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

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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 generalisablity 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 review[20] 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 statement[21] and an adapted checklist for economic

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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 intervals[25] 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

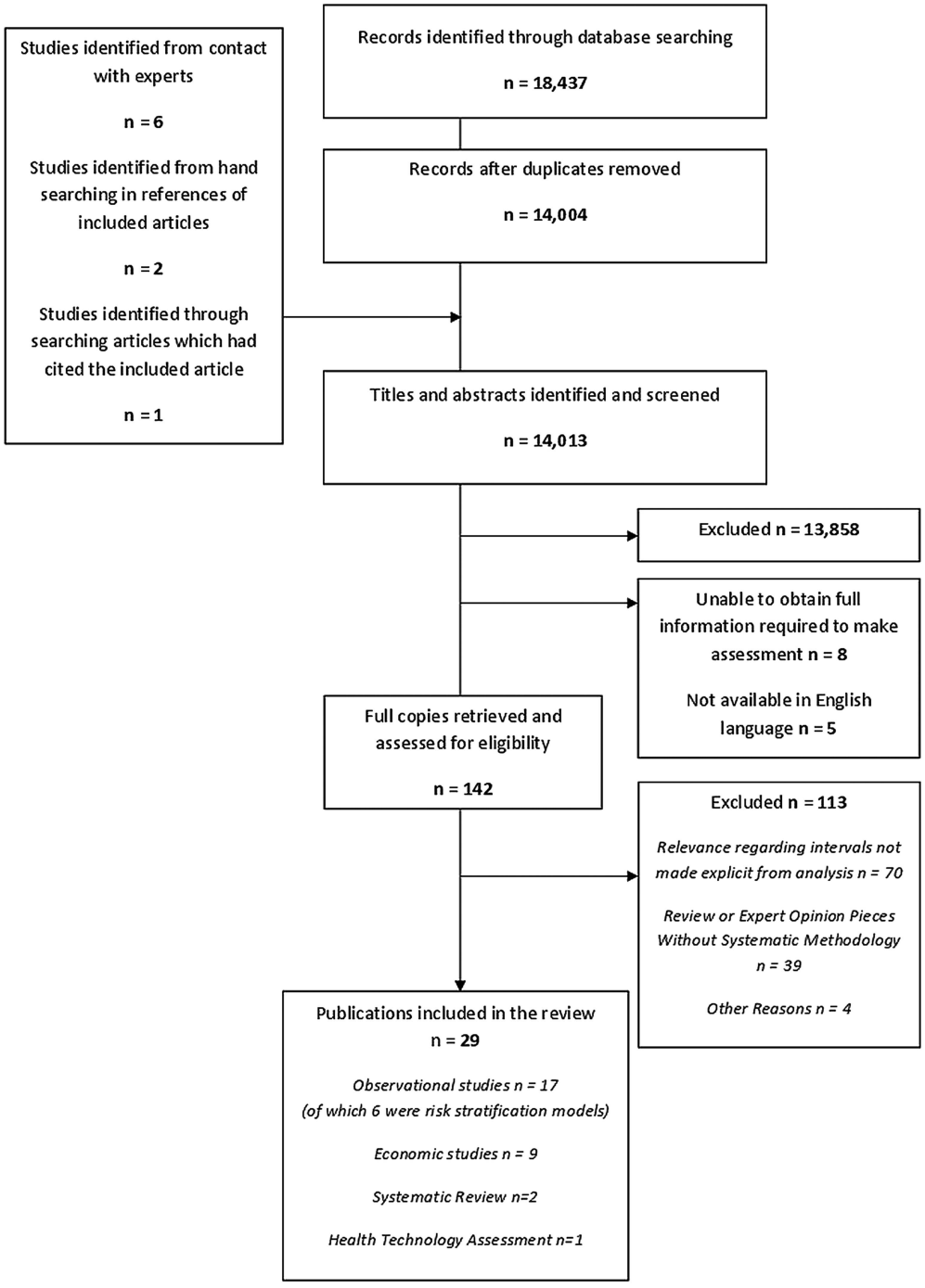

Figure 1 PRISMA flow chart of systematic review.

