National Institute for Health and Care Excellence

Final

Diabetic retinopathy: management and monitoring

[K] Evidence review for diagnostic accuracy of ultrawide-field fundus photography and optical coherence tomography

NICE guideline NG242

Evidence review underpinning recommendations 1.5.10 and 1.6.11, and research recommendation 14 in the NICE guideline

August 2024

Final

These evidence reviews were developed by NICE

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1 Evidence review for diagnostic accuracy of ultrawide-field fundus imaging and optical coherence tomography

1.1 Review question

What is the diagnostic test accuracy of ultrawide-field imaging and optical coherence tomography for monitoring of:

- **people diagnosed with non-proliferative diabetic retinopathy, whose care is managed under the hospital eye services, but who are not having treatment?**
- **people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema, who are having treatment or have had previous treatment?**

1.1.1 Introduction

Diabetic retinopathy is a significant cause of vision loss in the United Kingdom. The risk of the development and progression of non-proliferative retinopathy to macular oedema or vision-threatening proliferative diabetic retinopathy requires classification with either imaging or microscopy. Emerging evidence suggests the potential of digital photographic and optical coherence tomography (OCT) surveillance, particularly in virtual clinics, where patients have already been referred to diabetic eye clinics. These technologies offer the possibility of remote specialist diagnosis.

Ultrawide-field fundus imaging, with its broader view of the eye compared to standard techniques, is being examined to determine if it leads to more accurate classification of proliferative or non-proliferative diabetic retinopathy. By capturing a wider area of the retina, ultrawide-field photography may enhance the detection and classification of diabetic retinopathy. Similarly, OCT allows for subjective assessment of macular oedema. The aim of this review is therefore to investigate the effectiveness of ultrawide-filed imaging for diagnosing proliferative diabetic retinopathy and of OCT for diagnosing macular oedema, compared to established methods such as fundus biomicroscopy or stereophotography. Comparing these test with established techniques will provide valuable insights into their diagnostic capabilities.

1.1.2 Summary of the protocol

Table 1: Diagnostic accuracy of ultrawide-field fundus photography and OCT

Population	Inclusion: 1. people diagnosed with non-proliferative diabetic retinopathy, who are not having treatment 2. people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema, who are having treatment or have had previous treatment
Index test	**Ultrawide-field fundus photography** • For the population with non-proliferative retinopathy, a positive index test will be defined as a classification of proliferative diabetic retinopathy indicated by ultrawide-field fundus photography. • For the population with proliferative retinopathy, a positive index test will be defined as a classification of high-risk proliferative retinopathy indicated by ultrawide-field fundus photography. **Optical coherence tomography**

Reference Standard	**Ultrawide-field fundus photography:** In order of preference: • Ultrawide-field angiography • Combination of Fundus photography and Fluorescein angiography (FA) • Fluorescein angiography (FA) • Slit lamp bio-microscopy. If studies report more than 1 reference standard, only data relating to 1 reference standard will be reported based on the listed order of preference above. **For the population with non-proliferative retinopathy:** a positive reference standard will be defined as a classification of proliferative diabetic retinopathy, diagnosed using one of the reference standard methods listed. **For the population with proliferative retinopathy**, a positive reference standard will be defined as a classification of high-risk proliferative retinopathy diagnosed using one of the reference standard methods listed. **OCT (as described in Cochrane review):** • Stereoscopic fundus photography • Contact lens or non-contact lens biomicroscopy of the fundus
Outcomes	• Sensitivity • Specificity • Likelihood ratios
	• Diagnostic test accuracy studies • Case-control studies will be included

For the full protocol see Appendix A.

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.

During development of the review question, a Cochrane systematic review (Virgili et al. 2015) was identified that included relevant diagnostic accuracy results, specifically for OCT. The review was judged to be high quality and directly applicable to the review (see Appendix D) and so information for this part of the review was taken directly from the Cochrane review, rather than undertaking a new literature search or data analysis (see Table 2 in the methods document). Analysis from the Cochrane review was used and forest plots, GRADE tables and evidence tables were used directly from that review. None of the data from the Cochrane review was reanalysed. Links to information on the analysis, results and risk of bias are presented throughout this review where relevant. A NICE search was used for evidence on ultrawide-field fundus photography.

For both OCT and ultrawide-field fundus photography, the committee used sensitivity and specificity as the primary outcomes. A sensitivity of 80% and specificity of 65% was considered sufficient for a test to be considered as a potential diagnostic and monitoring tool for proliferative diabetic retinopathy or diabetic macular oedema.

The review searched for evidence for ultrawide-field fundus photography for people with non-proliferative diabetic retinopathy who are not having treatment and for people with proliferative diabetic retinopathy who are having treatment, or who have had previous treatment. Positive results from these tests are used to diagnose:

- People with non-proliferative diabetic retinopathy who have progressed to having proliferative diabetic retinopathy.
- People with proliferative diabetic retinopathy who have progressed to high-risk proliferative diabetic retinopathy.

Evidence for the use of OCT was for people who have proliferative diabetic retinopathy or diabetic macular oedema who are having treatment or have had previous treatment. A positive result from this test is used to diagnose:

- People who have proliferative diabetic retinopathy who have progressed to having diabetic macular oedema.
- People who have diabetic macular oedema who have progressed to having clinically significant diabetic macular oedema.

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

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

Ultrawide-field fundus photography

A systematic search carried out to identify relevant studies found 5487 references (see Appendix B) for the literature search strategy). Priority screening was used and the initial stopping criteria was reached after 3543 references were screened. However, only 24 studies were included based on their title and abstract and so the full database was sifted, based on the criteria stated in the protocol. No additional studies were identified in the rest of the sift. The 24 studies were assessed using full-text screening and one met the criteria specified in the review protocol (Appendix A). This study considered the use of ultrawide-field fundus photography for people who have previously had treatment for proliferative diabetic retinopathy. No evidence was identified for the use of ultrawide-field fundus photography for people who have non-proliferative diabetic retinopathy.

Re-run searches identified 231 additional records, but none met the inclusion criteria for the review. For a summary of the single included study see Table 2. The clinical evidence study selection is presented as a PRISMA diagram in Appendix C.

Optical coherence tomography

For information on study selection for OCT, see the Cochrane systematic review (Virgili et al. 2015) The Cochrane review included 10 studies that were relevant to this review. The search for studies was conducted until June 2013, and no additional searches were performed thereafter. The Cochrane review concluded that OCT is now widely recognized as a reference standard for evaluating diabetic macular oedema, and thus, further updates to the review were deemed unnecessary. The committee agreed with these conclusions and so no further searches were performed as part of the NICE review. Of the included studies, 3 reported on the use of OCT to evaluate progression to diabetic macular oedema, and 9 reported on the use of OCT to evaluate progression to clinically significant macular oedema.

For a summary of the Cochrane review and the included study see Table 2 and Table 4. The clinical evidence study selection is presented as a PRISMA diagram in Appendix C.

See section 1.1.13 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in Appendix J.

1.1.5 Summary of studies included in the diagnostic evidence

Table 2 Ultrawide-field fundus imaging for the detection of proliferative diabetic retinopathy in people with previously treated diabetic retinopathy

PDR: Proliferative diabetic retinopathy

Study details	Population inclusion criteria	Population exclusion criteria	Index test	Reference standard	Mean diabetes duration (SD) – years	Risk of bias
Lois 2021[1] N = 281 EMERALD: A Multicentre, case-referent, cross-sectional, diagnostic accuracy study from a prospectively recruited cohort.	Adults with diabetes (type 1 or 2) with previously successfully treated proliferative diabetic retinopathy in one or both eyes.	People unable to speak or understand English and those unable to provide informed consent.	**Main analysis:** Ophthalmic graders referral for PDR based on ultrawide-field fundus images Sensitivity analyses (SENA[1]) and additional post-hoc analysis where ophthalmologist graded fundus images, not ophthalmic graders (Additional): **SENA 1:** Ophthalmic graders identified active PDR based on ultrawide-field fundus images **Additional 1:** Ophthalmic assessment identified active PDR based on ultrawide-field fundus images	**Main analysis:** Slit lamp biomicroscopy - face-to-face evaluation of patients by ophthalmologists using slit-lamp biomicroscopy Sensitivity analyses (SENA) and additional post-hoc analysis where ophthalmologist graded fundus images, not ophthalmic graders (Additional): **SENA1:** Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye **Additional 1:** Ophthalmologist face-to-face clinical evaluation using slit-lamp	Not reported	Low

Study details	Population inclusion criteria	Population exclusion criteria	Index test	Reference standard	Mean diabetes duration (SD) – years	Risk of bias
				biomicroscopy to assess active PDR in either eye		
			SENA 2: Ophthalmic graders referral for PDR based on ultrawide-field fundus images	**SENA2:** Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye		
			SENA 4: Ophthalmic graders referral for PDR based on ultrawide-field fundus images	**SENA 4**: Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR with preretinal or vitreous haemorrhage in either eye		
			Additional 2: Ophthalmologist assessment identified active PDR based on ultrawide-field fundus images	**Additional 2:** Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR with preretinal or vitreous haemorrhage in either eye		
			SENA 6: Ophthalmic graders referral for PDR based on ultrawide-field fundus images in routine clinic	**SENA6:** Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess		

Study details	Population inclusion criteria	Population exclusion criteria	Index test	Reference standard	Mean diabetes duration (SD) – years	Risk of bias
				active PDR in either eye in routine clinic		

1. Other subgroups were reported for people with diabetic macular oedema but these are not reported in this evidence review, as the part of this review for people with macular oedema was covered by the Cochrane review. Other subgroups were also reported with an enhanced reference standard, but this included the use of ultrawide-field imaging which was the index test for this review. Subgroups that included comparisons with the enhanced reference standard were therefore not reported in this review.

Table 3 Summary of Cochrane review used for diagnostic effectiveness evidence – OCT for the detection of macular oedema or clinically significant macular oedema for people with diabetic retinopathy

OCT: Optical coherence tomography; DMO: Diabetic macular oedema; CSMO: Clinically significant diabetic macular oedema

Study	Number of included studies	Inclusion criteria	Exclusion criteria	Index test	Reference standard
Virgili et al. 2015	10 studies	Prospective and retrospective consecutive series of patients and case-control studies that evaluated the accuracy of OCT for diagnosing DMO or CSMO in people with diabetic retinopathy who were referred to eye clinics	Case control studies	OCT, regardless of the generation of development of the instrument (low or high resolution, three-dimensional or spectral-domain OCTs)	Stereoscopic fundus photography and contact lens or non-contact lens biomicroscopy of the fundus

Table 4 Summary of primary studies included in the diagnostic effectiveness evidence – OCT for the detection of macular oedema or clinically significant macular oedema for people with diabetic retinopathy

All studies for OCT were taken from the Cochrane review (for full evidence tables, see the Characteristics of included studies section of the Cochrane review (Virgili et al. 2015)

OCT: Optical coherence tomography; DMO: Diabetic macular oedema; CSMO: Clinically significant diabetic macular oedema

Study	Population inclusion criteria	Population exclusion criteria	Index test	Reference standard	Mean diabetes duration (SD) – years	Risk of bias
Brown 2004 N= 172 eyes	Diabetic patients with varying levels of retinopathy, examined during a 6-week period; 59/95 severe non-proliferative or proliferative diabetic retinopathy	Presence of any retinal or choroidal disease, other than diabetes, that could affect retinal thickness or preclude identification of oedema involving the centre of the macula	Stratus OCT	CSMO diagnosed with fundus biomicroscopy	19	Moderate
Browning 2004 N = 143 eyes Prospective case series	Patients with central or non-central CSMO in one or both eyes seen in a private retina practice	Patients with media opacities, poor pupillary dilation, high refractive error, or otherwise technically unsatisfactory studies with poor foveal thickness reproducibility were excluded.	Stratus OCT	CSMO diagnosed with stereoscopic slit-lamp biomicroscopy	NR	Moderate
Campbell 2007 N = 65 eyes Prospective	Adult with type 1 or type 2 diabetes and diabetic retinopathy ('the degree of	Patients were excluded if they exhibited clinical evidence of any retinal disease other than diabetic retinopathy.	Stratus OCT	CSMO diagnosed with fundus biomicroscopy and sterophoto	NR	Low

Study	Population inclusion criteria	Population exclusion criteria	Index test	Reference standard	Mean diabetes duration (SD) – years	Risk of bias
	diabetic retinopathy in the sample was representative of the spectrum of this disease)					
Davis 2008 N = 462 eyes Prospective consecutive case series	People with diabetic retinopathy selected among those enrolled in a randomised trial on treatment of DMO at retina clinics. Participants had to be gradable for both OCT and fundus photography.	People whose eyes were not gradable for both OCT and fundus photography.	Stratus OCT	CSMO diagnosed by stereophotography at photograph reading centre.	14	Moderate
Goebel 2006 N = 124 eyes + 13 control	Patients with diabetic retinopathy of any level seen at a university-based clinic in Germany Thirteen eyes of 13 subjects without diabetes mellitus or other vascular	13 eyes with ungradable fundus photograph and 6 with ungradable OCT	OCT 2000 Scanner (Zeiss)	CSMO or DMO diagnosed with digital stereoscopic fundus photography	Not reported	Moderate

Study	Population inclusion criteria	Population exclusion criteria	Index test	Reference standard	Mean diabetes duration (SD) – years	Risk of bias
	diseases and normal central retina shown by stereo biomicroscopy served as controls.					
Hee 1998 N = 182 eyes	Patients with diabetic retinopathy seen at the New England Eye Center of Tufts University	Not reported	Early, non-commercial OCT model and software (Early zeiss prototype)	CSMO or DMO diagnosed with fundus biomicroscopy	Not reported	High
Medina 2012 N = 62 prospective	Patients with diabetes without recent loss of vision (in the 6 months before enrolment)	Patients with significant corneal opacities that could result in a poor OCT signal, patients with any ocular disease other than diabetes, and patients who had undergone any intraocular surgery, including cataract surgery	Three commercially available SD OCT devices (Topcon 3d-1000, Cirrus HD OCT, Spectralis OCT)	Noncontact lens biomicroscopy of the fundus	Not reported	Moderate
Nunes 2010 N = 62 eyes Case series	Patients with type 2 diabetes classified on stereocolour fundus photography at an independent	Eyes with photocoagulation treatment within the 3 months before inclusion in the study and eyes with cataract or any other eye disease that may	Cirrus HD-OCT	Central (type 1) CSMO diagnosed with stereocolour fundus photography.	10.8 (6.8)	High

Study	Population inclusion criteria	Population exclusion criteria	Index test	Reference standard	Mean diabetes duration (SD) – years	Risk of bias
	reading centre, as having clinically significant macular oedema using the ETDRS classification	interfere with fundus examination were excluded from the study.				
Sadda 2006 N = 71 eyes Retrospective	People with a diagnosis of DMO who underwent OCT imaging. No other clinical characteristics of sample population were reported.	Not reported	Stratus OCT	CSMO or DMO diagnosed with fundus photography	Not reported	High
Strom 2002 N = 96 eyes Case series	Diagnosed as having diabetic macular oedema less severe than CSME or as having untreatable CSME	Not reported	OCT 2000 (Zeiss)	CSMO or DMO diagnosed with fundus photography	Type 1: 13.8 Type 2 : 23.5	High

See Appendix D for full evidence tables.

