National Institute for Health and Care Excellence

Guideline version (Draft)

Diabetic Retinopathy: management and monitoring

[J] Evidence reviews for the effectiveness of different monitoring frequencies

NICE guideline <number>

Evidence reviews underpinning recommendations 1.3.1 to 1.3.2, 1.4.9 to 1.4.12 and 1.5.16 to 1.5.17 and research recommendations in the NICE guideline

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Draft for Consultation

These evidence reviews were developed by Guideline Development Team

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Evidence review for effectiveness of different monitoring frequencies

1.1 Review question

What is the effectiveness of different monitoring frequencies for people with non-proliferative diabetic retinopathy whose care is managed under the hospital eye services but who are not having treatment?

What is the effectiveness of different monitoring frequencies for people with proliferative diabetic retinopathy or diabetic macular oedema who are receiving treatment or have had previous treatment?

1.1.1 Introduction

Diabetic retinopathy is a significant cause of vision loss in adults. The risk of the development and progression of non-proliferative retinopathy to macular oedema or vision-threatening proliferative diabetic retinopathy requires timely intervention to improve patient outcomes and reduce the risk of loss of vision.

Early detection of disease progression can play a significant role in timely treatment. Current recommendations in the Royal College of Ophthalmologists guidelines (2012) include 4-6 monthly monitoring for people with moderately severe to very severe non-proliferative retinopathy. The aim of this review was to establish the risks and benefits of different monitoring frequencies to effectively detect potentially vision-threatening changes in:

- People with moderate, severe, and very severe non-proliferative diabetic retinopathy without macular oedema, whose care is managed under hospital eye services.
- People with proliferative diabetic retinopathy or diabetic macular oedema who are receiving treatment or have had previous treatment**.**

The protocols for the evidence reviews are summarised in Table 1. Please see full protocols in Appendix A.

1.1.2 Summary of the protocol

Table 1: PICO for people with non-proliferative diabetic retinopathy

Population	People with moderate, severe, and very severe non-proliferative diabetic retinopathy, without macular oedema who are not receiving treatment.
Interventions	Increased/decreased monitoring frequency relative to standard monitoring
Comparator	Standard monitoring frequency (as defined by the study)
Outcomes	**Primary outcomes** • Progression to proliferative diabetic retinopathy • Progression to macular oedema **Secondary outcomes** • Best corrected visual acuity • Peripheral vision, assessed using visual field measurement • Quality of life, measured using a validated tool (the overall score as well as mental health domain scores will be reported separately) • Adherence (defined as mean percentage of monitoring visits attended)

	Outcomes will be reported at the latest time point reported by the study.

Table 2: PICO for people with proliferative diabetic retinopathy or diabetic macular oedema

Population	People with proliferative diabetic retinopathy or diabetic macular oedema who are receiving or who have received treatment
Interventions	Increased/decreased monitoring frequency relative to standard monitoring
Comparator	Standard monitoring frequency (as defined by the study)
Outcomes	**Primary outcomes** • Best corrected visual acuity *Population with proliferative diabetic retinopathy:* • Progression to macular oedema *Population with macular oedema:* • Recurrence of macular oedema following treatment • Progression to macular ischaemia **Secondary outcomes** • Peripheral vision, assessed using visual field measurement • Quality of life, measured using a validated tool (the overall score as well as mental health domain scores will be reported separately) • Adherence (defined as mean percentage of monitoring visits attended) *Population with proliferative diabetic retinopathy:* • progression to diabetic macular ischaemia • progression to proliferative diabetic retinopathy in fellow eye *Population with diabetic macular oedema:* • progression to diabetic macular oedema in fellow eye • progression to proliferative diabetic retinopathy in either eye Outcomes will be reported at the latest time point reported by the study.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual and the methods document for the diabetic retinopathy guideline.

Declarations of interest were recorded according to NICE's conflicts of interest policy. Methods specific to this review question are described in the review protocol in Appendix A. Additionally:

- A modified version of the NICE economics studies checklist was used to critically appraise modelling studies. Items 1.4, 1.6, 1.7, 2.6, 2.7, 2.8 and 2.9 were removed as they relate to economic aspects which are not applicable to this review.
- A modified GRADE approach was used to assess the certainty in the evidence from modelling studies. The approach to GRADE for assessing the effectiveness of interventions outlined in the methods document for the diabetic retinopathy guideline was used, with the exception that evidence from modelling studies was started with a GRADE rating of 'high'.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A single systematic literature search was conducted to cover both review questions. The search included randomised controlled trials (RCTs), comparative observational studies and modelling studies comparing monitoring frequencies. No date limit was applied, and the search yielded 2,686 references. These were screened on title and abstract, with 38 full-text papers ordered as potentially relevant studies.

Studies were excluded if they did not match the protocol outlined in Appendix A.

A single paper (DCCT/EDIC Research, 2017) was included after full text screening for the review question on monitoring frequencies for non-proliferative diabetic retinopathy. No studies were included for the review question on monitoring frequencies for proliferative diabetic retinopathy or diabetic macular oedema.

For the study selection process, please see PRISMA flow diagram in Appendix C

For the full evidence tables and full GRADE profiles for included studies, please see Appendix D and Appendix E.

1.1.4.2 Excluded studies

See Appendix I for a list of excluded studies with reasons for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 3:Studies included in the effectiveness evidence

Short Title	Title	Study characteristics	Outcomes
DCCT/EDIC Research, 2017 United States and Canada	Frequency of Evidence-Based Screening for Retinopathy in Type 1 Diabetes.	Study type Modelling study, A longitudinal Markov model Study dates from 1983 - 1989 Sources of funding (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; DCCT/EDIC ClinicalTrials.gov numbers, NCT00360893 and NCT00360815.) The DCCT enrolled 1441 patients with type 1 diabetes who were 13 to 39 years of age. • The primary prevention cohort (726 patients) had diabetes for 1 to 5 years and no retinopathy detected by means of stereoscopic fundus photography at baseline. • The secondary intervention cohort (715 patients) had diabetes for 1 to 15 years and very mild to moderate non-proliferative diabetic retinopathy Duration of follow-up: A maximum of 28.7 years of follow-up (mean, 23.5 years) Inclusion criteria People with minimal background retinopathy) Duration of IDDM between 1-15 years, Presence of at least one microaneurysm in either eye with or without other diabetes-related lesions, but less retinopathy than that which would characterize either eye as P2 or worse based on central grading of stereo fundus photographs using ETDRS standards, Visual acuity of 45 letters (20/32	Study (N = 1441) Progression from Lower Levels of Retinopathy (States 1 through 4) to State 5 Retinopathy (Proliferative Diabetic Retinopathy or Clinically Significant Macular Oedema) State 3 to State 5 (N = not reported) State 3 -corresponds to moderate non-proliferative diabetic retinopathy, State 4 -corresponds to severe non-proliferative diabetic retinopathy State 5 - Corresponded to any of the following: proliferative diabetic retinopathy, clinically significant macular oedema, or previous self-reported treatment with panretinal or focal photocoagulation, intraocular glucocorticoids, or anti-VEGF agents State 4 to State 5 (N = not reported) State 4 -corresponds to severe non-proliferative diabetic retinopathy State 5 - Corresponded to any of the following: proliferative diabetic retinopathy, clinically significant macular oedema, or previous self-reported treatment with panretinal or focal photocoagulation, intraocular glucocorticoids, or anti-VEGF agents Modelled screening Intervals: • 1,2,3,6,9 Months • 1,2,3,4,5 Years

Short Title	Title	Study characteristics	Outcomes
		Snellen equivalent) or better in both eyes., Less than or equal to 200 mg albumin/24 h on a 4-h urine collection, Basal plasma C-peptide <0.2 pmol/ml and for patients with duration >5 yr, stimulated plasma C-peptide <0.2 pmol/ml. Only a subset of this population matches the review protocol (people with moderate, severe, or very severe diabetic retinopathy). However, results were presented separately for progression from moderate and severe retinopathy and so these data were included in the review. Exclusion criteria The presence of diabetic retinopathy sufficient to categorize either eye as P2 or worse based on central grading of stereo fundus photographs. Eyes with new vessels were classified worse than P2. Eyes without new vessels that met any one of the three criteria listed below were classified as P2. Standard photos referred to below are those of the Modified Airlie House Classification. (a) Soft exudates (SE), venous beading (VB), and intraretinal microvascular abnormalities (IRMA) were each definitely present in at least two of fields 4 through 7. (b) Two of the above three lesions (SE, VB, or IRMA) were present in at least two of fields 4 through 7, and haemorrhages/ microaneurysms (HMa) were present in all four fields, equalling or exceeding standard photograph 2A in at least one of them. (c) IRMA were present in all four of these fields and were equal to or exceeded standard photograph 8A in at least two of them.	

67 See Appendix D for full evidence tables.

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1.1.6 Summary of the Effectiveness evidence

Probability over a given follow-Up interval of progression from lower levels of retinopathy to higher grade of retinopathy

Table 4:Modelled risk of progression from moderate diabetic retinopathy to proliferative retinopathy or clinically significant macular oedema

No. of studies	Risk of progression between monitoring visits in percent (95% CI)	Quality	Interpretation of effects
Interval of Follow-Up - 1 month			
1 study	1.1 (0–1.3)	Low	1.1% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 1-month interval.
Interval of Follow-Up - 2 month			
1 study	2.3 (2.0–2.6)	Low	2.3% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 2-month interval.
Interval of Follow-Up - 3 month			
1 study	3.4 (3.1–3.8)	Low	3.4% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a3-month interval.
Interval of Follow-Up – 6 months			
1 study	6.6 (6.0–7.3)	Low	6.6% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after 6-month interval.
Interval of Follow-Up - 9 month			
1 study	9.6 (8.8–10.5)	Low	9.6% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 9-month interval.
Interval of Follow-Up - 1 Year			
1 study	12.3 (11.3–13.5)	Low	12.3% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 1-year interval.
Interval of Follow-Up – 2 Year			
1 study	20.5 (18.9–22.3)	Low	20.5% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 2-year interval.
Interval of Follow-Up - 3 Year			
1 study	25.9 (23.9–28.2)	Low	25.9% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 3-year interval.
Interval of Follow-Up - 4 Year			

No. of studies	Risk of progression between monitoring visits in percent (95% CI)	Quality	Interpretation of effects
1 study	29.7 (27.6–32.2)	Low	29.7% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 4 -year interval.
Interval of Follow-Up - 5 Year			
1 study	32.5 (30.2–35.3)	Low	32.5% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 5 -year interval.