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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] Australia[34] 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 study[1] 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 model[37] 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 algorithm[37] 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 checklist[21] were well reported (see online supplementary appendix 4). Using the Phillips[24] 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

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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 *et al*[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 *et al*[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 *et al*[29]	Yes	No information	No information	No information	Yes	No information	No information	No information	No information
Looker *et al*[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 *et al*[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 *et al*[25]	As Jones *et al*								
Olafsdóttir and Stefánsson[30]	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		

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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?
						on a Snellen chart at 6 m with the best refractive correction			
Soto-Pedre *et al*[31]	No Information	One fundus photograph centred on the macula of each eye taken with 45° non-mydriatic retinal camera	Instant film Polaroid	Canon CR4-45NM	No	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 *et al*[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 *et al*[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-mydriatic 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 *et al*[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 *et al*[36]	As Younis 2003b								

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

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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 *et al* (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 *et al* (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 *et al* (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 *et al* (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 *et al* (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

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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
			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		focal) ICER: None stated Sensitivity analyses: One-way	examination alone, more years of sight are saved than less frequent examination.
Javitt *et al* (1994)[6]	EE: CEA Model: Simulation model using PROPHET	Hypothetical cohort of patients with T2DM 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	Outcomes: Person years of sight saved Costs: Screening and treatment and cost of blindness ICER: None stated Sensitivity analyses: One-way	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 *et al* (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 *et al* (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 *et al* (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.

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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 set[37] 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 intervals[49]). 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 these[20] did not identify six of the papers we have presented in this paper including two of the largest cohorts with 14 554[39] and 155 114[40] patients with diabetes. For one study[43] authors have misinterpreted biannual (every 6 months) as biennial (every 24 months). Echouffo-Tcheugui[20] 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 report[50] 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

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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.