1.1.6 Summary of the diagnostic evidence

Ultrawide-field fundus imaging for the detection of proliferative diabetic retinopathy in people with previously treated diabetic retinopathy.

Table 5. Ultrawide-field fundus imaging vs Slit lamp biomicroscopy.
PDR: Proliferative diabetic retinopathy
Interpretation of effect: A positive likelihood ratio greater than 1 indicates an increase in the probability of disease, while a negative likelihood ratio less than 1 indicates a decrease in the probability of disease.

Index test	Reference Standard	No. of studies and n	Sensitivity	Specificity	LR+	LR-	Interpretation (sensitivity)	Interpretation (specificity)	Quality
Ultrawide-field Fundus photography (main analysis)[1]	Slit lamp biomicroscopy	1 (Lois 2021) n=265	0.83 (0.75, 0.89)	0.54 (0.46, 0.61)	LR+ 1.79 (1.48, 2.16)	LR- 0.32 (0.20, 0.50)	The sensitivity of ultrawide-field fundus imaging is above the pre-set level to recommend this test for classifying PDR (lower CI is below the threshold for recommending)	The specificity of ultrawide-field fundus imaging is below the pre-set level to recommend this test for classifying PDR (upper CI is below the threshold for recommending)	High
Ultrawide-field Fundus photography : SENA1 [2]	Slit-lamp biomicroscopy	1 (Lois 2021) n=264	0.63 (0.53 , 0.71)	0.73 (0.60 , 0.79)	LR+ 2.32 (1.73 , 3.12)	LR- 0.51 (0.39 , 0.66)	The sensitivity of ultrawide-field fundus imaging is below the pre-set level to recommend this test for classifying PDR (CIs are below the threshold for recommending)	The specificity of ultrawide-field fundus imaging is above the pre-set level to recommend this test for classifying PDR (lower CI is below the threshold for recommending)	High

Ultrawide-field Fundus photography : Additional 1[3]	Slit-lamp biomicroscopy	1 (Lois 2021) n=262	0.72 (0.62 , 0.80)	0.86 (0.80 , 0.91)	LR+ 5.19 (3.46 , 7.80)	LR- 0.33 (0.24 , 0.45)	The sensitivity of ultrawide-field fundus imaging is below the pre-set level to recommend this test for classifying PDR (Upper CI meets the threshold for recommending)	The specificity of ultrawide-field fundus imaging is above the pre-set level to recommend this test for classifying PDR (CIs are above the threshold for recommending)	High
Ultrawide-field Fundus photography : SENA2[4]	Slit-lamp biomicroscopy	1 (Lois 2021) n=265	0.86 (0.77 , 0.91)	0.52 (0.45 , 0.59)	LR+ 1.78 (1.49 , 2.13)	LR- 0.28 (0.16 , 0.47)	The sensitivity of ultrawide-field fundus imaging is above the pre-set level to recommend this test for classifying PDR (lower CI is below the17hresholdd for recommending)	The specificity of ultrawide-field fundus imaging is below the pre-set level to recommend this test for classifying PDR (CIs are below the threshold for recommending)	High
Ultrawide-field Fundus photography : SENA4[5]	Slit-lamp biomicroscopy	1 (Lois 2021) n=264	0.87 (0.78 , 0.93)	0.49 (0.42 , 0.56)	LR+ 1.72 (1.46 , 2.03)	LR- 0.26 (0.14 , 0.48)	The sensitivity of ultrawide-field fundus imaging is above the pre-set level to recommend this test for classifying PDR (lower CI is below the threshold for recommending)	The specificity of ultrawide-field fundus imaging is below the pre-set level to recommend this test for classifying PDR (lower CI is below the threshold for recommending)	High
Ultrawide-field Fundus photography : Additional 2[6]	Slit-lamp biomicroscopy	1 (Lois 2021) n=262	0.81 (0.71 , 0.89)	0.80 (0.73 , 0.85)	LR+ 4.01 (2.96 , 5.42)	LR- 0.23 (0.14 , 0.38)	The sensitivity of ultrawide-field fundus imaging is above the pre-set level to recommend	The specificity of ultrawide-field fundus imaging is above the pre-set level to	High

							this test for classifying PDR (lower CI is below the threshold for recommending)	recommend this test for classifying PDR (CIs are above the threshold for recommending)	
Ultrawide-field Fundus photography : SENA6[7]	Slit-lamp biomicroscopy	1 (Lois 2021) n=169	0.82 (0.72 , 0.89)	0.51 (0.41 , 0.61)	LR+ 1.67 (1.32 , 2.11)	LR- 0.36 (0.21 , 0.60)	The sensitivity of ultrawide-field fundus imaging is above the pre-set level to recommend this test for classifying PDR (lower CI is below the threshold for recommending)	The specificity of ultrawide-field fundus imaging is below the pre-set level to recommend this test for classifying PDR (CIs are below the threshold for recommending)	High

1. Main analysis (Ophthalmic graders referral for PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists)
2. SENA1 (Ophthalmic graders identified active PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists to identify active PDR)
3. Additional 1 (Ophthalmologist assessment identifying active PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists to identify active PDR)
4. SENA 2 (Ophthalmic graders referral for PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists to identify active PDR)
5. SENA4 (Ophthalmic graders referral for PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists to assess active PDR with preretinal or vitreous haemorrhage
6. Additional 2 (Ophthalmologist identified active PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists to assess active PDR with preretinal or vitreous haemorrhage)
7. SENA6 (Ophthalmic graders referral for PDR based on ultrawide-field fundus images in routine clinic vs slit lamp biomicroscopy by ophthalmologists to assess active PDR in routine clinic)

OCT for the detection of macular oedema for people with diabetic retinopathy – from Cochrane review (Virgili et al. 2015)

Table 6 OCT vs stereoscopic fundus photography or contact lens or non-contact lens biomicroscopy of the fundus for diabetic macular oedema (based on ETDRS definition).

OCT: Optical coherence tomography; DMO: Diabetic macular oedema; CSMO: Clinically significant diabetic macular oedema
Interpretation of effect: A positive likelihood ratio greater than 1 indicates an increase in the probability of disease, while a negative likelihood ratio less than 1 indicates a decrease in the probability of disease.

Index test	Reference Standard	No. of studies and n	Sensitivity	Specificity	LR+	LR-	Interpretation (sensitivity)	Interpretation (specificity)	Quality
Optical coherence tomography	Stereoscopic fundus photography or contact lens or non-contact lens biomicroscopy of the fundus	1 (Goebel 2006) n=111 eyes	0.78 (0.66, 0.87)	0.82 (0.66, 0.92)	LR+ 4.33 (1.94, 10.87	LR- 0.26 (0.14, 0.51)	The sensitivity of OCT is below the pre-set level to recommend this test for classifying DMO (upper CI is above the threshold for recommending)	The specificity of OCT is above the pre-set level to recommend this test for classifying DMO (CIs are above the threshold for recommending)	Moderate
OCT	Stereoscopic fundus photography or contact lens or non-contact lens biomicroscopy of the fundus	1 (Sadda2006) n=63 eyes	0.84 (0.70, 0.93)	0.79 (0.54, 0.94)	LR+ 4.00 (1.52, 15.50)	LR- 0.20 (0.07, 0.55)	The sensitivity of OCT is above the pre-set level to recommend this test for classifying DMO (lower CI is below the threshold for recommending)	The sensitivity of OCT is above the pre-set level to recommend this test for classifying DMO (lower CI is below the threshold for recommending)	Low
OCT	Stereoscopic fundus photography or contact lens or non-contact	1 (Strom 2002) n=84 eyes	1.00 (0.77, 1.00)	1.00 (0.95, 1.00)	Not calculable	Not calculable	The sensitivity of OCT is above the pre-set level to recommend this test for	The sensitivity of OCT is above the pre-set level to recommend this test for	Low

	lens biomicroscopy of the fundus						classifying DMO (lower CI is below the threshold for recommending)	classifying DMO (CIs are above the threshold for recommending)	

OCT for detection of clinically significant macular oedema for people with diabetic retinopathy – from Cochrane review (Virgili et al. 2015)

Table 7 OCT vs stereoscopic fundus photography or contact lens or non-contact lens biomicroscopy of the fundus for clinically significant diabetic macular oedema (based on ETDRS definition).

OCT: Optical coherence tomography; DMO: Diabetic macular oedema; CSMO: Clinically significant diabetic macular oedema

Interpretation of effect: A positive likelihood ratio greater than 1 indicates an increase in the probability of disease, while a negative likelihood ratio less than 1 indicates a decrease in the probability of disease.

Index test	Reference Standard	No. of studies and n	Sensitivity	Specificity	LR+	LR-	Interpretation (sensitivity)	Interpretation (specificity)	Quality
OCT	Stereoscopic fundus photography or contact lens or non-contact lens biomicroscopy of the fundus	9 (n= 1303 eyes)	0.81 (0.74, 0.84)	0.85 (0.75, 0.91)	LR+ 5.30 (3.20, 8.70)	LR- 0.23 (0.18, 0.30)	The sensitivity of OCT is above the pre-set level to recommend this test for classifying DMO (lower CI is below the threshold for recommending)	The specificity of OCT is above the pre-set level to recommend this test for classifying DMO (CIs are above the threshold for recommending)	Low

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 672 studies. Based on title and abstract screening, 669 studies could confidently be excluded for this review question and a further 2 studies excluded following the full-text review. Thus, one relevant health economic study included in the review (see Appendix G).

1.1.7.2 Excluded studies

Two studies were excluded at full text review.

See Appendix J for excluded studies and reasons for exclusion.

1.1.8 Summary of included economic evidence

Table 6 provides a summary of the included economic evidence. Further details are included in Appendix H.

Table 8: Economic evidence profile

Study	Applicability	Limitations	Other comments	Costs	Consequences	Uncertainty
Lois et al (2021) Multimodal imaging interpreted by graders to detect re-activation of diabetic eye disease in previously treated patients: the EMERALD diagnostic accuracy study	Partially applicable (Not all interventions are relevant; Only cost-consequence rather than cost utility study)	Potentially serious limitations (Cost consequence study; No specific time horizon; No probabilistic sensitivity analysis)	PDR: Intervention: Ultrawide-field imaging assessed by graders Standard of care: ophthalmologist face-to-face examination with slit-lamp microscopy DMO: Intervention: OCT assessed by graders Standard of care: ophthalmologist face-to-face examination with slit-lamp microscopy and OCT	PDR: Cost savings per 100 patients (Ultrawide-field imaging compared with Standard of care): £1,189 DMO: Cost savings per 100 patients (OCT assessed by graders compared with Standard of care): £1390	Standard of care: assumed sensitivity 100% and specificity 100% PDR (Ultrawide-field imaging): sensitivity 83% and specificity of 54% DMO (Grader assessed OCT): sensitivity 97%, specificity 31%	Scenario 1: When the diagnostic performance of graders was assessed based on active PDR only, specificity improved but sensitivity was reduced, meaning more patients with active disease would be missed. Scenario 2: Grader pathway assessed by how well identified eyes requiring treatment. Sensitivity increased to 86% and specificity reduced to 54% with a

Study	Applicability	Limitations	Other comments	Costs	Consequences	Uncertainty
						cost saving compared with standard care of £1,131.

1.1.9 Economic model

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

1.1.10 Unit costs

Table 9: Unit costs

Resource	Unit cost	Source
Optical coherence tomography	£101.80	NHS Reference Costs 2019/2020. Consultant led non-admitted face-to-face attendance, follow-up. Code 130 (ophthalmology).

