomic review report
Crijns, H; Casparie, A F; Hendrikse, F (1999) Continuous computer simulation analysis of the cost-effectiveness of screening and treating diabetic retinopathy. International journal of technology assessment in health care 15(1): 198-206	• Population - diabetes NOT diabetic macular oedema • Costs only no outcome data
Cutino, Antonio, Green, Kenneth, Kendall, Robyn et al. (2015) Economic evaluation of a fluocinolone acetonide intravitreal implant for patients with DME based on the FAME study. The American journal of managed care 21(4suppl): 63-72	• Includes productivity costs which is outside NICE reference case
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	• Not applicable – interventions • The only interventions which it is possible to estimate an ICER based on the cost per QALY is relative to triamcinolone which is not a relevant comparator for this

Study	Reason for exclusion
macular edema. Ophthalmology 119(8): 1679-84	review question
Foglia, Emanuela, Ferrario, Lucrezia, Bandello, Francesco et al. (2018) Diabetic macular edema, innovative technologies and economic impact: New opportunities for the Lombardy Region healthcare system?. Acta ophthalmologica 96(4): e468-e474	• Costs only no outcome data
Holden, Sarah E; Currie, Craig J; Owens, David R (2017) Health-economic evaluation of fluocinolone acetonide 190 microg implant in people with diabetic macular edema. Current medical research and opinion 33(sup2): 45-52	• Costs only no outcome data
Javitt J C, Aiello L P (1996) Cost-effectiveness of detecting and treating diabetic retinopathy. Annals of Internal Medicine 124(1 Part 2): 164-169	• Not applicable - US study, pre-1990 analysis different from current UK setting • Population - diabetes NOT diabetic macular oedema • Not applicable - inappropriate comparison of interventions
Javitt, J C; Canner, J K; Sommer, A (1989) Cost effectiveness of current approaches to the control of retinopathy in type I diabetics. Ophthalmology 96(2): 255-64	• Not applicable - US study, pre-1990 analysis different from current UK setting • Population - diabetes NOT diabetic macular oedema
Kourlaba, G., Relakis, J., Mahon, R. et al. (2016) Cost-utility of ranibizumab versus aflibercept for treating Greek patients with visual impairment due to diabetic macular edema. Cost Effectiveness and Resource Allocation 14(1): 7	• Not applicable Greek population • Adaption of the study by Regnier et al 2015, using exactly the same inputs other than Greek costs
Lois, Noemi, Campbell, Christina, Waugh, Norman et al. (2023) Diabetic Macular Edema and Diode Subthreshold Micropulse Laser: A Randomized Double-Masked Noninferiority Clinical Trial. Ophthalmology 130(1): 14-27	• Duplication, summary paper of another include, the paper with the most detail has been selected for inclusion
Montes Rodriguez, P., Mateo Gabas, J., Esteban Floria, O. et al. (2022) Cost-effectiveness of dexamethasone compared with aflibercept in naive diabetic macular edema. Cost Effectiveness and Resource Allocation 20(1): 61	• Not applicable – societal perspective
Mukkamala, Lekha; Bhagat, Neelakshi; Zarbin, Marco (2017) Practical Lessons from Protocol T for the Management of Diabetic Macular Edema. Developments in ophthalmology 60: 109-124	• US study • Very serious limitations

Study	Reason for exclusion
Navarro-Navarro, A, Salom, D, Martinez-Toldos, J et al. (2017) The diabetic retinopathy clinical research network analysis of the cost-effectiveness of aflibercept, bevacizumab and ranibizumab for the treatment of diabetic macular oedema and its application in Spain. Archivos de la Sociedad Espanola de Oftalmologia 92(5): 245-246	• Non-English language
Patel, N.A., Yannuzzi, N.A., Lin, J. et al. (2021) A Cost-Effectiveness Analysis of Intravitreal Aflibercept for the Prevention of Progressive Diabetic Retinopathy. Ophthalmology Retina	• Population for non-proliferative diabetic retinopathy not diabetic macular oedema • Not applicable - non-QALY outcomes • Not applicable - discounting not applied
Pershing, Suzann, Enns, Eva A, Matesic, Brian et al. (2014) Cost-effectiveness of treatment of diabetic macular edema. Annals of internal medicine 160(1): 18-29	• Not applicable – unable to separate from the societal perspective
Pesonen, Mari; Kankaanpaa, Eila; Vottonen, Pasi (2021) Cost-effectiveness of dexamethasone and triamcinolone for the treatment of diabetic macular oedema in Finland: A Markov-model. Acta ophthalmologica 99(7): e1146-e1153	• Not applicable - irrelevant comparator • Triamcinolone is not included as an intervention within the protocol
Ramsey, D.J., Poulin, S.J., Lamonica, L.C. et al. (2021) Early conversion to aflibercept for persistent diabetic macular edema results in better visual outcomes and lower treatment costs. Clinical Ophthalmology 15: 31-39	• US population • Very serious limitations, unclear modelling methods
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	• Population – people with diabetes rather than diabetic macular oedema
Ross, Eric L, Hutton, David W, Stein, Joshua D et al. (2016) Cost-effectiveness of Aflibercept, Bevacizumab, and Ranibizumab for Diabetic Macular Edema Treatment: Analysis From the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trial. JAMA ophthalmology 134(8): 888-96	• Partially applicable US population • Very serious limitations with model structure
Ruiz-Moreno, J M; de Andres-Nogales, F; Oyaguez, I (2020) Cost-consequence analysis of extended loading dose of anti-VEGF treatment in	• Interventions not relevant to question • Severe limitations – only considers 6 months • Cost consequence not cost utility

Study	Reason for exclusion
diabetic macular edema patients. BMC ophthalmology 20(1): 37	
Schauwvlieghe, A M E, Dijkman, G, Hooymans, J M et al. (2015) Comparing the effectiveness and costs of Bevacizumab to Ranibizumab in patients with Diabetic Macular Edema: a randomized clinical trial (the BRDME study). BMC ophthalmology 15: 71	• Protocol study – no results
Smiddy, William E (2011) Economic considerations of macular edema therapies. Ophthalmology 118(9): 1827-33	• Not applicable – one year duration with no modelling and unclear methods
Vondeling, H (1993) Evaluation of argon laser treatment of diabetic retinopathy and its diffusion in The Netherlands. Health policy (Amsterdam, Netherlands) 23(12): 97-111	• Not applicable - US study, pre-1990 analysis different from current UK setting

Appendix L Network meta-analysis

Network meta-analyses were conducted for the outcomes ‘change in visual acuity’ and ‘change in central retinal thickness’ to allow the evidence across comparisons to be combined into a single internally consistent model. Seven network meta-analyses were conducted, all for people with centre-involving macular oedema. The populations and outcomes where there was sufficient data for network meta-analyses were:

- Whole centre-involving population
    - Change in visual acuity at 12 months
    - Change in visual acuity at 24 months
    - Change in central retinal thickness at 12 months
    - Change in central retinal thickness at 24 months

- Subgroup analysis: People with central retinal thickness >400 µm at baseline
    - Change in visual acuity at 12 months
    - Change in visual acuity at 24 months
    - Change in central retinal thickness at 12 months

L.1 Implementation

We undertook hierarchical Bayesian network meta-analysis using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk/). We used the WinBUGS code provided in the appendices of TSD 2 without substantive alteration to specify synthesis models. We used a normal likelihood with correction for multi-arm trials. Non-informative prior distributions were used for all parameters. Priors were normally distributed with a mean of 0 and variance of 10,000, except for the standard deviation between trials for the random effects meta-analyses which had a uniform prior distribution ranging from 0 to 5 for the visual acuity outcomes and from 0 to 1000 for the central retinal thickness outcomes. Standard threshold laser treatment was used as the reference treatment as this treatment has a high number of links with other nodes in the network and is

commonly used as first-line treatment. For full details of the methods used, see the sections on Data synthesis for intervention studies and Appraising the quality of the evidence (Intervention studies) in the methods document.

We report results summarising 50,000 samples from the posterior distribution of each model, having first run and discarded 50,000 'burn-in' iterations. Three separate chains with different initial values were used.

Some treatments had evidence for all timepoints in the NMA, while others only had evidence for either 12 or 24 months. Table 121 and Table 122 outlines where each treatment was included in the NMAs for visual acuity.

Table 133. Treatments included in the full population NMAs

Treatment	Visual acuity 12_months	Visual acuity_24_months	Central retinal thickness 12 months	Central retinal thickness 24 months
Standard threshold laser (reference treatment)	Included	Included	Included	Included
Subthreshold laser	Included	Not included	Included	Included
Bevacizumab	Included	Included	Included	Included
Ranibizumab	Included	Included	Included	Included
Aflibercept	Included	Included	Included	Included
Faricimab	Included	Not included	Not included	Not included
Brolucizumab	Included	Not included	Included	Not included
Conbercept	Included	Not included	Included	Not included
Pegaptanib	Included	Not included	Not included	Not included
Dexamethasone	Included	Included	Included	Included
Triamcinolone	Included	Included	Included	Included
Fluocinolone	Not included	Included	Included	Included

Ranibizumab and standard threshold laser	Included	Included	Included	Included
Bevacizumab and standard threshold laser	Included	Not included	Included	Not included
Triamcinolone and standard threshold laser	Included	Included	Not included	Not included
Bevacizumab and triamcinolone	Included	Not included	Included	Not included
Ranibizumab and dexamethasone	Included	Not included	Included	Not included
Bevacizumab and dexamethasone	Included	Not included	Included	Not included
Sham	Included	Included	Included	Included
Total treatments in network	18	10	16	10

Table 134. Treatments included in the subgroup NMAs for people with central retinal thickness of 400 micrometres or more

Treatment	**Visual acuity_12_months**	**Visual acuity_24_months**	**Central retinal thickness 12 months**
Standard threshold laser (reference treatment)	Included	Included	Included
Subthreshold laser	Not included	Not included	Included
Bevacizumab	Included	Included	Included
Ranibizumab	Included	Included	Included
Aflibercept	Included	Included	Included
Faricimab	Included	Not included	Not included

Brolucizumab	Included	Not included	Included
Conbercept	Included	Not included	Included
Pegaptanib	Included	Not included	Not included
Dexamethasone	Included	Included	Included
Triamcinolone	Included	Included	Included
Fluocinolone	Not included	Included	Included
Ranibizumab and standard threshold laser	Included	Included	Included
Bevacizumab and standard threshold laser	Not included	Not included	Included
Triamcinolone and standard threshold laser	Included	Included	Included
Bevacizumab and triamcinolone	Included	Not included	Included
Ranibizumab and dexamethasone	Not included	Not included	Not included
Bevacizumab and dexamethasone	Not included	Not included	Included
Sham	Included	Included	Included
Total treatments in network	14	10	16

L.2 WinBUGS code

Fixed effects model for continuous data (visual acuity)

```
# Normal likelihood, identity link
# Fixed effects model
model{                                # *** PROGRAM STARTS
for(i in 1:ns){                       #   LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)            # vague priors for all trial baselines
    for (k in 1:na[i]) {              #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)    # calculate variances
        prec[i,k] <- 1/var[i,k]       # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
# model for linear predictor
        theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
  }
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
# Provide estimates of treatment effects T[k] on the natural scale


for(k in 1:nt){ #calcuate rank and probability of each rank for each treatment
                                                    #rk[k] <- nt+1-rank(d[],k)
                                                    rk[k] <- rank(d[],k)
                                                    for (j in 1:nt){
                                                    rankprobs[k,j]<-equals(rk[k],j)
                                                    }

                                          }

#calculate mean differences
```

```
for (c in 1:nt-1)
        {for (k in (c+1):nt)
                {diff[c,k]<-d[k]-d[c]
                }
        }

}                                       # *** PROGRAM ENDS
```

Random effects model for continuous data (visual acuity)

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         #   LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
    for (k in 1:na[i]) {                #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)    # calculate variances
        prec[i,k] <- 1/var[i,k]       # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {                # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
```

```
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)


for(k in 1:nt){ #calcuate rank and probability of each rank for each treatment
                                                        #rk[k] <- nt+1-rank(d[],k)
                                                        rk[k] <- rank(d[],k)
                                                        for (j in 1:nt){
                                                        rankprobs[k,j]<-equals(rk[k],j)
                                                        }
                                            }

#calculate mean differences
for (c in 1:nt-1)
        {for (k in (c+1):nt)
                {diff[c,k]<-d[k]-d[c]
                }
        }

}                                           # *** PROGRAM ENDS
```

Random effects model for continuous data (central retinal thickness)

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         #   LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
    for (k in 1:na[i]) {             #  LOOP THROUGH ARMS
```

```
        var[i,k] <- pow(se[i,k],2)    # calculate variances
        prec[i,k] <- 1/var[i,k]       # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,1000)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
```

```
for(k in 1:nt){ #calcuate rank and probability of each rank for each treatment
                                                    #rk[k] <- nt+1-rank(d[],k)
                                                    rk[k] <- rank(d[],k)
                                                    for (j in 1:nt){
                                                    rankprobs[k,j]<-equals(rk[k],j)
                                                    }
                                          }

#calculate mean differences
```

```
for (c in 1:nt-1)
        {for (k in (c+1):nt)
                {diff[c,k]<-d[k]-d[c]
                }
        }

}                                       # *** PROGRAM ENDS
```

L.2.1 Centre-involving population: Change in visual acuity

Figure 61. Network diagram. Line thickness indicates number of trials comparing treatments for change in visual acuity at 12 months for people with centre-involving macular oedema. Nodes are scaled to indicate number of trials involving each treatment

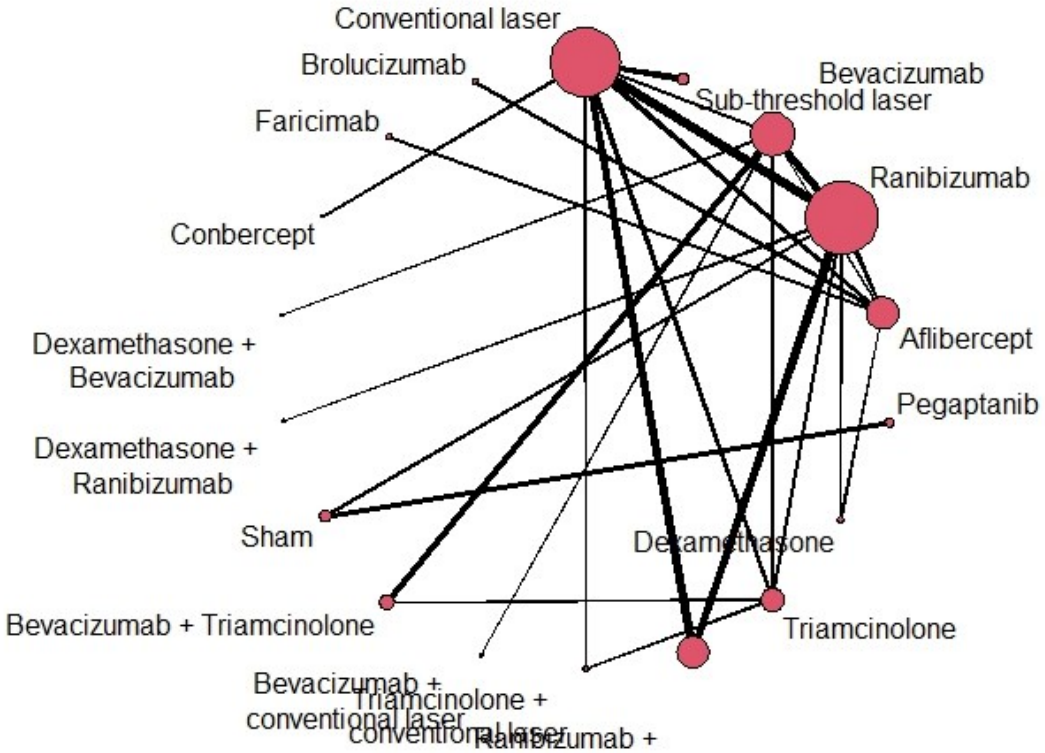
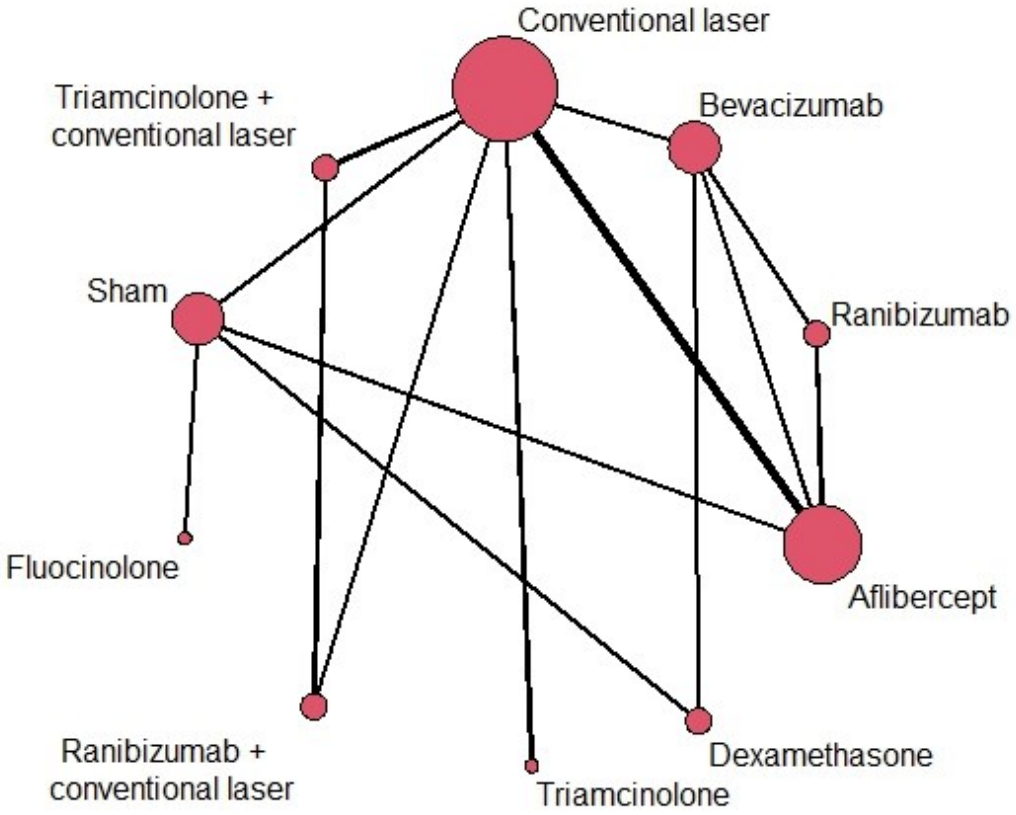


Figure 62. Network diagram. Line thickness indicates number of trials comparing treatments for change in visual acuity at 24 months for people with centre-involving macular oedema. Nodes are scaled to indicate number of trials involving each treatment



L.2.1.1 Model selection for mean change in visual acuity at 12 and 24 months

The data were fitted and random effects models, and the goodness of fit evaluated by calculating the total residual deviance (a calculation of the model's ability to predict the individual data points underlying it – a well-fitting model will have a total residual deviance approximately equal to the number of data points) and the deviance information criteria (an estimate of deviance that is 'penalised' according to the number of parameters in the model, and is useful for comparing models), The total residual deviance and deviance information criteria for the fixed and random effects models are shown in Table 137 and Table 138.