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REFERENCES

1 Thomas RL, Dunstan F, Luzio SD, *et al*. Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis. *BMJ* 2012;344:e874.
2 Saadine JB, Fong DS, Yao J. Factors associated with follow-up eye examinations among persons with diabetes. *Retina* 2008;28:195–200.
3 Scanlon PH. The English national screening programme for sight-threatening diabetic retinopathy. *J Med Screen* 2008;15:1–4.
4 Agardh E, Agardh CD, Hansson-Lundblad C. The five-year incidence of blindness after introducing a screening programme for early detection of treatable diabetic retinopathy. *Diabet Med* 1993;10:555–9.
5 Stefansson E, Bek T, Porta M, *et al*. Screening and prevention of diabetic blindness. *Acta Ophthalmol Scand* 2000;78:374–85.
6 Javitt JC, Aiello LP, Chiang Y, *et al*. Preventive eye care in people with diabetes is cost-saving to the federal government: implications for health-care reform. *Diabetes Care* 1994;17:909–17.
7 Backlund LB, Algvere PV, Rosenqvist U. New blindness in diabetes reduced by more than one-third in Stockholm County. *Diabet Med* 1997;14:732–40.
8 Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010;376:124–36.
9 Tung TH, Shih HC, Chen SJ, *et al*. Economic evaluation of screening for diabetic retinopathy among Chinese type 2 diabetics: a community-based study in Kinmen, Taiwan. *J Epidemiol* 2008;18:225–33.
10 Scanlon PH, Malhotra R, Greenwood RH, *et al*. Comparison of two reference standards in validating two field mydriatic digital photography as a method of screening for diabetic retinopathy. *Br J Ophthalmol* 2003;87:1258–63.
11 Olson JA, Strachan FM, Hipwell JH, *et al*. A comparative evaluation of digital imaging, retinal photography and optometrist examination in screening for diabetic retinopathy. *Diabet Med* 2003;20:528–34.
12 Mitchell P, Foran S, Wong TY, *et al*. *Guidelines for the Management of Diabetic Retinopathy*. Australia: Australian Diabetes Society for the National Health & Medical Research Council, 2008. Contract No: 4176.
13 Stefánsson E. Diabetic retinopathy screening. *Pediatrics* 2006;117:586.
14 Socialstyrelsen. National guidelines for diabetes. Stockholm, Sweden, Socialstyrelsen. 2010. http://wwwsocialstyrelsense (accessed May 2011).
15 Hutchinson A, McIntosh A, Peters J, *et al*. *Clinical guidelines and evidence review for Type 2 diabetes: diabetic retinopathy: early management and screening*. Sheffield: ScHARR, University of Sheffield, 2001.
16 Diabetic Retinopathy Summary Benchmark—2013. American Academy of Opthalmology, 2013.
17 Ting D, Ng J, Morlet N, *et al*. Diabetic retinopathy-screening and management by Australian GPs. *Aust Fam Physician* 2011;40:233–8.
18 Stratton IM, Aldington SJ. Risk stratification for diabetic eye screening. *Diabetologia* 2014;57:259.
19 McGhee S, Harding SP, Wong D. Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy by Aspelund et al(2011) *Diabetologia* 54:2525–2532. *Graefes Arch Clin Exp Ophthalmol* 2012;250:477–8.
20 Echouffo-Tcheugui JB, Ali MK, Roglic G, *et al*. Screening intervals for diabetic retinopathy and incidence of visual loss: a systematic review. *Diabet Med* 2013;30:1272–92.
21 Husereau D, Drummond M, Petrou S, *et al*. Consolidated health economic evaluation reporting standards (CHEERS) statement. *BMC Med* 2013;11:80.
22 Philips Z, Bojke L, Sculpher M, *et al*. Good practice guidelines for decision-analytic modelling in health technology assessment. *Pharmacoeconomics* 2006;24:355–71.
23 Unit PHR. *The critical skills appraisal programme: making sense of evidence*. England: Public Health Resource Unit, 2006. http://www.casp-uk.net/
24 Steyerberg EW, Moons KG, van der Windt DA, *et al*. Prognosis research strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 2013;10:e1001381.
25 Misra A, Bachmann M, Greenwood R, *et al*. Trends in yield and effects of screening intervals during 17 years of a large UK community-based diabetic retinopathy screening programme. *Diabet Med* 2009;26:1040–7.
26 Jones CD, Greenwood RH, Misra A, *et al*. Incidence and progression of diabetic retinopathy during 17 years of a population-based screening program in England. *Diabetes Care* 2012;35:592–6.
27 Mehlsen J, Erlandsen M, Poulsen PL, *et al*. Identification of independent risk factors for the development of diabetic retinopathy requiring treatment. *Acta Ophthalmol* 2011;89:515–21.
28 Mehlsen J, Erlandsen M, Poulsen PL, *et al*. Individualized optimization of the screening interval for diabetic retinopathy: A new model. *Acta Ophthalmol* 2012;90:109–14.
29 Kristinsson JK, Gudmundsson JR, Stefansson E, *et al*. Screening for diabetic retinopathy. Initiation and frequency. *Acta Ophthalmol Scand* 1995;73:525–8.
30 Olafsdóttir E, Stefánsson E. Biennial eye screening in patients with diabetes without retinopathy: 10-year experience. *Br J Ophthalmol* 2007;91:1599–601.
31 Soto-Pedre E, Hernaez-Ortega MC, Vazquez JA. Six-year retrospective follow-up study of safe screening intervals for sight-threatening retinopathy in patients with diabetes mellitus. *J Diabetes Sci Technol* 2009;3:812–18.
32 Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. *Diabetes Care* 2011;34:1318–9.
33 Kohner EM, Stratton IM, Aldington SJ, *et al*. Relationship between the severity of retinopathy and progression to photocoagulation in patients with Type 2 diabetes mellitus in the UKPDS (UKPDS 52). *Diabet Med* 2001;18:178–84.
34 Maguire A, Chan A, Cusumano J, *et al*. The case for biennial retinopathy screening in children and adolescents. *Diabetes Care* 2005;28:509–13.