1.1.11 Evidence statements

One published cost-consequence study for the monitoring of people with previously treated proliferative diabetic retinopathy (PDR) and previously treated diabetic macular oedema (DMO) (Lois et al. 2021) was identified. This study compared ultrawide-field imaging by a grader compared with the current standard of care which was an ophthalmologist face-to-face examination with slit-lamp microscopy for PDR and compared spectral domain optical coherence tomography (SD-OCT) to standard of care which was an ophthalmologist face-to-face examination with slit-lamp microscopy and SD-OCT for DMO. In people with PDR it was estimated that the use of grader-assessed ultrawide-field imaging could lead to cost savings of £1,189 per 100 people, however at a reduced specificity and sensitivity (83% and 54% compared with an assumed 100% for standard of care). In people with DMO it was estimated that the use of grader-assessed SD-OCT could lead to cost savings of £1,390 per 100 people, however at a reduced specificity and sensitivity (97% and 31% compared with an assumed 100% for standard of care).

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The assessment of diagnostic accuracy for OCT and ultrawide-field imaging involved considering sensitivity, specificity, and likelihood ratios. The committee thought that sensitivity and specificity were the most important outcomes, as accurately identifying someone as having, or not having, proliferative diabetic retinopathy or diabetic macular oedema is crucial for ensuing that people have the correct follow-up and monitoring.

The committee discussed the potential impact of true positive, true negative, false positive, and false negative outcomes. Sensitivity and true positives were considered important as they enable clinicians to identify individuals who require timely treatment, thereby reducing the severe complications associated with untreated proliferative diabetic retinopathy or diabetic macular oedema. The committee also noted that avoiding false negatives is crucial to ensure that signs of progression are not overlooked, as this could lead to people missing important

monitoring and treatment. Neglecting such measures might result in individuals experiencing more serious effects related to diabetic retinopathy and macular oedema, including vision loss.

False positives were also considered, as these can lead to additional follow-up appointments that may not have been needed. However, the committee thought this was less of a concern than people missing out on treatment because of false negative results. If someone is identified as having features of proliferative diabetic retinopathy or macular oedema by a diagnostic test, this would be followed up by a clinical examination, and so false positives are unlikely to result in people receiving unnecessary treatment.

The committee noted that the classification of diabetic retinopathy or macular oedema is also based on the ophthalmologist's assessment of several clinical components, which can mean that the accuracy of the reference standard varies between studies.

1.1.12.2 The quality of the evidence

Ultrawide-field fundus imaging for the detection of proliferative diabetic retinopathy in people with non-proliferative diabetic retinopathy.

No evidence was found for the use of ultrawide-field fundus imaging for people with non-proliferative diabetic retinopathy.

Ultrawide-field fundus imaging for the detection of proliferative diabetic retinopathy in people with previously treated diabetic retinopathy.

A single study, (Lois 2021, EMERALD) assessed the diagnostic accuracy of multimodal imaging, interpreted by graders, for detecting the re-activation of diabetic eye disease in patients who had previously received treatment. The study used various imaging techniques, such as OCT, ultrawide-field imaging, and fluorescein angiography, to evaluate the presence and severity of diabetic eye disease.

The EMERALD study was a high-quality cross-sectional study conducted in the UK. It focused on assessing the diagnostic accuracy of ultrawide-field fundus photography in adults with diabetes (type 1 or 2) who had previously undergone successful treatment for diabetic macular oedema or proliferative diabetic retinopathy in one or both eyes. The committee considered the study's design to be applicable to routine care within the NHS in the UK, and therefore directly applicable to the review.

The EMERALD study reported both a main analysis and several sensitivity analyses. The main analysis compared referral decisions for proliferative diabetic retinopathy made by non-specialist graders using ultrawide-field fundus imaging, with those made by ophthalmologists using slit-lamp biomicroscopy. The sensitivity analyses explored the diagnostic accuracy in various scenarios. These scenarios included the identification of active retinopathy and the use of ultrawide-field fundus imaging by ophthalmologists instead of non-specialist graders. Some of the sensitivity analyses used an enhanced reference standard, which involved incorporating ultrawide-field imaging and 7-field ETDRS images. However, these additional imaging modalities did not meet the inclusion criteria for this review and so the results of these comparisons were not considered by the committee.

The committee discussed the relevance and significance of both the main analysis and the sensitivity subgroups. They decided that the comparisons involving referral decisions for proliferative diabetic retinopathy, using ultrawide-field fundus imaging versus slit lamp biomicroscopy, were particularly relevant to the review question. As a result, the committee decided to concentrate their discussion primarily on the main analysis and one of the sensitivity analyses (SENA2). These analyses were deemed to provide the most applicable insights for the review.

OCT for the detection of diabetic macular oedema or clinically significant diabetic macular oedema for people with diabetic retinopathy

The Cochrane review (Virgili et al. 2015) included 10 studies published between 1998 and 2012, with a total of 830 participants and 1387 eyes. Many of the studies were at moderate or high risk of bias, partly due to the selection of the study population and because of the exclusion of participants who had poor-quality images. It was noted that many of the studies included both eyes of participant in the analyses as if they were independent, which could affect the results.

In the nine studies that provided data on clinically significant diabetic macular oedema, the analysis was pooled. However, for the detection of diabetic macular oedema, data from three studies (180 participants, 343 eyes) were not pooled. This approach was justified by the authors of the Cochrane review based on the small number of studies, and because one of these studies indicated that OCT had perfect sensitivity and specificity.

Some studies in the review used different generations of OCTs, however the committee thought they were all applicable to current practice. The committee were confident in the OCT devices in the evidence base, as while newer devices may offer enhanced features or improved imaging capabilities, the fundamental principles and underlying mechanisms of OCT technology remains consistent across generations.

1.1.12.3 Imprecision and clinical importance of effects

Ultrawide-field fundus imaging for the detection of proliferative diabetic retinopathy in people with previously treated diabetic retinopathy.

The main analysis and the subgroup analysis (SENA 2) that the committee considered most important for decision making in the EMERALD study (Lois, 2021) both had sensitivity above the pre-specified threshold (80%) for effectively identifying someone who has signs of proliferative diabetic retinopathy. It was noted that the lower 95% confidence interval for each of these analyses was below this threshold (75% and 77%). However, the committee did not think this was enough to rule out the use of ultrawide-field imaging as an additional diagnostic tool for proliferative diabetic retinopathy. Specificity for both analyses was below the threshold of 65%, but as the committee thought that true positives were the most important outcome, they did not think this should prevent the use of ultrawide-field imaging. Although there was only one study which evaluated the effectiveness of ultrawide-field imaging, it was high quality and the confidence intervals were relatively narrow, and so the committee thought this represented the true accuracy of the test.

OCT for the detection of diabetic macular oedema or clinically significant diabetic macular oedema for people with diabetic retinopathy

Sensitivity and specificity were both above the pre-set thresholds which the committee thought were sufficient to recommend the use of OCT as a diagnostic tool. The committee thought that the confidence intervals were narrow enough that they could be confident in the ability of OCT as a diagnostic tool for clinically significant diabetic macular oedema. Data was not pooled for the evaluation of people with diabetic macular oedema that was not clinically significant, but the specificity of each of the studies was above the pre-set threshold of 65% (0.82, 0.79 and 1.00). The confidence intervals for 2 of the studies were relatively wide, but as the committee were less concerned about false positives, they did not think this was a major issue. Confidence intervals were narrower for sensitivity, and 2 of the studies reported a sensitivity above the pre-set threshold of 80% (84% and 100%). The committee thought this reflected sufficient diagnostic accuracy to recommend the use of the test.

1.1.12.4 Benefits and harms

Ultrawide-field fundus imaging for the detection of proliferative diabetic retinopathy in people with non-proliferative diabetic retinopathy.

No evidence was identified for detecting people with non-proliferative diabetic retinopathy. The committee recognised that it is crucial to monitor individuals with non-proliferative diabetic retinopathy to detect any progression of the disease and to begin appropriate interventions in a timely manner to prevent vision loss. Given the lack of evidence, they made a research recommendation to understand how effective ultrawide-field imaging is for diagnosing progression to proliferative diabetic retinopathy in people who have non-proliferative diabetic retinopathy (See Appendix K for more details).

Ultrawide-field fundus imaging for the detection of proliferative diabetic retinopathy in people with previously treated diabetic retinopathy.

There was only one study reporting on the accuracy of ultrawide-field fundus imaging to detect proliferative diabetic retinopathy. In their main analysis, the EMERALD study (Lois, 2021) reported that non-specialist graders using ultrawide-field fundus imaging identified 83% (95% CI 75%-89%) of people for referral who were identified as having diabetic retinopathy using slit lamp biomicroscopy (see Table 5). 54% (95% CI 46%-61%) of those who were classed as negative by slit lamp biomicroscopy were also identified as not needing referral by the graders. When ophthalmologists used ultrawide-field fundus imaging (SENA 2 analysis), 86% (95% CI 77%-91%) of those identified as having proliferative diabetic retinopathy using slit lamp biomicroscopy were identified for referral. 52% (95%CI 45%-59%) of those identified as not having proliferative diabetic retinopathy using slit lamp biomicroscopy were also identified as not needing referral using ultrawide-field imaging. Likelihood ratios from both analyses suggested that a positive result from ultrawide-field imaging indicated a slight increase in the probability of a person having proliferative diabetic retinopathy, and a negative result indicated a moderate decrease in the probability of the disease.

The study's findings suggest that ultrawide-field imaging, when used by both non-specialist graders (main analysis) and ophthalmologists (SENA 2), has a sensitivity above the threshold they considered sufficient for them to recommend using as a test to detect proliferative diabetic retinopathy. The specificity was below the pre-set threshold, meaning that there is a higher chance of false positives, which can result in individuals being identified for referral who may not yet require treatment. However, the committee acknowledged that this is preferable to the risk of missing individuals who do require treatment. The committee believed that the sensitivity of ultrawide-field imaging was sufficient to consider it as an additional diagnostic test alongside other methods used for diagnosing diabetic retinopathy.

The committee discussed the use of ultrawide-field imaging as a standalone diagnostic test for proliferative diabetic retinopathy but acknowledged its limitations. They recognised that using ultrawide-field imaging alone may not identify all individuals who would be referred based on slit lamp biomicroscopy, which is considered a standard technique. Additionally, they were concerned that this imaging modality might miss important indications, such as rubeosis which can be detected by other standard techniques like slit lamp biomicroscopy. Based on these factors, and the lower specificity of the test, the committee recommended that ultrawide-field imaging should be used alongside other methods of clinical examination, such as slit lamp biomicroscopy, for the diagnosis of proliferative diabetic retinopathy. This could be during face-to face appointments with a clinician, or at virtual clinics, where imaging takes place and is reviewed later by the clinician. By combining both approaches, the likelihood of detecting important indications, including rubeosis, is increased. The committee were also aware that current methods of clinical examination can miss some people who are progressing, and so the use of more than one diagnostic tool can ensure comprehensive patient assessment. This

increases the chances of identifying indications of proliferative retinopathy and enhances the quality of care provided to patients.

It was noted that the evidence focused on people who have proliferative diabetic retinopathy that has previously been treated. This is a small section of the population who have proliferative diabetic retinopathy. However, the committee thought that this evidence could be extrapolated to the wider population who have not yet had treatment for proliferative retinopathy, as the imaging will be identifying the same markers for progression. Given that ultrawide-field imaging is being recommended alongside other standard clinical techniques, the committee did not think there was a risk of people in this wider group being missed for treatment. They highlighted that anyone who is identified as having signs of progression via ultrawide-field imaging would have a follow-up appointment with an ophthalmologist for further assessment and decision making about whether treatment is necessary. However, given that this evidence was based on one study that only included a subgroup of the population, they decided that ultrawide-field imaging should be considered, rather than offered, as an additional test.

The committee were aware that diagnostic accuracy is not the only consideration when deciding on which tests should be recommended. While ultrawide-field imaging can be efficient, it is often performed in diagnostic testing centres, where people are seen by clinicians, but not necessarily ophthalmologists. This means that patients may miss out on the opportunity to interact with the specialists who they would otherwise see as part of standard clinical techniques. By not seeing ophthalmologists as frequently, people may miss out on information and support that they would otherwise receive. This may lead to increased patient anxiety and the inability to address questions or concerns regarding the test results. Recognising the importance of patient support and reassurance, the committee emphasised the value of maintaining the involvement of healthcare professionals in the diagnostic process. This supported their decision not to recommend ultrawide-field imaging as the sole method of diagnosing proliferative diabetic retinopathy.

OCT for the detection of diabetic macular oedema or clinically significant diabetic macular oedema for people with diabetic retinopathy

OCT measurement of central retinal thickness detected 81% (95% CI 74%-84%) of people with clinically significant macular oedema, as determined by conventional ETDRS assessment using fundus examination or photography. Additionally, OCT correctly identified 85% (95% CI 75%-91%) of individuals who were not considered to have clinically significant oedema based on the index tests (fundus examination or photography). The committee were satisfied that these findings highlight the potential of OCT as a reliable method for detecting and assessing clinically significant diabetic macular oedema in clinical practice.

Three studies provided information on the accuracy of OCT for detecting diabetic macular oedema. The sensitivity of OCT in these studies ranged from 78% to 100% (see Table 4), indicating the ability of OCT to correctly identify individuals with diabetic macular oedema. The specificity ranged from 79% to 100%, suggesting that OCT can effectively rule out diabetic macular oedema in most individuals without the condition. Positive likelihood ratios indicated a large increase in the probability of an individual having clinically significant macular oedema or diabetic macular oedema, and negative likelihood ratios indicated a large decrease in the probability of these conditions.

