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Extending the diabetic retinopathy screening interval beyond 1 year: systematic review

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bjophthalmol-2014-305938>).

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Received 2 August 2014
Revised 21 November 2014
Accepted 14 December 2014
Published Online First
13 January 2015

ABSTRACT

To determine whether the recommended screening interval for diabetic retinopathy (DR) in the UK can safely be extended beyond 1 year. Systematic review of clinical and cost-effectiveness studies. Nine databases were searched with no date restrictions. Randomised controlled trials (RCTs), cohort studies, prognostic or economic modelling studies which described the incidence and progression of DR in populations with type 1 diabetes mellitus or type 2 diabetes mellitus of either sex and of any age reporting incidence and progression of DR in relation to screening interval (vs annual screening interval) and/or prognostic factors were included. Narrative synthesis was undertaken. 14 013 papers were identified, of which 11 observational studies, 5 risk stratification modelling studies and 9 economic studies were included. Data were available for 262 541 patients of whom at least 228 649 (87%) had type 2 diabetes. There were no RCTs. Studies concluded that there is little difference between clinical outcomes from screening 1 yearly or 2 yearly in low-risk patients. However there was high loss to follow-up (13–31%), heterogeneity in definitions of low risk and variation in screening and grading protocols for prior retinopathy results. Observational and economic modelling studies in low-risk patients show little difference in clinical outcomes between 1-year and 2-year screening intervals. The lack of experimental research designs and heterogeneity in definition of low risk considerably limits the reliability and validity of this conclusion. Cost-effectiveness findings were mixed. There is insufficient evidence to recommend a move to extend the screening interval beyond 1 year.

INTRODUCTION

Diabetic retinopathy (DR) is a serious complication of diabetes mellitus and a major cause of visual loss globally.^{1,2} Prevalence of DR is rising.² Early detection and timely treatment of sight-threatening DR have reduced the incidence and progression of visual loss.^{3–8} Screening for DR (using ophthalmoscopy and fundus photography) is accurate, safe and cost-effective.^{9–11}

DR screening is recommended in many countries.^{12–16} However there is often no complete register of patients and non-uniformity of interval, coverage, uptake, screening methods and grading.^{17,18} The generalisability of findings from one country to another has been questioned.¹⁹ There has been considerable international debate about extending the screening interval in the UK and the USA. A previous systematic review²⁰ advocated a longer screening interval as a cost saving measure with various caveats but the authors did

not formally critically appraise the evidence base, and two studies have since been published.

This systematic review aims to investigate the effects of longer screening intervals (vs an annual screening interval) in people with diabetes in order to inform screening decisions in the UK.

METHODS

Study eligibility criteria

Randomised controlled trials (RCTs), cohort studies, prognostic or economic modelling studies which described the incidence and progression of DR in populations with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) of either sex and of any age investigating annual with longer intervals were eligible (articles where annual screening is compared with a shorter interval were also included, because for some patient groups this interval may have to be more frequent). Studies investigating DR but not related to screening intervals, full text non-English publications, editorials, letters or commentaries were excluded.

Search strategy

Electronic searches were performed on 1 October 2013 in nine databases including Medline, SCOPUS, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, and the National Health Service (NHS) Economic Evaluation Database. No date or language restrictions were applied. Search terms were left deliberately broad. Reference lists of relevant systematic reviews were checked. Online supplementary appendix 1 gives details of the search strategy.

Study selection

Abstracts from the different databases were merged and duplicates removed. Two reviewers independently screened abstracts using prepiloted eligibility criteria and also independently reviewed the identified full texts. Differences were discussed and agreed with the input of a third adjudicator where necessary.

Data extraction and assessment of methodological quality

Two independent reviewers extracted data including: study characteristics, population characteristics, screening data, postscreening data, outcome measures and conclusions. Economic appraisals data were extracted and assessed using Consolidated Health Economic Evaluation Reporting Standards statement²¹ and an adapted checklist for economic



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To cite: Taylor-Phillips S, Mistry H, Leslie R, et al. *Br J Ophthalmol* 2016;**100**: 105–114.

models was also used.²² Observational studies were assessed using the Critical Appraisal Skills Programme tool.²³ Risk prediction studies were evaluated, but focused on external validation and impact on outcomes.²⁴ Disagreements were resolved through discussion with a third reviewer.

Data synthesis and analysis

Evidence was synthesised narratively, because of heterogeneity in populations, screening intervals, measurement methods, outcomes and uptake. Evidence on incidence and/or progression of DR was synthesised separately in relation to (A) screening intervals and (B) risk factors.