Table 5: Modelled risk of progression from severe diabetic retinopathy to proliferative retinopathy or clinically significant macular oedema

No. of studies	Risk of progression between monitoring visits in percent (95% CI)	Quality	Interpretation of effect
Interval of Follow-Up - 1 month			
1 study	5.7 (3.6–8.8)	Low	5.7% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 1-month interval.
Interval of Follow-Up - 2 month			
1 study	10.4 (6.5–16.0)	Low	10.4% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 2-month interval.
Interval of Follow-Up - 3 month			
1 study	14.4 (9.4–22.0)	Low	14.4% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 3-month interval.
Interval of Follow-Up – 6 months			
1 study	23.0 (15.8–32.7)	Low	23.0% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 6-month interval.
Interval of Follow-Up - 9 month			
1 study	28.6 (20.9–38.4)	Low	28.6% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after 9-month interval.
Interval of Follow-Up - 1 Year			
1 study	32.5 (23.8–44.2)	Low	32.5% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after 1-year interval.
Interval of Follow-Up – 2 Year			

1 study	41.2 (32.6–50.6)	Low	41.2% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 2-year interval.
Interval of Follow-Up - 3 Year			
1 study	45.9 (38.2–55.7)	Low	45.9% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 3-year interval.
Interval of Follow-Up - 4 Year			
1 study	49.0 (42.0–58.0)	Low	49% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 4-year interval.
Interval of Follow-Up - 5 Year			
1 study	51.3 (44.6–60.8)	Low	51.3% chance of progressing to proliferative retinopathy or clinically significant macular oedema if the next examination is conducted after a 5-year interval.

76 See Appendix E 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, 670 of the studies could confidently be excluded for these questions. Two studies were excluded following the full-text review. No relevant health economic studies were included.

1.1.7.2 Excluded studies

See Appendix I for excluded studies and reasons for exclusion.

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

1.1.8 Summary of included economic evidence

No relevant health economic studies were identified to be included.

1.1.9 Economic model

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

1.1.10 Unit costs

Table 6: Unit cost of screening visits

Resource	Unit cost	Source
Diabetic eye screening visit	£38.34	Cost of screening within the diabetic eye service. Scanlon et al (2015): £32 (2012/2013 prices) inflated to 2019/2020 prices.
Monitoring visit during treatment	£101.80	NHS Reference Costs 2019/2020. Consultant led non-admitted face-to-face attendance, follow-up. Code 130 (ophthalmology). Assumption used in TA294.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee agreed that progression to proliferative diabetic retinopathy was an important outcome in people diagnosed with non-proliferative diabetic retinopathy because this can have very serious consequences, including retinal detachment and irreversible and severe vision loss, if not treated. Other outcomes were also considered to be important (progression of diabetic macular oedema, best corrected visual acuity, peripheral vision, adherence, and health related quality of life) but no evidence was found for these outcomes. The committee wanted the data to be separated by subgroups including pregnancy, age, and severity of disease, however the evidence available did not allow for stratification by subgroups.

1.1.11.2 The quality of the evidence

Only one study was identified for people with non-proliferative retinopathy that matched the review protocol. The quality of the evidence for the outcomes was low, with the main reasons for downgrading being a lack of information on whether the models adjusted for confounders and the data not allowing for stratification by risk factors.

The data reported combined progression of proliferative diabetic retinopathy and diabetic macular oedema as one outcome and there was no information on the relative proportions of people with the two outcomes. The committee considered this a major limitation because delaying treatment for proliferative diabetic retinopathy has more serious consequences than delaying treatment for diabetic macular oedema. Delaying treatment for proliferative diabetic retinopathy can result in retinal detachment and irreversible sight loss. Delaying treatment for diabetic macular oedema could also result in sight loss, but this is likely to be less severe and reversible in comparison to sight loss secondary to proliferative diabetic retinopathy.

The committee were also concerned that the lack of clarity on whether the model was stratified by those who received intensive glycaemic control intervention and those that received no treatment.

The evidence was downgraded for indirectness as the population in the study was limited to people with type 1 diabetes. However, the committee agreed that they did not expect a large difference in outcomes between people with type 1 and type 2 diabetes.

No evidence was identified on the effectiveness of different monitoring frequencies for people who are receiving treatment or who have previously received treatment for proliferative diabetic retinopathy or diabetic macular oedema.

1.1.11.3 Imprecision and the clinical importance of effects

The evidence identified was modelled based on a large sample, and so the 95% confidence intervals were narrow enough to allow useful comparisons between monitoring frequencies. As noted in the section above, the committee found it difficult to determine what percentage of progression between monitoring visits would be acceptable because of the composite nature of the outcome and the different clinical consequences of progression to proliferative diabetic retinopathy and diabetic macular oedema.

1.1.11.4 Benefits and harms

The committee discussed that monitoring is needed to check for disease progression that requires treatment, so that treatment can begin promptly if progression occurs. They also noted that people with diabetic retinopathy and diabetic macular oedema often attend a large number of hospital appointments to manage their diabetes care. They often have other diabetes-related complications that also require hospital visits, and so it is important to make sure that monitoring is not more frequent than necessary to reduce this burden.

Non-proliferative retinopathy

Based on their expertise and the modelling evidence, the committee made different recommendations, depending on severity of disease and risk of progression. The committee made a weaker ‘consider’ recommendation based on the limitations in the evidence that was identified in the quality of the evidence section. However, it should be noted that the choice of consider rather than offer in this recommendation is in relation to the frequency of monitoring, rather than the need for any monitoring at all. It was decided that the recommendations should

be separated by people who have moderate non-proliferative retinopathy and those with severe to very severe non-proliferative diabetic retinopathy. People who have moderate non-proliferative diabetic retinopathy can be seen less frequently, with lower risk of progression between appointments, while those who have severe or very severe non-proliferative diabetic retinopathy will need more frequent appointments.

The committee discussed monitoring every 6-12 months for people with moderate non-proliferative retinopathy who are not being currently treated or have not been previously treated. It was noted that people under hospital eye services who are not receiving treatment occupy a lot of clinic time. It was agreed that progression of disease in this population is relatively slow and the evidence indicates that a 6–12-month window means that people have between 6.6% (6.0%-7.3%) and 12.3% (11.3%-13.5%) chance of progressing to proliferative retinopathy or clinically significant macular oedema between appointments. The committee thought that 6-12 months between appointments is therefore appropriate and should not allow for any major progression of the disease between appointments.

The committee agreed that people with severe or very severe non-proliferative diabetic retinopathy who are not being currently treated should be seen more frequently, as they are more at risk of progression than those who have moderate non-proliferative retinopathy. They noted that this group have a 14.4% (9.4%-22.0%) chance of progression if they have monitoring appointments every 3 months. It was highlighted that more frequent appointments would further reduce the risk of progression. For instance, appointments every 2 months would mean that someone only had a 10.4% (6.5%-16.0%) chance of progression. However, the committee were concerned that it may not be practical to see all of these patients more frequently than every 3 months. They also discussed how people with diabetic retinopathy have to attend a number of different appointments including these monitoring appointments for their eye disease as well as appointments for other complications associated with their diabetes. As such, very frequent appointments might be unmanageable for some people. Three months was therefore considered an appropriate follow-up time. It was also highlighted that while 3 months is ideal, some people will still not be able to attend appointments this frequently and might instead be at risk of missing appointments, which would have a greater impact on progression than less frequent monitoring. The committee therefore decided that monitoring should take place between 3 and 6 months for this group, giving a maximum risk of 23% (15.8%-32.7%) chance of progression between appointments. This time scale also reflects current practice.

Due to the limited evidence to inform recommendations on the timing of monitoring, the committee also made a research recommendation on the most effective monitoring frequencies for people with non-proliferative retinopathy who have not started treatment. The ideal study design to inform this research would be a randomised controlled trial comparing outcomes in people monitored at different frequencies. However, such a study would be difficult to carry out because it would need long follow up times and people may need to be allocated to follow up intervals that are longer than current practice. Modelling studies that report data on progression of diabetic retinopathy and diabetic macular oedema would therefore be a feasible alternative. For details of the research recommendation see Appendix J.

Proliferative retinopathy and diabetic macular oedema

No evidence was found for people who have proliferative diabetic retinopathy or diabetic macular oedema. The committee noted that monitoring during treatment would be determined by the treatment protocol and so did not make recommendations for this area. However, the committee agreed that some guidance would be useful for monitoring frequency after

treatment is completed. This was based on their clinical experience that an appropriate monitoring time can vary between individuals depending on their risk factors for progression, and the need to ensure that appointments are not so frequent that there is the risk of non-attendance. After 12 months, they thought the risk of progression was lower and therefore this is an appropriate time to consider discharge back to hospital services.

The committee agreed that people who have received treatment for proliferative diabetic retinopathy or diabetic macular oedema, whose disease has regressed should be monitored under the care of hospital eye services for 12 months. They specified that the frequency of monitoring during this time should be individualised depending on the treatment that had been given and on a person's response to treatment. The committee also agreed that after 12 months, people who have had treatment for proliferative diabetic retinopathy or diabetic macular oedema whose disease has regressed can be discharged back to the diabetic retinopathy annual screening programme. Those that have features that would prompt immediate re-referral to hospital eye services should remain under the care of hospital eye services for monitoring. Based on their clinical knowledge and experience the committee decided that monitoring every 12 months would be appropriate in this case.