A random effects model was preferred for both 12 month and 24 month analyses. The total residual deviance for the random effects model was closer to the number of unconstrained data points, and the deviance information criterion was lower. Reported results are based on the random effects NMA only.

Table 135: Measures of goodness of fit of fixed- and random-effects models for change in visual acuity at 12 months

Measure of goodness of fit	Fixed effect model	Random effects model
Total Residual deviance*	124.7	101.2
Deviance information criterion (DIC)	-346.6	-356.1
Between trial standard deviation (95% credible intervals)	-	0.026 (0.008 to 0.026)
*Compared to 94 data points		

Table 136: Measures of goodness of fit of fixed- and random-effects models for change in visual acuity at 24 months

Measure of goodness of fit	Fixed effect model	Random effects model
Total Residual deviance*	81.2	22.3
Deviance information criterion (DIC)	-44.8	-99.9
Between trial standard deviation (95% credible intervals)	-	0.11 (0.05 to 0.38)
*Compared to 23 data points		

The quality of evidence from the network meta-analysis was assessed using a modified version of the GRADE approach to quality rating. Each GRADE domain was rated as 'no serious', 'serious' or 'very serious' and an overall quality rating was derived for the evidence from the network meta-analysis as whole. The GRADE profile for the network meta-analysis can be found in Appendix F. For a description of how the GRADE criteria were applied to the network meta-analysis, see the Methods document.

L.2.1.2 Results

Table 137: Relative effectiveness showing all pair-wise combinations for mean change in visual acuity for people with central-involving macular oedema at 12 months

The values given are mean differences. The segment below the shaded cells is derived from the network meta-analysis and shows the mean difference as the row treatment minus the column treatment. Values in parentheses are 95% credible intervals. The segment above the shaded cells shows pooled direct evidence (random effects pairwise meta-analysis), where available, and shows the mean difference as the column treatment minus the row treatment.

	Standard threshold laser	Sub-threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Pegaptanib	Dexamethasone	Triamcinolone	Ranibizumab + standard	Triamcinolone + standard	Bevacizumab + standard	Bevacizumab + triamcinolone	Sham	Dexamethasone +	Dexamethasone +	Conbercept	Faricimab	Brolucizumab
Standard threshold laser		0.01 (-0.04, 0.05)	-0.20 (-0.30, -0.09)	-0.11 (-0.15, -0.08)	-0.21 (-0.25, -0.16)	N/A	N/A	-0.03 (-0.09, 0.02)	-0.10 (-0.15, -0.06)	-0.02 (-0.17, 0.13)	N/A	N/A	N/A	N/A	N/A	-0.17 (-0.24, -0.10)	N/A	N/A
Sub-threshold laser	0.00 (-0.05, 0.06)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bevacizumab	-0.12 (-0.16, -0.08)	-0.12 (-0.19, -0.06)		-0.02 (-0.06, 0.02)	-0.06 (-0.12, -0.01)	N/A	N/A	0.16 (0.03, 0.29)	N/A	N/A	-0.04 (-0.17, 0.10)	0.03 (-0.02, 0.09)	N/A	N/A	-0.01 (-0.18, 0.17)	N/A	N/A	N/A
Ranibizumab	-0.13 (-0.16, -0.10)	-0.13 (-0.19, -0.07)	-0.01 (-0.05, 0.02)		-0.05 (-0.09, 0.00)	N/A	0.07 (0.01, 0.12)	0.20 (0.08, 0.32)	0.01 (-0.02, 0.04)	N/A	N/A	N/A	0.24 (0.14, 0.33)	0.01 (-0.07, 0.08)	N/A	N/A	N/A	N/A
Aflibercept	-0.18 (-0.22, -0.15)	-0.18 (-0.25, -0.12)	-0.06 (-0.11, -0.02)	-0.05 (-0.09, -0.01)		N/A	0.05 (0.00, 0.10)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-0.02 (-0.05, 0.02)	0.02 (-0.03, 0.08)
Pegaptanib	0.01 (-0.11, 0.13)	0.01 (-0.12, 0.14)	0.13 (0.01, 0.25)	0.15 (0.03, 0.26)	0.19 (0.07, 0.32)		N/A	N/A	N/A	N/A	N/A	N/A	0.09 (0.05, 0.13)	N/A	N/A	N/A	N/A	N/A

	Standard threshold laser	Sub-threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Pegaptanib	Dexamethasone	Triamcinolone	Ranibizumab + standard	Triamcinolone + standard	Bevacizumab + standard	Bevacizumab + triamcinolone	Sham	Dexamethasone +	Dexamethasone +	Conbercept	Faricimab	Brolucizumab
Dexamethasone	-0.10 (-0.15, -0.05)	-0.10 (-0.18, -0.03)	0.02 (-0.04, 0.08)	0.03 (-0.02, 0.08)	0.08 (0.03, 0.13)	-0.11 (-0.24, 0.01)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Triamcinolone	-0.03 (-0.08, 0.02)	-0.03 (-0.11, 0.04)	0.09 (0.03, 0.14)	0.10 (0.05, 0.15)	0.15 (0.09, 0.21)	-0.04 (-0.17, 0.08)	0.07 (0.00, 0.14)		N/A	N/A	N/A	0.02 (-0.09, 0.14)	N/A	N/A	N/A	N/A	N/A	N/A
Ranibizumab + standard threshold laser	-0.11 (-0.15, -0.08)	-0.12 (-0.18, -0.06)	0.00 (-0.04, 0.05)	0.02 (-0.01, 0.05)	0.07 (0.02, 0.11)	-0.13 (-0.25, -0.01)	-0.02 (-0.07, 0.04)	-0.08 (-0.14, -0.03)		0.09 (0.05, 0.15)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Triamcinolone + standard threshold laser	-0.02 (-0.07, 0.03)	-0.02 (-0.10, 0.05)	0.10 (0.04, 0.16)	0.11 (0.06, 0.17)	0.16 (0.10, 0.22)	-0.03 (-0.16, 0.10)	0.08 (0.01, 0.15)	0.01 (-0.06, 0.08)	0.10 (0.04, 0.15)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bevacizumab + standard threshold laser	-0.16 (-0.31, -0.02)	-0.16 (-0.32, -0.01)	-0.04 (-0.18, 0.10)	-0.03 (-0.17, 0.11)	0.02 (-0.13, 0.17)	-0.17 (-0.36, 0.01)	-0.06 (-0.21, 0.09)	-0.13 (-0.28, 0.02)	-0.04 (-0.19, 0.10)	-0.14 (-0.30, 0.01)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bevacizumab + triamcinolone	-0.08 (-0.15, -0.01)	-0.08 (-0.17, 0.00)	0.04 (-0.02, 0.10)	0.05 (-0.01, 0.12)	0.10 (0.03, 0.17)	-0.09 (-0.23, 0.04)	0.02 (-0.06, 0.10)	-0.05 (-0.12, 0.03)	0.04 (-0.04, 0.11)	-0.06 (-0.14, 0.02)	0.08 (-0.07, 0.23)		N/A	N/A	N/A	N/A	N/A	N/A
Sham	0.10 (-0.01, 0.21)	0.10 (-0.02, 0.22)	0.22 (0.11, 0.33)	0.23 (0.13, 0.34)	0.28 (0.17, 0.39)	0.09 (0.04, 0.14)	0.20 (0.09, 0.32)	0.13 (0.02, 0.25)	0.22 (0.11, 0.33)	0.12 (0.00, 0.24)	0.26 (0.09, 0.44)	0.18 (0.06, 0.31)		N/A	N/A	N/A	N/A	N/A
Dexamethasone + ranibizumab	-0.12 (-0.21, -0.04)	-0.13 (-0.23, -0.03)	-0.01 (-0.10, 0.08)	0.01 (-0.08, 0.09)	0.06 (-0.03, 0.15)	-0.14 (-0.28, 0.00)	-0.03 (-0.12, 0.07)	-0.09 (-0.19, 0.00)	-0.01 (-0.10, 0.08)	-0.11 (-0.21, -0.01)	0.04 (-0.13, 0.20)	-0.05 (-0.15, 0.06)	-0.23 (-0.36, -0.10)		N/A	N/A	N/A	N/A
Dexamethasone + bevacizumab	-0.13 (-0.30, 0.04)	-0.13 (-0.31, 0.05)	-0.01 (-0.18, 0.16)	0.00 (-0.17, 0.17)	0.05 (-0.12, 0.23)	-0.14 (-0.35, 0.06)	-0.03 (-0.21, 0.15)	-0.10 (-0.27, 0.08)	-0.01 (-0.19, 0.16)	-0.11 (-0.29, 0.07)	0.03 (-0.19, 0.25)	-0.05 (-0.23, 0.13)	-0.23 (-0.43, -0.03)	0.00 (-0.19, 0.19)		N/A	N/A	N/A

	Standard threshold laser	Sub-threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Pegaptanib	Dexamethasone	Triamcinolone	Ranibizumab + standard	Triamcinolone + standard	Bevacizumab + standard	Bevacizumab + triamcinolone	Sham	Dexamethasone +	Dexamethasone +	Conbercept	Faricimab	Brolucizumab
Conbercept	-0.17 (-0.25, -0.09)	-0.17 (-0.27, -0.08)	-0.05 (-0.14, 0.04)	-0.04 (-0.12, 0.04)	0.01 (-0.08, 0.10)	-0.19 (-0.32, -0.04)	-0.07 (-0.16, 0.02)	-0.14 (-0.23, -0.05)	-0.06 (-0.14, 0.03)	-0.15 (-0.25, -0.06)	-0.01 (-0.17, 0.16)	-0.09 (-0.20, 0.01)	-0.27 (-0.41, -0.14)	-0.05 (-0.16, 0.07)	-0.04 (-0.23, 0.15)		N/A	N/A
Faricimab	-0.20 (-0.26, -0.14)	-0.20 (-0.28, -0.12)	-0.08 (-0.14, -0.02)	-0.07 (-0.13, -0.01)	-0.02 (-0.06, 0.03)	-0.21 (-0.34, -0.08)	-0.10 (-0.17, -0.03)	-0.17 (-0.24, -0.09)	-0.08 (-0.15, -0.02)	-0.18 (-0.26, -0.10)	-0.04 (-0.19, 0.12)	-0.12 (-0.20, -0.03)	-0.30 (-0.42, -0.18)	-0.07 (-0.17, 0.03)	-0.07 (-0.25, 0.11)	-0.03 (-0.13, 0.07)		N/A
Brolucizumab	-0.20 (-0.29, -0.12)	-0.21 (-0.31, -0.11)	-0.09 (-0.17, 0.00)	-0.07 (-0.16, 0.01)	-0.02 (-0.10, 0.05)	-0.22 (-0.36, -0.08)	-0.11 (-0.19, -0.02)	-0.17 (-0.27, -0.08)	-0.09 (-0.18, -0.01)	-0.19 (-0.28, -0.09)	-0.04 (-0.21, 0.12)	-0.13 (-0.23, -0.02)	-0.31 (-0.44, -0.18)	-0.08 (-0.20, 0.04)	-0.08 (-0.26, 0.11)	-0.03 (-0.15, 0.08)	-0.01 (-0.09, 0.08)	

Table 138: Relative effectiveness showing all pair-wise combinations for mean change in visual acuity for people with central-involving macular oedema at 24 months

The values given are mean differences. The segment below the shaded cells is derived from the network meta-analysis and shows the mean difference as the row treatment minus the column treatment. Values in parentheses are 95% credible intervals. The segment above the shaded cells shows pooled direct evidence (random effects pairwise meta-analysis), where available, and shows the mean difference as the column treatment minus the row treatment.

	Standard threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Fluocinolone	Sham	Triamcinolone + standard threshold laser
Standard threshold laser		-0.18 (-1.45, 1.11)	N/A	-0.09 (-0.83, 0.65)	N/A	0.08 (-1.19, 1.36)	-0.12 (-1.38, 1.15)	N/A	N/A	N/A
Bevacizumab	-0.12 (-0.36, 0.11)		N/A	-0.06 (-1.34, 1.23)	0.08 (-1.15, 1.37)	N/A	N/A	N/A	N/A	N/A
Ranibizumab	-0.13 (-0.46, 0.20)	-0.01 (-0.32, 0.30)		-0.01 (-1.27, 1.24)	N/A	N/A	N/A	N/A	N/A	N/A
Aflibercept	-0.11 (-0.29, 0.07)	0.01 (-0.22, 0.25)	0.03 (-0.28, 0.33)		N/A	N/A	N/A	N/A	0.03 (-1.25, 1.32)	N/A
Dexamethasone	-0.06 (-0.38, 0.25)	0.06 (-0.22, 0.34)	0.07 (-0.32, 0.47)	0.05 (-0.26, 0.37)		N/A	N/A	N/A	0.04 (-1.24, 1.29)	N/A
Triamcinolone	0.08 (-0.25, 0.41)	0.20 (-0.20, 0.61)	0.21 (-0.26, 0.68)	0.19 (-0.18, 0.57)	0.14 (-0.31, 0.60)		N/A	N/A	N/A	N/A
Ranibizumab + standard threshold laser	-0.12 (-0.45, 0.21)	0.00 (-0.40, 0.41)	0.02 (-0.45, 0.48)	-0.01 (-0.38, 0.37)	-0.06 (-0.51, 0.40)	-0.20 (-0.67, 0.27)		N/A	N/A	0.10 (-1.18, 1.37)
Fluocinolone	-0.08 (-0.51, 0.34)	0.04 (-0.40, 0.48)	0.05 (-0.46, 0.56)	0.02 (-0.40, 0.45)	-0.02 (-0.45, 0.41)	-0.16 (-0.70, 0.37)	0.03 (-0.51, 0.58)		0.06 (-1.19, 1.36)	N/A
Sham	-0.03 (-0.30, 0.24)	0.10 (-0.20, 0.39)	0.11 (-0.28, 0.49)	0.08 (-0.19, 0.35)	0.03 (-0.24, 0.31)	-0.11 (-0.54, 0.32)	0.09 (-0.34, 0.51)	0.06 (-0.27, 0.38)		N/A
Triamcinolone + standard threshold laser	-0.02 (-0.35, 0.31)	0.10 (-0.30, 0.51)	0.12 (-0.35, 0.58)	0.09 (-0.28, 0.47)	0.04 (-0.42, 0.50)	-0.10 (-0.57, 0.37)	0.10 (-0.23, 0.43)	0.07 (-0.48, 0.61)	0.01 (-0.42, 0.44)	

Table 139: Median rankings for each treatment with 95% credible intervals for mean change in visual acuity for people with central-involving macular oedema at 12 months

	Median rank (95% CrI)
Standard threshold laser	15 (14 to 17)
Sub-threshold laser	16 (12 to 18)
Bevacizumab	8 (5 to 11)
Ranibizumab	7 (5 to 9)
Aflibercept	4 (2 to 6)
Pegaptanib	16 (10 to 17)
Dexamethasone	10 (5 to 13)
Triamcinolone	13 (11 to 17)
Ranibizumab + standard threshold laser	9 (5 to 12)
Triamcinolone + standard threshold laser	14 (11 to 17)
Bevacizumab + standard threshold laser	5 (1 to 14)
Bevacizumab + triamcinolone	11 (6 to 14)
Sham	18 (16 to 18)
Dexamethasone + ranibizumab	8 (2 to 13)
Dexamethasone + bevacizumab	7 (1 to 17)
Conbercept + sham	4 (1 to 11)
Faricimab	2 (1 to 6)

	Median rank (95% CrI)
Brolucizumab	2 (1 to 7)

Table 140: Median rankings for each treatment with 95% credible intervals for mean change in visual acuity for people with central-involving macular oedema at 24 months

	Median rank (95% CrI)
Standard threshold laser	8 (4 to 10)
Bevacizumab	3 (1 to 8)
Ranibizumab	3 (1 to 10)
Aflibercept	4 (1 to 8)
Dexamethasone	6 (1 to 10)
Triamcinolone	10 (2 to 10)
Ranibizumab + standard threshold laser	4 (1 to 10)
Fluocinolone	5 (1 to 10)
Sham	7 (2 to 10)
Triamcinolone + standard threshold laser	7 (1 to 10)

Figure 63: Change in visual acuity at 12 months (logMAR). Relative effect of all treatments compared with standard threshold laser. Squares indicate the median of the posterior distribution for each effect, and lines indicate 95% Credible intervals.