RESULTS

Fourteen thousand and thirteen records were identified after duplicates were removed and 142 were screened at full text level. Of these 113 were excluded, leaving 29 eligible records, reporting on 26 unique studies (figure 1).^{1 6 9 25-47} One study was reported in two publications: one reporting prevalence of DR in relation to screening intervals²⁵ and the other incidence and progression of DR in relation to prognostic factors.²⁶ A study by Mehlsen *et al* was reported in two publications.^{27 28} Analyses from two other publications were based on the same study population.^{29 30} To avoid a potential for double-counting, the abovementioned six publications were considered as three

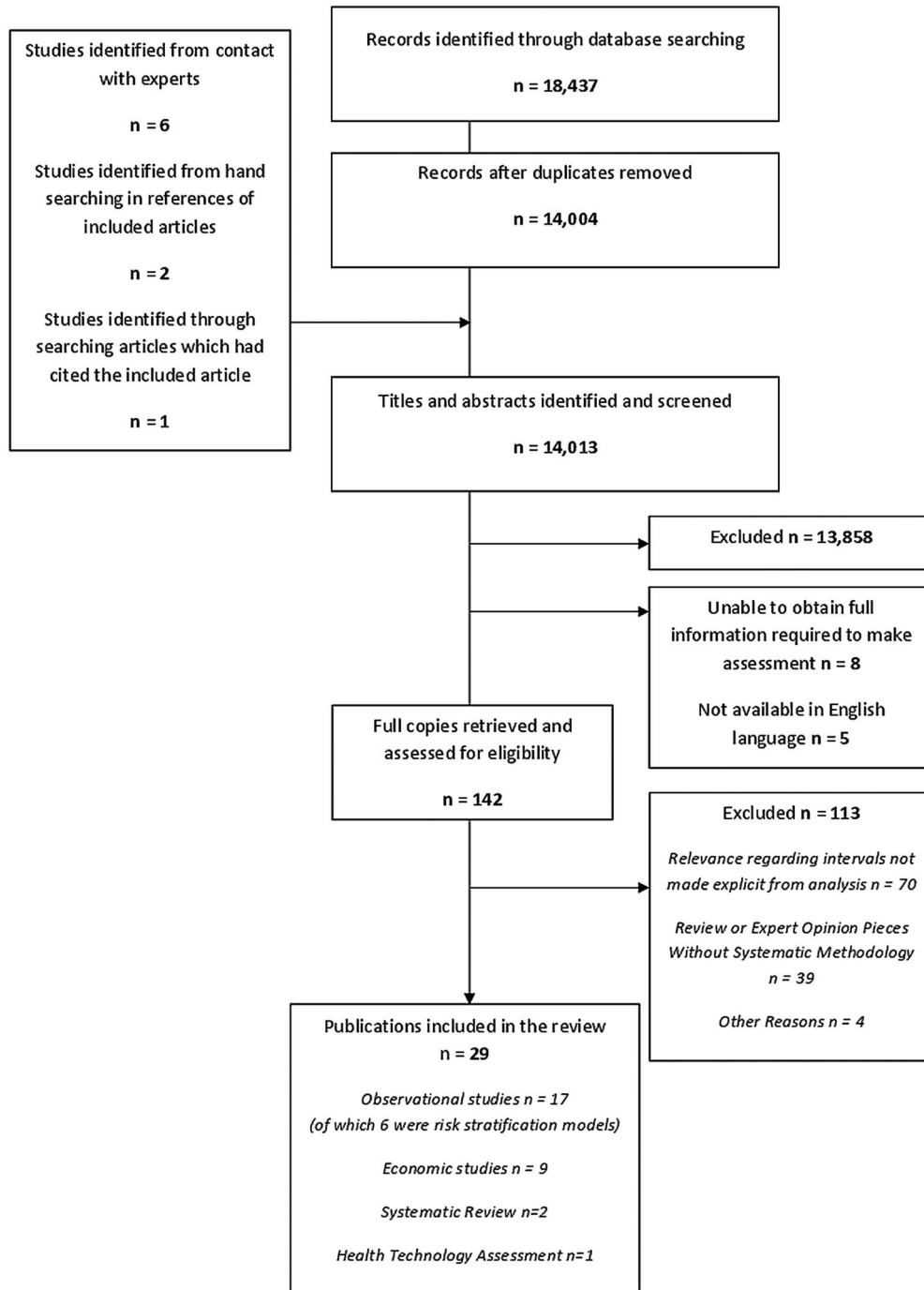


Figure 1 PRISMA flow chart of systematic review.

unique studies. One additional study was identified from searching of reference lists.³¹

Incidence and progression of DR

Incidence and/or progression of DR was reported in 15 studies.^{1 25–40} There were no randomised or non-randomised comparative studies. Ten observational studies followed progression of retinopathy in single populations with defined screening intervals.^{1 25 26 29–36} Five studies described risk stratification algorithms. None were externally validated.^{27 28 37–40}

Most observational studies used annual screening protocols^{25 26 34–36} although actual screening intervals varied. Two studies described screening every 3 years^{31 33} and one every 2 years.³⁰ Populations studied were from UK,^{1 25 26 33 35 36} Iceland,^{29 30} Australia³⁴ and Sweden.³² Different strategies for grading retinopathy were employed (see table 1).