Given the lack of evidence, the committee made a second research recommendation for people with proliferative diabetic retinopathy or diabetic macular oedema who have previously received treatment (see Appendix J). This should enable future guidelines to make more precise recommendations on the most effective monitoring frequencies.

1.1.11.5 Cost effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost effectiveness of different monitoring frequencies for people with a diagnosis of non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, or diabetic macula oedema. The committee noted that patients with a non-proliferative diabetic retinopathy diagnosis make up a large proportion of those seen within clinic, which led to the research recommendation being made for this population. The committee agreed that the recommendations made to monitor disease progression would not be expected to have a resource impact as they reflect current practice.

The committee discussed assessing disease regression in people who have received treatment for proliferative retinopathy or diabetic macular oedema would happen within a monitoring visit 2-3 months after treatment has ended. The committee discussed this currently happens within clinical practice and would not expect a resource impact other than improving consistency of practice across the country.

The committee discussed people with proliferative diabetic retinopathy or diabetic macula oedema whose disease has regressed or resolved after treatment and noted that they should still be monitored for twelve months to ensure any progression of disease is captured early. The committee also agreed that after 12 months people should be discharged back to the diabetic screening programme, however if the persons retina has features that make them ineligible for the screening programme they should continue to be monitored under the care of hospital eye services every 12 months. This is not expected to be a change in practice, and if implemented consistently may lead to a reduction in monitoring visits as only those whose disease has not improved would continue to be monitored after 12 months. Additionally any early signs of disease progression would likely be detected and lead to prompt treatment rather than more intensive treatment later when the persons disease has progressed further.

1.1.11.6 Other factors the committee took into account

The committee did not review any evidence that allowed them to clearly differentiate and stratify evidence for people 18 and under or pregnant women. However, the committee agreed that the same recommendations should apply to people under 18 as, although risk of developing diabetic retinopathy is lower in this group, if it is identified it should be monitored in the same way. The committee noted that there are existing recommendations on monitoring diabetic retinopathy in pregnancy in the NICE's guideline on diabetes in pregnancy, so they agreed to refer to this guideline.

The committee were also aware of the recommendations in the Royal College of Ophthalmologists guidelines (2012) for 4-6 monthly monitoring for people with moderately severe to very severe non-proliferative retinopathy. The NICE recommendations are broadly in line with those recommendations, although they acknowledge that some people with severe to very severe non-proliferative diabetic retinopathy could benefit from monitoring as often as every 3 months. The committee also thought it was important to highlight that some of the people who are within the recommendation from the Royal College of Ophthalmologists, but who have the least severe disease, may not need to be seen as frequently as every 6 months. For this reason, they thought the additional recommendation for monitoring every 6-12 months for people who have moderate non-proliferative diabetic retinopathy was important.

1.1.12 Recommendations supported by this evidence review

This evidence review supports Recommendations 1.3.1 to 1.3.2, 1.4.9 to 1.4.12 and 1.5.16 to 1.5.17 and the research recommendations on monitoring frequencies for people with non-proliferative diabetic retinopathy who are not receiving treatment, and for people with proliferative diabetic retinopathy or diabetic macular oedema who have received treatment.

1.1.13 References – included studies

1.1.13.1 Clinical evidence

DCCT/EDIC Research, Group, Nathan, David M, Bebu, Ionut et al. (2017) Frequency of Evidence-Based Screening for Retinopathy in Type 1 Diabetes. The New England journal of medicine 376(16): 1507-1516

Appendices

Appendix A – Review protocols

Review protocol for the most effective monitoring frequencies for people diagnosed with non-proliferative diabetic retinopathy whose care is managed under the hospital eye services but who are not having treatment

ID	Field	Content
0.	PROSPERO registration number	CRD42022335361
1.	Review title	Frequency of monitoring for people with non-proliferative diabetic retinopathy whose care is managed under the hospital eye services but who are not having treatment
2.	Review question	What is the effectiveness of different monitoring frequencies for people with non-proliferative retinopathy whose care is managed under the hospital eye services but who are not having treatment?
3.	Objective	To determine what are the most effective monitoring frequencies for people diagnosed with moderate, severe, or very severe non-proliferative diabetic retinopathy without macular oedema, who are not having treatment. The aim is to inform recommendations for people managed under hospital eye services and this population broadly matches that group.
4.	Searches	The following databases will be searched for the clinical review: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • HTA (legacy records)

		• INAHTA • MEDLINE • Medline in Process • Medline EPub Ahead of Print For the economics review the following databases will be searched on population only: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA Searches will be restricted by: • Studies reported in English • Study design RCT, observational and prognostic filters will be applied, with additional terms to ensure that modelling studies are identified. • 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: People with moderate, severe, and very severe non-proliferative diabetic retinopathy (according to the early treatment of diabetic retinopathy study (ETDRS) classification) without macular oedema who are not receiving treatment. The population specified in the scope of the guideline is limited to people cared for under hospital eye services for management of their diabetic retinopathy. The population in this review broadly matches this group, as people with mild diabetic retinopathy would not usually be cared for under hospital eye services in the UK, Studies with mixed populations will be included if more than 50% meet the inclusion criteria.
7.	Intervention	Increased/decreased monitoring frequency relative to standard monitoring

8.	Comparators	Standard monitoring frequency (as defined by the study): Note that standard monitoring frequencies are recommended in existing Royal college of Ophthalmology guidelines (2012) as follows: - Annual monitoring (moderate non-proliferative retinopathy) - 4-6 monthly monitoring (severe or very severe non-proliferative retinopathy)
9.	Types of study to be included	- Randomised controlled trials - Comparative observational studies - Modelling studies comparing monitoring frequencies
10.	Other exclusion criteria	• Studies that were not reported in English • Studies where more than 50% of participants do not match the population described in section 8.
11.	Context	Diabetic retinopathy is an important cause of sight loss in adults in the United Kingdom. The risk of the development and progression of retinopathy can be reduced substantially by intensive glycaemic management. Moreover, if clinically significant macular oedema or proliferative diabetic retinopathy develops, timely intervention with laser photocoagulation or with intraocular glucocorticoids or anti–vascular endothelial growth factor (VEGF) agents can substantially reduce loss of vision. Thus, the goal of retinopathy monitoring is the timely detection of retinopathy or clinically significant macular oedema, both of which require timely intervention to preserve vision.
12.	Primary outcomes (critical outcomes)	• Progression to proliferative diabetic retinopathy o Number of people receiving treatment for proliferative diabetic retinopathy will be extracted as a surrogate measure for this outcome, when the outcome is not reported in a study directly.

		• Progression to macular oedema ○ Number of people receiving treatment for macular oedema will be extracted as a surrogate measure for this outcome, when the outcome is not reported in a study directly.

13.	Secondary outcomes (important outcomes)	• Best corrected visual acuity,
		  ○ Best correct visual acuity will be presented per eye when this data is available in the study.
		  ○ Per patient data will only be extracted when this data is not presented in a study.
		
		• Peripheral vision, assessed using visual field measurement
		• Quality of life, measured using a validated tool (the overall score as well as mental health domain scores will be reported separately)
		• Adherence (defined as mean percentage of monitoring visits attended)
		
		Outcomes will be reported at the latest time point reported by the study.

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 not make use of the priority screening functionality within the EPPI-reviewer software because the database size is expected to be small.10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Extracted information for the quantitative review will include: study type; study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; inclusion and exclusion criteria; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using appropriate checklists as described in Developing NICE guidelines: the manual. Risk of bias in RCTs will be assessed using the Cochrane risk of bias version 2 tool. Risk of bias in comparative observational studies will be assessed using the ROBINS-I checklist.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Where analysis is based on SMDs, effect sizes will be converted back to an interpretable scale to aid interpretation. Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$, when random effects models will be used instead. A modified version of GRADE will be used to assess the quality of the outcomes. Imprecision will not be assessed in the GRADE profile but will be summarised narratively in the committee

		discussion section of the evidence review. Outcomes using evidence from RCTs and comparative observational studies assessed with ROBINS-I will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered.
17.	Analysis of sub-groups	Data will be presented separately for the following groups: • Pregnant women If data is available a subgroup analysis will be conducted by: • Ethnicity • People with a learning disability • Type 1 vs type 2 diabetes • 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)
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery

		☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	April 2022		
22.	Anticipated completion date	April 2024		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐

		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** NICE Guideline Development Team **5b Named contact e-mail** diabeticretinopathy@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and NICE Guideline Development Team		
25.	Review team members	From the Guideline development team: • Kathryn Hopkins • Ahmed Yosef • Syed Mohiuddin • Hannah Lomax • Kirsty Hounsell • Jenny Craven • Jenny Kendrick		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline development team which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of		

		interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10160
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diabetic retinopathy, monitoring frequency
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒Ongoing ☐Completed but not published ☐Completed and published ☐Completed, published and being updated

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

Review protocol for the most effective monitoring frequencies for people diagnosed with proliferative diabetic retinopathy and diabetic macular oedema that are receiving treatment or who have had previous treatment

ID	Field	Content
0.	PROSPERO registration number	CRD42022335370
1.	Review title	Frequency of monitoring for proliferative diabetic retinopathy and diabetic macular oedema
2.	Review question	What is the effectiveness of different monitoring frequencies for people with proliferative or diabetic macular oedema that are receiving treatment or have had previous treatment?
3.	Objective	• To determine what are the most effective monitoring frequencies for people diagnosed with proliferative diabetic retinopathy or macular oedema who are receiving treatment or have had previous treatment
4.	Searches	The following databases will be searched for the clinical review: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • HTA (legacy records) • INAHTA

		• MEDLINE • Medline in Process • Medline EPub Ahead of Print For the economics review the following databases will be searched on population only: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA Searches will be restricted by: • Studies reported in English • Study design RCT, observational and prognostic filters will be applied, with additional terms to ensure that modelling studies are identified. • 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 and macular oedema
6.	Population	Inclusion: People with proliferative diabetic retinopathy or diabetic macular oedema who are receiving or who have received treatment
7.	Intervention	Increased/decreased monitoring frequency relative to standard monitoring (where standard monitoring is as defined by the study)
8.	Comparators	Standard monitoring frequency (as defined by the study)
9.	Types of study to be included	- Randomised controlled trials - Comparative observational studies - Modelling studies comparing monitoring frequencies
10.	Other exclusion criteria	• Trials that were not reported in English • Studies where more than 50% of participants do not match the population described in section 8.
11.	Context	Diabetic retinopathy is an important cause of blindness in adults in the United Kingdom. The risk of the development and progression of retinopathy can be reduced substantially by optimisation of glycaemic control. Moreover, if clinically significant macular oedema or proliferative diabetic retinopathy develops, timely intervention with laser photocoagulation or with intraocular glucocorticoids or anti–vascular endothelial growth factor (VEGF) agents can substantially reduce loss of vision. Thus, the goal of retinopathy monitoring is the timely detection of retinopathy or clinically significant macular oedema, both of which require timely intervention to preserve vision.