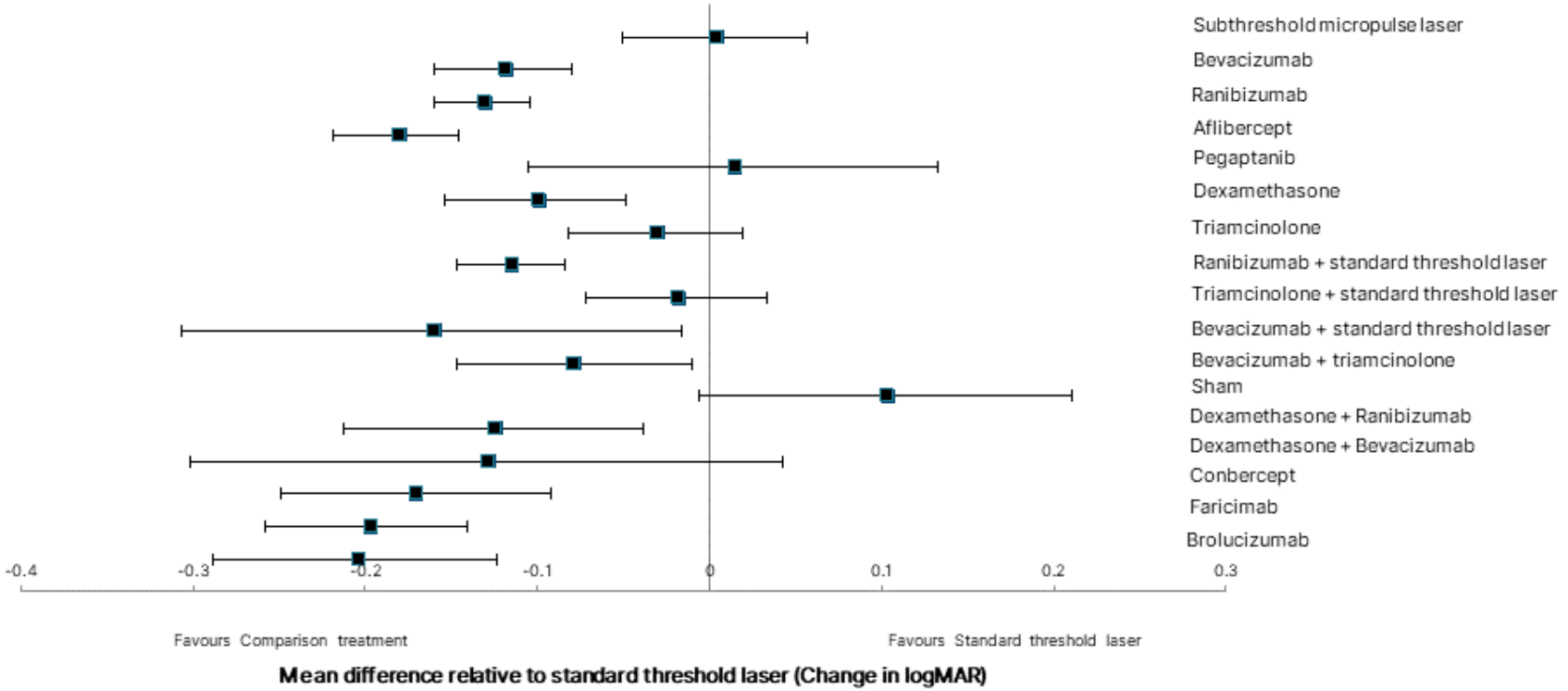
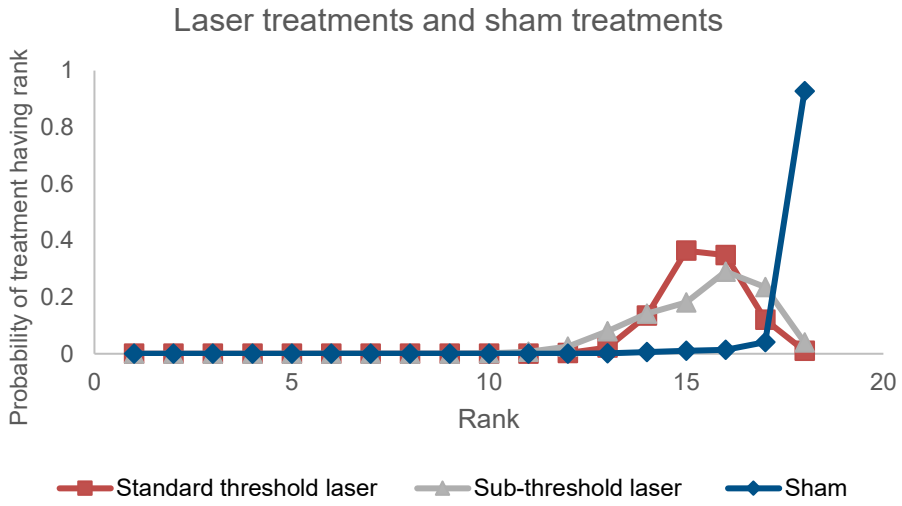
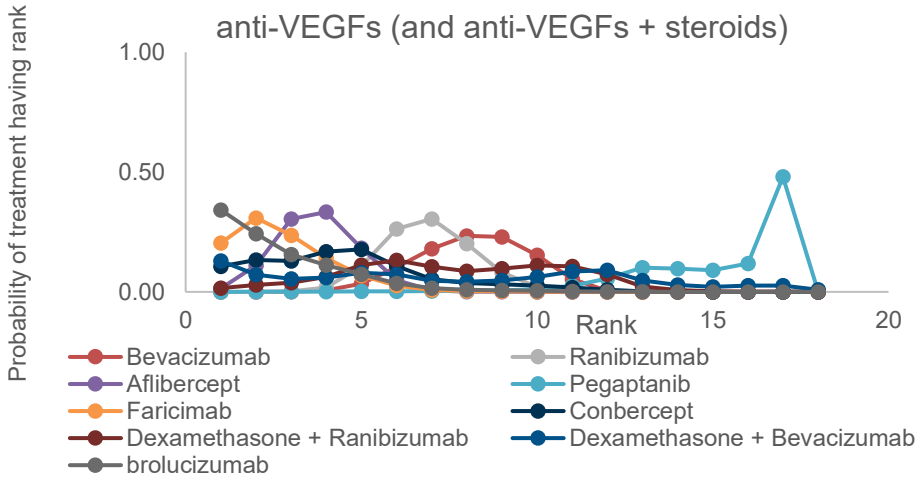
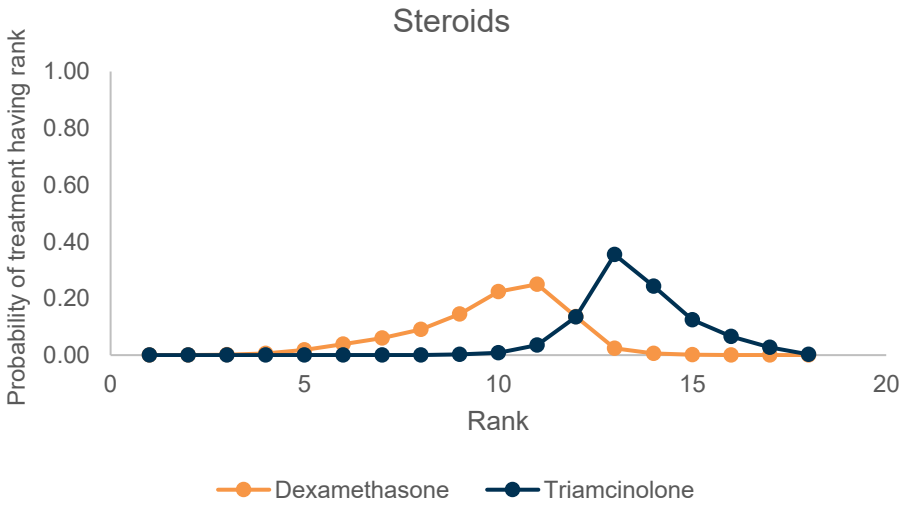


Figure 64: Rank probability plots for each treatment at 12 months. The probability of each treatment assuming each rank (1 to 18, with 1 as the most effective treatment) is plotted. Each line indicates a different treatment.







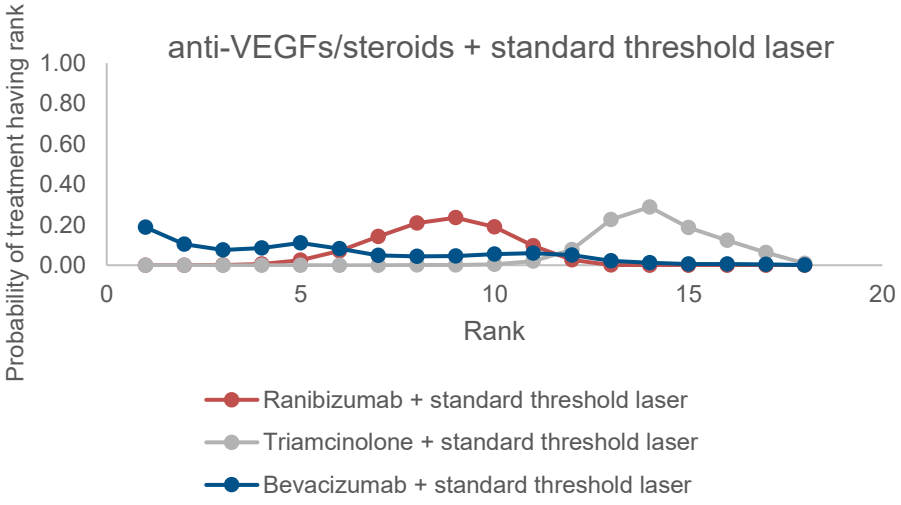


Figure 65: Change in visual acuity at 24 months (logMAR). Relative effect of all treatments compared with standard threshold laser. Squares indicate the median of the posterior distribution for each effect, and lines indicate 95% Credible intervals.

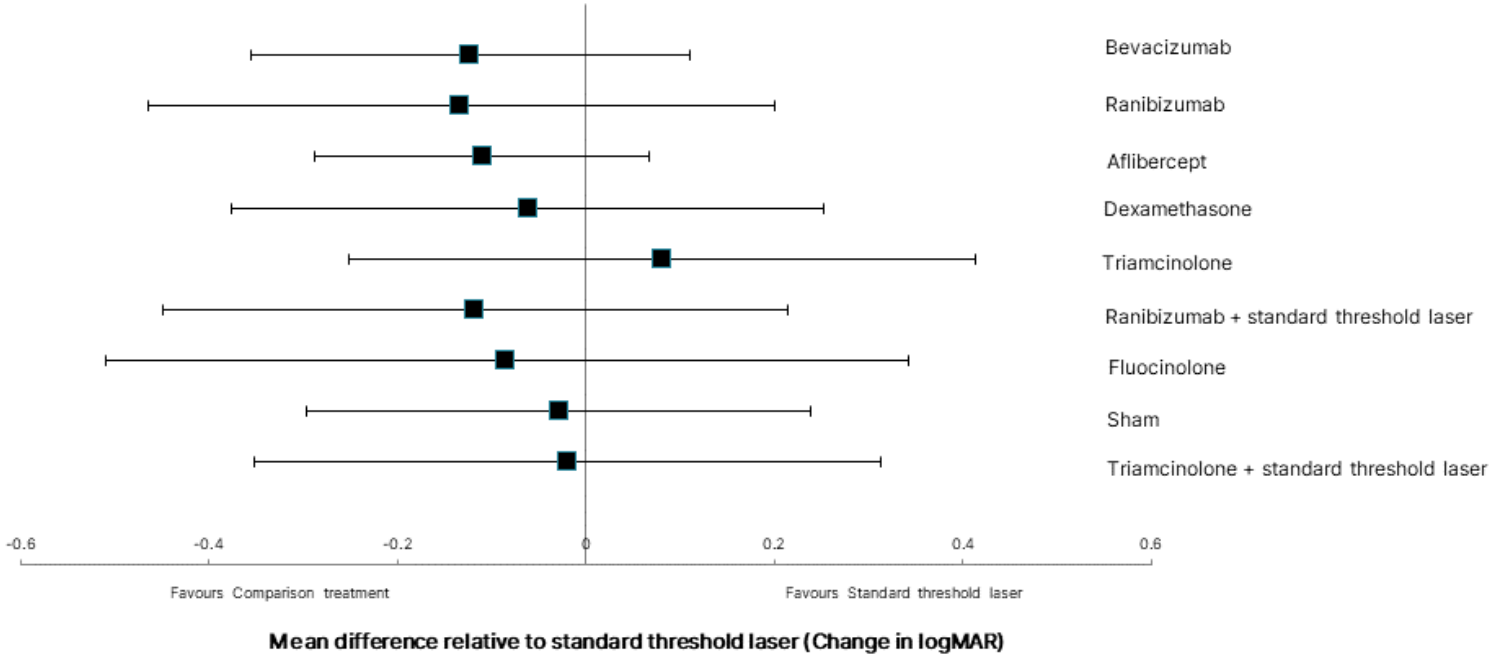
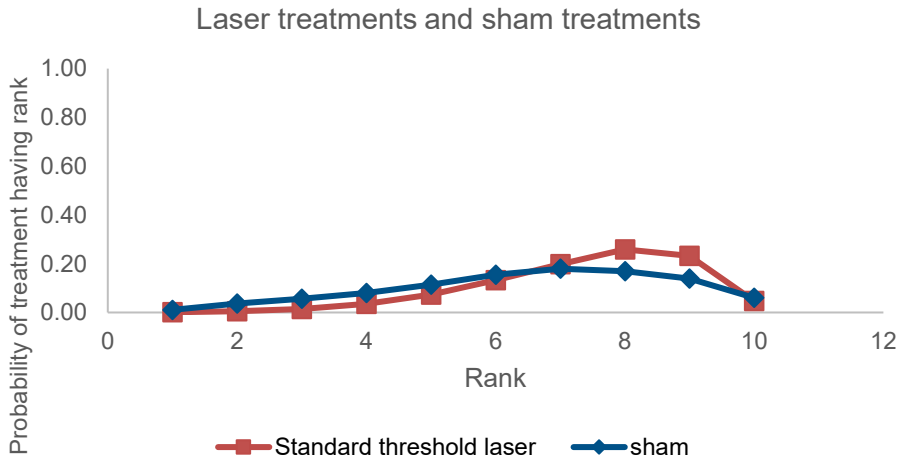
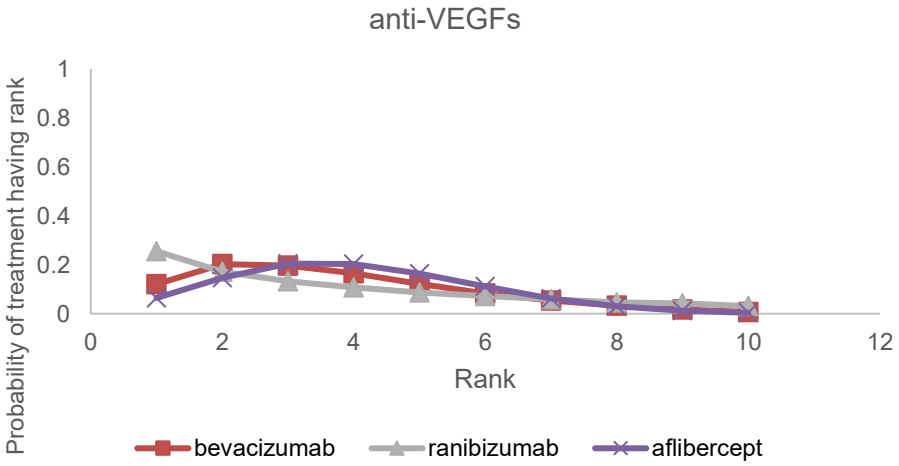
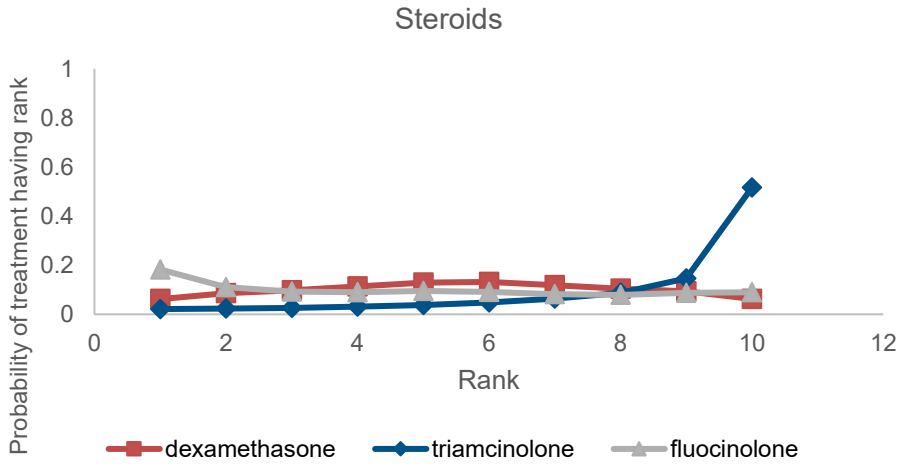
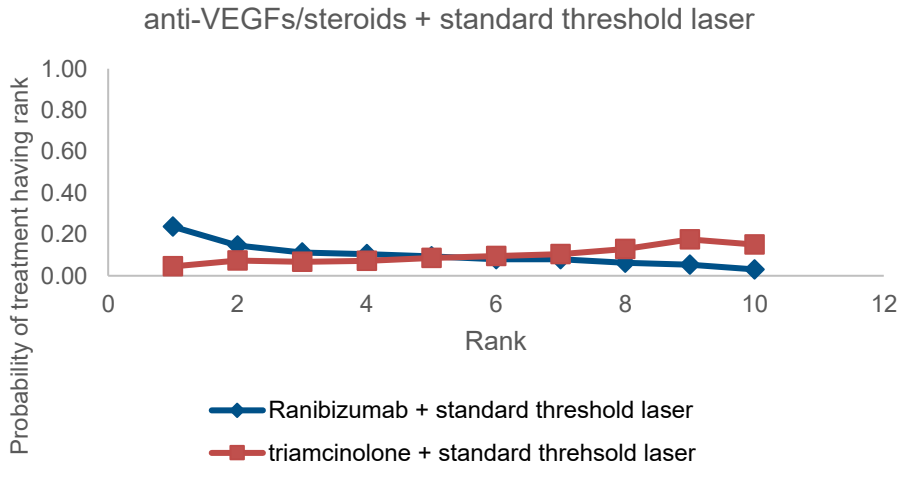


Figure 66: Rank probability plots at 24 months. The probability of each treatment assuming each rank (1 to 10, with 1 as the most effective treatment) is plotted. Each line indicates a different treatment.