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35 Younis N, Broadbent DM, Harding SP, *et al*. Incidence of sight-threatening retinopathy in Type 1 diabetes in a systematic screening programme. *Diabet Med* 2003;20:758–65.
36 Younis N, Broadbent DM, Vora JP, *et al*. Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: A cohort study. *Lancet* 2003;361:195–200.
37 Aspelund T, Thornorisdottir O, Olafsdottir E, *et al*. Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy. *Diabetologia* 2011;54:2525–32.
38 Semeraro F, Parrinello G, Cancarini A, *et al*. Predicting the risk of diabetic retinopathy in type 2 diabetic patients. *J Diabetes Complications* 2011;25:292–7.
39 Stratton IM, Aldington SJ, Taylor DJ, *et al*. A simple risk stratification for time to development of sight-threatening diabetic retinopathy. *Diabetes Care* 2013;36:580–5.
40 Looker HC, Nyangoma SO, Cromie DT, *et al*. Predicted impact of extending the screening interval for diabetic retinopathy: the Scottish Diabetic Retinopathy Screening programme. *Diabetologia* 2013;56:1716–25.
41 Brailsford SC, Gutjahr WJ, Rauner MS, *et al*. Combined discrete-event simulation and ant colony optimisation approach for selecting optimal screening policies for diabetic retinopathy. *Computational Management Science* 2007;4:59–83.
42 Chalk D, Pitt M, Vaidya B, *et al*. Can the Retinal Screening Interval Be Safely Increased to 2 Years for Type 2 Diabetic Patients Without Retinopathy? *Diabetes Care* 2012;35:1663–8.
43 Dasbach EJ, Fryback DG, Newcomb PA, *et al*. Cost-effectiveness of strategies for detecting diabetic retinopathy (Structured abstract). *Med Care* 1991;29:20–39.
44 Davies R, Roderick P, Canning C, *et al*. The evaluation of screening policies for diabetic retinopathy using simulation. *Diabet Med* 2002;19:762–70.
45 Javitt J, Canner J, Frank R, *et al*. Detecting and treating retinopathy in patients with type I diabetes mellitus. A health policy model. *Ophthalmology* 1990;97:483–94; discussion 94-5.
46 Rein DB, Wittenborn JS, Zhang X, *et al*. The cost-effectiveness of three screening alternatives for people with diabetes with no or early diabetic retinopathy. *Health Serv Res* 2011;46:1534–61.
47 Vijan S, Hofer TP, Hayward RA. Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus. *JAMA* 2000;283:889–96.
48 Vickers AJ, Cronin AM. Everything you always wanted to know about evaluating prediction models (but were too afraid to ask). *Urology* 2010;76:1298–301.
49 Jones S, Edwards R. Diabetic retinopathy screening: a systematic review of the economic evidence. *Diabet Med* 2009;27:249–56.
50 Mellanby A, Milne R. Research WIfH, Development SD, Committee E. *Reducing the interval for diabetic retinal screening*. Wessex Institute for Health Research and Development, 1999.

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Appendix 1: Search Strategy Terms

Table A: Search strategy terms		
Rows combined individually with 'OR'. Results of individual Row searches (Rows A, B and C) combined with 'AND'		
ROW A	**ROW B**	**ROW C**
Retinopathy.mp. or exp Diabetic Retinopathy/	screening.mp. or exp Mass Screening/	polic*.mp.
exp Diabetes Mellitus, Type 2/ or exp Diabetes Mellitus/ or diabet*.mp. or exp Diabetes Mellitus, Type 1/	screen*.mp.	. exp Policy Making/ or exp Public Policy/ or policy.mp. or exp Health Policy/ or exp Policy/
exp Diabetic Retinopathy/ or retinopath*.mp.		intervention*.mp. or exp Intervention Studies/
		frequenc*.mp.
		. interval*.mp.