12.	Primary outcomes (critical outcomes)	• Best corrected visual acuity
		  ○ Best correct visual acuity will be presented per eye when this data is available in the study.
		  ○ Per patient data will only be extracted when this data is not presented in a study.
		
		Population with proliferative diabetic retinopathy:
		• Progression to macular oedema
		  ○ Number of people receiving treatment for macular oedema will be extracted as a surrogate measure for this outcome, when the outcome is not reported in a study directly.
		
		Population with macular oedema:
		• Recurrence of macular oedema following treatment
		• Progression to macular ischaemia

13.	Secondary outcomes (important outcomes)	• Peripheral vision, assessed using visual field measurement • Quality of life, measured using a validated tool (the overall score as well as mental health domain scores will be reported separately) • Adherence (defined as mean percentage of monitoring visits attended) **Population with proliferative diabetic retinopathy:** • progression to diabetic macular ischaemia • progression to proliferative diabetic retinopathy in fellow eye **Population with diabetic macular oedema:** • progression to diabetic macular oedema in fellow eye • progression to proliferative diabetic retinopathy in either eye Outcomes will be reported at the latest time point reported by the study.
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 not make use of the priority screening functionality within the EPPI-reviewer software because the database size is anticipated to be small.10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Extracted information for the quantitative review will include: study type; study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; inclusion and exclusion criteria; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using appropriate checklists as described in Developing NICE guidelines: the manual. Risk of bias in RCTs will be assessed using the Cochrane risk of bias version 2 tool. Risk of bias in comparative observational studies will be assessed using the ROBINS-I checklist.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Where analysis is based on SMDs, effect sizes will be converted back to an interpretable scale to aid interpretation. Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as I2≥50%, when random effects models will be used instead.

		A modified version of GRADE will be used to assess the quality of the outcomes. Imprecision will not be assessed in the GRADE profile but will be summarised narratively in the committee discussion section of the evidence review. Outcomes using evidence from RCTs and comparative observational studies assessed with ROBINS-I will be rated as high quality initially and downgraded from this point. Reasons for upgrading the certainty of the evidence will also be considered.
17.	Analysis of sub-groups	Data will be presented separately for the following groups: • Pregnant women • Proliferative retinopathy and 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 over 80 • Type 1 vs Type 2 diabetes • severity of proliferative disease
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery

		☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	April 2022		
22.	Anticipated completion date	April 2024		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐

		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** NICE Guideline Development Team **5b Named contact e-mail** Diabeticretinopathy@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and NICE Guideline Development Team		
25.	Review team members	From the Guideline development team: • Kathryn Hopkins • Ahmed Yosef • Syed Mohiuddin • Hannah Lomax • Kirsty Hounsell • Jenny Craven • Jenny Kendrick		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline development team which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a		

		senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10160
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diabetic retinopathy, monitoring, diabetic macular oedema
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated

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

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 May 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:

RCTs

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

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

Observational studies

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

Prognosis

Wilczynski NL, Haynes RB; The Hedges Team. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE. *BMC Medicine*. 2004;2:23 (5 pages). (Sensitive filter)

Clinical search strategies

Database	Date searched	Database Platform	Database segment or version
Cochrane Central Register of Controlled Trials (CENTRAL)	09/05/2022	Wiley	Issue 4 of 12, April 2022
Cochrane Database of Systematic Reviews (CDSR)	09/05/2022	Wiley	Issue 5 of 12, May 2022
Embase	09/05/2022	Ovid	1974 to 2022 May 06
Epistemonikos	09/05/2022	Epistemonikos	Search run on 09 May 2022
HTA	09/05/2022	CRD	Search run on 09 May 2022
INAHTA	09/05/2022	N/A	Search run on 09 May 2022
MEDLINE	09/05/2022	Ovid	1946 to May 06, 2022
MEDLINE-in-Process	09/05/2022	Ovid	1946 to May 06, 2022
MEDLINE ePub Ahead-of-Print	09/05/2022	Ovid	May 06, 2022

Database: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)		
#1	MeSH descriptor: [Diabetic Retinopathy] explode all trees	1543
#2	MeSH descriptor: [Macular Edema] explode all trees	1253
#3	(diabet* NEAR/6 (retin* or eye* or macular*)):ti,ab,kw	5479
#4	#1 or #2 or #3	5915

#5 MeSH descriptor: [Monitoring, Physiologic] this term only 2297
#6 ((increas* or expan* or additional* or raise* or decreas* or reduc* or lower* or fewer* or routine* or standard* or frequen* or regular* or rate or rates or optim* or repeat*) near/4 (monitor* or assess* or surveil* or observ* or exam* or follow-up* or followup* or check-up* or checkup*)):ti,ab,kw 121418
#7 monitor*:ti 10710
#8 #5 or #6 or #7 130743
#9 #4 and #8 568

Database: Embase

1 diabetic retinopathy/46299
2 macular edema/ 6065
3 (diabet* adj6 (retin* or eye* or macular*)).tw. 51110
4 1 or 2 or 3 69496
5 *physiologic monitoring/ 1592
6 ((increas* or expan* or additional* or raise* or decreas* or reduc* or lower* or fewer* or routine* or standard* or frequen* or regular* or rate or rates or optim* or repeat*) adj4 (monitor* or assess* or surveil* or observ* or exam* or follow-up* or followup* or check-up* or checkup*)).tw. 1199787
7 monitor*.ti. 189066
8 or/5-7 1362038
9 4 and 8 4247
10 nonhuman/ not human/ 4999122
11 9 not 10 4009
12 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5193621
13 11 not 12 2889
14 limit 13 to english language 2532
15 random:.tw. 1795360
16 placebo:.mp. 495361
17 double-blind:.tw. 230583
18 or/15-17 2063362
19 Clinical study/ 158254
20 Case control study/ 188544
21 Family study/25437
22 Longitudinal study/ 173116
23 Retrospective study/ 1252946
24 comparative study/ 952485
25 Prospective study/ 769147
26 Randomized controlled trials/ 227608
27 25 not 26 760188
28 Cohort analysis/ 848023
29 cohort analy$.tw. 16609

30	(Cohort adj (study or studies)).tw.	394965
31	(Case control$ adj (study or studies)).tw.	158090
32	(follow up adj (study or studies)).tw.	69385
33	(observational adj (study or studies)).tw.	217674
34	(epidemiologic$ adj (study or studies)).tw.	116057
35	(cross sectional adj (study or studies)).tw.	290372
36	case series.tw.	129967
37	prospective.tw.	1000579
38	retrospective.tw.	1099175
39	or/19-24,27-38	4842516
40	incidence.sh.	502975
41	exp mortality/	1249456
42	follow-up studies.sh.	107
43	prognos:.tw.	1076751
44	predict:.tw.	2497220
45	course:.tw.	922391
46	exp statistical model/	264359
47	or/40-46	5459526
48	18 or 39 or 47	10015884
49	14 and 48	1637

Database: Epistemonikos

(title:(Diabetic retinopath* OR macular edema OR macular oedema) OR abstract:(Diabetic retinopath* OR macular edema OR macular oedema))
AND
(title:(increas* OR expan* OR additional* OR raise* OR decreas* OR reduc* OR lower* OR fewer* OR routine* OR standard* OR frequen* OR regular* OR rate OR rates OR optim* OR repeat*) OR abstract:(increas* OR expan* OR additional* OR raise* OR decreas* OR reduc* OR lower* OR fewer* OR routine* OR standard* OR frequen* OR regular* OR rate OR rates OR optim* OR repeat*))
AND
(title:(monitor* OR assess* OR surveil* OR observ* OR exam* OR follow-up* OR followup* OR check-up* OR checkup*) OR abstract:(monitor* OR assess* OR surveil* OR observ* OR exam* OR follow-up* OR followup* OR check-up* OR checkup*))

Database: Health Technology Assessment (HTA)

1	MeSH DESCRIPTOR Diabetic Retinopathy EXPLODE ALL TREES	118
2	MeSH DESCRIPTOR Macular Edema EXPLODE ALL TREES	82
3	((diabet* NEAR (retin* or eye* or macular*)))	225
4	#1 OR #2 OR #3	254

5	MeSH DESCRIPTOR Monitoring, Physiologic EXPLODE ALL TREES 814	
6	(((increas* or expan* or additional* or raise* or decreas* or reduc* or lower* or fewer* or routine* or standard* or frequen* or regular* or rate or rates or optim* or repeat*) near (monitor* or assess* or surveil* or observ* or exam* or follow-up* or followup* or check-up* or checkup*)))	5168
7	(monitor*):TI	632
8	#5 OR #6 OR #7	6056
9	#4 AND #8	32
10	* IN HTA	17351
11	#9 AND #10	5