The Critical Appraisal Skills Programme tool (see online supplementary appendix 2) indicated that observational studies reported well. Completeness of follow-up varied, with attrition reaching up to 31% in two studies.^{25 36} Three studies had lower losses to follow-up (under 25%^{32 29 35}), and reported that baseline characteristics did not differ between responders/completers and those lost to follow-up. In one study¹ for which the rate of non-attendance for a repeat screen was relatively low (13%), the authors reported that non-attendees tended to be older with a longer duration of diabetes in comparison with attendees. Completeness of follow-up data was not reported for four studies.^{26 30 33 34}

Incidence and/or progression of DR in relation to screening intervals was reported in six observational studies (see online supplementary appendix 3).^{25 26 28 34–37 40} All six studies suggested that the annual screening interval for patients with T1DM/T2DM at low risk (ie, no visible DR at baseline, adequate diabetes control) could be safely extended to 2 years or beyond. In three studies the incidence and progression of DR, either actual or predicted, were similar between annual and 2-yearly screening.^{25 28 34} Younis *et al*,^{35 36} found that about 95% of patients with T1DM-T2DM with no DR at initial screening remained free of sight threatening diabetic retinopathy (STDR) for the mean screening interval of 5.4 years. In a large single arm study in more than 20 000 patients, no significant association between a longer screening interval (18–24 months vs 12–18 months) and prevalence of referable DR (OR=0.93, 95% CI 0.82 to 1.05) or STDR/maculopathy (OR=1.05, 95% CI 0.72 to 1.52) was found.²⁵ In the largest study, of 155 000 patients,⁴⁰ predicted risk of progression in patients with T2DM with no DR at two consecutive screens for the 2-year screening interval was 0.15% or less compared with 0.03% or less for the annual interval. Studies which investigated 2-year screening intervals for patient subgroups at increased risk of progression (eg, visible DR of any grade, poorly controlled diabetes, duration of DM >10 years), suggested that these subgroups may need to be screened more frequently.

Incidence and/or progression of DR in relation to prognostic factors were reported in 13 studies (see online supplementary appendix 3).^{1 25–27 29–36 38–40} Most studies showed that patients with baseline DR (vs no DR) were at higher risk of progressing to referable DR or STDR.^{26 33 35–37 39 40} In one study of patients with T2DM,²⁶ the presence of baseline background DR (vs no background DR) was associated with an increased risk of pre-DR or proliferative DR (HR=5.00, 95% CI 4.40 to 5.60). Mehlsen *et al*,²⁷ also found the number of retinal haemorrhages to be a significant risk factor for progression to STDR in patients with T1DM (OR=2.68, 95% CI 1.83 to 3.91) and

T2DM (OR=2.37, 95% CI 1.84 to 3.06). Grade of baseline DR was also a significant predictor of progression to referable DR or STDR.^{33 35–37} Clinical risk factors for progression to STDR were found to be longer with duration of diabetes,^{1 26 27 34 35 37 38 40} insulin use,^{1 26 36 38} higher level of HbA1c,^{27 30 34 37 38} raised systolic blood pressure^{37 38} and hypertension treatment.²⁶

Six studies^{27 28 37–40} describe risk stratification models to determine the most effective screening interval based on identified risk factors. These were developed using either Cox proportional hazards models, non-parametric survival models or logistic regression with data from different screening programmes.^{27 28 37–40} None of the models were externally validated on a UK data set, although one model³⁷ was externally validated on a Danish database. All other models were internally validated tending to overestimate performance in comparison with external validation, due to statistical overfitting and potential lack of generalisability.⁴⁸ The Danish screening programme model^{27 28} indicated that screening could be prolonged 2.9 times for patients with T1DM and 1.2 times for patients with T2DM without increasing STDR. The Aspelund risk prediction algorithm³⁷ when externally validated on the same Danish data set could reduce the number of visits by 59% without increasing overall risk using the predictors of disease type (1 or 2), HbA1c, systolic blood pressure, gender and presence of non-proliferative DR. The current Danish screening system has screening intervals dependent on risk factors, so generalisability to the UK is problematic. Risk stratification based on two consecutive negative screens had the potential to reduce the number of screening visits in the Scottish screening service by up to 40%.⁴⁰ However, probability of referable retinopathy would be higher with a 2 year interval, increasing from 0.7% to 1.2% in the English model (where screening includes mydriasis and two fields per eye)³⁹ and from 0.05% to 0.25% in men with 10 years duration of diabetes in the Scottish model (where screening includes one field per eye).⁴⁰ These rates were higher when any referable disease was included.