The committee agreed with the findings of the Cochrane review that these results confirm the value of OCT in identifying and assessing diabetic macular oedema. The committee recognised the widespread acceptance of OCT as the reference standard for diagnosing diabetic macular oedema and agreed that the evidence accurately reflects clinical practice. Despite the presence of false positives in OCT testing, the committee acknowledged that this is a result of the technology's ability to detect subclinical macular oedema. This is considered

important as it allows for the identification of individuals who may require treatment in the future as they reach a threshold of clinical significance.

The committee discussed how, in addition to the benefits of ensuring that people are not missed when they need treatment, there are minimal risks associated with the use of OCT scans. Based on their discussions and considering the findings of the systematic review, the committee reached a consensus that OCT should be recommended as the primary method for diagnosing diabetic macular oedema. This recommendation highlights the importance of OCT in accurately detecting DMO, aiding in timely diagnosis and appropriate management decisions.

1.1.12.5 Cost effectiveness and resource use

No economic evidence was identified for non-proliferative diabetic retinopathy. However, no resource impact would be anticipated for this population given only research recommendations were made for this population, and in the in the absence of this research it is expected that current practice would continue.

The committee considered the one economic evaluation identified which addressed the cost-effectiveness of the diagnostic accuracy of grader-assessed ultrawide-field fundus photography for monitoring of people with previously treated proliferative diabetic retinopathy (PDR). The EMERALD study by Lois et al (2021) estimated that grader-assessed ultrawide-field imaging compared with the current standard of care (ophthalmologist face-to-face examination with slit-lamp microscopy) could save £1,189 per 100 visits for PDR based on a sensitivity of 83% and specificity of 54% for grader evaluating ultrawide-field images compared with an assumed sensitivity and specificity of 100% for standard of care. Grader-assessed ultrawide-field imaging is less costly than current standard of care due to staff costs, and is low enough that even with a proportion of patients being referred for face-to-face ophthalmology appointments (based on the specificity of 54%) this method of imaging is less costly overall.
The committee felt that given the current resource constraints faced, the use of ultrawide-field imaging by graders could offer both a cost saving alternative for monitoring PDR and help relieve capacity for the ophthalmologists by reducing the number of referrals they receive. The committee were concerned by the comparably lower specificity by the graders pathway and discussed concerns of variability in practice between ophthalmologists and graders and whether this could lead to inequality of outcomes between patients and could lead to missed reactivation of PDR which could put patients at risk of loss of eyesight and lead to delayed resource impact. Given the EMERALD study is only a short-term study of two years, the committee did not feel confident on offering ultrawide-field imaging particularly given the large reduction in specificity; however, they did feel it offered a resource saving opportunity which should be considered.

Lois et al (2021) also included analysis on the cost-effectiveness of grader-assessed OCT compared with standard of care (ophthalmologist face-to-face examination with slit-lamp microscopy and OCT) in DMO, and found that the grader-assessed OCT could save £1,390 per 100 visits for DMO based on a sensitivity of 97% and specificity of 31% compared with the assumed sensitivity and specificity of 100% for standard of care. The committee considered that OCT is recognised as the current standard of care and therefore recommended that OCT should be used for monitoring DMO.

1.1.13 Recommendations supported by this evidence review.

This evidence review supports recommendations 1.5.10 and 1.6.15 and the research recommendation on diagnostic test accuracy of ultrawide-field fundus imaging for people with non-proliferative diabetic retinopathy.

1.1.14 References – included studies

1.1.14.1 Clinical evidence

Ultra-wide fundus photography

Lois, Noemi, Cook, Jonathan A, Wang, Ariel et al. (2021) Evaluation of a New Model of Care for People with Complications of Diabetic Retinopathy: The EMERALD Study. Ophthalmology 128(4): 561-573

Optical coherence tomography

For a list of included studies, see the Cochrane review (Virgili et al. 2015).

Virgili G, Menchini F, Casazza G, Hogg R, Das RR, Wang X, Michelessi M. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. Cochrane Database Syst Rev. 2015 Jan 7;1:CD008081. Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1.1.14.2 Economic

Lois, Noemi, Cook, Jonathan, Wang, Ariel et al. (2021) Multimodal imaging interpreted by graders to detect re-activation of diabetic eye disease in previously treated patients: the EMERALD diagnostic accuracy study. Health technology assessment (Winchester, England) 25(32): 1-104

Appendices

Appendix A – Review protocols

Review protocol for diagnostic accuracy of ultrawide-field fundus photography and OCT

ID	Field	Content
1.	Review title	The diagnostic test accuracy of ultrawide-field imaging for monitoring of: • people diagnosed with non-proliferative diabetic retinopathy, whose care is managed under the hospital eye services, but who are not having treatment • people diagnosed with proliferative diabetic retinopathy who are having treatment or have had previous treatment
2.	Review question	What is the diagnostic test accuracy of ultrawide-field imaging and optical coherence tomography for monitoring of: • people diagnosed with non-proliferative diabetic retinopathy, whose care is managed under the hospital eye services, but who are not having treatment? • people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema, who are having treatment or have had previous treatment?
3.	Objective	To determine the diagnostic accuracy of ultrawide-field imaging and optical coherence tomography for monitoring the progression of: • people diagnosed with non-proliferative diabetic retinopathy, whose care is managed under the hospital eye services, but who are not having treatment • people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema, who are having treatment or have had previous treatment?
4.	Searches	A Cochrane review has been identified, which will used to provide evidence on the diagnostic accuracy of optical coherence tomography:

		Virgili G, Menchini F, Casazza G, Hogg R, Das RR, Wang X, Michelessi M. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. Cochrane Database of Systematic Reviews 2015 A systematic search will not be conducted for this aspect of the review. Despite the review being published in 2015, an update search will not be conducted because the Cochrane review concluded an update should not be conducted as OCT was increasingly used in routine practice and was considered by many to be the new reference standard. The aspect of the review relating to ultrawide-field imaging will be covered by a new systematic search. 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 diagnostic accuracy filters will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • No date limit will be set unless specified by the protocol • Cost Utility (specific) and Cohort Studies for the economic search Other searches: • None identified The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for all databases will be published in the final review.
5.	Condition or domain being studied	Diabetic retinopathy
6.	Population	Inclusion: 1. people diagnosed with non-proliferative diabetic retinopathy, who are not having treatment 2. people diagnosed with proliferative diabetic retinopathy or diabetic macular oedema, who are having treatment or have had previous treatment
7.	Index Test	• **Ultrawide-field fundus photography** For the population with non-proliferative retinopathy, a positive index test will be defined as the presence of proliferative diabetic retinopathy indicated by ultrawide-field fundus photography.

		For the population with proliferative retinopathy, a positive index test will be defined as the presence of high-risk proliferative retinopathy indicated by ultrawide-field fundus photography. • **Optical coherence tomography**
8.	Reference Standard	**Ultrawide-field fundus photography:** In order of preference: • Ultrawide-field angiography • Combination of Fundus photography and Fluorescein angiography (FA) • Fluorescein angiography (FA) • Slit lamp bio-microscopy If studies report more than 1 reference standard, only data relating to 1 reference standard will be reported based on the listed order of preference above. For the population with non-proliferative retinopathy, a positive reference standard will be defined as the presence of proliferative diabetic retinopathy, diagnosed using one of the reference standard methods listed. For the population with proliferative retinopathy, a positive reference standard will be defined as the presence of high-risk proliferative retinopathy diagnosed using one of the reference standard methods listed. **Optical coherence tomography (as described in Cochrane review):** • Stereoscopic fundus photography • Contact lens or non-contact lens biomicroscopy of the fundus
9.	Types of study to be included	• Diagnostic test accuracy studies • Case-control studies will be included

10.	Other exclusion criteria	Studies that were not reported in English
11.	Context	Diabetic retinopathy is an important cause of sight loss in adults in the United Kingdom. This review will inform a new guideline on diabetic retinopathy that is currently being developed by NICE.
12.	Primary outcomes (critical outcomes)	• Sensitivity • Specificity • Likelihood ratios
13.	Secondary outcomes (important outcomes)	None
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. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. 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). The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Extracted information for the quantitative review will include: study type; study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; inclusion and exclusion criteria; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using appropriate checklists as described in Developing NICE guidelines: the manual. **Ultrawide-field imaging**

		Risk of bias in for diagnostic accuracy studies will be assessed using the QUADAS-2 checklist. **Optical coherence tomography** Risk of bias judgments made as part of the Cochrane review process will be used directly.
16.	Strategy for data synthesis	**Ultrawide-field imaging:** Meta-analyses of diagnostic test accuracy data will be conducted for all diagnostic tests that are reported by more than one study, with reference to the Cochrane Handbook for systematic reviews of diagnostic test accuracy. Random-effects models will be fitted for all analyses. A bivariate model will be fitted when 5 or more studies are available to be meta-analysed. A univariate model will be fitted when there are fewer than 5 studies available. • Bivariate meta-analyses will be performed in R using the 'mada' package • Univariate meta-analysis will be performed in R using the metafor package. 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 will be initially rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered. **Optical coherence tomography:** Data from the identified Cochrane review will be reported directly, without further synthesis.
17.	Analysis of sub-groups	**Ultrawide-field imaging** Data will be presented separately for the following groups: • Pregnant women • Non-proliferative retinopathy, proliferative retinopathy, 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) • Severity of non-proliferative retinopathy (moderate, severe, and very severe) **Optical coherence tomography:**

		Subgroup analysis has not been conducted by the identified Cochrane review. No further subgroup analysis will be completed, because, given the overall conclusions of the Cochrane review, subgroup analysis is unlikely to result in useful information for decision making.
18.	Type and method of review	☐ ☒ ☐ ☐ ☐ ☐ ☐
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	April 2022
22.	Anticipated completion date	April 2024
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: • Clare Dadswell • 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.
33.	Details of existing review of same topic by same authors	None
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 November 2022. This search report is compliant with the requirements of PRISMA-S.

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

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

Review Management

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

Limits and restrictions

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

Limits to exclude, 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:

Observational studies

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

Diagnostic test accuracy

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

Clinical search strategies

Database	Date searched	Database Platform	Database segment or version
Cochrane Central Register of Controlled Trials (CENTRAL)	21/11/2022	Wiley	Issue 11 of 12, November 2022
Cochrane Database of Systematic Reviews (CDSR)	21/11/2022	Wiley	Issue 11 of 12, November 2022
Embase	22/11/2022	Ovid	1974 to 2022 November 18
Epistemonikos	22/11/2022	Epistemonikos	n/a
HTA	22/11/2022	CRD	n/a
INAHTA	22/11/2022	n/a	n/a
MEDLINE	22/11/2022	Ovid	1946 to November 21, 2022
MEDLINE-in-Process	22/11/2022	Ovid	1946 to November 21, 2022
MEDLINE ePub Ahead-of-Print	22/11/2022	Ovid	November 21, 2022

Database: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)		
#1	MeSH descriptor: [Diabetic Retinopathy] explode all trees	1583
#2	MeSH descriptor: [Macular Edema] explode all trees	1286
#3	(diabet* near/6 (retin* or eye* or macular* or maculopath*)):ti,ab,kw	5690
#4	{or #1-#3}	6135
#5	MeSH descriptor: [Fluorescein Angiography] this term only	898

#6 ((fluoresc* or fundus*) near/2 (angiograph* or contrast* or imag* or scan* or photo* or exam* or test* or auto-fluorescen* or autofluorescen*)):ti,ab,kw 3995
#7 fluoroangiograph*:ti,ab,kw 7
#8 (Ultra-wide* or Ultrawide* or UWF or UWFA):ti,ab,kw 78
#9 (slit lamp near/2 (bio-microscop* or biomicroscop* or microscop* or exam* or test*)):ti,ab,kw 1105
#10 slitlamp:ti,ab,kw 804
#11 (BM 900 or BM-900 or BQ 900 or BQ-900 or BX 900 or BX-900):ti,ab,kw 14
#12 Retinal thickness analy*:ti,ab,kw 1024
#13 {or #5-#12} 6072
#14 #4 and #13 1492
#15 "conference":pt or (clinicaltrials or trialsearch):so 650308
#16 #14 not #15 992

Database: Embase

1 diabetic retinopathy/ 48037
2 macular edema/ 6498
3 (diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw. 53150
4 or/1-3 72224
5 *fluorescence angiography/ 3498
6 ((fluoresc* or fundus*) adj2 (angiograph* or contrast* or imag* or scan* or photo* or exam* or test* or auto-fluorescen* or autofluorescen*)).tw. 94009
7 fluoroangiograph*.tw. 157
8 (Ultra-wide* or Ultrawide* or UWF or UWFA).tw. 2756
9 (slit lamp adj2 (bio-microscop* or biomicroscop* or microscop* or exam* or test*)).tw. 8749
10 slitlamp.tw. 1293
11 (BM 900 or BM-900 or BQ 900 or BQ-900 or BX 900 or BX-900).tw. 13
12 Retinal thickness analy*.tw. 169
13 or/5-12 105297
14 4 and 13 7835
15 Nonhuman/ not Human/ 5095339
16 14 not 15 7506
17 limit 16 to english language 6593
18 (sensitiv: or diagnos:).mp. or di.fs. 8972650
19 Clinical study/ 161049
20 Case control study/ 195405
21 Family study/ 25715
22 Longitudinal study/ 181456
23 Retrospective study/ 1339939
24 comparative study/ 978807
25 Prospective study/ 809445
26 Randomized controlled trials/ 238877
27 25 not 26 799840
28 Cohort analysis/ 920982
29 cohort analy$.tw. 17687
30 (Cohort adj (study or studies)).tw. 421333
31 (Case control$ adj (study or studies)).tw. 163207