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

9	#8 AND #4	34
8	#7 OR #6 OR #5	5872
7	(monitor*)[Title]	334
6	((increas* or expan* or additional* or raise* or decreas* or reduc* or lower* or fewer* or routine* or standard* or frequen* or regular* or rate or rates or optim* or repeat*) AND (monitor* or assess* or surveil* or observ* or exam* or follow-up* or followup* or check-up* or checkup*))	5674
5	"Monitoring, Physiologic"[mh]	98
4	#3 OR #2 OR #1	94
3	(diabet* AND (retin* or eye* or macular*))	86
2	"Macular Edema"[mh]	27
1	"Diabetic Retinopathy"[mh]	40

Database: Ovid MEDLINE(R)

1	Diabetic Retinopathy/	27983
2	Macular Edema/	8360
3	(diabet* adj6 (retin* or eye* or macular*)).tw.	32187
4	1 or 2 or 3	42461
5	*Monitoring, Physiologic/	24687
6	((increas* or expan* or additional* or raise* or decreas* or reduc* or lower* or fewer* or routine* or standard* or frequen* or regular* or rate or rates or optim* or repeat*) adj4 (monitor* or assess* or surveil* or observ* or exam* or follow-up* or followup* or check-up* or checkup*)).tw.	727003
7	monitor*.ti.	125252
8	or/5-7	845800
9	4 and 8	2271
10	Animals/ not Humans/	4981528

11	9 not 10	2120
12	limit 11 to english language	1910
13	randomized controlled trial.pt.	569781
14	randomi?ed.mp.	918499
15	placebo.mp.	216917
16	or/13-15	974298
17	Observational Studies as Topic/	7900
18	Observational Study/	128156
19	Epidemiologic Studies/	9109
20	exp Case-Control Studies/	1326798
21	exp Cohort Studies/	2356876
22	Cross-Sectional Studies/	428798
23	Controlled Before-After Studies/	697
24	Historically Controlled Study/	222
25	Interrupted Time Series Analysis/	1631
26	Comparative Study.pt.	1911177
27	case control$.tw.	130722
28	case series.tw.	75221
29	(cohort adj (study or studies)).tw.	237550
30	cohort analy$.tw.	9042
31	(follow up adj (study or studies)).tw.	49568
32	(observational adj (study or studies)).tw.	117817
33	longitudinal.tw.	251700
34	prospective.tw.	585638
35	retrospective.tw.	567724
36	cross sectional.tw.	374325
37	or/17-36	4916008
38	incidence.sh.	293225
39	exp mortality/	418318
40	follow-up studies.sh.	685518
41	prognos:.tw.	614514
42	predict:.tw.	1555912
43	course:.tw.	598843
44	exp models, statistical/	444625
45	or/38-44	3770251
46	16 or 37 or 45	7480858
47	12 and 46	1355

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*)).tw.	5
4	1 or 2 or 3	5

5	*Monitoring, Physiologic/	0
6	((increas* or expan* or additional* or raise* or decreas* or reduc* or lower* or fewer* or routine* or standard* or frequen* or regular* or rate or rates or optim* or repeat*) adj4 (monitor* or assess* or surveil* or observ* or exam* or follow-up* or followup* or check-up* or checkup*)).tw.	270
7	monitor*.ti.	38
8	or/5-7	305
9	4 and 8	1
10	Animals/ not Humans/	0
11	9 not 10	1
12	limit 11 to english language	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*)).tw.	568
4	1 or 2 or 3	568
5	*Monitoring, Physiologic/	0
6	((increas* or expan* or additional* or raise* or decreas* or reduc* or lower* or fewer* or routine* or standard* or frequen* or regular* or rate or rates or optim* or repeat*) adj4 (monitor* or assess* or surveil* or observ* or exam* or follow-up* or followup* or check-up* or checkup*)).tw.	12487
7	monitor*.ti.	1757
8	or/5-7	13968
9	4 and 8	27
10	Animals/ not Humans/	0
11	9 not 10	27
12	limit 11 to english language	27

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-Feb-22	OVID	<1886 to February 13, 2022>
Embase (filters applied: specific cost utility filter, cohort terms plus OECD filter)	16-Feb-22	Ovid	<1974 to 2022 February 16>
HTA	16-Feb-22	CRD	16-Feb-2022
INAHTA	16-Feb-22	INAHTA	16-Feb-2022
MEDLINE (filters applied: specific cost utility filter, cohort terms plus OECD filter)	16-Feb-22	Ovid	<1946 to February 16, 2022>
MEDLINE-in-Process (filters applied: specific cost utility filter, cohort terms)	16-Feb-22	Ovid	<1946 to February 16, 2022>
MEDLINE Epub Ahead-of-Print (filters applied: specific cost utility filter, cohort terms)	16-Feb-22	Ovid	<February 16, 2022>
NHS EED	16-Feb-22	CRD	N/A

Database: EconLit

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

Database: Embase

Cost utility search:

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

Cohort studies:

1 diabetic Retinopathy/ 45440
2 macular Edema/ 5828
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 47762
4 or/1-3 66388
5 cohort analysis/ 811098
6 Retrospective study/ 1206857
7 Prospective study/ 748103
8 (Cohort adj (study or studies)).tw. 380594
9 (cohort adj (analy* or regist*)).tw. 16437
10 (follow up adj (study or studies)).tw. 68508
11 longitudinal.tw. 384899
12 prospective.tw. 981024
13 retrospective.tw. 1068301

14 or/5-13 3358085
15 4 and 14 13743
16 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ 1511773
17 exp "organisation for economic co-operation and development"/ 1933
18 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ 3545238
19 european union/ 29144
20 developed country/ 34415
21 or/17-20 3576072

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

Database: Health Technology Assessment (HTA)

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

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

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

Database: Ovid MEDLINE(R)

Cost utility search:

1 Diabetic Retinopathy/ 27250
2 Macular Edema/ 8126
3 (diabet* adj4 (retin* or eye* or macular*)).tw. 29608
4 1 or 2 or 3 40314
5 Cost-Benefit Analysis/ 88398
6 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 13197
7 ((incremental* adj2 cost*) or ICER).tw. 13599
8 (cost adj2 utilit*).tw. 5176

9 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 1698
10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 17986
11 (cost and (effect* or utilit*)).ti. 30223
12 or/5-11 100083
13 4 and 12 287
14 animals/ not humans/ 4924997
15 13 not 14 287

Cohort studies:

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

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

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

Cost utility search:

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

10 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 242
11 (cost and (effect* or utilit*)).ti. 286
12 or/5-11 450
13 4 and 12 2
14 animals/ not humans/ 0
15 13 not 14 2

Cohort studies:

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

Database: Ovid MEDLINE(R) Epub Ahead of Print

Cost utility search:

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

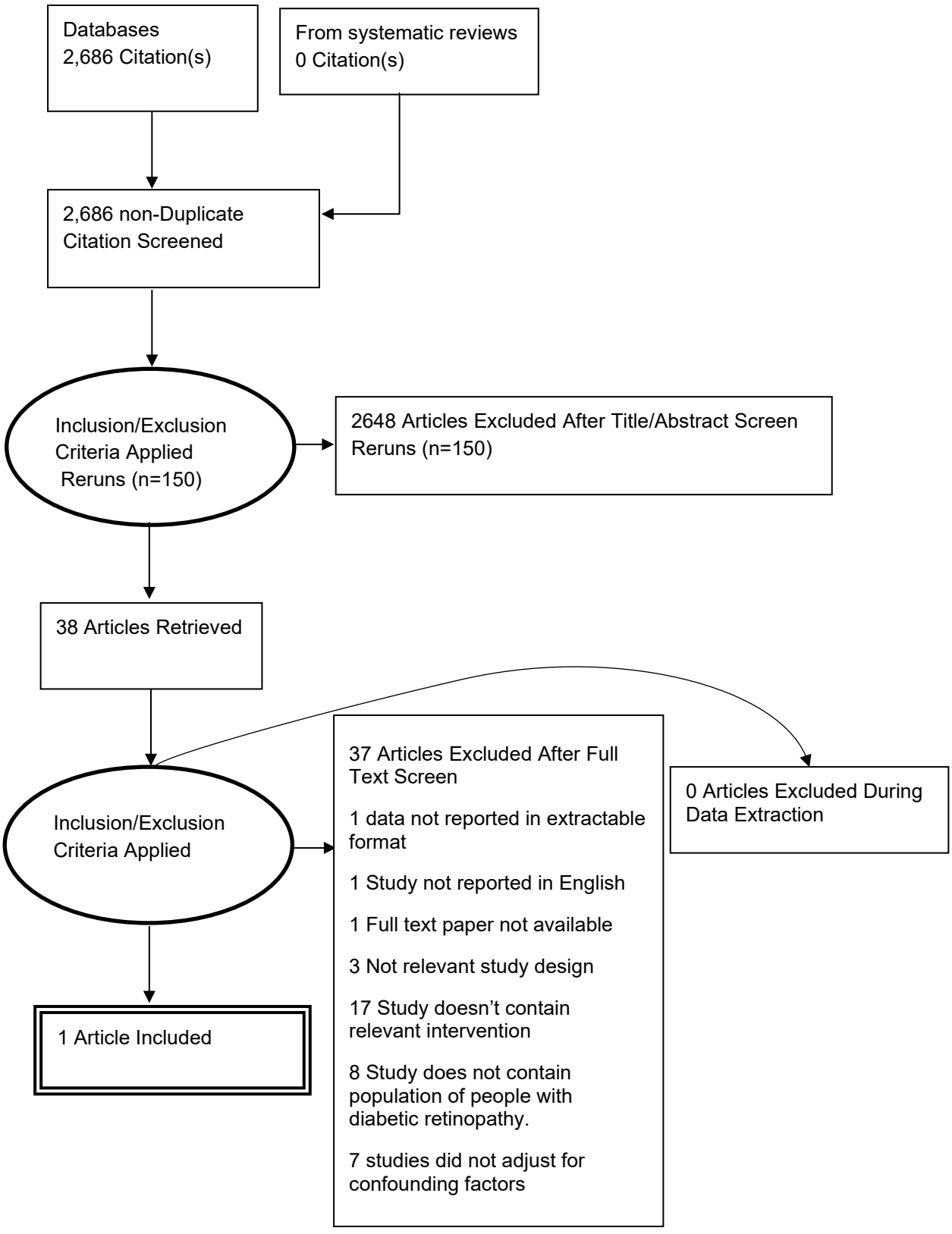
Cohort studies:

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

Database: NHS Economic Evaluation Database

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

Appendix C –Effectiveness evidence study selection



Appendix D – Effectiveness evidence

DCCT/EDIC Research, 2017

Bibliographic Reference	DCCT/EDIC Research, Group; Nathan, David M; Bebu, Ionut; Hainsworth, Dean; Klein, Ronald; Tamborlane, William; Lorenzi, Gayle; Gubitosi-Klug, Rose; Lachin, John M; Frequency of Evidence-Based Screening for Retinopathy in Type 1 Diabetes.; The New England journal of medicine; 2017; vol. 376 (no. 16); 1507-1516

Study details

Secondary publication of another included study- see primary study for details	Diabetes Control and Complications Trial (DCCT) and its longitudinal follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study
Study location	United States and Canada
Study dates	From 1983 - 1989
Sources of funding	(Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; DCCT/EDIC ClinicalTrials.gov numbers, NCT00360893 and NCT00360815.)
Inclusion criteria	People with minimal background retinopathy) Duration of IDDM between 1-15 years, Presence of at least one microaneurysm in either eye with or without other diabetes-related lesions, but less retinopathy than that which would characterize either eye as P2 or worse based on central grading of stereo fundus photographs using ETDRS standards, Visual acuity of 45 letters (20/32 Snellen equivalent) or better in both eyes., Less than or equal to 200 mg albumin/24 h on a 4-h urine collection, Basal plasma C-peptide <0.2 pmol/ml and for patients with duration >5 yr, stimulated plasma C-peptide <0.2 pmol/ml.
Exclusion criteria	The presence of diabetic retinopathy sufficient to categorize either eye as P2 or worse based on central grading of stereo fundus photographs. Eyes with new vessels were classified worse than P2. Eyes without new vessels that met any one of the three criteria listed below were classified as P2. Standard photos referred to below are those of the Modified Airlie House Classification. (a) Soft exudates (SE), venous beading (VB), and intraretinal microvascular abnormalities (IRMA) were each definitely present in at least two of fields 4 through 7. (b) Two of the above three lesions (SE, VB, or IRMA) were present in at least two of fields 4 through 7, and haemorrhages/ microaneurysms (HMa) were present in all four fields, equalling or exceeding standard photograph 2A in at least one of them. (c) IRMA were present in all four of these fields and were equal to or exceeded standard photograph 8A in at least two of them.

	Only a subset of the population matched the population in the review protocol (people with non-proliferative diabetic retinopathy that is moderate severity or greater). Data was presented separately for this group and so has been included in the review.
Intervention(s)	Modelled follow up durations of 1,2,3,6.9 and 12 months and 5 yearswith a maximum of 28.7 years of follow-up (mean, 23.5 years)
Comparator	All of the modelled followed durations listed under 'intervention' were compared.
Outcome measures	Progression from Lower Levels of Retinopathy (States 1 through 4) to State 5 Retinopathy (Proliferative Diabetic Retinopathy or Clinically Significant Macular Oedema). Only progression from states 3 and 4 to state 5 matches the review protocol for this review.
Number of participants	The DCCT enrolled 1441 patients with type 1 diabetes who were 13 to 39 years of age. The primary prevention cohort (726 patients) had diabetes for 1 to 5 years and no retinopathy detected by means of stereoscopic fundus photography at baseline. The secondary intervention cohort (715 patients) had diabetes for 1 to 15 years and very mild to moderate non-proliferative diabetic retinopathy
Duration of follow-up	After the DCCT ended in 1993, a total of 1375 patients (95% of the cohort) joined the observational EDIC follow-up study. Data on fundus photography obtained from 1983 through 2012, with a maximum of 28.7 years of follow-up (mean, 23.5 years),
Loss to follow-up	95% of the Patients' data was obtained
Methods of analysis	A longitudinal Markov model – models included recognized risk factors for progression of retinopathy. Age, sex, duration of diabetes, current smoking status, BMI, hypertension, hyperlipidaemia, and treatment group had some significant unadjusted associations with possible transition. Data collected as please of the diabetes control and complications trial (which compared intensive insulin treatment with standard therapy was used to model different durations of follow up.
Additional comments	The EDIC baseline measurement stratified by sex delineates multiple cardiovascular disease risk factor differences such as age (older in men), waist-to-hip ratio (higher in men), HDL cholesterol (lower in men), hypertension (more prevalent in men), and maximum intimal-medial thickness of common and internal carotid arteries (thicker in men). Of the original conventional treatment group,

Study arms

State 3 to State 5 (N = Not reported)
State 3 -corresponds to moderate non-proliferative diabetic retinopathy, State 4 -corresponds to severe non-proliferative diabetic retinopathy State 5 - Corresponded to any of the following: proliferative diabetic retinopathy, clinically significant macular oedema, or previous self-reported treatment with panretinal or focal photocoagulation, intraocular glucocorticoids, or anti-VEGF agents

State 4 to State 5 (N =Not reported)
State 4 -corresponds to severe non-proliferative diabetic retinopathy State 5 - Corresponded to any of the following: proliferative diabetic retinopathy, clinically significant macular oedema, or previous self-reported treatment with panretinal or focal photocoagulation, intraocular glucocorticoids, or anti-VEGF agents

Characteristics

Study-level characteristics

Characteristic	Study (N = 1441)
% Female	n = 653; % = 47.6

DCCT/EDIC Research, 2017

Bibliographic Reference	DCCT/EDIC Research, Group; Nathan, David M; Bebu, Ionut; Hainsworth, Dean; Klein, Ronald; Tamborlane, William; Lorenzi, Gayle; Gubitosi-Klug, Rose; Lachin, John M; Frequency of Evidence-Based Screening for Retinopathy in Type 1 Diabetes.; The New England journal of medicine; 2017; vol. 376 (no. 16); 1507-1516

Critical appraisal - GDT Crit App - Modified checklist for decision-analytic models

Section	Question	Answer
Section 1: Applicability (relevance to specific review questions and the NICE reference case	1.8 Overall judgement:	Partially applicable *(The secondary intervention cohort (715 patients) had diabetes for 1 to 15 years and very mild to moderate non-proliferative diabetic retinopathy.) Only a subset of this population matches the review protocol (people with moderate, severe, or very severe diabetic retinopathy). However, results were presented separately for progression from moderate and severe retinopathy and so these data were included in the review.*
Section 2: Study limitations (the level of methodological quality)	2.3 Are all important and relevant outcomes included?	Moderate *(lack of information on whether the models adjusted for confounders, data was not stratified by risk factors, the outcome was combined progression of proliferative diabetic retinopathy and diabetic macular oedema)*

Appendix E – GRADE tables

Modelled risk of progression from moderate diabetic retinopathy to proliferative retinopathy or clinically significant macular oedema

Table 7: Interpretation of effect: higher percentage indicates higher risk of progression in-between interval of follow up

No. of studies	Study design	Sample size	Effect size Percent (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
Interval of Follow-Up - 1 month							
1 study	Modelling study	NR	1.1 (0–1.3)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up - 2 month							
1 study	Modelling study	NR	2.3 (2.0–2.6)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up - 3 month							
1 study	Modelling study	NR	3.4 (3.1–3.8)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up – 6 months							
1 study	Modelling study	NR	6.6 (6.0–7.3)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up - 9 month							
1 study	Modelling study	NR	9.6 (8.8–10.5)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up - 1 Year							
1 study	Modelling study	NR	12.3 (11.3–13.5)	Serious[1]	N/A	Serious[3]	Low
Interval of Follow-Up – 2 Year							
1 study	Modelling study	NR	20.5 (18.9–22.3)	Serious[1]	N/A[2]	serious	Low
Interval of Follow-Up - 3 Year							
1 study	Modelling study	NR	25.9 (23.9–28.2)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up - 4 Year							
1 study	Modelling study	NR	29.7 (27.6–32.2)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up – 5 Year							
1 study	Modelling study	NR	32.5 (30.2–35.3)	Serious[1]	N/A[2]	Serious[3]	Low