Economic evaluation of screening intervals

Nine papers assessed cost-effectiveness of differing screening intervals for identification of DR/prevention of DR complications.^{6 9 41–47} Studies used various types of simulation models conducted on hypothetical cohorts of patients with diabetes using data from existing data sets and literature.

Table 2 highlights key characteristics, methods and findings. Not all studies reported a viewpoint. The most common outcomes were sight years saved/gained, and two studies used quality-adjusted life years.^{46 47} Two studies did not discount.^{42 44} Four studies did not provide an incremental cost-effectiveness ratio.

Most items in the Consolidated Health Economic Evaluation Reporting Standards checklist²¹ were well reported (see online supplementary appendix 4). Using the Phillips²⁴ checklist, publications reported a clear statement of the decision problem, objectives, data sources, model, methods and assumptions. They also reported costs including sources, and most also adequately compared results with previous models (see online supplementary appendix 5).

In general, the cost-effectiveness studies suggested that screening every 2 years could be safely adopted for those with no background or mild retinopathy,^{6 42 46 47} without increased risk of visual loss, and this reduces screening costs by ~25%,⁴² and has no detrimental effect on years of sight saved.⁶ When taking into account the ability to detect other eye conditions screening

Table 1 Differences in screening and grading protocols for detecting diabetic retinopathy

	Was mydriasis used?	How many and which retinal fields were taken?	Photographs or digital retinal photographs	Which cameras were used?	Were patients tested using slit lamp (biomicroscopy)	What grading protocol was used?	Were screeners and graders trained and/or accredited?	Was grading quality assured?/ Was grading assessed elsewhere?	How many times were images graded?
Agardh and Tababat-Khani ³²	No information	One central and one nasal 50° field per eye.	Red free digital images	No information	No information	International Diabetic Retinopathy and Macula Edema Severity Scales	Performed by specially trained ophthalmic nurses	No information	No information
Jones <i>et al</i> ²⁶	Both pupils were dilated with 1% tropicamide drops	Two photographs of each eye were taken, one centred on the optic nerve and the other on the fovea. Images taken by trained retinal screeners	Mixed Before 2000: colour transparency film From 2000: digital imaging	Mobile retinal cameras: Canon 45NM or 46NM fundus cameras (Canon UK, Reigate, UK) with 458 fields and Orion Eyecap and DRSS digital imaging software.	No information	1990–2002: Descriptive grading system based on European guidelines From 2003: U.K. National Screening Committee grading system After 2006: NSC grading system Described as 'virtually identical'	Before 2000: diabetologist with a specialist interest in retinopathy From 2000: seven primary graders	Yes. Nationally accredited arbitration grader	No information
Kohner <i>et al</i> ³³	Yes	Four-field 30° retinal photographs taken as stereo pairs	No information	No information	No information	Allocated to a retinopathy severity level using the Early Treatment of Diabetic Retinopathy Study (ETDRS) final scale, modified for four standard fields. Retinopathy severity categorised as no retinopathy, MA only in one eye, MA in both eyes or more severe retinopathy features.	No information	Only patients with a set of good quality images of both eyes were included in the study.	No information
Kristinsson <i>et al</i> ²⁹	Yes	No information	No information	No information	Yes	No information	No information	No information	No information
Looker <i>et al</i> ⁴⁰	If required	Single field	Digital photograph	No information	Slit lamp outcomes were not available for all patients, but where available, results were used.	Scottish grading system	No information	No information	No information
Maguire <i>et al</i> ³⁴	Yes—1% cyclopentolate and 2.5% phenylephrine	Stereoscopic fundal photography of seven fields. Non-simultaneous photographic pairs for each eye	Viewed with a Donaldson Stereoviewer providing a 3D representation of the fundus.	Topcon fundus camera	Yes. Slit lamp examination of the anterior segment.	ETDRS adaption of the modified Ailie House classification of diabetic retinopathy.	Graded by an ophthalmologist with a large sample graded by a second grader independently.	When necessary, a grading supervisor was used to adjudicate. Agreement between two graders was statistically assessed.	No information
Misra <i>et al</i> ²⁵ Olafsdóttir and Stefánsson ³⁰	As Jones <i>et al</i> Yes		Colour photographs taken with a 90-diopter lens		Yes	Visual acuity reported by the better eye. Retinopathy level determined as the stage of the worse eye. Visual acuity measured	Screened by an ophthalmologist		