L.2.2 Centre-involving population - subgroup with central retinal thickness >400 µm at baseline: Change in visual acuity

Figure 67: Network diagram. Line thickness indicates number of trials comparing treatments for change in visual acuity at 12 months for people with centre-involving macular oedema and central retinal thickness >400 µm at baseline. Nodes are scaled to indicate number of trials involving each treatment

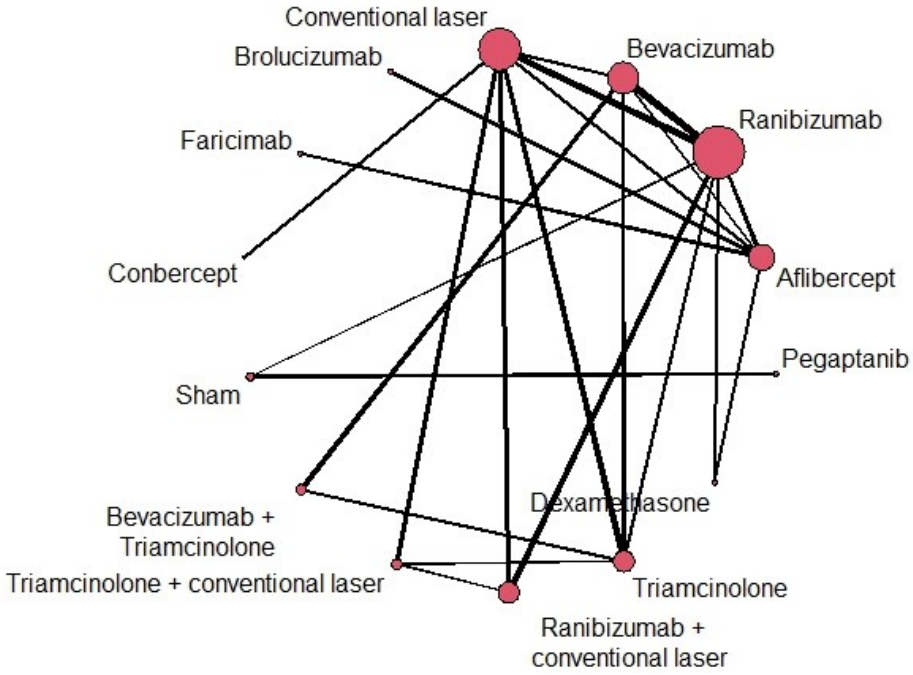
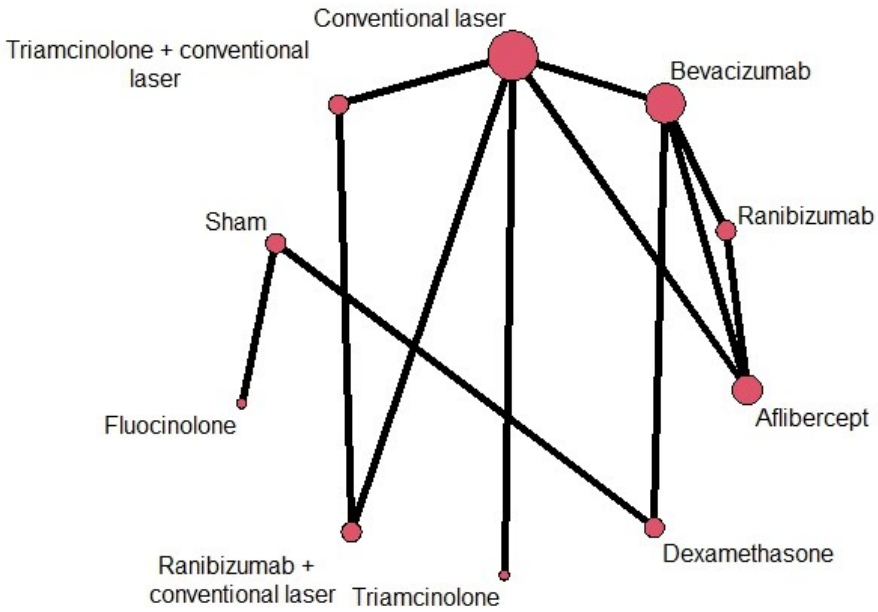


Figure 68: Network diagram. Line thickness indicates number of trials comparing treatments for change in visual acuity at 24 months for people with centre-involving macular oedema and central retinal thickness >400 µm at baseline. Nodes are scaled to indicate number of trials involving each treatment



L.2.2.1 Model selection for mean change in visual acuity at 12 and 24 months (subgroup with central retinal thickness >400µm)

The data were fitted and random effects models, and the goodness of fit evaluated by calculating the total residual deviance (a calculation of the model's ability to predict the individual data points underlying it – a well-fitting model will have a total residual deviance approximately equal to the number of data points) and the deviance information criteria (an estimate of deviance that is 'penalised' according to the number of parameters in the model, and is useful for comparing models), The total residual deviance and deviance information criteria for the fixed and random effects models are shown in Table 141 and Table 142.

A random effects model was preferred. The total residual deviance for the random effects model was closer to the number of unconstrained data points, and the deviance information criterion was lower. Reported results are based on the random effects NMA only.

Change in visual acuity at 12 months (logMAR) in population with baseline central retinal thickness >400um

Table 141: Measures of goodness of fit of fixed- and random-effects models

Measure of goodness of fit	Fixed effect model	Random effects model
Total Residual deviance*	97.9	69.6
Deviance information criterion (DIC)	-255.2	-271.41
Between trial standard deviation (95% credible intervals)	-	0.03 (0.01 to 0.05)
*Compared to 70 data points		

Change in visual acuity at 24 months (logMAR) in population with baseline central retinal thickness >400um

Table 142: Measures of goodness of fit of fixed- and random-effects models

Measure of goodness of fit	Fixed effect model	Random effects model
Total Residual deviance*	16.3	17.1
Deviance information criterion (DIC)	-72.6	-70.9
Between trial standard deviation (95% credible intervals)	-	0.21 (0.003 to 4.2)
*Compared to 18 data points		

A fixed effects model was preferred. The total residual deviance for both models were close to the number of unconstrained data points, and the deviance information criterion was lower for the random effects model. Subsequent results present data from the fixed effects model only.

The quality of evidence from the network meta-analysis was assessed using a modified version of the GRADE approach to quality rating. Each GRADE domain was rated as 'no serious', 'serious' or 'very serious' and an overall quality rating was derived for the evidence from the network

meta-analysis as whole. The GRADE profile for the network meta-analysis can be found in Appendix F. For a description of how the GRADE criteria were applied to the network meta-analysis, see the Methods document.

L.2.2.2 Results

Table 143: Relative effectiveness showing all pair-wise combinations for mean change in visual acuity for people with central-involving macular oedema and central retinal thickness >400 µm at baseline at 12 months

The values given are mean differences. The segment below the shaded cells is derived from the network meta-analysis and shows the mean difference as the row treatment minus the column treatment. Values in parentheses are 95% credible intervals. The segment above the shaded cells shows pooled direct evidence (random effects pairwise meta-analysis), where available, and shows the mean difference as the column treatment minus the row treatment.

	Standard threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Pegaptanib	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Triamcinolone + standard threshold laser	Bevacizumab + triamcinolone	Sham	Conbercept	Faricimab	Brolucizumab
Standard threshold laser		-0.19 (-0.30, -0.09)	-0.10 (-0.15, -0.06)	-0.24 (-0.30, -0.19)	N/A	N/A	-0.02 (-0.09, 0.02)	-0.13 (-0.19, -0.08)	-0.01 (-0.17, 0.13)	N/A	N/A	-0.17 (-0.23 -0.09)	N/A	N/A
Bevacizumab	-0.13 (-0.18, -0.09)		-0.02 (-0.06, 0.02)	-0.06 (-0.12, -0.07)	N/A	N/A	0.15 (0.03, 0.28)	N/A	N/A	0.04 (-0.02, 0.10)	N/A	N/A	N/A	N/A
Ranibizumab	-0.15 (-0.18, -0.11)	-0.01 (-0.05, 0.02)		-0.04 (-0.09, 0.00)	N/A	0.06 (0.01, 0.11)	0.19 (0.07, 0.32)	0.00 (-0.03, 0.04)	N/A	N/A	0.23 (0.13, 0.33)	N/A	N/A	N/A
Aflibercept	-0.20 (-0.25, -0.15)	-0.07 (-0.12, -0.02)	-0.05 (-0.10, -0.01)		N/A	0.04 (-0.00, 0.10)	N/A	N/A	N/A	N/A	N/A	N/A	-0.01 (-0.05, 0.02)	-0.00 (-0.04, 0.04)

	Standard threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Pegaptanib	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Triamcinolone + standard threshold laser	Bevacizumab + triamcinolone	Sham	Conbercept	Faricimab	Brolucizumab
Pegaptanib	0.00 (-0.13, 0.14)	0.13 (0.00, 0.27)	0.15 (0.02, 0.28)	0.20 (0.06, 0.34)		N/A	N/A	N/A	N/A	N/A	0.08 (0.02, 0.14)	N/A	N/A	N/A
Dexamethasone	-0.12 (-0.18, -0.05)	0.02 (-0.05, 0.08)	0.03 (-0.03, 0.09)	0.08 (0.03, 0.14)	-0.12 (-0.26, 0.03)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Triamcinolone	-0.04 (-0.09, 0.02)	0.10 (0.03, 0.15)	0.11 (0.05, 0.17)	0.16 (0.09, 0.23)	-0.04 (-0.18, 0.10)	0.08 (0.00, 0.16)		N/A	N/A	0.02 (-0.08, 0.14)	N/A	N/A	N/A	N/A
Ranibizumab + standard threshold laser	-0.13 (-0.18, -0.09)	0.00 (-0.05, 0.05)	0.01 (-0.03, 0.05)	0.06 (0.01, 0.12)	-0.14 (-0.27, 0.00)	-0.02 (-0.09, 0.05)	-0.10 (-0.16, -0.03)		0.09 (0.00, 0.17)	N/A	N/A	N/A	N/A	N/A
Triamcinolone + standard threshold laser	-0.04 (-0.12, 0.04)	0.09 (0.00, 0.18)	0.10 (0.02, 0.19)	0.16 (0.07, 0.25)	-0.04 (-0.20, 0.11)	0.07 (-0.02, 0.17)	0.00 (-0.09, 0.09)	0.09 (0.01, 0.17)		N/A	N/A	N/A	N/A	N/A
Bevacizumab + triamcinolone	-0.08 (-0.16, 0.00)	0.05 (-0.01, 0.13)	0.07 (-0.01, 0.15)	0.12 (0.04, 0.21)	-0.08 (-0.23, 0.07)	0.04 (-0.06, 0.13)	-0.04 (-0.13, 0.05)	0.06 (-0.03, 0.14)	-0.04 (-0.14, 0.07)		N/A	N/A	N/A	N/A

	Standard threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Pegaptanib	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Triamcinolone + standard threshold laser	Bevacizumab + triamcinolone	Sham	Conbercept	Faricimab	Brolucizumab
Sham	0.09 (-0.03, 0.20)	0.22 (0.10, 0.34)	0.23 (0.12, 0.34)	0.29 (0.17, 0.40)	0.09 (0.01, 0.16)	0.20 (0.08, 0.33)	0.12 (0.00, 0.25)	0.22 (0.10, 0.34)	0.13 (-0.01, 0.27)	0.17 (0.03, 0.30)		N/A	N/A	N/A
Conbercept	-0.17 (-0.26, -0.08)	-0.04 (-0.13, 0.06)	-0.02 (-0.12, 0.07)	0.03 (-0.07, 0.13)	-0.17 (-0.33, -0.01)	-0.05 (-0.16, 0.05)	-0.13 (-0.23, -0.03)	-0.04 (-0.13, 0.06)	-0.13 (-0.24, -0.01)	-0.09 (-0.21, 0.03)	-0.26 (-0.40, -0.11)		N/A	N/A
Faricimab	-0.22 (-0.29, -0.15)	-0.08 (-0.16, -0.01)	-0.07 (-0.14, 0.00)	-0.02 (-0.07, 0.04)	-0.22 (-0.36, -0.07)	-0.10 (-0.18, -0.02)	-0.18 (-0.26, -0.09)	-0.08 (-0.16, -0.01)	-0.17 (-0.28, -0.07)	-0.14 (-0.24, -0.04)	-0.30 (-0.43, -0.17)	-0.05 (-0.16, 0.06)		N/A
Brolucizumab	-0.20 (-0.27, -0.13)	-0.07 (-0.14, 0.01)	-0.05 (-0.12, 0.02)	0.00 (-0.06, 0.06)	-0.20 (-0.35, -0.05)	-0.08 (-0.16, 0.00)	-0.16 (-0.25, -0.07)	-0.06 (-0.14, 0.02)	-0.16 (-0.26, -0.05)	-0.12 (-0.22, -0.02)	-0.29 (-0.42, -0.15)	-0.03 (-0.14, 0.08)	0.02 (-0.06, 0.10)	

Table 144: Relative effectiveness showing all pair-wise combinations for mean change in visual acuity for people with central-involving macular oedema and central retinal thickness >400 µm at baseline at 24 months

The values given are mean differences. The segment below the shaded cells is derived from the network meta-analysis and shows the mean difference as the row treatment minus the column treatment. Values in parentheses are 95% credible intervals. The segment above the shaded cells shows pooled direct evidence (random effects pairwise meta-analysis), where available, and shows the mean difference as the column treatment minus the row treatment.

	Standard threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Fluocinolone	Sham	Triamcinolone + standard threshold laser
Standard threshold laser		-0.18 (-6.33, -5.98)	N/A	-0.23 (-6.36, 6.00)	N/A	-0.01 (-6.15, 6.19)	-0.12 (-6.26, 6.04)	N/A	N/A	N/A
Bevacizumab	-0.18 (-0.21, -0.15)		N/A	-0.06 (-6.23, 6.13)	0.08 (-6.15, 6.25)	N/A	N/A	N/A	N/A	N/A
Ranibizumab	-0.23 (-0.27, -0.18)	-0.05 (-0.09, 0.00)		-0.01 (-6.19, 6.21)	N/A	N/A	N/A	N/A	N/A	N/A
Aflibercept	-0.24 (-0.27, -0.20)	-0.06 (-0.09, -0.02)	-0.01 (-0.05, 0.03)		N/A	N/A	N/A	N/A	N/A	N/A
Dexamethasone	-0.10 (-0.22, 0.02)	0.08 (-0.03, 0.19)	0.13 (0.00, 0.24)	0.14 (0.02, 0.25)		N/A	N/A	N/A	0.05 (-6.05, 6.22)	N/A
Triamcinolone	0.00 (-0.26, 0.26)	0.18 (-0.08, 0.44)	0.23 (-0.04, 0.49)	0.23 (-0.03, 0.50)	0.10 (-0.19, 0.39)		N/A	N/A	N/A	N/A
Ranibizumab + standard threshold laser	-0.12 (-0.17, -0.07)	0.06 (0.00, 0.12)	0.11 (0.04, 0.17)	0.12 (0.06, 0.18)	-0.02 (-0.14, 0.11)	-0.12 (-0.39, 0.15)		N/A	N/A	0.10 (-6.09, 6.31)
Fluocinolone	-0.11 (-0.24, 0.02)	0.07 (-0.05, 0.19)	0.12 (-0.02, 0.25)	0.13 (0.00, 0.25)	-0.01 (-0.06, 0.04)	-0.11 (-0.40, 0.18)	0.01 (-0.13, 0.14)		0.06 (-6.19, 6.16)	N/A
Sham	-0.05 (-0.18, 0.07)	0.13 (0.00, 0.24)	0.17 (0.04, 0.30)	0.18 (0.05, 0.31)	0.05 (0.00, 0.09)	-0.05 (-0.34, 0.24)	0.07 (-0.07, 0.20)	0.06 (0.03, 0.08)		N/A
Triamcinolone + standard threshold laser	-0.02 (-0.07, 0.03)	0.16 (0.10, 0.22)	0.21 (0.14, 0.28)	0.22 (0.15, 0.28)	0.08 (-0.05, 0.21)	-0.02 (-0.29, 0.25)	0.10 (0.05, 0.15)	0.09 (-0.05, 0.23)	0.03 (-0.10, 0.17)	

Table 145: Median rankings for each treatment with 95% credible intervals for mean change in visual acuity for people with central-involving macular oedema and central retinal thickness >400 µm at baseline at 12 months

	Median rank (95% CrI)
Standard threshold laser	12 (11 to 14)
Bevacizumab	7 (4 to 9)
Ranibizumab	5 (3 to 7)
Aflibercept	3 (1 to 4)
Pegaptanib	12 (7 to 13)
Dexamethasone	8 (4 to 10)
Triamcinolone	11 (9 to 13)
Ranibizumab + standard threshold laser	6 (4 to 9)
Triamcinolone + standard threshold laser	11 (8 to 13)
Bevacizumab + triamcinolone	9 (5 to 12)
Sham	14 (12 to 14)
Conbercept + sham	4 (1 to 9)
Faricimab	1 (1 to 5)
Brolucizumab	3 (1 to 7)

Table 146: Median rankings for each treatment with 95% credible intervals for mean change in visual acuity for people with central-involving macular oedema and central retinal thickness >400 µm at baseline at 24 months

	Median rank (95% CrI)
Standard threshold laser	9 (7 to 10)
Bevacizumab	3 (3 to 6)
Ranibizumab	2 (1 to 3)
Aflibercept	1 (1 to 3)
Dexamethasone	6 (3 to 8)
Triamcinolone	9 (1 to 10)
Ranibizumab + standard threshold laser	5 (4 to 8)
Fluocinolone	5 (2 to 8)
Sham	7 (5 to 10)
Triamcinolone + standard threshold laser	8 (5 to 10)

Figure 69: Change in visual acuity for people with central-involving macular oedema and central retinal thickness >400 µm at baseline at 12 months (logMAR). Relative effect of all treatments compared with standard threshold laser. Squares indicate the median of the posterior distribution for each effect, and lines indicate 95% Credible intervals.