32 (follow up adj (study or studies)).tw. 70927
33 (observational adj (study or studies)).tw. 231022
34 (epidemiologic$ adj (study or studies)).tw. 118284
35 (cross sectional adj (study or studies)).tw. 308769
36 prospective.tw. 1037944
37 retrospective.tw. 1158813
38 or/19-24,27-37 4992542
39 18 or 38 12276317
40 17 and 39 5161
41 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5372445
42 40 not 41 3833

Database: Epistemonikos

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

AND

(title:(Fluoresc* angiograph* OR fluoroangiograph* OR Ultra-wide* OR Ultrawide* OR UWF OR UWFA) OR abstract:(Fluoresc* angiograph* OR fluoroangiograph* OR Ultra-wide* OR Ultrawide* OR UWF OR UWFA))

Database: Health Technology Assessment (HTA)

1 MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES 118 Delete
2 MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES 82 Delete
3 ((diabet* near (retin* or eye* or macular* or maculopath*))) 225 Delete
4 #1 OR #2 OR #3 254 Delete
5 MeSH DESCRIPTOR Fluorescein Angiography EXPLODE ALL TREES 14 Delete
6 (((fluoresc* or fundus*) near (angiograph* or contrast* or imag* or scan* or photo* or exam* or test* or auto-fluorescen* or autofluorescen*))) 76 Delete
7 (fluoroangiograph*) 1 Delete
8 ((Ultra-wide* or Ultrawide* or UWF or UWFA)) 1 Delete
9 ((slit lamp near (bio-microscop* or biomicroscop* or microscop* or exam* or test*))) 5 Delete
10 (slitlamp) 0 Delete
11 ((BM 900 or BM-900 or BQ 900 or BQ-900 or BX 900 or BX-900)) 0 Delete
12 (Retinal thickness analy*) 2 Delete
13 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 85 Delete

14	#4 AND #13	24	Delete
15	* IN HTA	17351	Delete
16	#14 AND #15	5	Delete

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

14	#13 AND #4	12	November 22 2022 10:01 AM
13	#12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5	72	November 22 2022 10:01 AM
12	Retinal thickness analy*	1	November 22 2022 10:00 AM
11	(BM 900 or BM-900 or BQ 900 or BQ-900 or BX 900 or BX-900)	28	November 22 2022 10:00 AM
10	slitlamp	0	November 22 2022 10:00 AM
9	(slit lamp AND (bio-microscop* or biomicroscop* or microscop* or exam* or test*))	5	November 22 2022 9:59 AM
8	(Ultra-wide* or Ultrawide* or UWF or UWFA)	2	November 22 2022 9:59 AM
7	fluoroangiograph*	0	November 22 2022 9:59 AM
6	(((fluoresc* or fundus*) AND (angiograph* or contrast* or imag* or scan* or photo* or exam* or test* or auto-fluorescen* or autofluorescen*)))	36	November 22 2022 9:59 AM
5	"Fluorescein Angiography"[mh]	3	November 22 2022 9:58 AM
4	#3 OR #2 OR #1	94	November 22 2022 9:58 AM
3	((diabet* AND (retin* or eye* or macular* or maculopath*)))	88	November 22 2022 9:57 AM
2	"Macular Edema"[mh]	27	November 22 2022 9:57 AM
1	"Diabetic Retinopathy"[mh]	41	November 22 2022 9:56 AM

Database: Ovid MEDLINE(R)

1	Diabetic Retinopathy/	28613
2	Macular Edema/	8631
3	(diabet* adj6 (retin* or eye* or macular* or maculopath*)).tw.	33136
4	or/1-3	43425
5	*Fluorescein Angiography/	5524
6	((fluoresc* or fundus*) adj2 (angiograph* or contrast* or imag* or scan* or photo* or exam* or test* or auto-fluorescen* or autofluorescen*)).tw.	63300
7	fluoroangiograph*.tw.	110
8	(Ultra-wide* or Ultrawide* or UWF or UWFA).tw.	1286
9	(slit lamp adj2 (bio-microscop* or biomicroscop* or microscop* or exam* or test*)).tw.	5576
10	slitlamp.tw.	1032
11	(BM 900 or BM-900 or BQ 900 or BQ-900 or BX 900 or BX-900).tw.	8
12	Retinal thickness analy*.tw.	133
13	or/5-12	72344
14	4 and 13	5114

15 Animals/ not Humans/ 5033472
16 14 not 15 4946
17 limit 16 to english language 4398
18 (sensitiv: or diagnos:).mp. or di.fs. 6566412
19 Observational Studies as Topic/ 8273
20 Observational Study/ 134687
21 Epidemiologic Studies/ 9193
22 exp Case-Control Studies/ 1369978
23 exp Cohort Studies/ 2417631
24 Cross-Sectional Studies/ 446870
25 Comparative Study.pt. 1911731
26 case control$.tw. 134121
27 (cohort adj (study or studies)).tw. 251588
28 cohort analy$.tw. 9530
29 (follow up adj (study or studies)).tw. 50401
30 (observational adj (study or studies)).tw. 123975
31 longitudinal.tw. 260890
32 prospective.tw. 602216
33 retrospective.tw. 592546
34 cross sectional.tw. 392625
35 or/18-34 9788077
36 17 and 35 3935

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. 10
4 or/1-3 10
5 *Fluorescein Angiography/ 0
6 ((fluoresc* or fundus*) adj2 (angiograph* or contrast* or imag* or scan* or photo* or exam* or test* or auto-fluorescen* or autofluorescen*)).tw. 15
7 fluoroangiograph*.tw. 0
8 (Ultra-wide* or Ultrawide* or UWF or UWFA).tw. 1
9 (slit lamp adj2 (bio-microscop* or biomicroscop* or microscop* or exam* or test*)).tw. 3
10 slitlamp.tw. 0
11 (BM 900 or BM-900 or BQ 900 or BQ-900 or BX 900 or BX-900).tw. 0
12 Retinal thickness analy*.tw. 0
13 or/5-12 18
14 4 and 13 2
15 Animals/ not Humans/ 0
16 14 not 15 2
17 limit 16 to english language 1
18 (sensitiv: or diagnos:).mp. or di.fs. 1223
19 Observational Studies as Topic/ 0
20 Observational Study/ 0
21 Epidemiologic Studies/ 0
22 exp Case-Control Studies/ 0

23 exp Cohort Studies/ 0
24 Cross-Sectional Studies/ 0
25 Comparative Study.pt. 0
26 case control$.tw. 63
27 (cohort adj (study or studies)).tw. 197
28 cohort analy$.tw. 6
29 (follow up adj (study or studies)).tw. 15
30 (observational adj (study or studies)).tw. 96
31 longitudinal.tw. 174
32 prospective.tw. 225
33 retrospective.tw. 362
34 cross sectional.tw. 367
35 or/18-34 2121
36 17 and 35 1

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. 501
4 or/1-3 501
5 *Fluorescein Angiography/ 0
6 ((fluoresc* or fundus*) adj2 (angiograph* or contrast* or imag* or scan* or photo* or exam* or test* or auto-fluorescen* or autofluorescen*)).tw. 1050
7 fluoroangiograph*.tw. 0
8 (Ultra-wide* or Ultrawide* or UWF or UWFA).tw. 68
9 (slit lamp adj2 (bio-microscop* or biomicroscop* or microscop* or exam* or test*)).tw. 88
10 slitlamp.tw. 5
11 (BM 900 or BM-900 or BQ 900 or BQ-900 or BX 900 or BX-900).tw. 0
12 Retinal thickness analy*.tw. 0
13 or/5-12 1165
14 4 and 13 71
15 Animals/ not Humans/ 0
16 14 not 15 71
17 limit 16 to english language 69
18 (sensitiv: or diagnos:).mp. or di.fs. 51201
19 Observational Studies as Topic/ 0
20 Observational Study/ 2
21 Epidemiologic Studies/ 0
22 exp Case-Control Studies/ 0
23 exp Cohort Studies/ 0
24 Cross-Sectional Studies/ 0
25 Comparative Study.pt. 0
26 case control$.tw. 2201
27 (cohort adj (study or studies)).tw. 8563
28 cohort analy$.tw. 304
29 (follow up adj (study or studies)).tw. 525

30	(observational adj (study or studies)).tw.	3964
31	longitudinal.tw.	6619
32	prospective.tw.	11012
33	retrospective.tw.	16947
34	cross sectional.tw.	10333
35	or/18-34	86243
36	17 and 35	44

Cost effectiveness searches

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

Limits and restrictions

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

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

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

Search filters

Cost utility

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

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

Cohort studies

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

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

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

Cost effectiveness search strategies

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

Database: EconLit	
1	Diabetic Retinopathy/ 0
2	Macular Edema/ 0

3 (diabet* adj4 (retin* or eye* or macular*)).tw. 14

4 1 or 2 or 3 14

Database: Embase

Cost utility search:

1 diabetic retinopathy/ 45217

2 macular edema/ 5687

3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47443

4 1 or 2 or 3 65931

5 cost utility analysis/ 10912

6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 26154

7 ((incremental* adj2 cost*) or ICER).tw. 26757

8 (cost adj2 utilit*).tw. 9655

9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 2715

10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 31906

11 (cost and (effect* or utilit*)).ti. 51363

12 or/5-11 81030

13 4 and 12 417

14 nonhuman/ not human/ 4929899

15 13 not 14 415

16 (conference abstract or conference paper or conference proceeding or "conference review").pt. 5091583

17 15 not 16 302

Cohort studies:

1 diabetic Retinopathy/ 45440

2 macular Edema/ 5828

3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47762

4 or/1-3 66388

5 cohort analysis/ 811098

6 Retrospective study/ 1206857

7 Prospective study/ 748103

8 (Cohort adj (study or studies)).tw. 380594

9 (cohort adj (analy* or regist*)).tw. 16437

10 (follow up adj (study or studies)).tw. 68508

11 longitudinal.tw. 384899

12 prospective.tw. 981024

13 retrospective.tw. 1068301

14 or/5-13 3358085

15 4 and 14 13743

16 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ 1511773

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

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

19 european union/ 29144

20 developed country/ 34415

21	or/17-20	3576072
22	16 not 21	1373176
23	15 not 22	12938
24	limit 23 to english language	12133
25	nonhuman/ not human/	4938000
26	24 not 25	12067
27	Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt.	7072757
28	26 not 27	8733
29	limit 28 to dc=20120101-20220228	6467

Database: 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

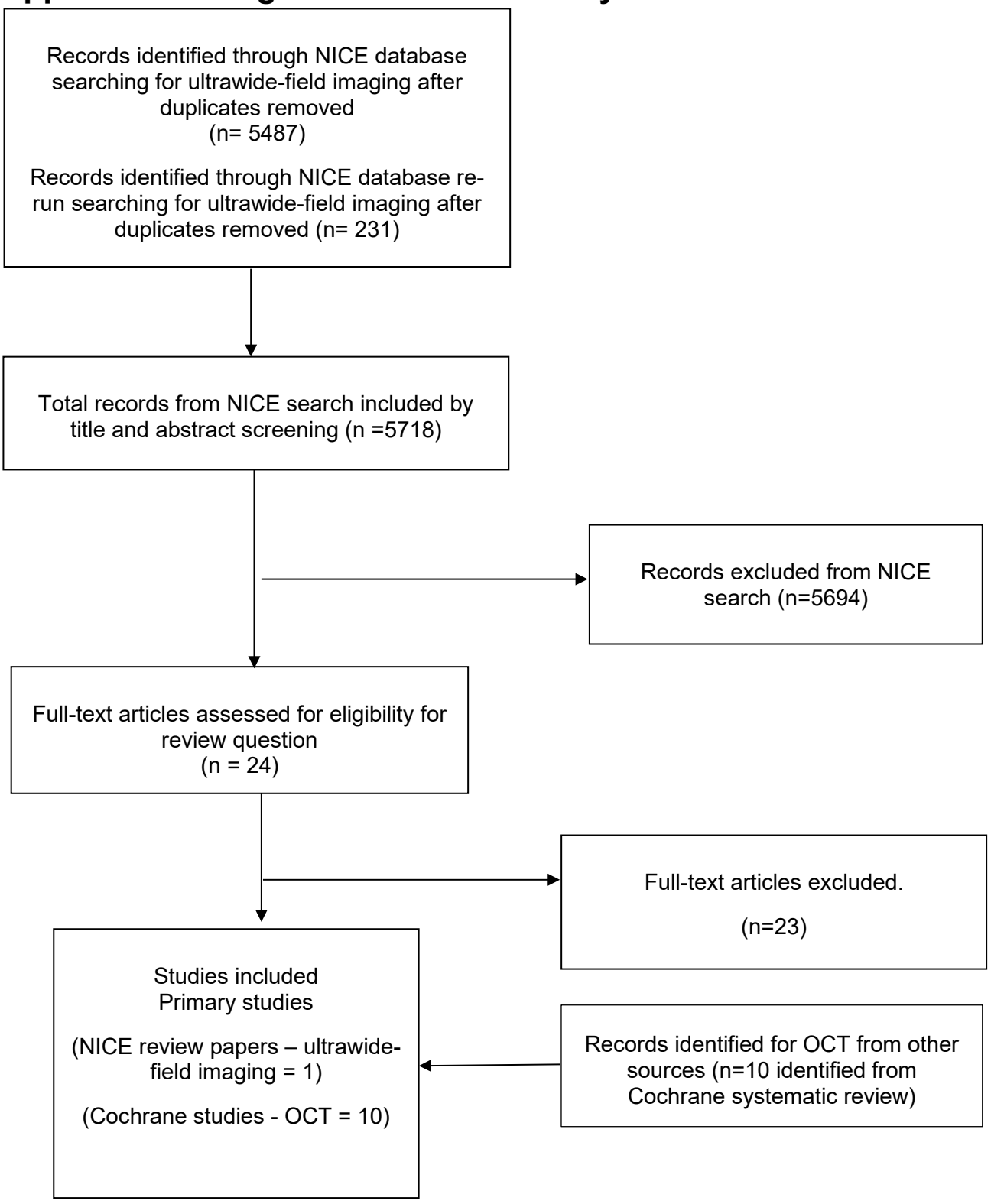
Cohort studies:

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 –Diagnostic evidence study selection



Appendix D –Diagnostic evidence

Ultrawide-field fundus imaging for the detection of proliferative diabetic retinopathy in people with previously treated diabetic retinopathy

Primary study

Lois, 2021

Bibliographic Reference	Lois, Noemi; Cook, Jonathan; Wang, Ariel; Aldington, Stephen; Mistry, Hema; Maredza, Mandy; McAuley, Danny; Aslam, Tariq; Bailey, Clare; Chong, Victor; Ghanchi, Faruque; Scanlon, Peter; Sivaprasad, Sobha; Steel, David; Styles, Caroline; Azuara-Blanco, Augusto; Prior, Lindsay; Waugh, Norman; Multimodal imaging interpreted by graders to detect re-activation of diabetic eye disease in previously treated patients: the EMERALD diagnostic accuracy study.; Health technology assessment (Winchester, England); 2021; vol. 25 (no. 32); 1-104

Study Characteristics

Study type	Cross-sectional study Multicentre, case-referent, cross-sectional, diagnostic accuracy study from a prospectively recruited cohort
Study details	Study location UK Setting 13 hospitals Study dates: Participants were recruited between October 26, 2017, and June 7, 2019. Sources of funding The EMERALD study was funded by the Health Technology Assessment of the National Institute for Health Research in the United Kingdom (identifier, 13/142/04).
Inclusion criteria	• Adults with diabetes • Previously treated for proliferative diabetic retinopathy • Successful treatment, in 1 or both eyes. Successful treatment = at the last visit in clinic, no further treatment had been indicated by the treating ophthalmologists because of lack of activity of PDR
Exclusion criteria	• Unable to speak or understand English • Unable to provide informed consent

Number of participants	281
Index test(s)	Ophthalmic graders referral for PDR based on ultra-widefield fundus images (referral included people who had active PDR, where the grader was unsure, or where images were ungradable)
Reference standard (s)	Standard care pathway: Standard-of-Care Pathway (Reference Standard). The standard-of-care pathway for PDR was the current standard of care: face-to-face evaluation of patients by ophthalmologists using slit-lamp biomicroscopy. Active or inactive PDR were judged by ophthalmologists based on clinical examination
Subgroup analyses	Referral for PDR based on UWF **Sensitivity analysis (SENA) 1** Index: Ophthalmic graders identified active PDR based on ultra-widefield fundus images Reference: Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye **Additional (post-hoc) analysis 1** Index: Ophthalmic assessment identified active PDR based on ultra-widefield fundus images Reference: Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye **SENA2** Index: Ophthalmic graders referral for PDR based on ultrawide-field fundus images Reference: Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye requiring treatment **SENA4** Index: Ophthalmic graders referral for PDR based on ultrawide-field fundus images Reference: Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR with preretinal or vitreous haemorrhage in either eye **Additional 2**

	Index: Ophthalmologist assessment identified active PDR based on ultra-widefield fundus images Reference: Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR with preretinal or vitreous haemorrhage in either eye **SENA6** Index: Ophthalmic graders referral for PDR based on ultra-widefield fundus images in routine clinic Reference: Ophthalmologist face-to-face clinical evaluation using slit-lamp biomicroscopy to assess active PDR in either eye in routine clinic **Other subgroups** Other subgroup analyses were included in the study (SENA 5 and Additional 3) but these were not included in this review as they did not match the inclusion criteria in the protocol. SENA 5 used an enhanced reference standard which included ultrawide-field fundus imaging (the index test in this review) and Additional 3 used a reference standard that also included ultrawide-field fundus imaging.
Additional comments	Other subgroups were reported for people with diabetic macular oedema, but these were not extracted for analysis in this evidence review, as the part of this review for people with macular oedema was covered by the Cochrane review.

Study arms

Patients have inactive PDR (N = 170)

Patients have active PDR (N = 111)

Study-level characteristics

Characteristic	Study (N = 281)
% Female	34
18-59	148
60 and older	133
White	234
Black	19

Characteristic	Study (N = 281)
Asian	20
Middle Eastern	5
Other	3

Critical appraisal - QUADAS-2 checklist

Section	Question	Answer
Overall risk of bias	Risk of Bias	Low
Overall directness	Directness	Directly applicable

OCT for the detection of macular oedema and clinically significant macular oedema for people with diabetic retinopathy

Systematic review

Virgili et al., 2015

Bibliographic Reference	Gianni Virgili, Francesca Menchini, Giovanni Casazza, Ruth Hogg, Radha R Das, Xue Wang AMM; Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy; 2015

Study Characteristics

Study design	Systematic review
Study details	Dates searched Until June 2013 Databases searched Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA) and the NHS Economic Evaluation Database (NHSEED) , Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to June 2013), EMBASE (January 1950 to June 2013), Web of Science Conference Proceedings Citation Index - Science (CPCI-S) (January 1990 to June 2013), BIOSIS Previews (January 1969 to June 2013), MEDION and the Aggressive Research Intelligence Facility database (ARIF Sources of funding None relevant
Inclusion criteria	Prospective and retrospective consecutive series of patients and case-control studies that evaluated the accuracy of OCT for diagnosing DMO or CSMO in people with diabetic retinopathy who were referred to eye clinics
Exclusion criteria	Case control studies
Intervention(s)	Index test: OCT, regardless of the generation of development of the instrument (low or high resolution, three-dimensional or spectral-domain OCTs) Reference standard: Stereoscopic fundus photography and contact lens or non-contact lens biomicroscopy of the fundus
Outcome(s)	Sensitivity

	Specificity Likelihood ratios
Number of studies included in the systematic review	10
Studies from the systematic review that are relevant for use in the current review	Brown 2004 Browning 2004 Campbell 2007 Davis 2008 Goebel 2006 Hee 1998 Medina 2012 Nunes 2010 Sadda 2006 Strom 2002
Studies from the systematic review that are not relevant for use in the current review	None - all are relevant and included in the NICE review

Systematic review risk of bias assessment (ROBIS)

Virgili G, Menchini F, Casazza G, Hogg R, Das RR, Wang X, Michelessi M. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. Cochrane Database Syst Rev. 2015 Jan 7;1:CD008081	
Overall study rating	High
Applicability	Directly applicable
Additional comments:	Link to review: Virgili et al. 2015

Primary studies

Evidence tables for the primary studies in the OCT review can be found in the Characteristics of included studies section of the Cochrane review (Virgili et al. 2015).

Appendix E – Forest plots

E.1.1 Ultrawide-field fundus imaging for the detection of proliferative diabetic retinopathy in people with previously treated diabetic retinopathy.

Ultra-wide fundus photography:

Figure 1: Sensitivity: Ultrawide-field fundus imaging vs Slit lamp biomicroscopy.

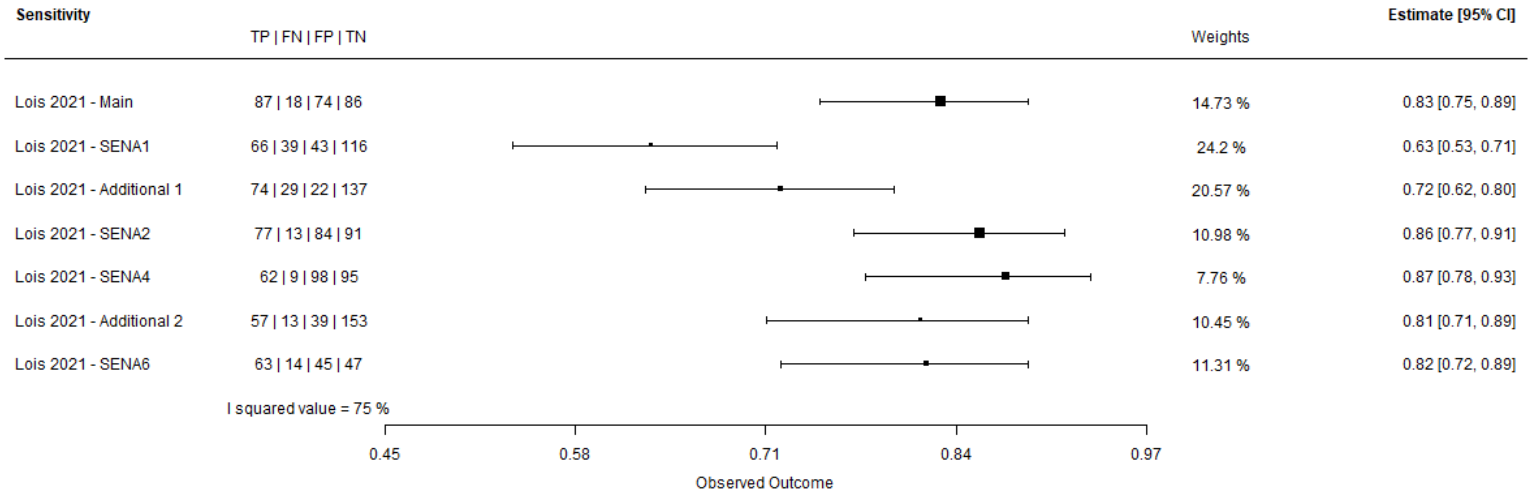


Figure 2: Specificity: Ultrawide-field fundus imaging photography vs Slit lamp biomicroscopy.

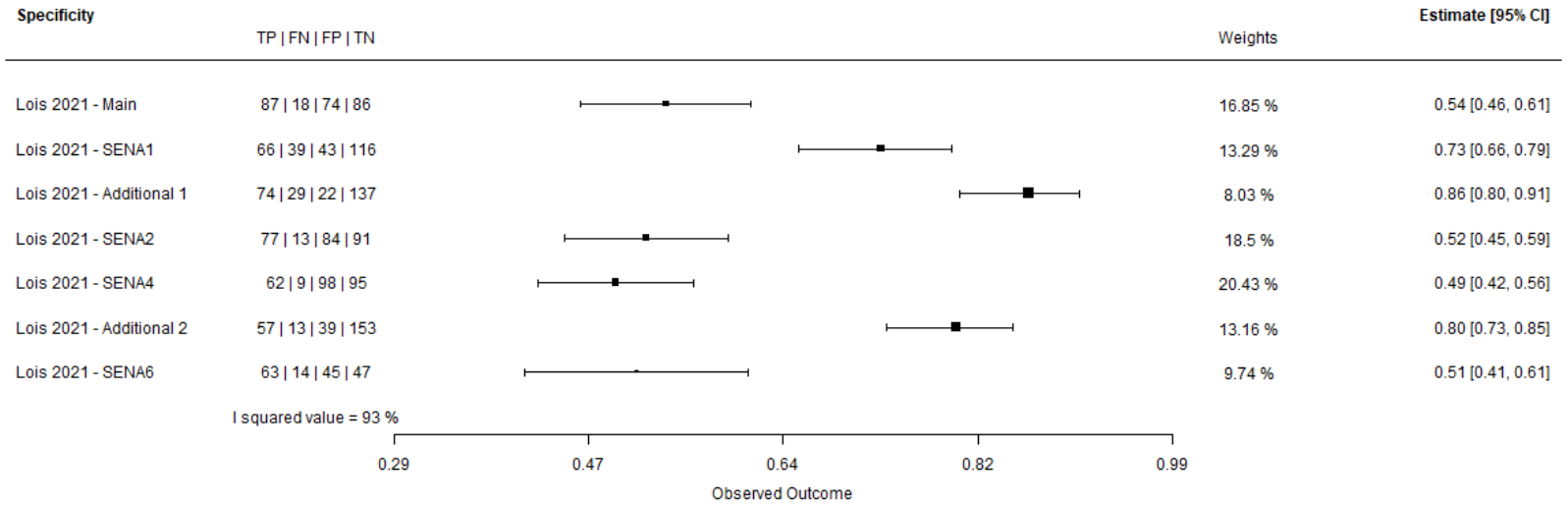


Figure 3: Positive likelihood ratios: Ultrawide-field fundus imaging vs Slit lamp biomicroscopy.