Appendix 2. Methodological quality of observational studies that evaluated screening programs (CASP appraisal checklist)

Item #	Agardh 2011[25]	Kohner 2001 [27]	Kristinsson 1995 [28] Olafsdottir 2007[31]	Looker 2013 [40]	Maguire 2005 [29]	Misra 2009 [30] Jones 2012 [26]	Soto-Pedre 2009 [32]	Stratton 2013 [39]	Thomas 2012 [1]	Younis 2003a [34] Younis 2003b [33]
Study design	Prospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Dynamic cohort study	Retrospective, two arm cohort	Retrospective cohort study with risk stratification	Retrospective cohort study	Retrospective cohort study
1. Did the study address a clearly focused issue?	To determine the incidence of STDR in T2DM patients without DR at baseline.	To establish the relationship between severity of DR and the progress to photocoagulation for T2DM patients.	Whether biennial examinations suffice for T1DM and T2DM patients without DR.	To establish whether there are any subgroups of the population at low risk of transition to a referable state of retinopathy in a 2 year interval.	To identify the optimum screening frequency for children and adolescents with T1DM.	To estimate incidence, prevalence, and progression rates of DR in relation to baseline DR severity and other prognostic factors in T2DM patients.	To estimate safe screening intervals for sight-threatening diabetic retinopathy.	To develop a simple model to estimate risk of STDR.	To determine the incidence of referable DR in people with T2DM over a 4 year period.	To investigate incidence of DR in relation to severity of DR in patients with T1DM and T2DM and calculate optimum screening intervals.
	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the cohort recruited in an acceptable way?	Study recruited cohort of T2DM patients at one hospital that fit criteria.	Cohort of 3,709 T2DM patients with good quality retinal photographs selected from a wider cohort.	Two Icelandic cohorts followed for comparison (81 children aged<15 and 185 adult patients with T1DM and T2DM with no retinopathy; selection process not clear, was this the total population of eligible participants?	Cohort of 155,114 people with T1DM and T2DM diagnosed before May 2008 who were screened by the Scottish Screening Service and had either no retinopathy, mild background retinopathy, observable background retinopathy or observable background maculopathy in the worst eye at baseline and at least one subsequent screen.	Cohort of 668 children and adolescents recruited from a hospital. All patients who had a baseline and at least one follow up screen before age 20 were included.	Cohort of all people with T2DM (n=20,788) identified through GP diabetes register were screened; patients with STDR were excluded. It was a dynamic cohort where individuals enter and leave the cohort at different times.	Two cohorts of patients referred to one hospital between 1998 and 2004 with at least one baseline screening and one subsequent screening. Cohort 1: (n-=286), no DR at baseline Cohort 2: Mild nonproliferative DR at baseline (n=144).	Population based cohort of 14,554 people aged 12 or over with T1DM and T2DM who were screened by the Gloucestershire Diabetic Eye Screening Service between 2005 and 2010 and had no DR or mild nonproliferative DR at two consecutive annual screenings.	Cohort of 57,199 patients with T2DM aged > 12 registered with a GP with no DR at baseline.	Cohort of all patients with T1DM (n=501) and T2DM (n=4,770) registered with GPs and screened with DR data available at baseline and at least one further screening.
	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Yes