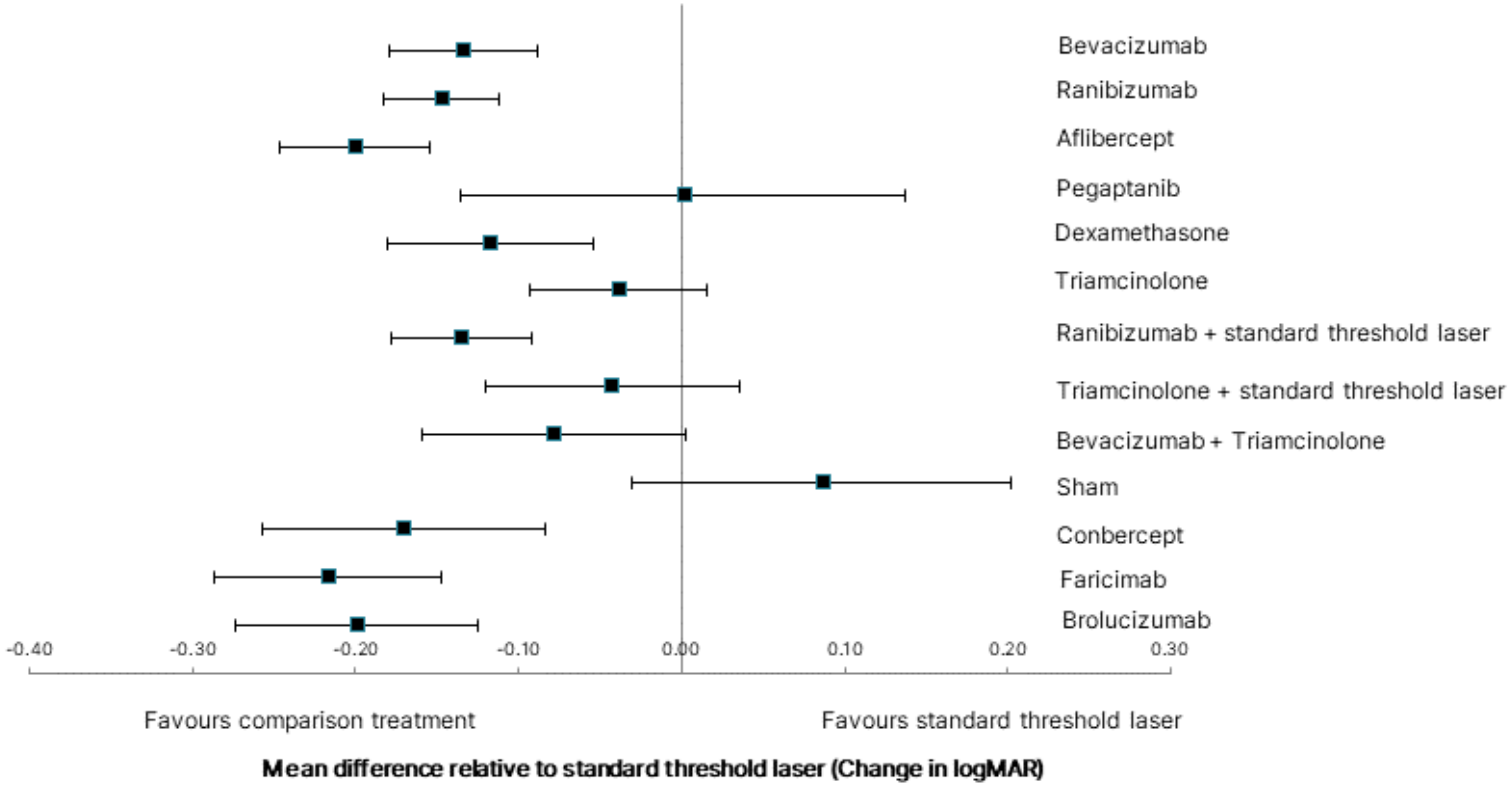
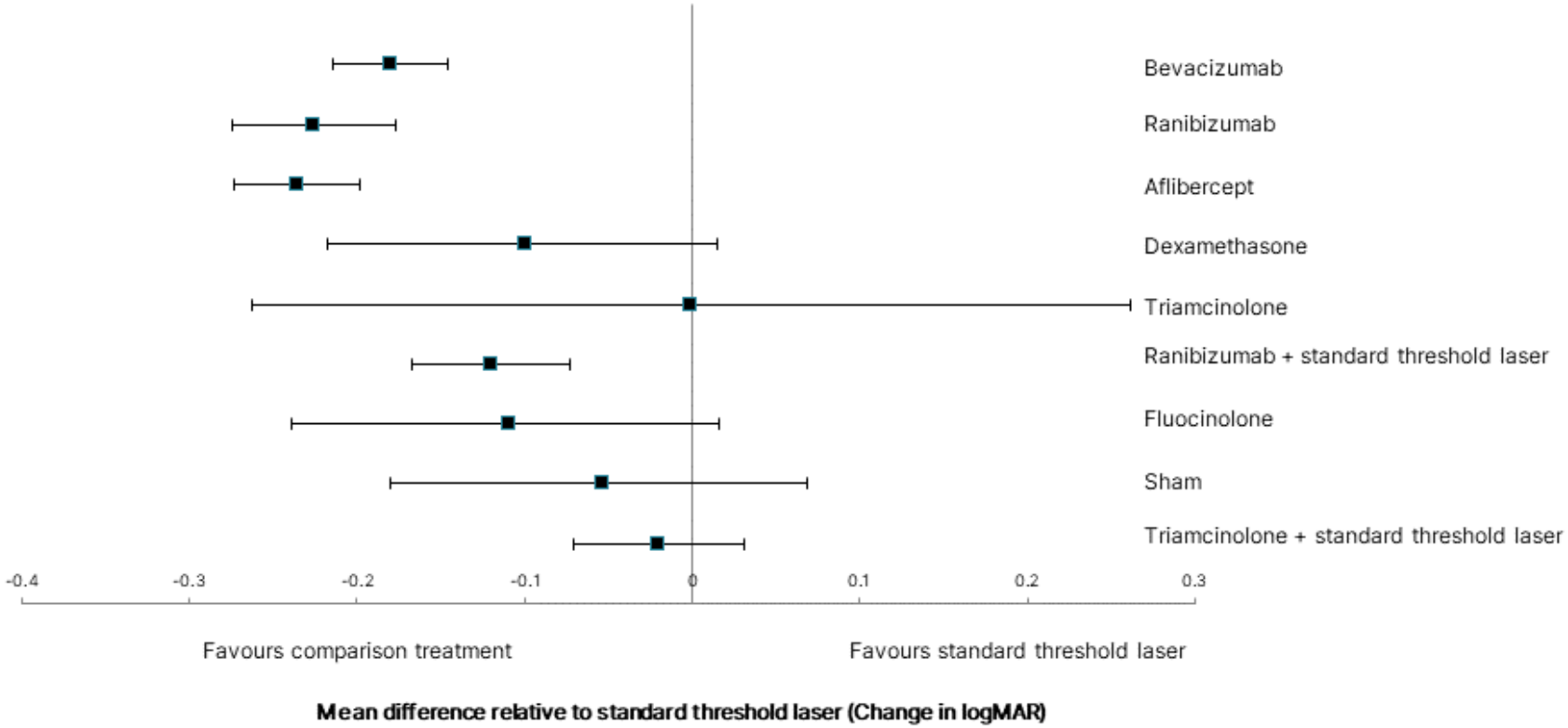
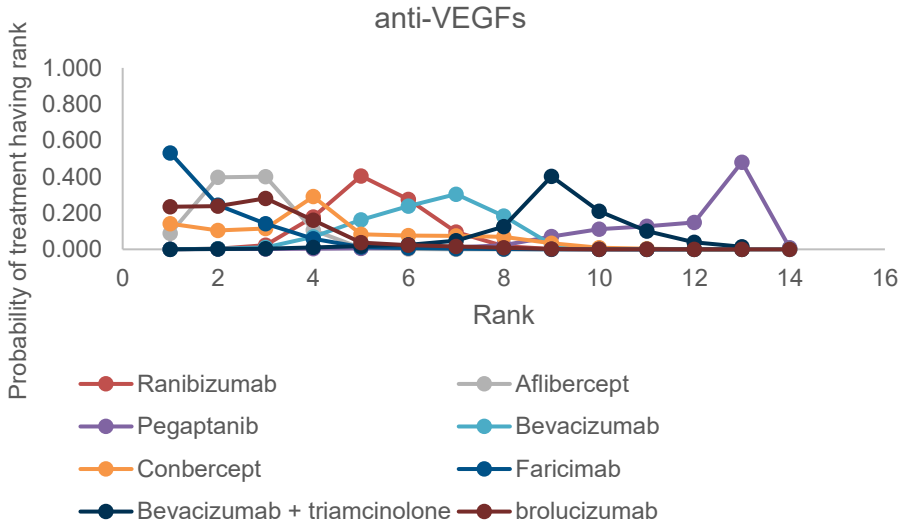
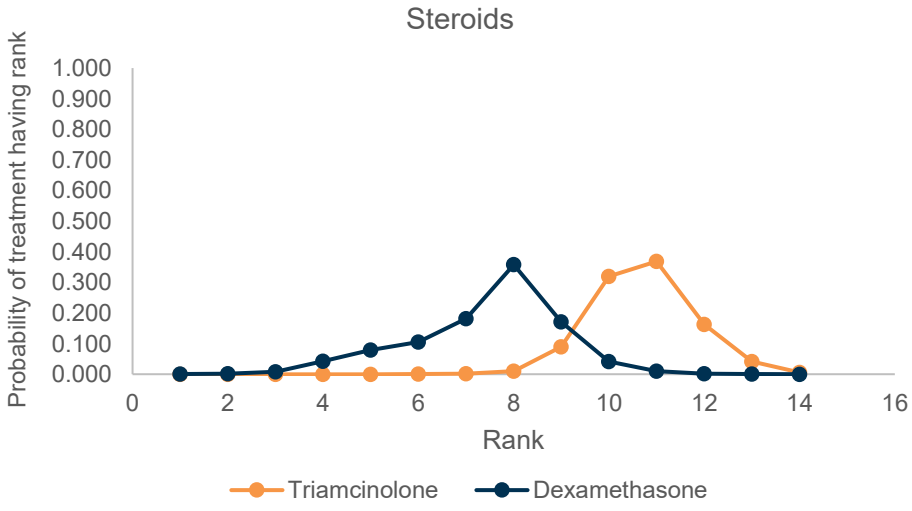


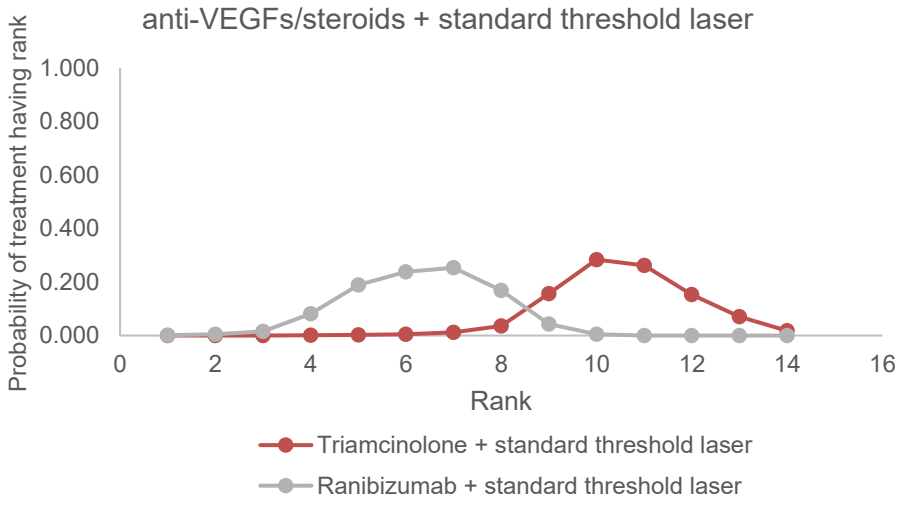
Figure 70: Change in visual acuity for people with central-involving macular oedema and central retinal thickness >400 µm at baseline at 24 months (logMAR). Relative effect of all treatments compared with standard threshold laser. Squares indicate the median of the posterior distribution for each effect, and lines indicate 95% Credible intervals.



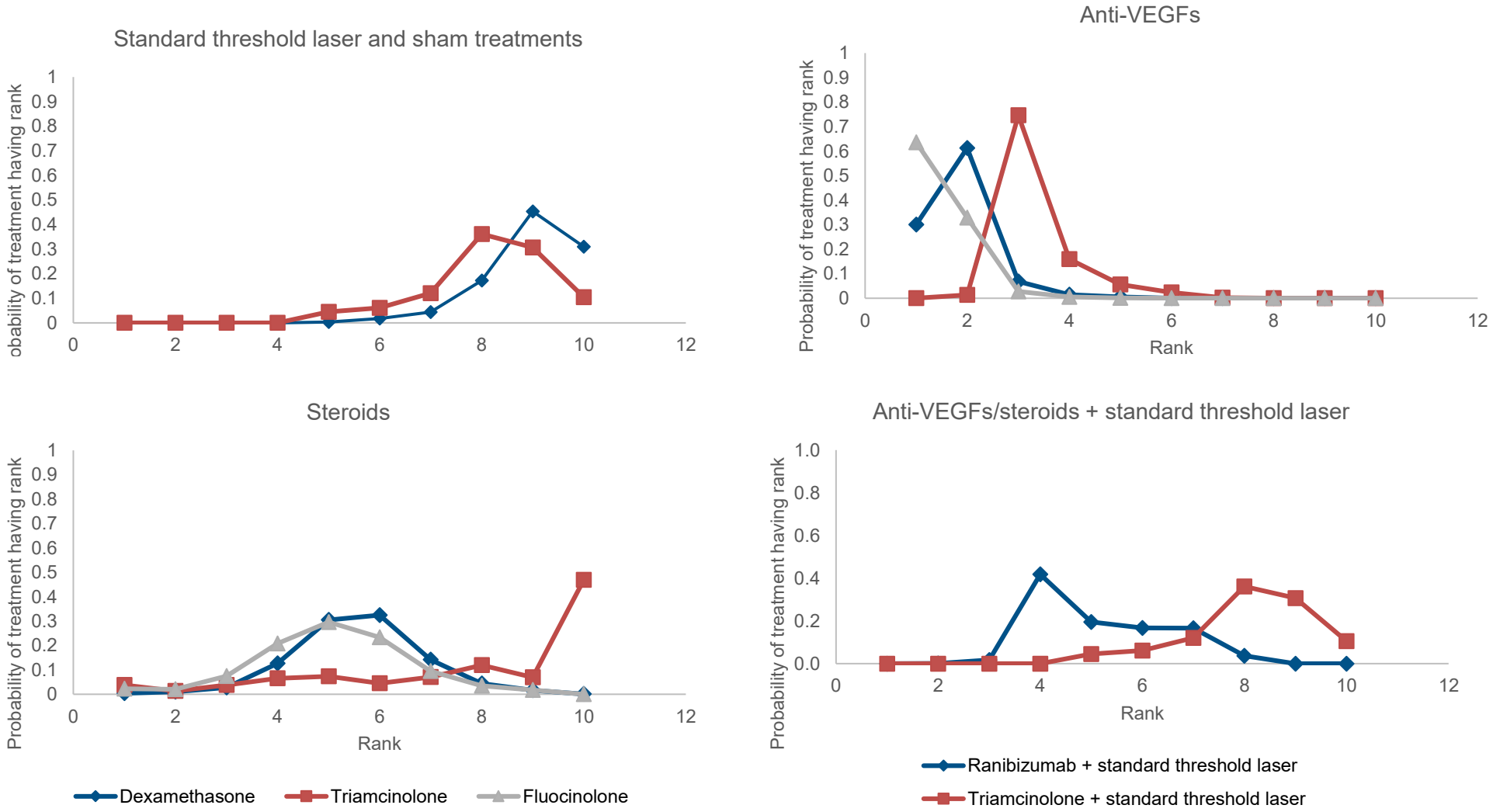
Rank probability plots at 12 months. The probability of each treatment assuming each rank (1 to 14, with 1 as the most effective treatment) is plotted. Each line indicates a different treatment. CRT>400







Rank probability plots at 24 months. The probability of each treatment assuming each rank (1 to 10, with 1 as the most effective treatment) is plotted. Each line indicates a different treatment. CRT>400



L.2.3 Centre-involving population: Change in central retinal thickness

Figure 71: Network diagram. Line thickness indicates number of trials comparing treatments for change in central retinal thickness at 12 months for people with centre-involving macular oedema. Nodes are scaled to indicate number of trials involving each treatment

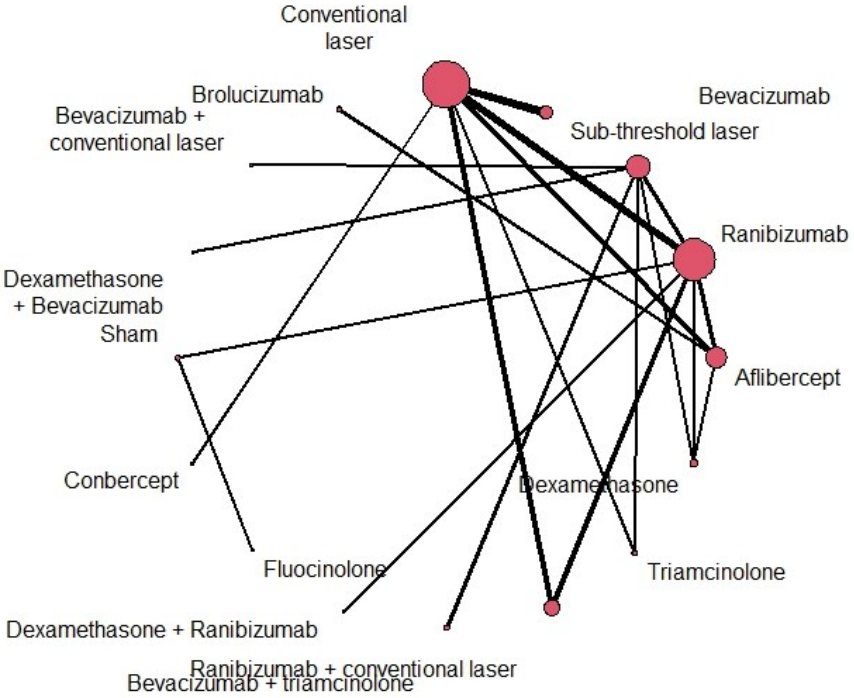
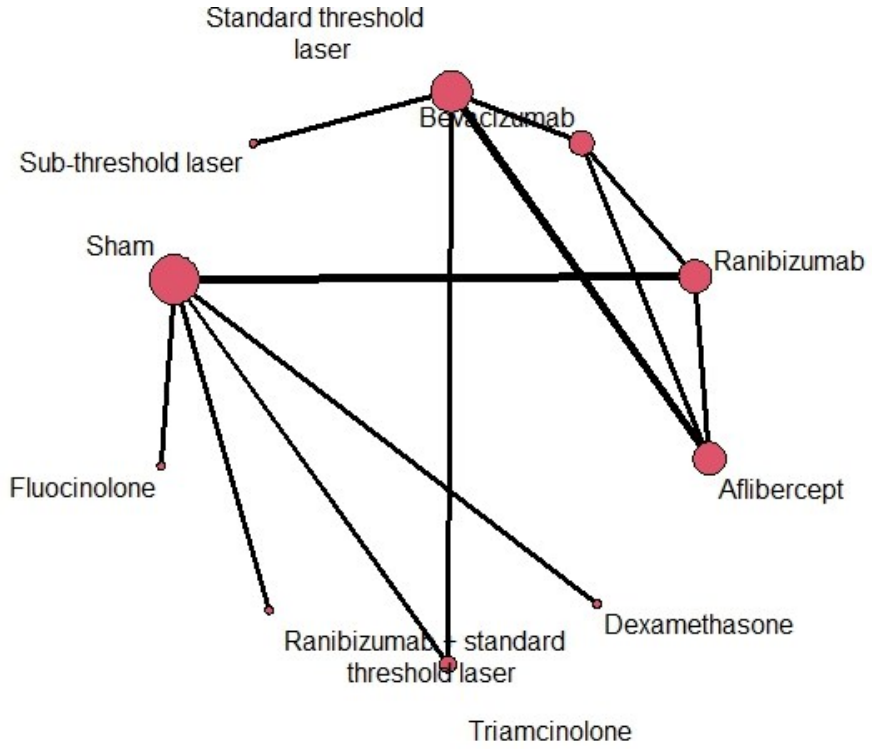


Figure 72: Network diagram. Line thickness indicates number of trials comparing treatments for change in central retinal thickness at 24 months for people with centre-involving macular oedema. Nodes are scaled to indicate number of trials involving each treatment



L.2.3.1 Model selection for mean change in central retinal thickness at 12 and 24 months

The data were fitted and random effects models, and the goodness of fit evaluated by calculating the total residual deviance (a calculation of the model's ability to predict the individual data points underlying it – a well-fitting model will have a total residual deviance approximately equal to the number of data points) and the deviance information criteria (an estimate of deviance that is 'penalised' according to the number of parameters in the model, and is useful for comparing models), The total residual deviance and deviance information criteria for the fixed and random effects models are shown in Table 147 and Table 148.