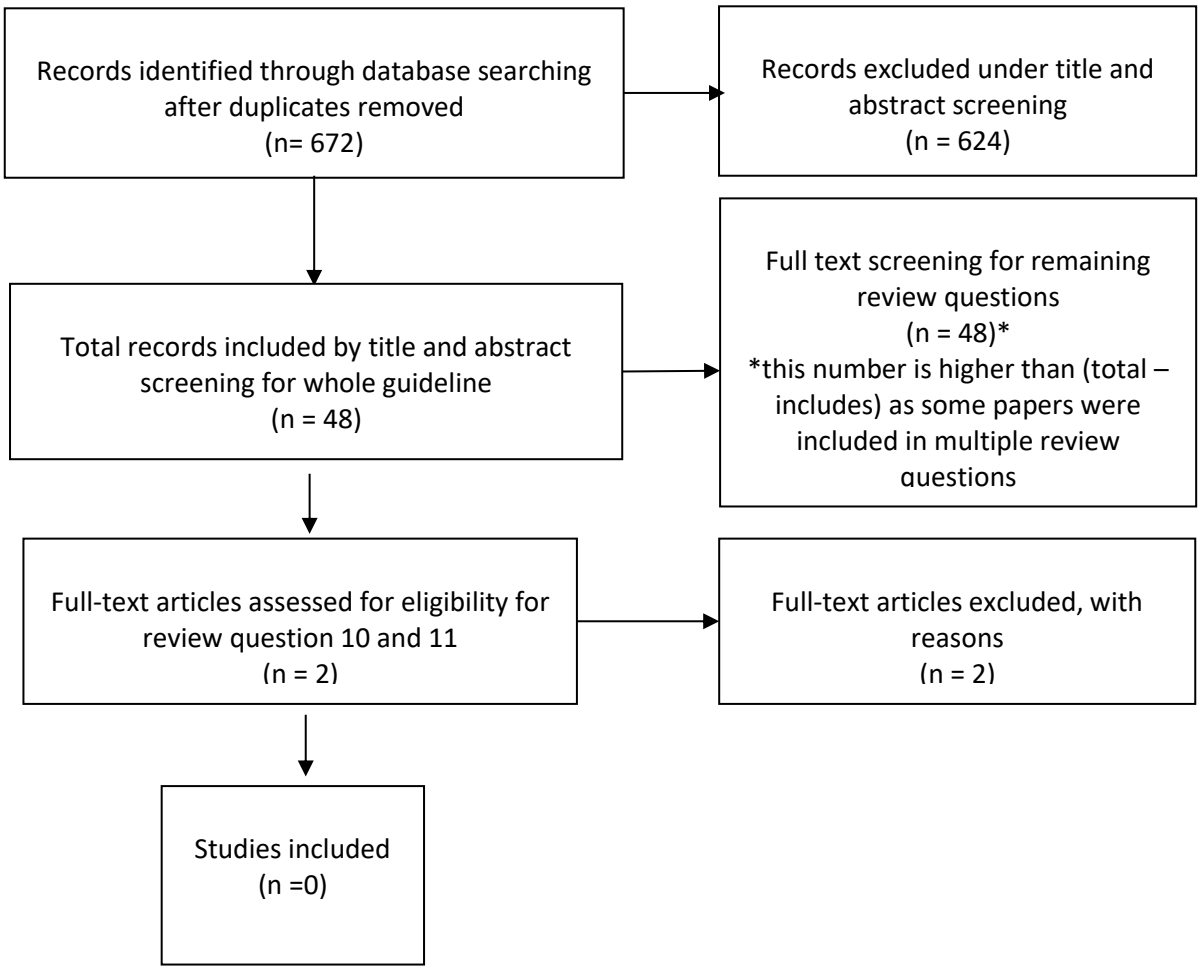
1 moderate risk of bias risk of bias assessed using a modified NICE appraisal checklist for economic evaluations)
2 Inconsistency not applicable for single study; Outcome reported from one study
3 Partially Applicable

Table 8: Modelled risk of progression from severe diabetic retinopathy to proliferative retinopathy or clinically significant macular oedema

No. of studies	Study design	Sample size	Effect size Percent (95% CI)	Risk of bias	Inconsistency	Indirectness	Quality
Interval of Follow-Up - 1 month							
1 study	Modelling study	NR	5.7 (3.6–8.8)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up - 2 month							
1 study	Modelling study	NR	10.4 (6.5–16.0)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up - 3 month							
1 study	Modelling study	NR	14.4 (9.4–22.0)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up – 6 months							
1 study	Modelling study	NR	23.0 (15.8–32.7)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up - 9 month							
1 study	Modelling study	NR	28.6 (20.9–38.4)	Serious[1]	N/A[2]	Serious[3]	Low
Interval of Follow-Up - 1 Year							
1 study	Modelling study	NR	32.5 (23.8–44.2)	Serious[1]	N/A[2]	Not serious	Low
Interval of Follow-Up – 2 Year							
1 study	Modelling study	NR	41.2 (32.6–50.6)	Serious[1]	N/A[2]	Not serious	Low
Interval of Follow-Up - 3 Year							
1 study	Modelling study	NR	45.9 (38.2–55.7)	Serious[1]	N/A[2]	Not serious	Low
Interval of Follow-Up - 4 Year							
1 study	Modelling study	NR	49.0 (42.0–58.0)	Serious[1]	N/A[2]	Not serious	Low
Interval of Follow-Up – 5 Year							
1 study	Modelling study	NR	51.3 (44.6–60.8)	Serious[1]	N/A[2]	Not serious	High

1 moderate risk of bias assessed using a Modified JBI checklist for economic studies no multivariate analysis conducted to adjust for confounders)
2 Inconsistency not applicable for single study; Outcome reported from one study.
3 Partially Applicable study includes a mixture of population and only reports composite outcome

Appendix F – Economic evidence study selection



Appendix G – Economic evidence tables

There are no included studies in this review question.

Appendix H – Health economic model

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

35 Appendix I – Excluded studies

36 Clinical studies

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Title	Reason for exclusion
Agardh, E, Agardh, C D, Hansson-Lundblad, C et al. (1996) The importance of early diagnosis of treatable diabetic retinopathy for the four-year visual outcome in older-onset diabetes mellitus. Acta ophthalmologica Scandinavica 74(2): 166-70	- Study does not contain a relevant intervention
Agardh, E; Agardh, CD; Hansson-Lundblad, C (1993) The five-year incidence of blindness after introducing a screening programme for early detection of treatable diabetic retinopathy. Diabetic medicine : a journal of the British Diabetic Association 10(6): 555-9	Does not contain a population of people with Diabetic Retinopathy
Askew, Deborah A, Crossland, Lisa, Ware, Robert S et al. (2012) Diabetic retinopathy screening and monitoring of early stage disease in general practice: design and methods. Contemporary clinical trials 33(5): 969-75	-Study does not contain a relevant intervention
Bourry, Julien, Courteville, Hugues, Ramdane, Nassima et al. (2021) Progression of Diabetic Retinopathy and Predictors of Its Development and Progression During Pregnancy in Patients With Type 1 Diabetes: A Report of 499 Pregnancies. Diabetes care 44(1): 181-187	Does not contain a population of people with DR/DMO
Broadbent, Deborah M, Wang, Amu, Cheyne, Christopher P et al. (2021) Safety and cost-effectiveness of individualised screening for diabetic retinopathy: the ISDR open-label, equivalence RCT. Diabetologia 64(1): 56-69	Does not contain a population of people with DR/DMO
Broadbent, DM, Harding, SP, Garcia-Finana, M et al. (2020) Safety, efficacy and cost effectiveness of individualised screening for diabetic retinopathy: the individualised screening for diabetic retinopathy (ISDR) single centre, open label, equivalence randomised controlled trial. European journal of ophthalmology 30(1suppl): 6-7	Does not contain a population of people with DR/DMO
Broadbent, DM, Wang, A, Cheyne, CP et al. (2019) Individualised screening for diabetic retinopathy: the ISDR study-a randomised controlled trial of safety, efficacy, and cost-effectiveness. Diabetes 68	Does not contain a population of people with DR/DMO
Creuzot-Garcher, C, Malvitte, L, Sicard, A C et al. (2010) How to improve screening for diabetic retinopathy: the Burgundy experience. Diabetes & metabolism 36(2): 114-9	- Study does not contain a relevant intervention

Title	Reason for exclusion
Crossland, L, Askew, D, Ware, R et al. (2016) Diabetic Retinopathy Screening and Monitoring of Early Stage Disease in Australian General Practice: tackling Preventable Blindness within a Chronic Care Model. Journal of diabetes research 2016: 8405395	- Study does not contain a relevant intervention
Datlinger, Felix, Datlinger, Anja, Pollreisz, Andreas et al. (2022) Intraprocedural OCT monitoring of the immediate treatment response during indocyanine green angiography-guided laser therapy of teleangiectatic capillaries in diabetic macular edema. Scientific reports 12(1): 2315	- Study does not contain a relevant intervention
Gabrielle, Pierre-Henry, Nguyen, Vuong, Bhandari, Sanjeeb et al. (2022) Initial observation or treatment for diabetic macular oedema with good visual acuity: two-year outcomes comparison in routine clinical practice: data from the Fight Retinal Blindness! Registry. Acta ophthalmologica 100(3): 285-294	Study does not contain a relevant intervention
Garcia-Finana, Marta, Hughes, David M, Cheyne, Christopher P et al. (2019) Personalized risk-based screening for diabetic retinopathy: A multivariate approach versus the use of stratification rules. Diabetes, obesity & metabolism 21(3): 560-568	- Does not contain a population of people with Diabetic Retinopathy
Hutchinson, A, McIntosh, A, Peters, J et al. (2000) Effectiveness of screening and monitoring tests for diabetic retinopathy--a systematic review. Diabetic medicine : a journal of the British Diabetic Association 17(7): 495-506	- Study does not contain a relevant intervention
ISRCTN87561257 (2014) Individual risk-based Screening for Diabetic Retinopathy. https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN87561257	- Study does not contain a relevant intervention
Januszewski, A.S., Velayutham, V., Benitez-Aguirre, P. et al. (2020) Assessing retinopathy screening frequency in adolescents with type 1 diabetes using Markov model. Diabetologia 63(suppl1): 37-s38	Study does not contain a relevant intervention. - Does not contain a population of people with DR/DMO
Kawaguchi, Atsushi, Sharafeldin, Noha, Sundaram, Aishwarya et al. (2018) Tele-Ophthalmology for Age-Related Macular Degeneration and Diabetic Retinopathy Screening: A Systematic Review and Meta-Analysis. Telemedicine journal and e-health : the official journal of the American Telemedicine Association 24(4): 301-308	Study does not contain a relevant intervention. - Does not contain a population of people with Diabetic Retinopathy