3. Was the exposure accurately measured to minimise bias?	All patients who were available for follow up invited for assessment after 3 years. Reminders were sent to non-responders, so some may have been followed up after a longer time period. This is not reported.	Participants of underwent a full medical examination, including retinal examination yearly.	Screening intervals for group 2 described as 'at least annually'; screening intervals for group 1 (children) not reported.	Patients screened yearly under a standard protocol.	Patients were followed longitudinally and different screening frequencies were observed. Interval lengths were recorded and patients were grouped by interval length for analysis.	All patients invited for screening annually, although people with clinical indications or those with questionable images or technical problems were rescreened at 6 months. It is not clear if non attendees were followed up or whether actually attendance was at sooner or later than the 12 month mark.	Study reviews all patients with a baseline screening and subsequent screening. It is not clear what the standard interval is for this cohort.	Patients screened yearly under a standard protocol.	Patients screened yearly under a standard procedure.	Patients with no DR or background DR were screened yearly. Patients with DR without sight threatening maculopathy were followed up every 6 months.
	Can't tell	Yes	Can't tell	Yes	Yes	Can't tell	Can't tell	Yes	Yes	Yes
4. Was the outcome accurately measured to minimise bias?	Eyes were assessed using the same method and graded by specially trained ophthalmic nurses using a validated international scale. HbA1c was measured using the same method.	The same protocol for screening and grading was used for the cohort. All images were graded by physicians at the Retinopathy Grading Centre.	Standardised examination and reporting method used across both patient groups. Retinopathy reported for each patient was based on the worst eye.	Methodology for screening and quality assurance is not described.	Outcomes were verified on a proportion of photographs graded independently by a second grader for quality control and 'good agreement' was found between the graders. Outcome classification was standardised.	Some measurement bias is possible over the period of the study. Two different methods of imaging and grading systems (scales) were used over the period of the study.	Standard procedure for screening described for all patients.	Standard protocol for screening and grading used for all patients.	Standard protocol for screening and grading used for all patients.	Standardised protocol for screening, grading (Wisconsin algorithm), and reporting DR. Provision for rescreening or validating results in place.
	Yes	Yes	Yes	Can't tell	Yes	No	Yes	Yes	Yes	Yes
5. Have the authors identified all important confounding factors?	The authors measured HbA1c at baseline showing no significant difference between attendees and non-attendees.	The study did not consider confounders such as HbA1c or therapy allocation.	For children (group 1), onset of puberty was considered. Age at onset and duration of disease were reported for adults in group 2.	At baseline, BMI, HbA1c, blood pressure were recorded nearest to the initial screening. Age, sex, and diabetes duration were recorded for T1DM and T2DM.	At each eye examination, height, weight, pubertal staging, blood pressure and HbA1c and DM duration were recorded. Other confounders	Age, duration of DM, DM treatment and hypertension treatment were measured at baseline. Smoking history, blood glucose, blood pressure,	At baseline, Age, sex, glycated hemoglobin level, type of DM, diabetes duration and treatment of DM were recorded. Number of	The study did not consider confounders, but are allocated to a group in accordance to identified risk factors.	Age at DM diagnosis, duration of DM, DM treatment and sex were recorded at baseline. HbA1c percentage was not used in the study.	The authors considered age, duration of DM, age at diagnosis, follow up duration, number of screening visits, sex and treatment at baseline.

	Age at diagnosis, duration of DM and DM treatment method were recorded.		HbA1c was not reported or analysed in either group.		such as DM treatment were not recorded.	sex and ethnicity were not recorded as part of the screening programme.	screening visits was not recorded.			
	Yes	No	No	Yes	Yes	No	Yes	No	No	Yes
6. Was the follow up of the subjects complete enough?	Of the 1,691 recruited subjects 1,322 were followed up. The authors state that HbA1c levels did not differ in those with and without follow up data.	The study only included patients who had all the required follow up images and data.	The study only included patients who were still alive at the end of the 10 year follow up period. There was no information on patients who may have died during the follow-up whose outcomes may have been different to the outcomes in the overall group.	The study only included patients who had all the required follow up images and data	Only patients with a baseline and follow up screen were included. It appears that screens were conducted as a diagnostic rather than as a screening programme, meaning that these findings could perhaps represent either more unwell children or children or families that were more likely to seek medical support.	Patients with evidence of retinopathy were referred to the hospital eye service and the authors report that the quality of data referring to risk factors and outcomes was poor meaning that they were unable to provide analysis for these patients.	The study only included patients who had all the required follow up images and data.	The study only included patients that met the criteria for recruitment	Of the 57,199 individuals recruited at baseline, 7,436 (13%) did not attend a further screening. Of the 7,436 subjects, 449 were not eligible for a second screen (recruited less than 12 months from the end of the study). It is unclear why the remaining 6,987 patients did not attend the second screen The authors stated that the non-attendees were more likely to be older and have a longer duration of DM.	A large proportion of patients (31%, n=2388) had not undergone a repeat screening by the end of the study period and were not included in the cohort analysis of baseline data plus one other screen. Non-attenders to a second appointment may have differed from attenders factors which could affect onset of DR. Non-participation rate in T1DM patients was high. Of the 1050 eligible patients, only 79% (n=831) accepted invitation for a baseline screen, of whom only 501 participated in a follow up screen.
	Yes	No	Can't tell	No	No	No	No	No	No	No
7. What are the results of this study?	See Table 1	See Table 1	See Table 1	See Table 1	See Table 1	See Table 1	See Table 1	See Table 1	See Table 1	See Table 1
8. How precise are	95% CIs not reported	The proportion of patients requiring	Only proportions of outcomes are	P-values were used when comparing	The authors used General Estimating	Annual incidence for was provided	95% CIs were reported for all	Hazard ratios that compare the risk	The reported incidence or	95% CIs were reported for all