A random effects model was preferred for the 12 month analysis and fixed effects for the 24 month analysis. The total residual deviance for the random effects model was closer to the number of unconstrained data points, and the deviance information criterion was lower. Reported results are based on the random effects NMA at 12 months and the fixed effects NMA at 24 months only.

Table 147: Measures of goodness of fit of fixed- and random-effects models for change in central retinal thickness at 12 months

Measure of goodness of fit	Fixed effect model	Random effects model
Total Residual deviance*	98.9	68.11
Deviance information criterion (DIC)	653.9	635.3
Between trial standard deviation (95% credible intervals)	-	26.9 (14.8 to 43.9)
*Compared to 69 data points		

Table 148: Measures of goodness of fit of fixed- and random-effects models for change in central retinal thickness at 24 months

Measure of goodness of fit	Fixed effect model	Random effects model
Total Residual deviance*	21.9	22.4
Deviance information criterion (DIC)	212.7	214.4
Between trial standard deviation (95% credible intervals)	-	11.3 (0.41 to 50.2)
*Compared to 25 data points		

The quality of evidence from the network meta-analysis was assessed using a modified version of the GRADE approach to quality rating. Each GRADE domain was rated as 'no serious', 'serious' or 'very serious' and an overall quality rating was derived for the evidence from the network meta-analysis as whole. The GRADE profile for the network meta-analysis can be found in Appendix G. For a description of how the GRADE criteria were applied to the network meta-analysis, see the Methods document.

L.2.3.2 Results

Table 149: Relative effectiveness showing all pair-wise combinations for mean change in central retinal thickness for people with central-involving macular oedema at 12 months

The values given are mean differences. The segment below the shaded cells is derived from the network meta-analysis and shows the mean difference as the row treatment minus the column treatment. Values in parentheses are 95% credible intervals. The segment above the shaded cells shows pooled direct evidence (random effects pairwise meta-analysis), where available, and shows the mean difference as the column treatment minus the row treatment.

	Standard threshold laser	Sub-threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Bevacizumab + triamcinolone	Dexamethasone + ranibizumab	Fluocinolone	Conbercept	Sham	Dexamethasone + bevacizumab	Bevacizumab + standard threshold laser	Brolucizumab
Standard threshold laser		-1.26 (-36.2, 34.75)	N/A	-39.6 (-69.2, -3.57)	-76.98 (-115.3, -28.48)	N/A	2.59 (-43.85, 48.77)	-48.68 (-98.16, 7.48)	N/A	N/A	N/A	-22.23 (-71.6, 30.14)	N/A	N/A	N/A	N/A
Sub-threshold laser	-2.07 (-42.09, 38.77)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bevacizumab	-22.76 (-59.94, 16.37)	-20.71 (-75.76, 35.27)		-26.31 (-62.6, 15.09)	N/A	-23.04 (-71.62, 28.9)	6.30 (-44.69, 56.32)	N/A	-0.90 (-44.2, 42.82)	N/A	N/A	N/A	N/A	-3.62 (-55.8, 48.3)	-0.29 (-47.7, 47.23)	N/A
Ranibizumab	-62.10 (-86.42, -33.97)	-59.81 (-106.90, -11.40)	-39.25 (-72.61, -4.72)		-11.82 (-52.03, 31.13)	-4.42 (-49.59, 42.61)	-0.05 (-62.61, 61.7)	-7.02 (-47.38, 34.26)	N/A	-20.91 (-66.8, 30.0)	N/A	N/A	52.48 (-5.3, 105.2)	N/A	N/A	N/A

	Standard threshold laser	Sub-threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Bevacizumab + triamcinolone	Dexamethasone + ranibizumab	Fluocinolone	Conbercept	Sham	Dexamethasone + bevacizumab	Bevacizumab + standard threshold laser	Brolucizumab
Aflibercept	-81.73 (-112.00, -48.48)	-79.62 (-129.80, -27.93)	-58.93 (-102.00, -14.78)	-19.69 (-52.23, 12.68)		-44.14 (-94.2, 11.95)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	13.81 (-26.94, 51.04)
Dexamethasone	-106.40 (-149.60, -59.93)	-104.20 (-163.60, -43.57)	-83.52 (-129.40, -37.47)	-44.35 (-86.00, -3.56)	-24.67 (-69.76, 19.86)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Triamcinolone	2.04 (-47.06, 50.60)	4.14 (-60.27, 66.57)	24.69 (-29.60, 76.91)	64.08 (9.59, 114.40)	83.79 (25.14, 138.40)	108.30 (44.07, 169.70)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ranibizumab + standard threshold laser	-78.56 (-112.70, -40.65)	-76.26 (-129.10, -21.72)	-55.78 (-102.80, -7.63)	-16.41 (-52.29, 19.39)	3.25 (-41.10, 47.53)	27.86 (-24.51, 81.29)	-80.41 (-138.00, -19.12)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bevacizumab + triamcinolone	-21.56 (-83.84, 42.79)	-19.42 (-93.93, 56.07)	1.26 (-51.66, 53.97)	40.44 (-21.76, 101.50)	60.18 (-7.41, 126.40)	84.76 (15.36, 153.60)	-23.44 (-96.62, 51.19)	56.90 (-13.46, 126.10)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Dexamethasone + ranibizumab	-98.95 (-162.10, -28.33)	-96.68 (-171.30, -16.79)	-76.21 (-143.80, -2.98)	-36.90 (-96.96, 27.12)	-17.29 (-84.25, 54.37)	7.48 (-63.99, 83.99)	-101.00 (-177.40, -16.35)	-20.48 (-89.21, 52.83)	-77.39 (-161.90, 12.45)		N/A	N/A	N/A	N/A	N/A	N/A
Fluocinolone	-4.27 (-88.96, 80.39)	-2.04 (-97.12, 91.08)	18.56 (-72.19, 107.30)	57.78 (-27.45, 139.50)	77.49 (-12.00, 163.80)	102.10 (8.69, 193.10)	-6.14 (-103.10, 90.92)	74.11 (-16.66, 162.90)	17.31 (-86.48, 119.50)	94.47 (-12.19, 195.40)		N/A	36.66 (-17.23, 81.79)	N/A	N/A	N/A

	Standard threshold laser	Sub-threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Bevacizumab + triamcinolone	Dexamethasone + ranibizumab	Fluocinolone	Conbercept	Sham	Dexamethasone + bevacizumab	Bevacizumab + standard threshold laser	Brolucizumab
Conbercept	-54.85 (-125.30, 17.72)	-52.80 (-134.60, 29.88)	-32.15 (-112.30, 48.86)	7.11 (-69.05, 82.82)	26.72 (-51.26, 104.40)	51.42 (-32.58, 136.00)	-56.86 (-142.10, 30.48)	23.49 (-56.21, 103.00)	-33.40 (-128.30, 62.00)	43.85 (-55.40, 139.60)	-50.38 (-160.40, 60.29)		N/A	N/A	N/A	N/A
Sham	70.93 (1.24, 140.30)	73.04 (-8.23, 152.60)	93.62 (18.24, 167.30)	132.80 (64.19, 198.40)	152.60 (77.77, 224.60)	177.30 (97.52, 254.40)	68.87 (-14.40, 153.00)	149.20 (72.88, 223.20)	92.26 (1.28, 182.20)	169.70 (74.67, 258.00)	75.21 (17.70, 132.40)	125.60 (25.77, 224.00)		N/A	N/A	N/A
Dexamethasone + bevacizumab	-28.84 (-115.10, 58.85)	-26.74 (-122.40, 69.36)	-6.17 (-87.82, 75.38)	33.08 (-53.44, 119.30)	52.66 (-37.49, 142.30)	77.42 (-14.36, 169.50)	-30.73 (-125.40, 65.44)	49.44 (-42.68, 140.90)	-7.42 (-104.30, 89.72)	69.93 (-37.04, 173.90)	-24.48 (-143.10, 95.47)	25.92 (-85.89, 137.90)	-99.83 (-207.50, 9.74)		N/A	N/A
Bevacizumab + standard threshold laser	-21.35 (-91.20, 51.43)	-19.12 (-100.40, 63.29)	1.41 (-61.01, 64.64)	40.66 (-29.37, 110.30)	60.27 (-14.54, 135.00)	84.95 (8.48, 161.90)	-23.28 (-103.00, 59.29)	57.04 (-20.27, 133.80)	0.25 (-81.14, 82.27)	77.66 (-17.67, 168.20)	-17.19 (-124.20, 93.09)	33.78 (-67.17, 133.70)	-92.29 (-187.30, 5.47)	7.72 (-94.81, 110.30)		N/A
Brolucizumab	-98.53 (-149.70, -41.49)	-96.25 (-161.10, -26.81)	-75.65 (-135.80, -12.54)	-36.38 (-89.82, 19.00)	-16.72 (-59.87, 29.35)	7.93 (-53.30, 72.53)	-100.40 (-168.90, -25.63)	-19.93 (-81.25, 43.67)	-76.94 (-155.10, 5.19)	0.55 (-82.12, 81.43)	-94.07 (-190.60, 7.32)	-43.35 (-131.10, 47.06)	-169.30 (-252.30, -81.03)	-69.21 (-168.50, 31.82)	-77.00 (-162.30, 10.80)	

Table 150: Relative effectiveness showing all pair-wise combinations for mean change in central retinal thickness for people with central-involving macular oedema at 24 months

The values given are mean differences. The segment below the shaded cells is derived from the network meta-analysis and shows the mean difference as the row treatment minus the column treatment. Values in parentheses are 95% credible intervals. The segment above the shaded cells shows pooled direct evidence (random effects pairwise meta-analysis), where available, and shows the mean difference as the column treatment minus the row treatment.

	Standard threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Fluocinolone	Sham	Sub-threshold laser
Standard threshold laser		-11.41 (-66.71, 45.58)	N/A	-41.41 (-95.31, 17.98)	N/A	16.06 (-41.43, 70.0)	N/A	N/A	N/A	-0.21 (-53.78, 53.65)
Bevacizumab	-65.47 (-96.59, -34.19)		N/A	-10.91 (-64.31, 45.7)	N/A	N/A	N/A	N/A	N/A	N/A
Ranibizumab	-92.13 (-123.70, -60.70)	-26.64 (-54.11, 0.71)		-4.91 (-58.85, 49.62)	N/A	N/A	N/A	N/A	48.28 (-13.46, 105.1)	N/A
Aflibercept	-109.70 (-132.90, -86.52)	-44.21 (-70.18, -18.37)	-17.55 (-43.46, 8.33)		N/A	N/A	N/A	N/A	N/A	N/A
Dexamethasone	-44.67 (-87.87, -2.08)	20.73 (-22.71, 63.32)	47.31 (11.32, 82.55)	64.98 (23.14, 105.90)		N/A	N/A	N/A	20.91 (-37.99, 76.45)	N/A

	Standard threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Fluocinolone	Sham	Sub-threshold laser
Triamcinolone	66.54 (42.15, 91.00)	132.00 (93.26, 170.90)	158.60 (120.00, 197.40)	176.30 (143.00, 209.40)	111.30 (64.42, 159.50)		N/A	N/A	-15.51 (-73.0, 42.72)	N/A
Ranibizumab + standard threshold laser	24.93 (-24.70, 73.77)	90.30 (40.42, 139.60)	116.90 (73.71, 159.90)	134.60 (86.27, 182.00)	69.65 (34.46, 104.90)	-41.63 (-95.31, 11.38)		N/A	2.52 (-51.9, 55.9)	N/A
Fluocinolone	-23.15 (-66.75, 20.09)	42.35 (-1.36, 85.36)	68.97 (32.55, 104.80)	86.57 (44.66, 128.00)	21.62 (-3.72, 46.94)	-89.69 (-137.70, -41.88)	-48.08 (-83.45, -12.25)		15.46 (-42.08, 68.64)	N/A
Sham	35.27 (-4.62, 74.69)	100.70 (60.72, 139.80)	127.30 (95.72, 158.40)	144.90 (106.70, 182.40)	79.98 (62.53, 97.52)	-31.27 (-76.22, 12.89)	10.23 (-20.25, 41.19)	58.35 (40.10, 76.49)		N/A
Sub-threshold laser	-0.59 (-13.95, 12.78)	64.91 (31.07, 98.79)	91.58 (57.33, 125.80)	109.10 (82.39, 135.90)	44.13 (-0.60, 89.61)	-67.10 (-95.00, -39.36)	-25.51 (-76.20, 26.23)	22.60 (-22.79, 68.17)	-35.80 (-77.53, 6.27)	

Table 151: Median rankings for each treatment with 95% credible intervals for mean change in central retinal thickness at 12 months for people with central-involving macular oedema

	Median rank (95% CrI)
Standard threshold laser	13 (9 to 5)
Sub-threshold laser	12 (8 to 15)
Bevacizumab	10 (7 to 13)
Ranibizumab	6 (4 to 9)
Aflibercept	4 (2 to 8)
Dexamethasone	2 (1 to 6)
Triamcinolone	13 (8 to 16)
Ranibizumab + standard threshold laser	5 (1 to 8)
Bevacizumab + triamcinolone	10 (4 to 15)
Dexamethasone + ranibizumab	3 (1 to 9)
Fluocinolone	12 (4 to 15)
Conbercept	7 (1 to 14)
Sham	16 (13 to 16)
Dexamethasone + bevacizumab	9 (2 to 16)
Bevacizumab + standard threshold laser	10 (4 to 15)
Brolucizumab	3 (1 to 8)

Table 152: Median rankings for each treatment with 95% credible intervals for mean change in central retinal thickness at 24 months for people with central-involving macular oedema

	Median rank (95% CrI)
Standard threshold laser	7 (5 to 8)
Bevacizumab	3 (2 to 5)
Ranibizumab	2 (1 to 3)
Aflibercept	1 (1 to 2)
Dexamethasone	4 (3 to 5)
Triamcinolone	10 (8 to 10)
Ranibizumab + standard threshold laser	8 (6 to 10)
Fluocinolone	5 (4 to 7)
Sham	9 (7 to 10)
Sub-threshold laser	6 (5 to 9)

Figure 73: Change in central retinal thickness for people with central-involving macular oedema at 12 months. Relative effect of all treatments compared with standard threshold laser. Squares indicate the median of the posterior distribution for each effect, and lines indicate 95% Credible intervals.