Continued

Table 1 Continued

	Was mydriasis used?	How many and which retinal fields were taken?	Photographs or digital retinal photographs	Which cameras were used?	Were patients tested using slit lamp (biomicroscopy)	What grading protocol was used?	Were screeners and graders trained and/or accredited?	Was grading quality assured?/ Was grading assessed elsewhere?	How many times were images graded?
Soto-Pedre <i>et al</i> ³¹	No Information	One fundus photograph centred on the macula of each eye taken with 45° non-mydratic retinal camera	Instant film Polaroid	Canon CR4-45NM	No	on a Snellen chart at 6 m with the best refractive correction International Diabetic Retinopathy and Macula Edema Severity Scales. Level of disease recorded for the worse eye.	Stored polaroid photographs were graded by the same retina specialist for this study.	No	Once for the purpose of this retrospective study
Stratton <i>et al</i> ³⁹	Yes	Two standard 45 fields—Macular and disc centred—per eye	Digital colour retinal photographs	No information	No information	Grading based on the ETDRS severity scale Background retinopathy defined using the R1M0 category on the English NHS Diabetic Eye Screening Programme.	Trained assessors in a central location to the screening venues	Internal and external quality-assured reading process that reaches national recommendations.	No information
Thomas <i>et al</i> ¹	Tropicamide (applied to each eye 15 min before screening)	Two 45° digital retinal images per eye—one macular centred and one nasal field	Non-mydratic Canon DGi camera			Screening undertaken by a trained photographer Grading undertaken by trained staff use an enriched version of English National Screening Protocol	Before screening, a trained healthcare assistant assesses visual acuity in both eyes using an illuminated 3 m Snellen chart		Retinal images transferred to a central reading centre for grading
Younis <i>et al</i> ³⁵	1% tropicamide with or without phenylephrine	Three overlapping non-stereoscopic 33 mm transparency photographs of each eye	Either Canon CR4-45NM with 45° fields or a Topcon TRC 50 SX camera with 50° fields.	No information	Patients with ungradable images or STDR invited for slit lamp biomicroscopy by specialists in medical retinal disease.	STDR defined as moderate preproliferative retinopathy or greater and/or significant maculopathy in any eye. Graded by trained graders with a modified Wisconsin algorithm.	No information	No information	No information
Younis <i>et al</i> ³⁶	As Younis 2003b								

NSC, National Screening Committee; MA, microaneurysms; STDR, sight threatening diabetic retinopathy.

Table 2 Characteristics and findings of cost-effectiveness studies investigating different DR screening intervals

Author (year)	Type of economic evaluation and model	Population studied	Comparators	Methods (perspective, time horizon and discount rate)	Methods (costs, outcomes, ICER and sensitivity analyses)	Results and main conclusions
Brailsford <i>et al</i> (2007) ⁴¹	EE: CEA Model: Discrete event simulation embedded in an optimisation model using POST	Hypothetical population of 100 000 people with T2DM	Two screening policies using different strategies vs no screening: 1. optometrist funduscopy 2. diabetologist ophthalmoscopy 3. GP ophthalmoscopy 4. mobile camera 5. mydriatic 7 field photography by ophthalmologist (gold standard). Screening interval was varied between 6 months and 36 months.	Study perspective: Not stated Time horizon: 100 years Discount rate: 0%, 3% 5% Currency/price year: UK £—year not stated	Outcomes: Total number of years of sight saved Costs: Direct costs of screening and treatment, outpatient visits ICER: Incremental cost per year of sight saved Sensitivity analyses: Not stated	Most cost-effective screening policy is where the optometrist carries out both screens (policy 2) and if screen 2 is positive this is confirmed by the gold standard test. Screening should be carried out at 30 month intervals.
Chalk <i>et al</i> (2012) ⁴²	EE: CEA Model: Simulation model using POST	Hypothetical population of 5000 people with T2DM without DR	Annual (or 6-monthly) screening vs a 2-year screening programme	Study perspective: Not stated Time horizon: 15 years Discount rate: Not stated Currency/price year: UK £—year not stated	Outcomes: Proportion of patients with diabetes with vision loss Costs: Screening test, ophthalmology visits and laser treatment ICER: None stated Sensitivity analyses: One-way	The 2-year screening costs were £1 360 516 and annual screening costs were £1 834 060, which represents a 25.8% reduction in screening costs. A screening test every 2 years was a safe and cost-effective strategy.
Dasbach <i>et al</i> (1991) ⁴³	EE: CEA Model: Simulation model using a Markov process	Hypothetical groups of a 1000 patients with onset diabetes: 1. younger patients; 2. older patients taking insulin; and 3. older patients, not taking insulin	Seven screening strategies: (1) no care (2) and (3) annual or biannual visits to a community healthcare professional (4) and (5) annual or biannual non-mydriatic camera screening (6) and (7) annual or biannual mydriatic camera screening	Study perspective: Societal Time horizon: 10 years and 60 years Discount rate: 5% (varied between 0% and 10%) Currency/price year: US\$ in 1989 prices	Outcomes: Sight years saved Costs: Screening and clinic visits, treatments and rehabilitation ICER: None stated Sensitivity analyses: One-way	60-year results: annual examination with mydriatic fundus photography for groups 1, 2 and 3 might save from 303 to 319, from 58 to 62 and from 19 to 21 sight years, respectively. The results suggest that screening annually compared with 6 monthly was favoured.
Davies <i>et al</i> (2002) ⁴⁴	EE: CEA Model: Discrete event simulation model using POST.	Hypothetical population of 500 000 people with T1DM or T2DM who could develop DR	Each scenario compared with no screening. Screening done by a mobile camera, diabetologist, optometrist or GP. Policy 1, screening every 12 months and a 6-month interval between visits once DR detected. Policy 2, screening every 12 months, even after the detection of background retinopathy, until treatable retinopathy is detected (every 6 months). Mydriatic seven-field photography by an ophthalmologist, screening every 6 months, with visits every 3 months after DR had been detected.	Study perspective: Not stated Time horizon: 25 years Discount rate: Not undertaken Currency/price year: UK £—year not stated	Outcomes: Average years of sight saved Costs: Screener, ophthalmology outpatient visits, treatment and mobile camera (including set-up costs). ICER: Costs per year of sight saved Sensitivity analyses: One-way	For both types of patients, the mobile camera (Policy 2) had the lowest costs at £449 200 per year and a cost per sight year saved of £2842. Policy 2 was more cost-effective than policy 1 as long as the screening sensitivity and compliance were relatively high. Results suggested there is little difference in the number of sight years saved between the different modes of screening when screening intervals are ≤ 1 year and compliance is high.
Javitt <i>et al</i> (1990) ⁴⁵	EE: CEA Model: Monte Carlo Simulation model using PROPHET	Hypothetical cohort of patients with T1DM	Five screening strategies all have dilated ophthalmoscopy: 1. every 2 years 2. annually 3. annually for patients with no DR	Study perspective: Government Time horizon: Lifetime Discount rate: 5% Currency/price year: US\$ in 1986 prices	Outcomes: Person years of sight saved Costs: Screening (eye examination, angiography) and treatment (laser pan retinal or	All strategies resulted in cost savings. There is an economic advantage in adding semiannual visits under strategy 3. Although it was slightly less cost-saving than annual