the results?		photocoagulation 95% CIs (reported only graphically) were wider for patients with severe DR, probably due to smaller numbers and as time progresses	reported for both groups. No further statistical analysis is provided. 95% CIs not reported	incidence data between patients with no visible retinopathy and mild background retinopathy and between no visible retinopathy and observable retinopathy and maculopathy.	Equations (GEEs) to compare risk of retinopathy at yearly intervals to the baseline based on the available data for the whole group and the two age divisions. P-values were used when comparing incidence data between patient groups for whom the corresponding estimates were less precise.	with 95% CIs, which are wider for non-proliferative DR as numbers are smaller, particularly as time progresses. 95% CIs were narrow for up to 4 years for patients with no retinopathy at baseline.	findings; although the sample size is much smaller than other studies.	of DR progression between groups are reported with 95% confidence intervals. P Values are used when comparing the incidence of more serious DR between groups.	progression of DR from 1 to 4 years had narrow 95% CIs.	findings; given the large study group, the reported estimates were precise.
	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Yes	Can't tell	Yes	Yes	Yes
9. Do you believe the results?	Measurement and grading methods are robust and characteristics of followed up and non-followed up patients are reported as not differing making the results believable.	The cohort is large and the design of the study is robust with each patient having the same data evaluated with the same protocol making the results believable.	For both groups, the study population is small. The lack of precision and short follow up periods would make the findings difficult to rely, however considered in the wider context of the review the findings are in line with other studies	Large cohort. As the screening and grading methodology is not clearly outlined, it is not possible to be assured of the results reported for individual patients.	The findings are in line with findings from other groups and significance is tested which makes the findings believable. However the numbers are much smaller than other studies which would promote caution if relying on these findings only.	The lack of description of the characteristics of those not attending for screening or taking part in the programme is concerning as they may have characteristics such greater non-compliance to diabetes treatment that may have affected progression to retinopathy.	The findings are in line with findings from other groups and significance is tested which makes the findings believable. It is useful to see the two cohorts analysed separately although the study population for each cohort is small. The authors report the limitations of the specificity of the screening methodology.	Large cohort with robust recruitment and measurement methods.	The cohort is large and the authors are careful to report any potential limitations of the study. The analysis of the results is robust, making the findings believable.	The study had a robust methodology and the authors acknowledge the limitations of the smaller sample size and the impact of the non-participants on the findings. The results are more believable for the larger group of patients with no DR than for those with mild pre-proliferative DR at baseline.
	Yes	Yes	No	Can't tell	Yes	Can't tell	Yes	Yes	Yes	Yes