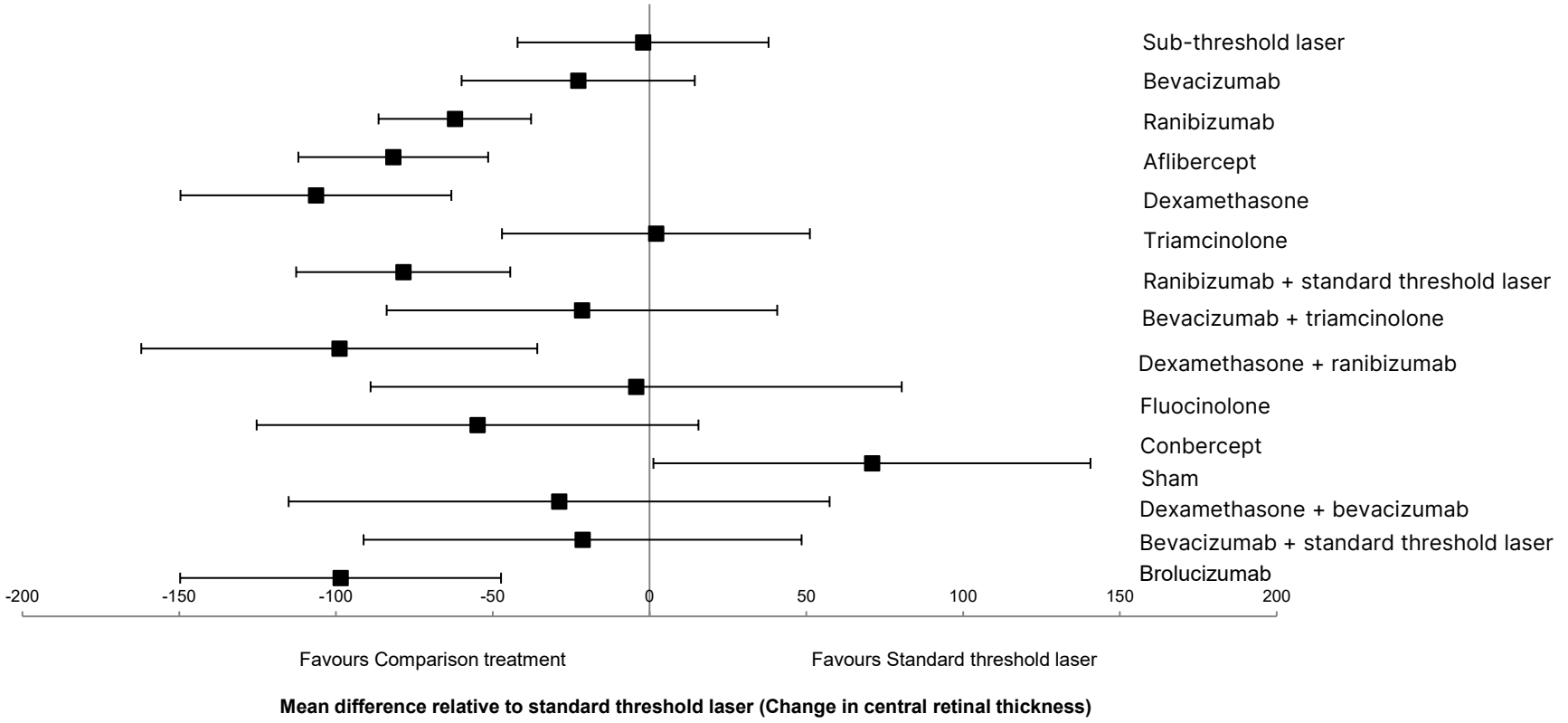
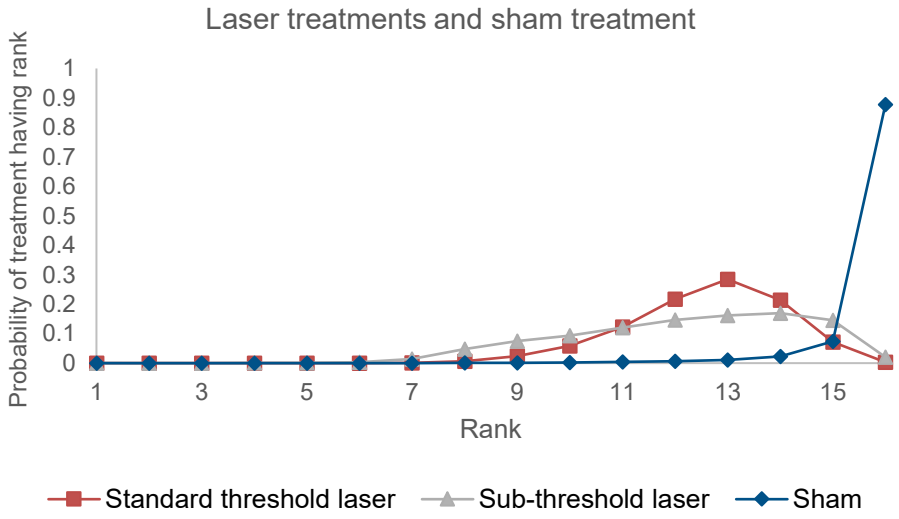
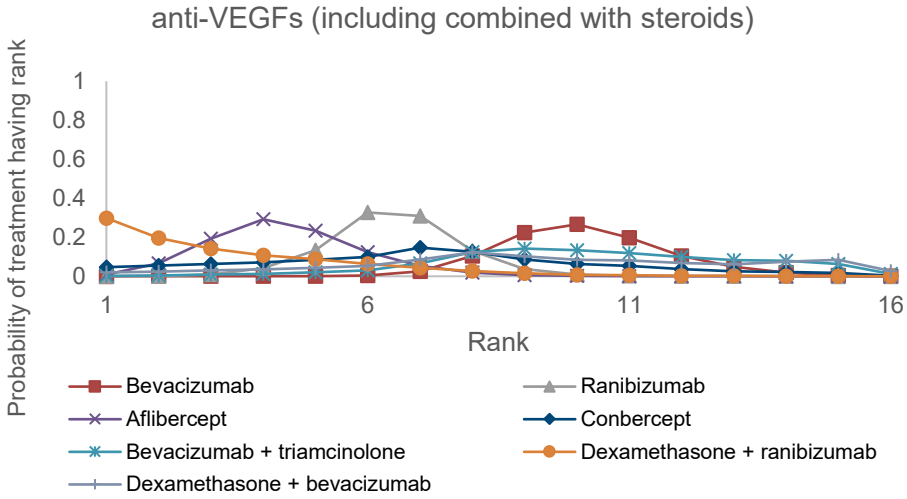
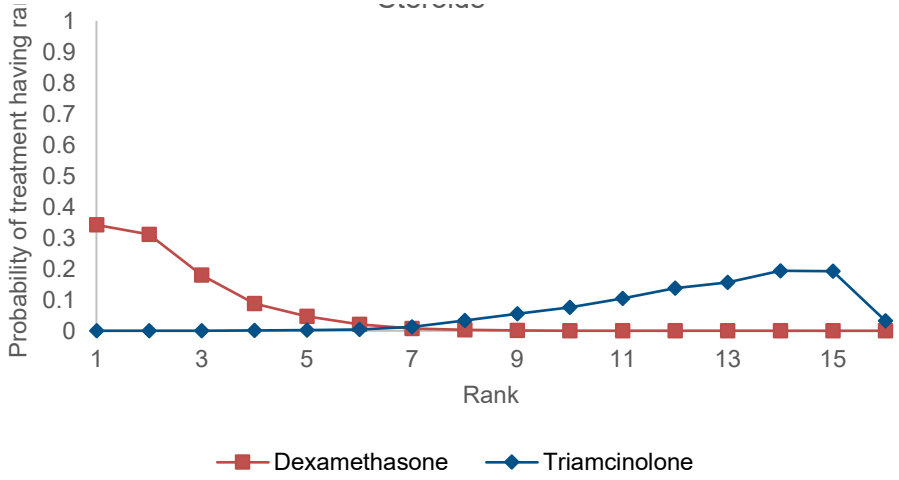


Figure 74: Rank probability plots at 12 months. The probability of each treatment assuming each rank (1 to 16, with 1 as the most effective treatment) is plotted. Each line indicates a different treatment.







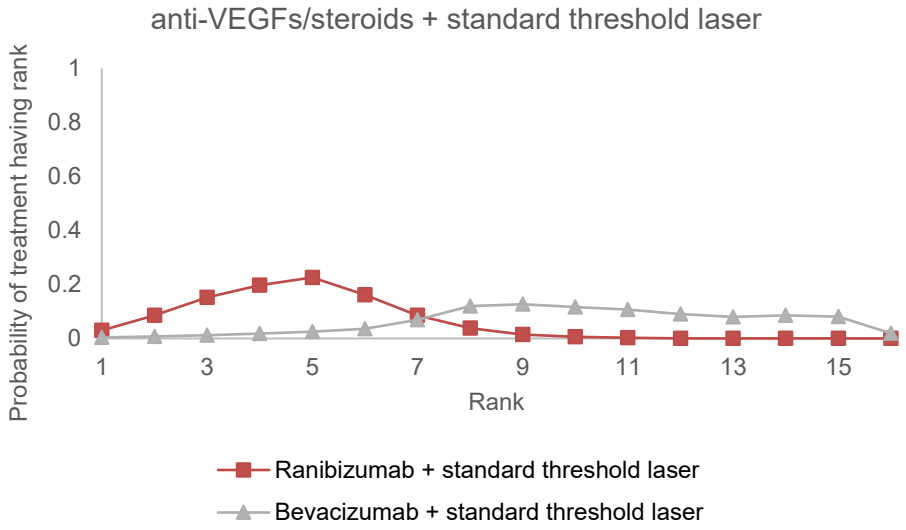


Figure 75: Change in central retinal thickness for people with central-involving macular oedema at 24 months. Relative effect of all treatments compared with standard threshold laser. Squares indicate the median of the posterior distribution for each effect, and lines indicate 95% Credible intervals.

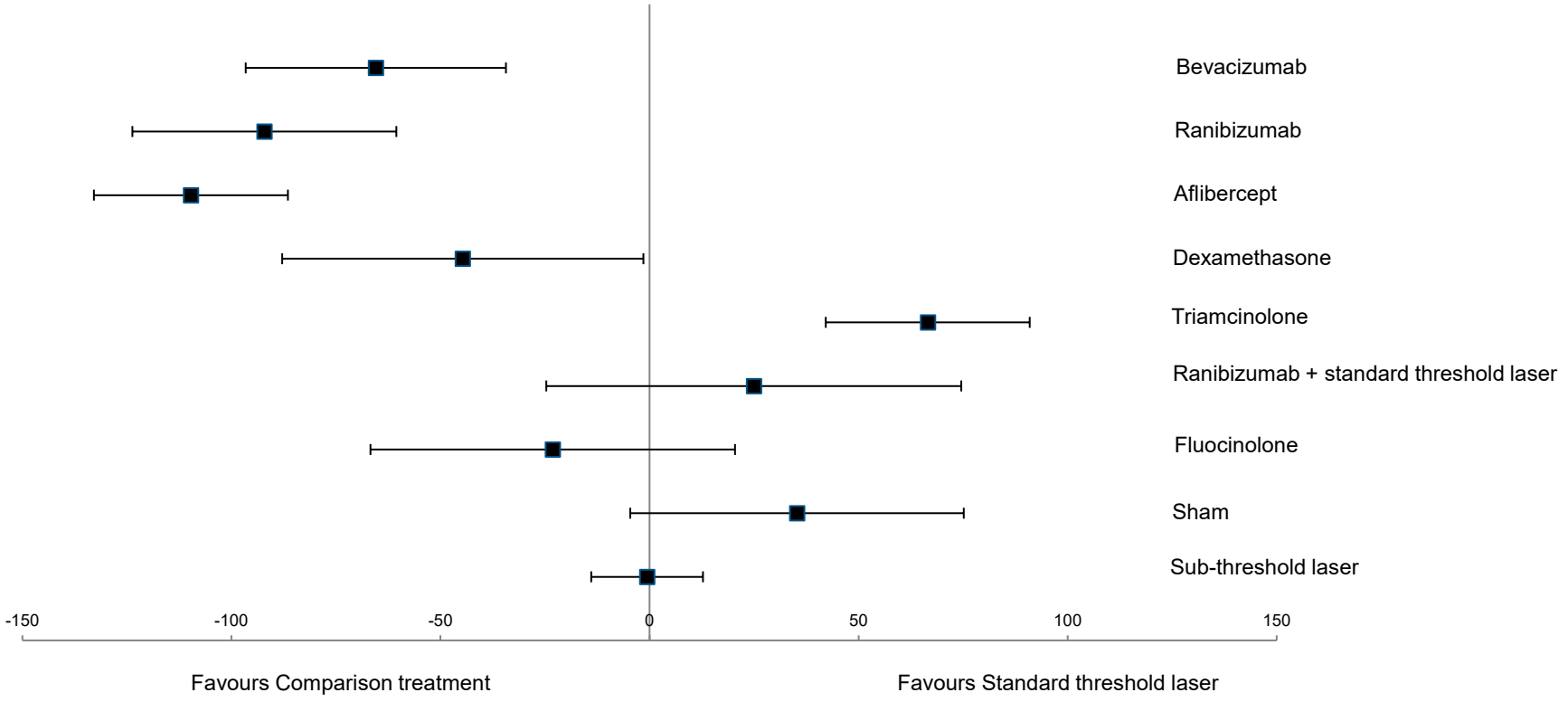
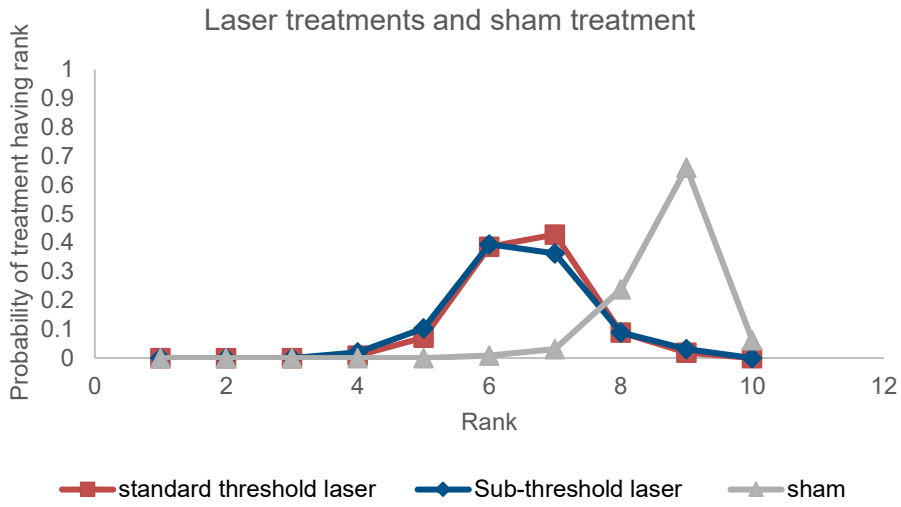
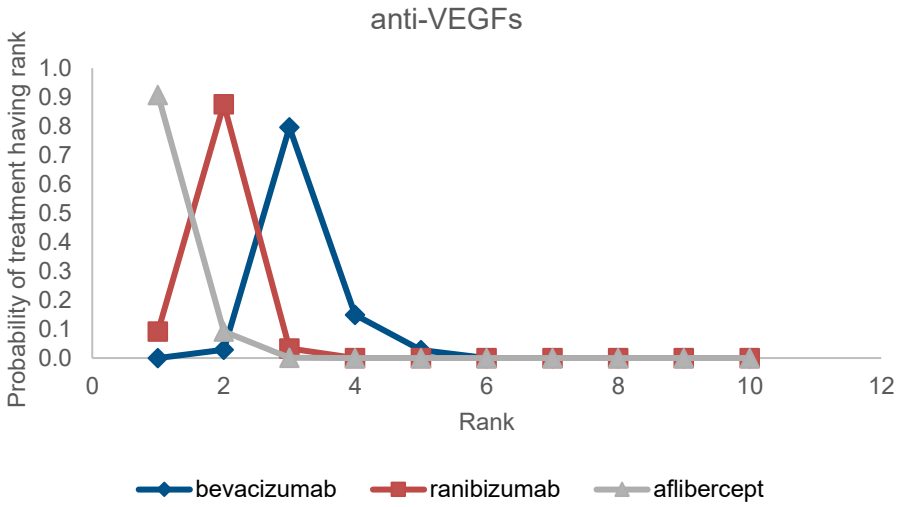
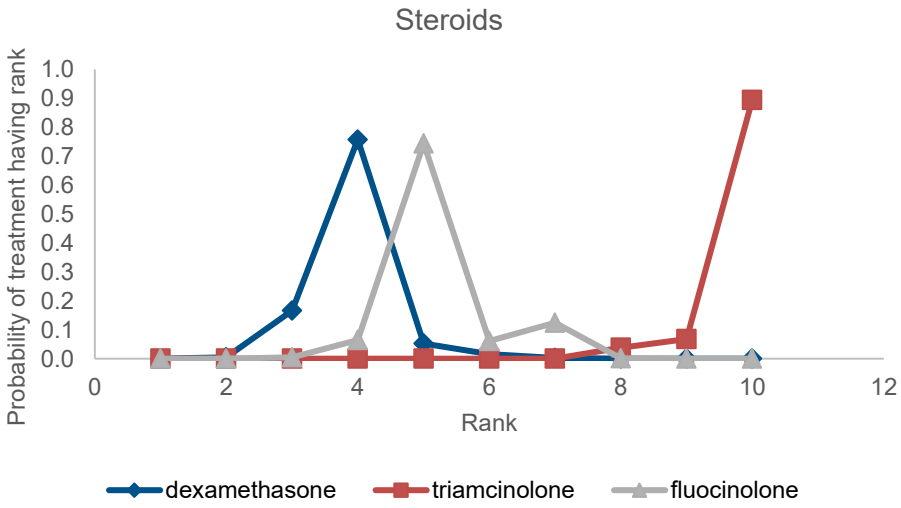
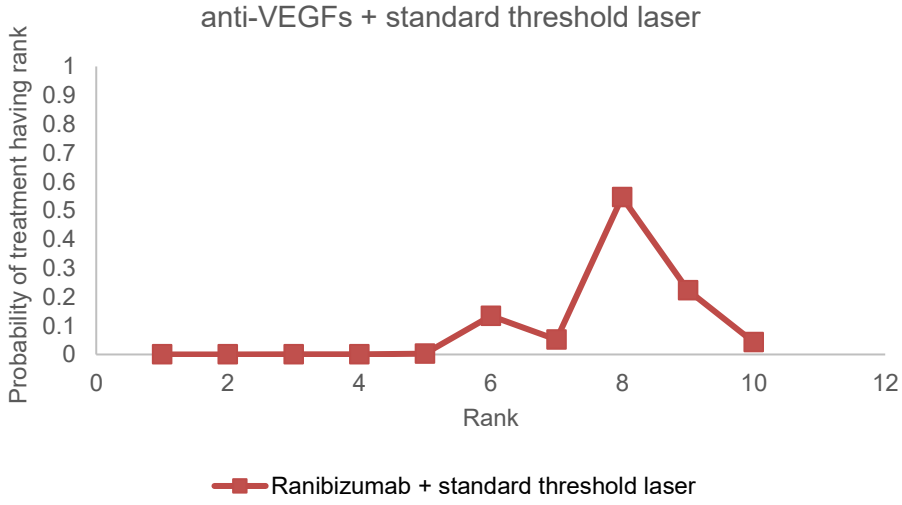


Figure 76: Rank probability plots at 24 months. The probability of each treatment assuming each rank (1 to 10, with 1 as the most effective treatment) is plotted. Each line indicates a different treatment.