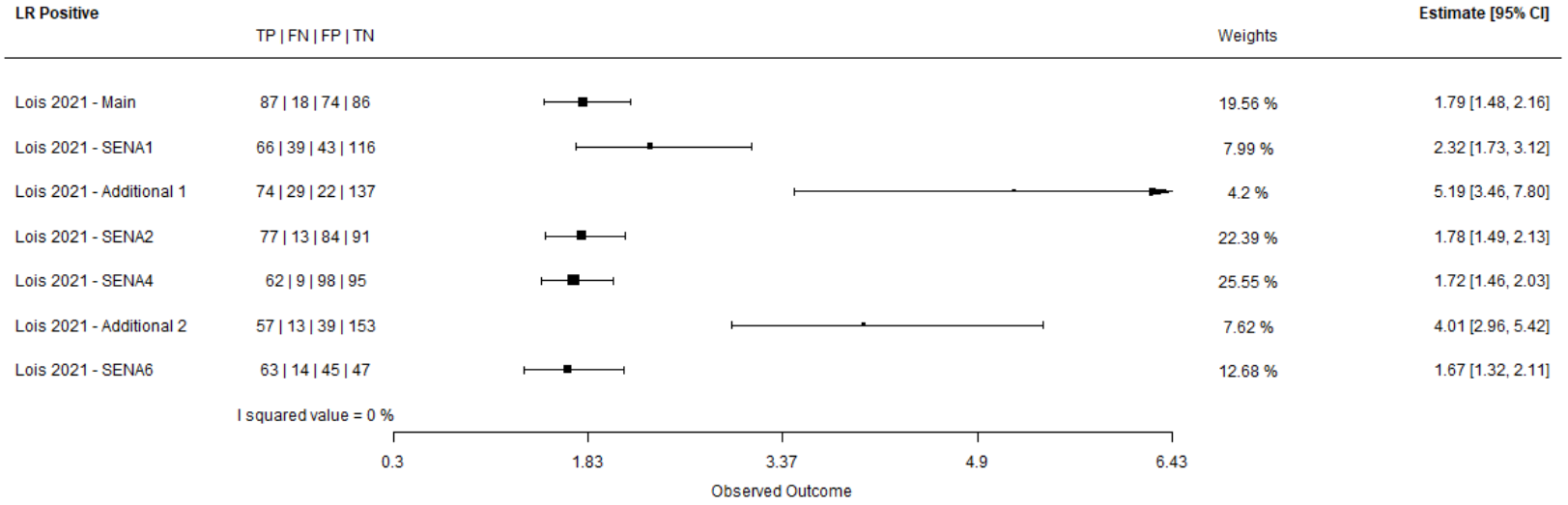
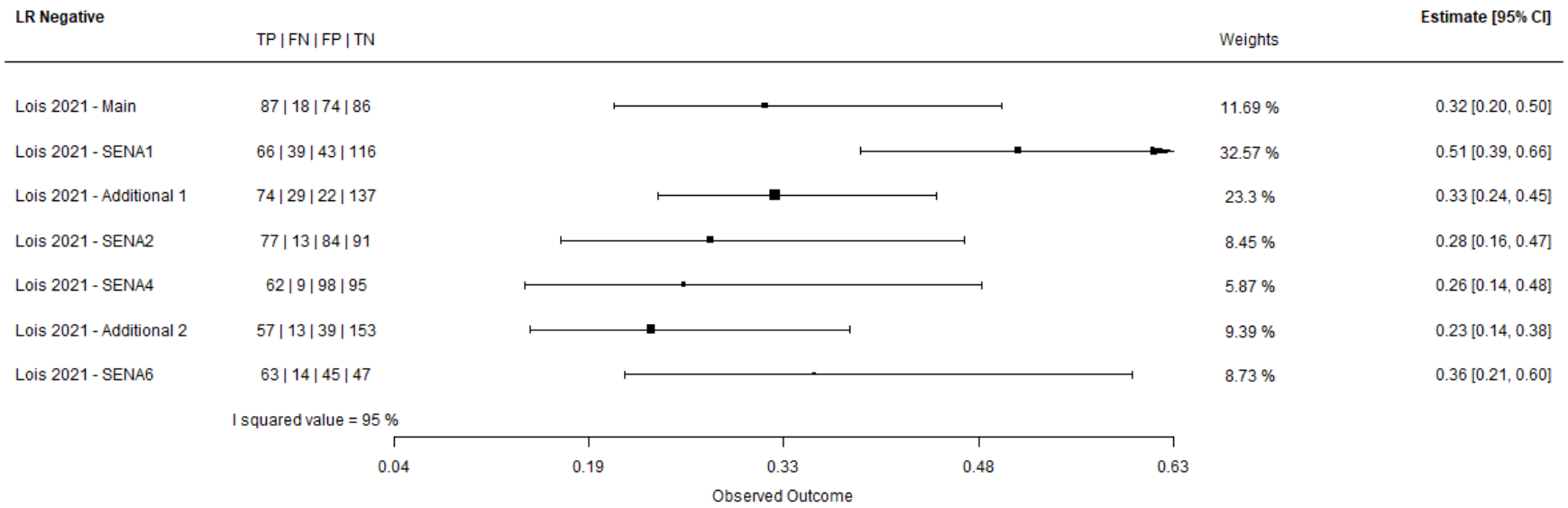


Figure 4: Negative likelihood ratios: Ultrawide-field fundus imaging vs Slit lamp biomicroscopy.



E.1.2 OCT for the detection of macular oedema or clinically significant macular oedema for people with diabetic retinopathy – from Cochrane review (Virgili et al. 2015)

Optical coherence tomography:

Forest plots for OCT data can be found in Figure 3 (Detection of clinically significant diabetic macular oedema) and Figure 5 (Detection of diabetic macular oedema) in the Cochrane review at: Virgili et al. 2015.

Appendix F – GRADE tables

F.1.1 Ultrawide-field fundus imaging for the detection of proliferative diabetic retinopathy in people with previously treated diabetic retinopathy.

UWF Photography vs slit lamp biomicroscopy.

Interpretation of effect: A positive likelihood ratio greater than 1 indicates an increase in the probability of disease, while a negative likelihood ratio less than 1 indicates a decrease in the probability of disease.

PDR – Proliferative diabetic retinopathy

Studies	Study design	N	Sensitivity	Specificity	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)	Risk of bias	Directness	Inconsistency	Quality
Main analysis (Ophthalmic graders referral for PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists)										
1 (Lois 2021)	Cross-sectional	265	0.83 (0.75, 0.89)	0.54 (0.46, 0.61)	1.79 (1.48, 2.16)	0.32 (0.20, 0.50)	not serious	not serious	NA[1]	High
SENA1 (Ophthalmic graders identified active PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists to identify active PDR)										
1 (Lois 2021)	Cross-sectional	264	0.63 (0.53, 0.71)	0.73 (0.66, 0.79)	2.32 (1.73, 3.12)	0.51 (0.39, 0.66)	not serious	not serious	NA[1]	High
Additional 1 (Ophthalmologist assessment identifying active PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists to identify active PDR)										

Studies	Study design	N	Sensitivity	Specificity	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)	Risk of bias	Directness	Inconsistency	Quality
1 (Lois 2021)	Cross-sectional	262	0.72 (0.62 , 0.80)	0.86 (0.80 , 0.91)	5.19 (3.46 ,7.80)	0.33 (0.24 , 0.45)	not serious	not serious	NA[1]	High
SENA 2 (Ophthalmic graders referral for PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists to identify active PDR)										
1 (Lois 2021)	Cross-sectional	265	0.86 (0.77 , 0.91)	0.52 (0.45 , 0.59)	1.78 (1.49 , 2.13)	0.28 (0.16, 0.47)	not serious	not serious	NA[1]	High
SENA4 (Ophthalmic graders referral for PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists to assess active PDR with preretinal or vitreous haemorrhage)										
1 (Lois 2021)	Cross-sectional	264	0.87 (0.78, 0.93)	0.49 (0.42 , 0.56)	1.72 (1.46 , 2.03)	0.26 (0.14, 0.48)	not serious	not serious	NA[1]	High
Additional 2 (Ophthalmologist identified active PDR based on ultrawide-field fundus images vs slit lamp biomicroscopy by ophthalmologists to assess active PDR with preretinal or vitreous haemorrhage)										
1 (Lois 2021)	Cross-sectional	262	0.81 (0.71 , 0.89)	0.80 (0.73 , 0.85)	4.01 (2.96 , 5.42)	0.23 (0.14 , 0.38)	not serious	not serious	NA[1]	High
SENA6 (Ophthalmic graders referral for PDR based on ultrawide-field fundus images in routine clinic vs slit lamp biomicroscopy by ophthalmologists to assess active PDR in routine clinic)										
1 (Lois 2021)	Cross-sectional	169	0.82 (0.72 , 0.89)	0.51 (0.41 , 0.61)	1.67 (1.32, 2.11)	0.36 (0.21, 0.60)	not serious	not serious	NA[1]	High

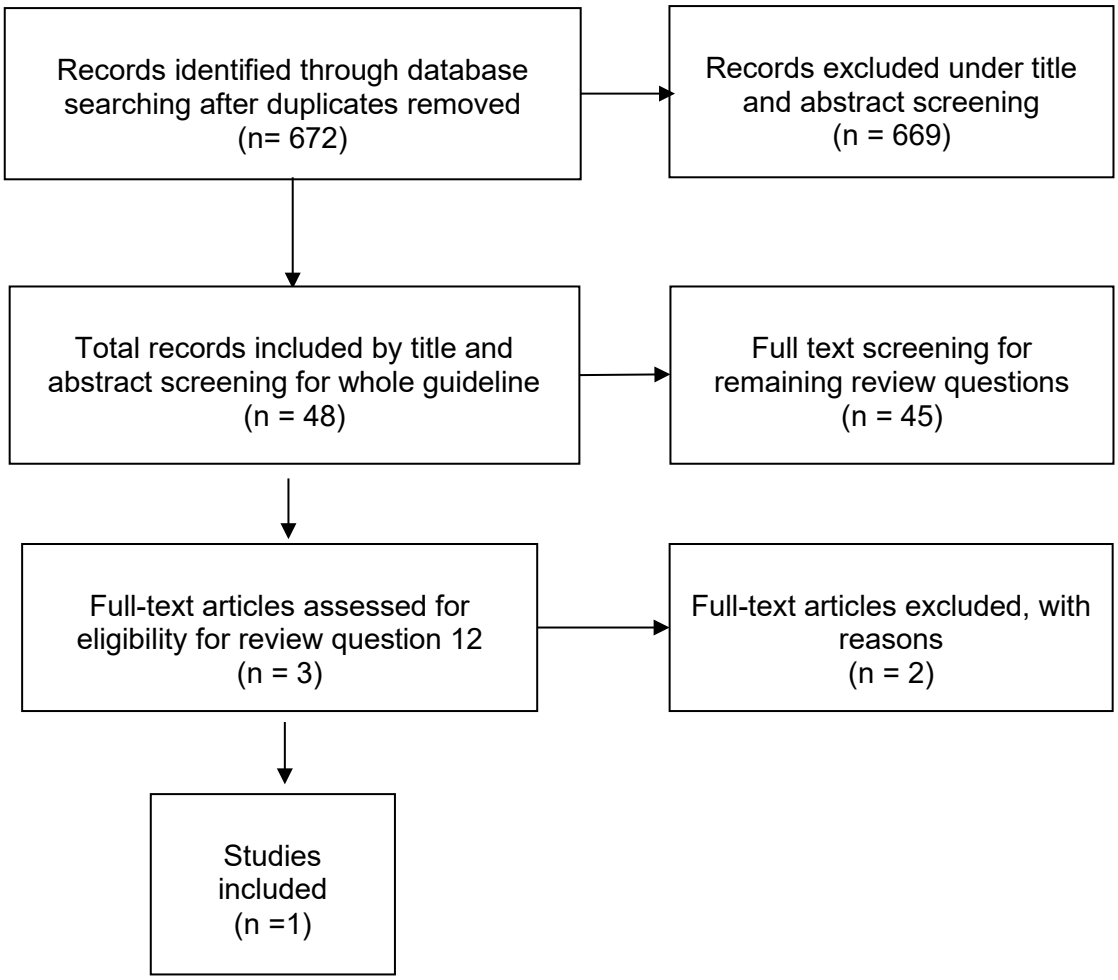
1. Only 1 study so no inconsistency

F.1.2 OCT for the detection of macular oedema or clinically significant macular oedema for people with diabetic retinopathy – from Cochrane review (Virgili et al. 2015)

Optical coherence tomography:

GRADE tables for OCT can be found in the summary of findings table (page 42) in the Cochrane review at the following link: Virgili et al. 2015

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Table 10: Economic evidence table

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
Lois et al (2021)	Economic analysis: Cost-consequence (outcomes were sensitivity and specificity of the imaging routes)	Setting: UK Perspective: NHS and PSS	Standard of care: ophthalmologist face-to-face examination with slit-lamp microscopy (and OCT for DMO) Interventions: PDR: Ultrawide-field imaging assessed by graders DMO: OCT assessed by graders	People with previously treated proliferative diabetic retinopathy and people with previously treated diabetic macular oedema	Discount rate: 3.5% per year Cost-consequence analysis based on evidence from the EMERALD clinical trial in PDR and in DMO Cost differences calculated per 100 patients based on sensitivity and specificity Costs based on the different equipment costs and the time estimated each staff level may take to estimate the costs associated with staff time based on the staff costs obtained from the PSSRU. Equipment costs consisted of	PDR Cost savings per 100 patients: Ultrawide-field imaging compared with Standard of care: £1,189 Sensitivity: Standard of care: assumed 100% Ultrawide-field imaging: sensitivity: 82% Specificity: Standard of care: assumed 100% Ultrawide-field imaging: 54% DMO Cost savings per 100 patients: OCT compared with Standard of care: £1,390 Sensitivity: Standard of care: assumed 100% OCT: 97% Specificity:	PDR Scenario 1: When the diagnostic performance of graders was assessed based on active PDR only, specificity improved but sensitivity was reduced, meaning more patients with active disease would be missed. Scenario 2: Grader pathway assessed by how well identified eyes requiring treatment. Sensitivity increased to 86% and specificity reduced to 54% with a cost saving compared with standard care of £1,131 DMO: In sensitivity analyses there were no significant differences found in	The costs in the grader pathway considered the specificity to calculate the costs of individuals who would still be referred to an ophthalmologist for monitoring after having been assessed by the grader.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					acquisition and maintenance costs divided by the expected lifetime of equipment and estimates of usage.	Standard of care: assumed 100% OCT: 31% Costs were driven by the number of ophthalmologist referrals avoided.	the sensitivity of grader-assessed OCT, but the specificity varied from 21% to 56% which would subsequently change the amount of cost savings associated with using graders.	