Title	Reason for exclusion
Khalid, Hagar, Schwartz, Roy, Nicholson, Luke et al. (2021) Widefield optical coherence tomography angiography for early detection and objective evaluation of proliferative diabetic retinopathy. The British journal of ophthalmology 105(1): 118-123	- Study does not contain a relevant intervention
Khurana, Rahul N, Hoang, Carol, Khanani, Arshad M et al. (2021) A Smart Mobile Application to Monitor Visual Function in Diabetic Retinopathy and Age-Related Macular Degeneration: The CLEAR Study. American journal of ophthalmology 227: 222-230	- Study does not contain a relevant intervention
Kozousek, V, Brown, M G, Cottle, R et al. (1993) Use of ophthalmologic services by diabetic patients in Nova Scotia. Canadian journal of ophthalmology. Journal canadien d'ophtalmologie 28(1): 7-10	- Does not contain a population of people with Diabetic Retinopathy
Li, B, Powell, AM, Hooper, PL et al. (2015) Prospective evaluation of teleophthalmology in screening and recurrence monitoring of neovascular age-related macular degeneration: a randomized clinical trial. JAMA ophthalmology 133(3): 276-282	- Study does not contain a relevant intervention
Mehlsen, Jesper, Erlandsen, Mogens, Poulsen, Per Logstrup et al. (2012) Individualized optimization of the screening interval for diabetic retinopathy: a new model. Acta ophthalmologica 90(2): 109-14	- Not a relevant study design(personalised risk stratification screening study)
Mellanby, A and Milne, R (1999) Reducing the interval for diabetic retinal screening.	- Not a relevant study design (non-comparative study)
NCT01257815 (2010) Ranibizumab Treatment of Diabetic Macular Oedema With Bimonthly Monitoring After a Phase of Initial Treatment. https://clinicaltrials.gov/show/NCT01257815	- Study does not contain a relevant intervention
Pareja-Rios, A, Bonaque-Gonzalez, S, Serrano-Garcia, M et al. (2017) Tele-ophthalmology for diabetic retinopathy screening: 8 years of experience. Archivos de la Sociedad Espanola de Oftalmologia 92(2): 63-70	- Study not reported in English
Park, Kyu Hyung, Kim, Yun Young, Jo, Young Joon et al. (2019) Healthcare Utilization and Treatment Patterns in Diabetic Macular Edema in Korea: a Retrospective Chart Review. Journal of Korean medical science 34(15): e118	Study does not contain a relevant intervention
Queiroz, Marcia Silva, de Carvalho, Jacira Xavier, Bortoto, Silvia Ferreira et al. (2020) Diabetic retinopathy screening in urban primary care setting with a handheld smartphone-based retinal camera. Acta diabetologica 57(12): 1493-1499	- Study does not contain a relevant intervention

Title	Reason for exclusion
Raman, V, Campbell, F, Holland, P et al. (2002) Retinopathy screening in children and adolescents with diabetes. Annals of the New York Academy of Sciences 958: 387-9	- Full text paper not available
Rosati, Renee; Ables, Adrienne Z; Warren, Petra (2017) Improving Diabetic Retinopathy in an Indigent Population. Journal of health care for the poor and underserved 28(2): 635-642	- Data not reported in an extractable format
Sharif, A.; Jendle, J.; Hellgren, K.-J. (2021) Screening for Diabetic Retinopathy with Extended Intervals, Safe and Without Compromising Adherence: A Retrospective Cohort Study. Diabetes Therapy 12(1): 223-234	- Does not contain a population of people with Diabetic Retinopathy
Singer, D E, Nathan, D M, Fogel, H A et al. (1992) Screening for diabetic retinopathy. Annals of internal medicine 116(8): 660-71	Study does not contain a relevant intervention
Souza, Grazielle Fialho de, Figueira, Renato Minelli, Alkmim, Maria Beatriz et al. (2020) Teleophthalmology Screening for Diabetic Retinopathy in Brazil: Applicability and Economic Assessment. Telemedicine journal and e-health : the official journal of the American Telemedicine Association 26(3): 341-346	Study does not contain a relevant intervention
Stone, LG; Grinton, ME; Talks, JS (2021) Delayed follow-up of medical retina patients due to COVID-19: impact on disease activity and visual acuity. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie	Study does not contain a relevant intervention
Tapp, R.J., Zimmet, P.Z., Harper, C.A. et al. (2004) Diabetes care in an Australian population: Frequency of screening examinations for eye and foot complications of diabetes. Diabetes Care 27(3): 688-693	people with diabeties but unclear on retinopathy at baseline
van der Heijden, Amber A W A, Walraven, Iris, van 't Riet, Esther et al. (2014) Validation of a model to estimate personalised screening frequency to monitor diabetic retinopathy. Diabetologia 57(7): 1332-8	-Does not contain a population of people with Diabetic Retinopathy
Wang, Sophia Y, Andrews, Chris A, Gardner, Thomas W et al. (2017) Ophthalmic Screening Patterns Among Youths With Diabetes Enrolled in a Large US Managed Care Network. JAMA ophthalmology 135(5): 432-438	Does not contain a population of people with Diabetic Retinopathy
Wilson, A., Baker, R., Thompson, J. et al. (2004) Coverage in screening for diabetic retinopathy according to screening provision: Results from a national survey in England and Wales. Diabetic Medicine 21(3): 271-278	Does not contain a population of people with Diabetic Retinopathy

38 Economic evidence

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	Title	Reason for exclusion
9536449	Crijns, H; Casparie, A F; Hendrikse, F; Continuous computer simulation analysis of the cost-effectiveness of screening and treating diabetic retinopathy.; International journal of technology assessment in health care; 1999; vol. 15 (no. 1); 198-206	Does not contain a population of people with Diabetic Retinopathy
9536429	Polak, B C P; Crijns, H; Casparie, A F; Niessen, L W; Cost-effectiveness of glycemic control and ophthalmological care in diabetic retinopathy.; Health policy (Amsterdam, Netherlands); 2003; vol. 64 (no. 1); 89-97	Does not contain a population of people with Diabetic Retinopathy

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Appendix J - Research Recommendation

J.1 Research recommendation

What is the most effective monitoring frequency for people with non-proliferative diabetic retinopathy who are cared for under hospital eye services and are not receiving treatment?

J.2 Why this is important

While there are general guidelines for monitoring individuals with this condition, specific evidence-based recommendations are needed for people with non-proliferative diabetic retinopathy who are under the care of hospital eye services and not receiving treatment. Non-proliferative diabetic retinopathy can progress to a more severe stage, such as proliferative diabetic retinopathy, which may require treatment. Regular monitoring can help detect early signs of disease progression and enable timely intervention, reducing the risk of vision loss. Research is therefore needed to ensure that people are monitored at the most effective frequency to ensure they can receive timely treatment.

J.3 Rationale for research recommendation

Importance to 'patients' or the population	Receiving appropriate monitoring is important to patients because it allows for the timely identification and treatment of disease progression.
Relevance to NICE guidance	Future guideline updates will be able to provide clinicians with guidance on the most effective monitoring frequencies.
Relevance to the NHS	Evidence on effective monitoring frequencies could allow reduced monitoring of groups who are at low risk of disease progression, allowing a possible resource saving.
National priorities	Moderate
Current evidence base	One low-quality modelling study that partially covers population was identified to inform recommendations in this area.
Equality considerations	No specific equality considerations were identified in relation to this question

J.4 Modified PICO table

Population	People with moderate, severe or very severe non-proliferative retinopathy who are not yet receiving treatment
Intervention	Increased or decreased monitoring frequency compared with standard monitoring frequency
Comparison	Standard monitoring frequency
Outcomes	Progression to proliferative retinopathy Progression to diabetic macular oedema
Study design	• Randomised controlled trial

	• Modelling study based on routinely collected healthcare data on timing of disease progression
Timeframe	• Long-term (up to 10 years)
Stratification	• Stratification based on disease severity at baseline (moderate, severe or very severe). • Stratification based on risk factors for progression (e.g. HbA1c at baseline)

J.1.5 Research recommendation

What is the most effective monitoring frequency for people with proliferative diabetic retinopathy or diabetic macular oedema who have received treatment?

J.1.6 Why this is important

The monitoring frequency for individuals with proliferative diabetic retinopathy or diabetic macular oedema who have received treatment is an important consideration for managing their condition effectively. The most effective monitoring frequency depends on various factors, including the severity of the condition, the type of treatment received, the stability of the patient's visual function, and the presence of any additional risk factors. Frequent monitoring is essential to detect any disease progression or recurrence early and initiate timely interventions. Research is therefore needed to ensure that people are monitored at the most effective frequency to ensure they can receive timely treatment.

J.1.7 Rationale for research recommendation

Importance to ‘patients’ or the population	Receiving appropriate monitoring is important to patients because it allows for the timely identification and treatment of disease progression.
Relevance to NICE guidance	Future guideline updates will be able to provide clinicians with guidance on the most effective monitoring frequencies.
Relevance to the NHS	Evidence on effective monitoring frequencies could allow reduced monitoring of groups who are at low risk of disease progression, allowing a possible resource saving.
National priorities	Moderate
Current evidence base	No evidence was found to inform current recommendations in this area.
Equality considerations	No specific equality considerations were identified in relation to this question

J.1.8 Modified PICO table

Population	People with proliferative diabetic retinopathy or diabetic macular oedema who have received treatment.

Intervention	Increased or decreased monitoring frequency compared with standard monitoring frequency
Comparison	Standard monitoring frequency
Outcomes	Progression of proliferative retinopathy Progression of diabetic macular oedema
Study design	• Randomised controlled trial. • Modelling study based on routinely collected healthcare data on timing of disease progression
Timeframe	• Long-term (up to 10 years)
Stratification	• Stratification based on disease severity at baseline (low or high risk proliferative diabetic retinopathy, centre involving or non-centre involving diabetic macular oedema). • Stratification based on risk factors for progression (e.g. HbA1c at baseline)

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