Continued

Table 2 Continued

Author (year)	Type of economic evaluation and model	Population studied	Comparators	Methods (perspective, time horizon and discount rate)	Methods (costs, outcomes, ICER and sensitivity analyses)	Results and main conclusions
Javitt <i>et al</i> (1994) ⁶	EE: CEA Model: Simulation model using PROPHET	Hypothetical cohort of patients with T2DM with DR	and examination every 6 months for those with DR 4. full fundus photographs annually 5. full fundus photographs annually for patients with no DR and examination every 6 months for those with DR Eight screening strategies: (1) and (2) screening every 2 years. Patients with background or more advanced DR seen semiannually under strategy 1 or annually under strategy 2. (3), (4) and (5) screening every 3 years. Patients with background DR scheduled every 6 months, 12 months or 18 months, respectively (6), (7) and (8) screening every 4 years. Patients with background DR scheduled every 6 months, 12 months or 24 months, respectively	Study perspective: Government Time horizon: Lifetime Discount rate: 5% (varied between 2.5% and 10%) Currency/price year: US\$ in 1990 prices	focal) ICER: None stated Sensitivity analyses: One-way Outcomes: Person years of sight saved Costs: Screening and treatment and cost of blindness ICER: None stated Sensitivity analyses: One-way	examination alone, more years of sight are saved than less frequent examination. Changing the frequency of screening for patients with no or mild background DR from 1 year to 2 years has no detrimental effect on years of sight saved while reducing costs. Once patients develop moderate non-proliferative or more advanced DR, savings in sight-years are sensitive to the screening interval.
Rein <i>et al</i> (2011) ⁴⁶	EE: CUA Model: Monte Carlo simulation	Hypothetical 10 million patients with T2DM with no or early DR	Four screening methods: 1. patient self-referral following visual symptoms 2. annual eye evaluation, 3. biennial eye evaluation 4. annual telemedicine screening in primary care settings	Study perspective: Societal Time horizon: Lifetime Discount rate: 3% Currency/price year: US\$ in 2010 prices	Outcomes: QALYs Costs: Intervention (including telemedicine) and treatment costs and productivity losses ICER: Cost per QALY gained Sensitivity analyses: Probabilistic	Current annual eye evaluation was costly compared with either treatment alternative. Self-referral offered the lowest costs and QALYs, followed by telemedicine, biennial evaluation and annual evaluation.
Tung <i>et al</i> (2008) ⁸	EE: CEA and CUA Model: Markov-decision type model	Community-based patients with T2DM	Five screening strategies compared with no screening: 1. annual screening 2. biennial screening 3. 3-year screening 4. 4-year screening 5-year screening	Study perspective: Not stated Time horizon: 10 years Discount rate: 5% Currency/price year: New Taiwan (NT) \$ in 2004 prices	Outcomes: Sight years saved and QALYs Costs: Direct costs of screening, drugs and treatment (laser photocoagulation and surgery) ICER: Cost per sight year saved and cost per QALY gained Sensitivity analyses: One-way	Annual screening should be conducted.
Vijan <i>et al</i> (2000) ⁴⁷	EE: CUA Model: Markov model.	Hypothetical T2DM patients	Four screening strategies compared with no screening: 1. annual screening 2. biennial screening 3. 3-year screening 4. 5-year screening	Study perspective: Third party payer (government and societal used in sensitivity analyses) Time horizon: Lifetime Discount rate: 3% Currency/price year: US\$—year not stated	Outcomes: QALYs Costs: Screening, ophthalmology visits, laser treatment and angiogram ICER: Cost per QALY gained Sensitivity analyses: One-way and multivariate	Screening every other year maybe the most cost-effective option. with the option of tailoring screening to the needs of different individuals.

CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DR, diabetic retinopathy; EE, economic evaluation; GP, General Practitioner; ICER, incremental cost-effectiveness ratio; POST, Patient Orientated Simulation Technique; PROPHET, PROspective Population Health Event Tabulation; QALY, quality-adjusted life year; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

every 2 years remained cost-effective.⁴⁶ For those who already have retinopathy a greater degree of surveillance would be required, but results were mixed, depending on models used and assumptions made. Once retinopathy was detected, the screening interval should be 6 months;^{44 45} in contrast, two studies concluded that annual screening should be used;^{9 43} and the final study found that the most cost-effective option was to carry out two screening tests at 30-month intervals.⁴¹

DISCUSSION

Principal findings

Studies broadly supported extending screening intervals beyond 1 year for patients with T2DM at low risk of progression to DR, such as those with well controlled diabetes on dietary treatment, with low HbA1c and no background retinopathy. Inevitably the lack of comparators in the evidence base introduces significant bias including selection bias and attrition bias—with those at least risk most likely to participate and those at most risk most likely to drop out. Both of these problems bias findings, that is, screening every 2 years will appear to be more beneficial and less risky than in fact it is. Other problems in the studies identified included heterogeneity in screening methods, in grading protocols, in defining risk, and uptake. Cost-effectiveness findings were conflicting. Three studies^{9 44 43} concluded that annual screening remains the most cost-effective. Risk stratification models show promise in providing tailored screening intervals based on individual risk factors, but none have been externally validated.

Strengths and weaknesses

This review is systematic with a priori study eligibility criteria and rigorous methods in selection, extraction, quality appraisal and synthesis of evidence. We were unable to pool evidence due to heterogeneity, and to assess publication bias. A thorough quality assessment was undertaken using recognised checklists.

None of the included studies allowed for direct comparison of different screening intervals in relation to the incidence of retinopathy or vision loss. Economic analyses were based on hypothetical simulation models. Strengths of the evidence base include: good reporting, real-world setting,^{1 26 32 34–36} large sample size,^{1 26 39 40} adequate methods of participant recruitment and sufficient follow-up.^{26 27 30 33 37 42} There were some notable limitations: high attrition,^{1 25 35 36} systematic differences between attendees and non-attendees and substantial heterogeneity between studies, making it difficult to compare results with regard to the occurrence or progression of retinopathy. Therefore patients with 'no existing background retinopathy' should be interpreted as 'patients in whom no evidence for background retinopathy has been found'.¹⁸ There were also difficulties in measuring other risk factors such as duration of diabetes. There may be limited applicability to adults with T1DM as only a small proportion of the studies covered this group. While we did not find sufficiently robust evidence to suggest that the screening interval could safely be extended beyond 1 year, it should be noted that equally we did not find persuasive evidence that it should not be extended. Only one risk prediction algorithm was externally validated and this was on a Danish data set³⁷ where there was a large amount of missing data, and where screening intervals are already stratified by risk so not applicable to a system such as the UK where uniform screening intervals currently pertain.