Table 11: Quality checklist

Study identification **Lois et al (2021) Multimodal imaging interpreted by graders to detect re-activation of diabetic eye disease in previously treated patients: the EMERALD diagnostic accuracy study**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	Study included people who had previously received treatment for diabetic retinopathy or diabetic macular oedema. The results are disaggregated by condition.
1.2 Are the interventions appropriate for the review question?	Partly	Standard of care of slit-lamp examination undertaken by ophthalmologist and ultrawide-field fundus photographs by trained ophthalmic graders. The Emerald study also included seven field ETDRS fundus photographs which was not included as an intervention within the review question protocol
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	NHS
1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS and personal social services perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	NHS and personal social services perspective, however cost consequence analysis
1.6 Are all future costs and outcomes discounted appropriately?	No	It was unclear how discounting was applied in the analysis as costs and outcomes are applied at one time point. From the results tables it did not appear that “future costs” of referral to ophthalmologists were applied in future.
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).	Not applicable	EQ-5d-5L scores, NEI VFQ-25 and VisQoL scores collected, however QALYs were not included as the main outcome
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	No model, uses staff time to identify the cost of each intervention and the specificity and sensitivity

Study identification Lois et al (2021) Multimodal imaging interpreted by graders to detect re-activation of diabetic eye disease in previously treated patients: the EMERALD diagnostic accuracy study		
Category	**Rating**	**Comments**
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	The analysis only looked at the costs of the imaging visits and the immediate consequences (sensitivity and specificity of tests, and whether people would be referred to further ophthalmology monitoring)
2.3 Are all important and relevant outcomes included?	No	QALYs were not included as specificity and sensitivity of tests was the main outcome. Future costs such as those associated with undetected disease were not included in the analysis. Only costs of imaging and monitoring were included.
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Clinical trial (EMERALD)
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	Clinical trial (EMERALD)
2.6 Are all important and relevant costs included?	No	Future costs associated with consequences of lower sensitivity and specificity were not included in the analysis
2.7 Are the estimates of resource use from the best available source?	Yes	Clinical trial (EMERALD)
2.8 Are the unit costs of resources from the best available source?	Yes	Staff costs were taken from nationally available sources (PSSRU, Pay and Conditions Circular) and equipment costs (i.e. cost of testing) were the purchase prices of the imaging equipment, alongside clinical expert estimates of use.
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	No	No incremental analysis was presented as the comparisons were pairwise, and an incremental analysis would not have been interpretable given the outcomes were sensitivity and specificity.
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analysis
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Appendix I – Health economic model

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

Appendix J – Excluded studies

Diagnostic evidence

Study	Reason
Ahsan, S., Haseeb, U., Memon, M.S. et al. (2022) Validity of Hand Held Fundus Camera by Optometrist using Slit lamp 90D bio microscopy as a reference standard for screening of Diabetes Retinopathy. Journal of the Pakistan Medical Association 72(11): 2189-2192	- Study does not contain ultrawide-field fundus photography *Hand held fundus camera is 50 degrees*
Ashraf, M., AbdelAl, O., Shokrollahi, S. et al. (2023) Evaluation of diabetic retinopathy severity on ultrawide field colour images compared with ultrawide fluorescein angiograms. The British journal of ophthalmology	- Does not contain a population of people with non-proliferative/proliferative diabetic retinopathy or diabetic macular oedema *People with type 1 or type 2 diabetes but not necessarily diabetic retinopathy*
Ashraf, Mohamed, Sampani, Konstantina, AbdelAl, Omar et al. (2020) Disparity of microaneurysm count between ultrawide field colour imaging and ultrawide field fluorescein angiography in eyes with diabetic retinopathy. The British journal of ophthalmology 104(12): 1762-1767	- No Primary outcomes *not looking at DTA outcomes*
Chen, A., Dang, S., Chung, M.M. et al. (2021) Quantitative Comparison of Fundus Images by 2 Ultra-Widefield Fundus Cameras. Ophthalmology Retina 5(5): 450-457	- Not a DTA or case-control study *Image comparison not DTA*
Cui, Ying, Zhu, Ying, Wang, Jay C et al. (2021) Comparison of widefield swept-source optical coherence tomography angiography with ultra-widefield colour fundus photography and fluorescein angiography for detection of lesions in diabetic retinopathy. The British journal of ophthalmology 105(4): 577-581	- Comparator in study does not match that specified in protocol *Detection of lesions, this combined with study design mean it doesn't match protocol.*
de Sonnaville, J J, van der Feltz van der Sloot, D, Ernst, L et al. (1996) Retinopathy screening in type 2 diabetes: reliability of wide angle fundus photography. Diabetic medicine : a journal of the British Diabetic Association 13(5): 482-6	- Study does not contain ultrawide-field fundus photography *60 degree = wide photo, not ultra-wide*
Fan, Zhun, Rong, Yibiao, Cai, Xinye et al. (2018) Optic Disk Detection in Fundus Image Based on Structured Learning. IEEE journal of biomedical and health informatics 22(1): 224-234	- Study does not contain ultrawide-field fundus photography

Study	Reason
Gunay, M., Tugcugil, E., Somuncu, A.M. et al. (2022) The clinical use of ultra - Wide field imaging and intravenous fluorescein angiography in infants with retinopathy of prematurity. Photodiagnosis and Photodynamic Therapy 37: 102658	- Does not contain a population of people with non-proliferative/proliferative diabetic retinopathy or diabetic macular oedema *No Diabetic retinopathy*
Hadziahmetovic, M., Nicholas, P., Jindal, S. et al. (2019) Evaluation of a Remote Diagnosis Imaging Model vs Dilated Eye Examination in Referable Macular Degeneration. JAMA Ophthalmology 137(7): 802-808	- Study does not contain ultrawide-field fundus photography *Normal fundus photography*
Haridas, Swathy, Indurkhya, Swati, Kumar, Sailesh et al. (2022) Sensitivity and specificity of pseudocolor ultrawide field imaging in comparison to wide field fundus fluorescein angiography in detecting retinal neovascularization in diabetic retinopathy. Eye (London, England) 36(10): 1940-1944	- Study does not contain ultrawide-field fundus photography *Index test does not match as UWP retinal photography being used to diagnose microvascularisation in diabetic retinopathy, not DR itself.*
Hussain, N., Edraki, M., Tahhan, R. et al. (2017) Telemedicine for diabetic retinopathy screening using an ultra-widefield fundus camera. Clinical Ophthalmology 11: 1477-1482	- Comparator in study does not match that specified in protocol *No clear comparison*
Khan, Rehana, Raman, Sundaresan, Karamcheti, Sri Krishna M et al. (2021) Comparison of Two Ultra-Widefield Cameras With High Image Resolution and Wider View for Identifying Diabetic Retinopathy Lesions. Translational vision science & technology 10(12): 9	- Comparator in study does not match that specified in protocol *Not looking at Classifying DR but at lesion detection.*
Kleinstein, R N, Roseman, J M, Herman, W H et al. (1987) Detection of diabetic retinopathy by optometrists. Journal of the American Optometric Association 58(11): 879-82	- Study does not contain ultrawide-field fundus photography *standard fundus photography*
Ku, Janice J-Y, Landers, John, Henderson, Tim et al. (2013) The reliability of single-field fundus photography in screening for diabetic retinopathy: the Central Australian Ocular Health Study. The Medical journal of Australia 198(2): 93-6	- Study does not contain ultrawide-field fundus photography *single field 60 degree photography*
Li, Jie, Wei, Dingyang, Mao, Mingzhu et al. (2022) Ultra-widefield color fundus photography combined with high-speed ultra-widefield swept-source optical coherence tomography angiography for non-invasive detection of	- Comparator in study does not match that specified in protocol *Not strictly a DTA. Doesn't stratify solely between UWF and FA*

Study	Reason
lesions in diabetic retinopathy. Frontiers in public health 10: 1047608	
Lim, Wei Sing, Grimaldi, Gabriela, Nicholson, Luke et al. (2021) Widefield imaging with Clarus fundus camera vs slit lamp fundus examination in assessing patients referred from the National Health Service diabetic retinopathy screening programme. Eye (London, England) 35(1): 299-306	- Does not contain a population of people with non-proliferative/proliferative diabetic retinopathy or diabetic macular oedema *People with type 1 or type 2 diabetes but not necessarily diabetic retinopathy*
Purbrick, R.M.J., Izadi, S., Gupta, A. et al. (2014) Comparison of Optomap ultrawide-field imaging versus slit-lamp biomicroscopy for assessment of diabetic retinopathy in a real-life clinic. Clinical Ophthalmology 8: 1413-1417	- Does not contain a population of people with non-proliferative/proliferative diabetic retinopathy or diabetic macular oedema *People with type 1 or type 2 diabetes but not necessarily diabetic retinopathy*
Roychowdhury, Sohini, Koozekanani, Dara D, Kuchinka, Sam N et al. (2016) Optic Disc Boundary and Vessel Origin Segmentation of Fundus Images. IEEE journal of biomedical and health informatics 20(6): 1562-1574	- Study does not contain ultrawide-field fundus photography
Rudnisky, Christopher J, Hinz, Brad J, Tennant, Matthew T S et al. (2002) High-resolution stereoscopic digital fundus photography versus contact lens biomicroscopy for the detection of clinically significant macular edema. Ophthalmology 109(2): 267-74	- Study does not contain ultrawide-field fundus photography *no ultrawide (30 degree)*
Spooner, K., Phan, L., Cozzi, M. et al. (2021) Comparison between two multimodal imaging platforms: Nidek Mirante and Heidelberg Spectralis. Graefe's Archive for Clinical and Experimental Ophthalmology 259(7): 1791-1802	- Does not contain a population of people with non-proliferative/proliferative diabetic retinopathy or diabetic macular oedema *Not looking specifically at DR pop*
Stino, Heiko, Riessland, Susanna, Sedova, Aleksandra et al. (2022) Comparison of two ultra-widefield color-fundus imaging devices for visualization of retinal periphery and microvascular lesions in patients with early diabetic retinopathy. Scientific reports 12(1): 17449	- No relevant primary outcomes

Optical coherence tomography

For excluded studies, see the excluded studies list in the Cochrane review (Virgili et al. 2015).

Economic evidence

Study	Reason
Leal, Jose, Luengo-Fernandez, Ramon, Stratton, Irene M et al. (2019) Cost-effectiveness of digital surveillance clinics with optical coherence tomography versus hospital eye service follow-up for patients with screen-positive maculopathy. Eye (London, England) 33(4): 640-647	- Exclude - not relevant intervention - Exclude - cost comparison only
Porta, M, Rizzitiello, A, Tomalino, M et al. (1999) Comparison of the cost-effectiveness of three approaches to screening for and treating sight-threatening diabetic retinopathy. Diabetes & metabolism 25(1): 44-53	- Exclude - screening population only

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

For people who are under the care of hospital eye services, what is the diagnostic test accuracy of ultrawide-field fundus imaging for diagnosing the progression of diabetic retinopathy to proliferative diabetic retinopathy?

K.1.2 Why this is important

Unmonitored progression of non-proliferative diabetic retinopathy to proliferative diabetic retinopathy can lead to sight loss if not found early. The eye screening test can identify clinical features before they become sight threatening. With increasing technology there have been new diagnostic tools being increasingly used to confirm the presence or absence of proliferative diabetic retinopathy. It is important to establish which of these are the most effective.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	There is uncertainty on the best methods of monitoring people who have non-proliferative diabetic retinopathy and are under hospital services. These people may progress without appropriate diagnosis at the time that they develop proliferative diabetic retinopathy ..
Relevance to NICE guidance	NICE guidance looked at the diagnostic accuracy of tools to detect proliferative diabetic retinopathy. However no evidence was available for people with non-proliferative diabetic retinopathy. This is an important population of people accessing services recommended by NICE.
Relevance to the NHS	Timely and accurate diagnosis would mean people can access timely treatment and preserve their vision for longer.
National priorities	Moderate
Current evidence base	No data for people with non-proliferative diabetic retinopathy was identified.
Equality considerations	None known

K.1.4 Modified PICO table

Population	People diagnosed with non-proliferative and proliferative diabetic retinopathy, who are not having treatment and have not been previously treated (treatment-naïve patients)
Index test	Ultrawide-field fundus imaging

Reference standard	• Ultrawide-field angiography • Combination of Fundus photography and Fluorescein angiography • Fluorescein angiography • Slit lamp bio-microscopy Combination of reference standards (slit lamp, ultrawide-field photography and angiography)
Outcome measures	• Diagnostic accuracy (Sensitivity, specificity, LR+, LR-)
Study design	Diagnostic test accuracy study
Timeframe	Long term (10 years)
Additional information	None