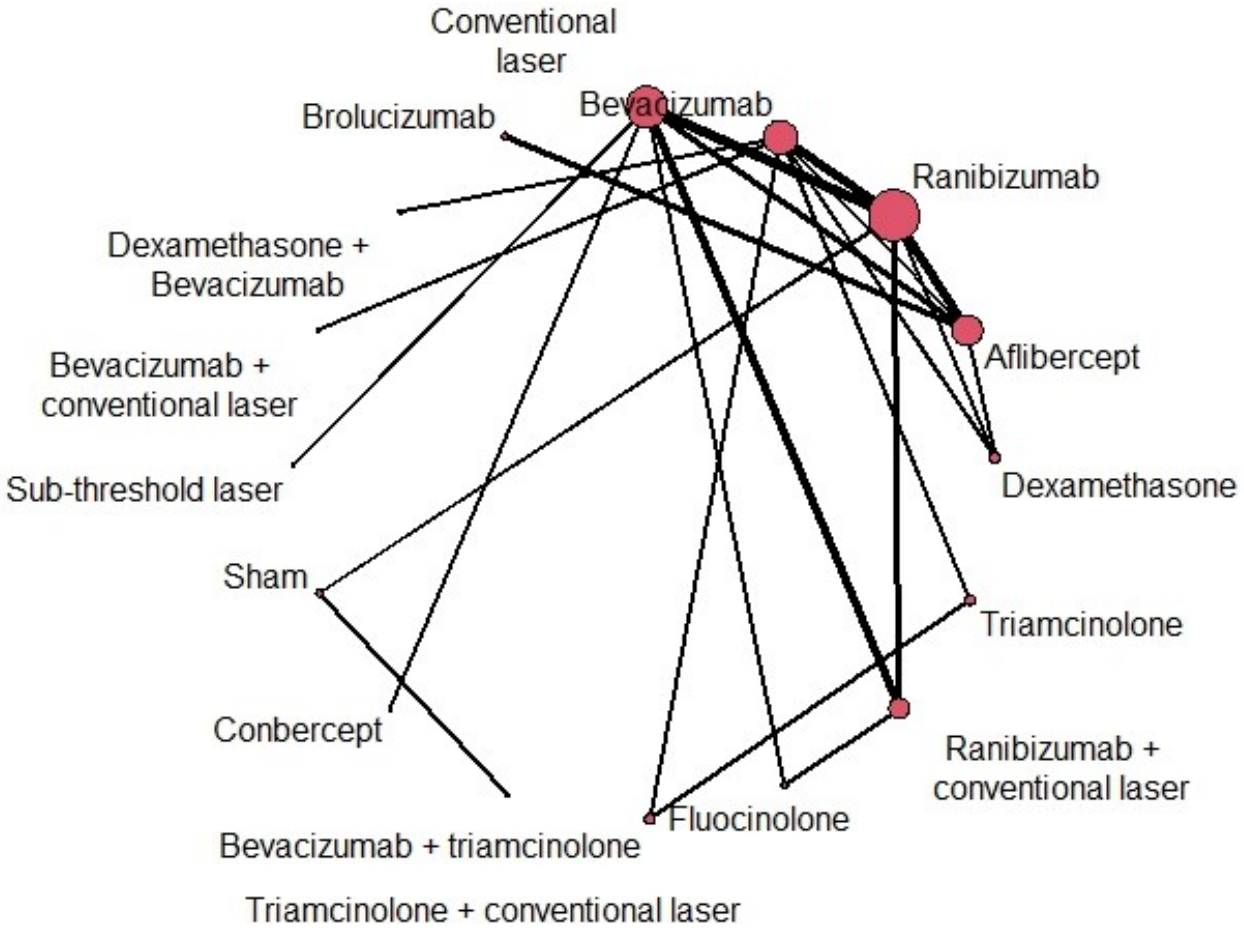






L.2.4 Centre-involving population - subgroup with central retinal thickness >400 µm at baseline: Change in central retinal thickness

Figure 77: Network diagram. Line thickness indicates number of trials comparing treatments for change in central retinal thickness at 12 months for people with centre-involving macular oedema and central retinal thickness >400 µm at baseline. Nodes are scaled to indicate number of trials involving each treatment



L.2.4.1 Model selection for mean change in central retinal thickness at 12 months (subgroup with central retinal thickness >400µm)

The data were fitted and random effects models, and the goodness of fit evaluated by calculating the total residual deviance (a calculation of the model's ability to predict the individual data points underlying it – a well-fitting model will have a total residual deviance approximately equal to the number of data points) and the deviance information criteria (an estimate of deviance that is 'penalised' according to the number of parameters in the model, and is useful for comparing models), The total residual deviance and deviance information criteria for the fixed and random effects models are shown in Table 153.

A random effects model was preferred. The total residual deviance for the random effects model was closer to the number of unconstrained data points, and the deviance information criterion was lower. Reported results are based on the random effects NMA only.

Change in central retinal thickness at 12 months in population with baseline central retinal thickness >400um

Table 153: Measures of goodness of fit of fixed- and random-effects models

Measure of goodness of fit	Fixed effect model	Random effects model
Total Residual deviance*	99.9	55.9
Deviance information criterion (DIC)	548.0	515.8
Between trial standard deviation (95% credible intervals)	-	32.06 (19.5 to 51.6)
*Compared to 57 data points		

The quality of evidence from the network meta-analysis was assessed using a modified version of the GRADE approach to quality rating. Each GRADE domain was rated as 'no serious', 'serious' or 'very serious' and an overall quality rating was derived for the evidence from the network meta-analysis as whole. The GRADE profile for the network meta-analysis can be found in Appendix F. For a description of how the GRADE criteria were applied to the network meta-analysis, see the Methods document.

L.2.4.2 Results

Table 154: Relative effectiveness showing all pair-wise combinations for mean change in central retinal thickness for people with central-involving macular oedema and central retinal thickness >400 µm at baseline at 12 months

The values given are mean differences. The segment below the shaded cells is derived from the network meta-analysis and shows the mean difference as the row treatment minus the column treatment. Values in parentheses are 95% credible intervals. The segment above the shaded cells shows pooled direct evidence (random effects pairwise meta-analysis), where available, and shows the mean difference as the column treatment minus the row treatment.

	Standard threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Triamcinolone + standard threshold laser	Bevacizumab + triamcinolone	Fluocinolone	Conbercept	Sham	Sub-threshold laser	Bevacizumab + standard threshold	Dexamethasone + bevacizumab	Brolucizumab
Standard threshold laser		N/A	-51.42 (-68.71, -33.21)	-127.4 (-148.9, -104.9)	N/A	N/A	-71.73 (-93.71, -50.33)	N/A	N/A	N/A	-35.61 (-75.13, 3.03)	N/A	16.04 (-32.47, 68.74)	N/A	N/A	N/A
Bevacizumab	-22.28 (-62.30, 21.66)		-41.47 (-64.61, -19.62)	-57.26 (-79.12, -35.07)	-37.51 (-75.13, 1.00)	N/A	N/A	N/A	-11.93 (-43.61, 21.70)	N/A	N/A	N/A	N/A	-0.30 (-31.26, 31.66)	-5.28 (-49.4, 39.62)	N/A
Ranibizumab	-63.56 (-93.06, -30.04)	-41.27 (-75.32, -7.45)		-15.7 (-33.6, 2.50)	-7.81 (-29.93, 14.68)	N/A	-10.77 (-35.39, 15.21)	N/A	N/A	N/A	N/A	84.71 (46.71, 124.2)	N/A	N/A	N/A	N/A
Aflibercept	-83.62 (-118.70, -43.30)	-61.32 (-102.80, -18.81)	-20.07 (-52.79, 14.13)		-74.47 (-107.8, -39.8)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	11.17 (-34.27, 54.37)
Dexamethasone	-107.70 (-156.90, -53.21)	-85.33 (-134.60, -35.57)	-44.03 (-89.84, 2.62)	-24.01 (-73.24, 24.90)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Standard threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Triamcinolone + standard threshold laser	Bevacizumab + triamcinolone	Fluocinolone	Conbercept	Sham	Sub-threshold laser	Bevacizumab + standard threshold	Dexamethasone + bevacizumab	Brolucizumab
Triamcinolone	-36.21 (-109.40, 41.46)	-14.05 (-81.47, 54.74)	27.17 (-45.60, 101.10)	47.22 (-29.91, 124.30)	71.13 (-10.72, 153.70)		N/A	N/A	5.36 (-21.65, 33.0)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ranibizumab + standard threshold laser	-74.24 (-112.40, -31.67)	-51.94 (-104.80, 0.49)	-10.61 (-54.09, 32.51)	9.40 (-42.15, 59.00)	33.44 (-27.96, 93.71)	-37.75 (-121.40, 43.56)		-4.59 (-36.63, 28.39)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Triamcinolone + standard threshold laser	-70.28 (-135.70, -0.94)	-48.06 (-125.20, 29.28)	-6.78 (-78.37, 64.86)	13.19 (-62.33, 87.94)	37.23 (-45.77, 119.60)	-33.81 (-134.70, 64.93)	3.78 (-64.49, 72.79)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bevacizumab + triamcinolone	-31.47 (-104.10, 45.91)	-9.33 (-76.39, 58.90)	32.06 (-40.19, 105.50)	52.02 (-24.96, 128.50)	75.99 (-5.27, 158.10)	4.78 (-50.77, 60.47)	42.73 (-38.41, 125.70)	38.73 (-59.71, 139.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fluocinolone	-6.49 (-98.95, 87.64)	15.74 (-82.62, 111.40)	57.07 (-35.89, 147.70)	77.07 (-21.07, 172.20)	101.10 (-2.63, 201.80)	29.94 (-88.31, 144.00)	67.70 (-32.63, 165.70)	63.77 (-51.49, 176.70)	25.22 (-93.35, 138.90)		N/A	68.33 (49.99, 86.47)	N/A	N/A	N/A	N/A
Conbercept	-52.80 (-130.00, 26.19)	-30.60 (-120.00, 56.84)	10.65 (-74.16, 93.76)	30.58 (-57.34, 116.10)	54.73 (-40.12, 147.40)	-16.67 (-126.00, 90.13)	21.26 (-66.95, 108.60)	17.44 (-86.66, 119.50)	-21.53 (-130.10, 84.92)	-46.65 (-167.30, 75.56)		N/A	N/A	N/A	N/A	N/A
Sham	68.40 (-6.94, 144.40)	90.50 (9.20, 168.80)	131.80 (58.39, 203.10)	151.70 (71.34, 228.80)	175.80 (88.90, 259.60)	104.70 (0.28, 205.20)	142.60 (58.38, 223.50)	138.70 (37.42, 237.30)	100.00 (-4.80, 199.60)	74.75 (8.18, 140.60)	121.40 (11.75, 229.30)		N/A	N/A	N/A	N/A

	Standard threshold laser	Bevacizumab	Ranibizumab	Aflibercept	Dexamethasone	Triamcinolone	Ranibizumab + standard threshold laser	Triamcinolone + standard threshold laser	Bevacizumab + triamcinolone	Fluocinolone	Conbercept	Sham	Sub-threshold laser	Bevacizumab + standard threshold	Dexamethasone + bevacizumab	Brolucizumab
Sub-threshold laser	40.46 (-56.57, 137.60)	62.42 (-44.57, 167.50)	103.60 (0.67, 204.70)	123.70 (18.07, 226.70)	147.70 (35.82, 256.70)	76.51 (-47.72, 198.40)	114.30 (7.85, 219.20)	110.60 (-8.92, 228.00)	71.77 (-51.75, 193.20)	46.97 (-87.37, 180.40)	93.61 (-32.27, 216.90)	-27.79 (-150.60, 93.99)		N/A	N/A	N/A
Bevacizumab + standard threshold laser	-20.43 (-97.03, 60.93)	1.96 (-68.55, 72.53)	43.24 (-33.06, 120.10)	63.29 (-17.61, 143.10)	87.21 (1.82, 171.70)	15.94 (-81.79, 113.20)	53.81 (-31.00, 140.00)	50.10 (-51.69, 152.20)	11.23 (-86.36, 108.00)	-13.71 (-131.20, 106.30)	32.50 (-77.18, 144.40)	-88.74 (-191.70, 17.14)	-60.83 (-184.30, 66.46)		N/A	N/A
Dexamethasone + bevacizumab	-27.83 (-119.40, 66.07)	-5.64 (-92.24, 80.20)	35.57 (-55.47, 126.50)	55.44 (-38.94, 148.40)	79.51 (-18.67, 177.40)	8.16 (-101.30, 116.50)	46.23 (-52.43, 144.80)	42.35 (-71.41, 155.10)	3.55 (-105.60, 111.80)	-21.35 (-148.40, 107.10)	24.89 (-95.82, 147.20)	-96.26 (-211.00, 20.39)	-68.44 (-202.00, 67.44)	-7.85 (-118.80, 103.60)		N/A
Brolucizumab	-98.68 (-156.60, -32.01)	-76.48 (-139.50, -9.30)	-35.14 (-92.65, 26.76)	-15.20 (-63.85, 37.10)	8.89 (-58.99, 80.67)	-62.36 (-152.80, 30.57)	-24.56 (-92.47, 48.19)	-28.22 (-115.90, 63.00)	-67.00 (-157.00, 25.63)	-91.95 (-197.40, 19.26)	-45.67 (-142.50, 56.14)	-166.90 (-256.60, -70.27)	-138.70 (-251.60, -20.78)	-78.35 (-170.70, 18.10)	-70.67 (-175.00, 37.17)	

Table 155: Median rankings for each treatment with 95% credible intervals for mean change in central retinal thickness for people with central-involving macular oedema and central retinal thickness >400 µm at baseline

	Median rank (95% CrI)
Standard threshold laser	13 (9 to 15)
Bevacizumab	11 (7 to 14)
Ranibizumab	6 (3 to 10)
Aflibercept	4 (2 to 8)
Dexamethasone	2 (1 to 6)
Triamcinolone	9 (2 to 15)
Ranibizumab + standard threshold laser	5 (1 to 10)
Triamcinolone + standard threshold laser	5 (1 to 13)
Bevacizumab + triamcinolone	10 (3 to 15)
Fluocinolone	12 (3 to 15)
Conbercept + sham	7 (1 to 14)
Sham	16 (13 to 16)
Sub-threshold laser	15 (7 to 16)
Bevacizumab + standard threshold laser	11 (3 to 15)
Dexamethasone + bevacizumab	10 (1 to 15)
Brolucizumab	2 (1 to 9)

Figure 78: Change in central retinal thickness for people with central-involving macular oedema and central retinal thickness >400 µm at baseline at 12 months (logMAR). Relative effect of all treatments compared with standard threshold laser. Squares indicate the median of the posterior distribution for each effect, and lines indicate 95% Credible intervals.

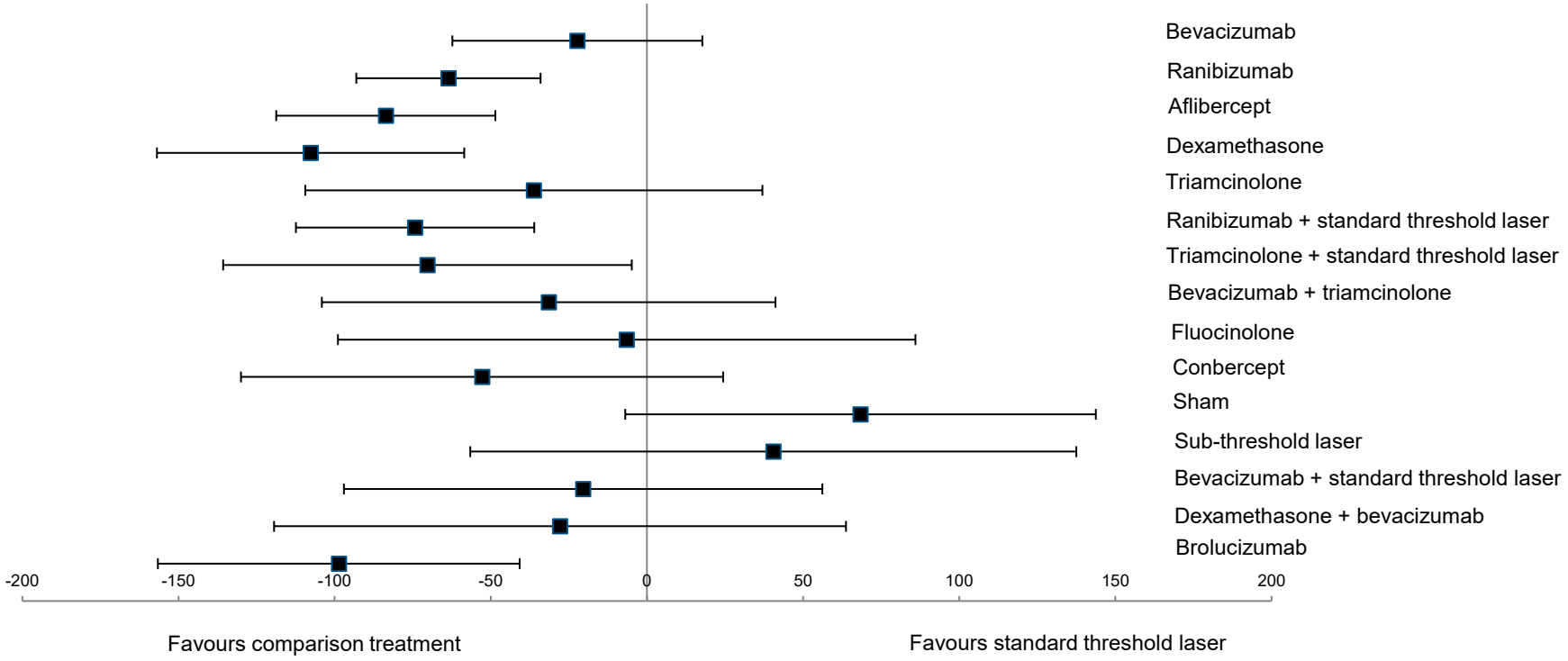


Figure 79: Rank probability plots at 12 months. The probability of each treatment assuming each rank (1 to 16, with 1 as the most effective treatment) is plotted. Each line indicates a different treatment.