Cost-effectiveness models were of considerable complexity and included various inputs such as: progression rates between disease stages, interval between screening visits, compliance and

sensitivity, and specificity of testing. In general, the models assumed equal treatment success irrespective of screening interval; most also assumed the same compliance rate and uncertainty in patient behaviour and compliance were not adequately included (eg, differential compliance with different screening intervals⁴⁹). Individual patient characteristics which potentially determine optimal screening interval and the practicalities of providing individualised screening intervals, were not included. Most studies did include benefits of detecting other eye disorders. The clinical outcomes and methodologies of the models were heterogeneous and precluded meaningful synthesis in meta-analysis. Some studies did not assign utility scores to differing degrees of sight loss and models used averaged progression rates obtained from studies such as the UK Prospective Diabetes Study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy, in which most patients do not progress quickly. Discrete Event Simulation models use such averages which are applied to a variety of patients whose risk of progression depends on their baseline characteristics. If this is the case, it may mean that individuals who progress at the fastest rate may not be effectively captured within the model; it is these individuals who would be most likely to influence any difference in outcomes between programmes. Three studies^{6 43 45} are over 20 years old, and their validity is questionable in light of medical advances, changing prevalence and costs.

Comparison of findings with other reviews

Three previous systematic reviews have been published.^{20 49 50} The most recent of these²⁰ did not identify six of the papers we have presented in this paper including two of the largest cohorts with 14 554³⁹ and 155 114⁴⁰ patients with diabetes. For one study⁴³ authors have misinterpreted biannual (every 6 months) as biennial (every 24 months). Echouffo-Tcheugui²⁰ concluded that the screening interval could safely be extended to 2 years. Jones *et al*⁴⁹ had broad aims and examined all aspects of cost-effectiveness of DR screening. The Wessex Institute report⁵⁰ also reviewed cost-effectiveness concluding that the limited evidence base suggests that more patients may lose their sight with a 2 year interval.

Recommendations for future research

Further research is needed on:

- ▶ how 'low-risk' patients should be identified,
- ▶ how different screening and grading protocols affect performance, and
- ▶ how extending the screening interval might affect uptake.
- ▶ An RCT randomising either individual patients or whole screening centres to a longer interval would provide robust data upon which to base policy decisions and underpin a rigorous cost-effectiveness analysis
- ▶ Risk stratification algorithms identified in this review showed considerable promise for optimising services and minimising costs, although the cost-effectiveness of such a strategy would need to be carefully considered, and risk algorithms validated.

Implications for clinicians and policymakers

Based on the strength of the evidence identified in this review, we cannot reliably predict the outcome of a change in screening intervals. While the invited interval might be 2 years, in practice with lower uptake the screening interval might extend well beyond this for some patients. Additionally, there would need to be a reliable and uniform method for identifying and recording risk of progression to STDR. Previous retinopathy screening

results allow for risk stratification. This is a powerful predictor of risk, but is not currently measured consistently across the UK.¹⁸ Detection and treatment for diabetes has improved in recent years, with diabetes more likely to be diagnosed and treated. This in turn will reduce the risk of progression of DR.

There is a broader question about the level of evidence required to make changes to an existing screening programme. While the best evidence would be from RCTs or meta-analysis of several trials, this is not a practical or affordable approach for every decision on a screening programme. Most often after implementation, the screening programme will be extended, either in frequency or in the eligible population, a phenomenon known as ‘mission creep’. Here, we considered the minimum level of evidence to be a two arm randomised or non-randomised trial investigating the effect of a 1-year interval vs a 2-year interval on retinopathy rates and uptake, with appropriate cost-effectiveness analysis. This was not available in the literature.

CONCLUSION

Observational and economic modelling studies in low-risk patients show little difference in clinical outcomes between screening intervals of 1 year or 2 years. The lack of experimental research design and heterogeneity in definition of those at low risk limits the reliability and validity of this conclusion. Cost-effectiveness literature provides mixed results. While we did not find sufficiently robust evidence to suggest that the screening interval could safely be extended beyond 1 year, it should be noted that equally we did not find persuasive evidence that it should not be extended. However we consider that current evidence does not support a move to extend the screening interval beyond 1 year.

Contributors RL performed the searches. RL and DT conducted the screening, data extraction and quality assessment for the clinical papers. HM led the data extraction and quality assessment for the cost-effectiveness papers. ST-P reviewed the risk stratification algorithms and drafted the paper. All authors were involved in reviewing, commenting, and editing drafts of the manuscript and all approved of the final manuscript and take responsibility for the integrity of the data and the accuracy of the data analysis. ST-P is guarantor.

Funding This work was supported by The Four Nations diabetic retinopathy steering group on behalf of the UK National Screening Committee, part of Public Health England. The funders provided feedback on the protocol and the draft report, but all decisions regarding study design; collection, analysis, and interpretation of data; the writing of the report; and submission for publication were taken independently by the study team. ST-P is supported by a postdoctoral fellowship from the National Institute for Health Research (NIHR). AC is supported by the NIHR Collaboration for Leadership in Applied Health Research and Care West Midlands at University Hospitals Birmingham NHS Foundation Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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