10. Can the results be applied to the population of England?	Compliance to screening has been reported to be higher in Sweden than in England meaning that non-compliance may lead to a longer than 3 year interval in a larger subgroup of a screening cohort.	Study uses a sample of UK patients making the findings applicable to the rest of England acceptable.	The study uses a small Icelandic population which makes the findings less applicable to the English population as characteristics such as screening compliance and DM control can vary	Study uses a Welsh population and is broadly applicable to a UK population.	The study is based in Australia, which in terms of access to care and treatment and overall patient characteristics is similar to an English population.	Study is of a large population in the UK, making application to the rest of England acceptable.	The study uses a Spanish population in one small area. No information is given about the screening policy or compliance in a Spanish population.	The study uses a population form Gloucestershire in England which is broadly comparable to the UK population	Study uses a Welsh population and is applicable to a UK population.	Study is of a large population in Liverpool, UK making application to the rest of England applicable.
	Can't tell	Yes	No	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes
11. Do the results fit with other evidence?	The authors conclude that longer screening interval is safe for low risk T2DM patients with no retinopathy; however, the recommendation for a 3 year interval is longer than other studies recommend.	As with other studies, the authors found that retinopathy incidence was low in patients without retinopathy over a 3 - 6 year period.	The authors conclude that biennial screening for both T1DM and T2DM without retinopathy is reasonable. Other studies have reported that people with T1DM should remain on yearly intervals.	As with other studies, the authors report lower risk of retinopathy in patients with T2DM and no background retinopathy and with no visible retinopathy at two consecutive screens. Although the study does not go as far as recommending biennial screening they state that the risk of low risk patients developing retinopathy is small.	This study in children, finds that STDR is unlikely to occur within an interval of 2 years in patients with no baseline DR. As with other studies, the authors recommend that upon detection of retinopathy, frequency should change to annual.	As with other studies, the authors find incidence of retinopathy over 5-10 years in patients with no retinopathy at first screen as low, recommending that intervals longer than one year may be appropriate for this group of people.	As with other studies, the authors report low incidence of retinopathy in patients with no retinopathy at baseline over a 6 year period. As with other studies, poor metabolic control is identified as a risk factor. The recommendation for a 3-4 year interval for patients with no retinopathy baseline is longer than other studies recommend.	As with other studies, the authors report that those in higher risk groups (defined by presence of DR at baseline or previous screen) are most likely to progress to more serious DR. The study does not make explicit recommendations on the frequency of screening.	Similarly to other studies, the authors recommend longer intervals for patients with no retinopathy at baseline. Identified risk factors were similar to those identified in other studies (age, insulin use and duration of diabetes).	Results of this generally fit with the other studies that include a small cohort of T1DM patients. Optimum screening interval of 5.7 years for a 95% likelihood of remaining free of STDR for those without DR at baseline is much longer than the intervals recommended by other studies Optimum screening interval for those with background retinopathy was 1.3 years, which is more in line with findings from other studies.
	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	STDR=sight-threatening diabetic retinopathy; T1DM= type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; DR=diabetic retinopathy; DM=diabetes mellitus ; 95% CI=95 percent confidence interval									

Appendix 3: 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, E. and P. Tababat-Khani	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 et.al	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, U.K.) with 458 fields and Orion Eyecap and DRSS digital imaging software.	No information	1990 to 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 (R.H.G.). From 2000: seven primary graders	Yes. Nationally accredited arbitration grader	No information
Kohner et.al	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	No information	Only patients with a set of good quality images of both eyes were included in the study.	No information

						features.			
Kristinsson, J. K., et al.	Yes	No information	No information	No information	Yes	No information	No information	No information	No information
Looker et al.	If required	Single field	Digital photograph	No information	Slit lamp outcomes were not available for all patients, but were available results were used.	Scottish grading system	No information	No information	No information
Maguire et.al	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.	Early Treatment Diabetic Retinopathy Study 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 et.al	AS JONES et al								
Ólafsdóttir et.al	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 on a snellen chart at 6 m with the best refractive correction	Screened by an ophthalmologist		
Soto-Pedre et al.	No Information	One fundus photograph centred on the macula of each eye taken with 45° nonmydriatic retinal camera	Instant film Polaroid	Canon CR4-45NM	No	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 et al.	Yes	Two standard 45 fields – Macular and	Digital colour retinal	No information	No information	Grading based on the Early Treatment	Trained assessors in a central location to	Internal and external quality	No information

		disc centred - per eye	photographs			of Diabetic Retinopathy Study (ETDRS) severity scale Background retinopathy defined using the R1M0 category on the English NHS Diabetic Eye Screening Programme.	the screening venues	assured reading process that reaches national recommendations.	
Thomas et.al	Tropicamide (applied to each eye 15 minutes before screening	Two 45 degree digital retinal images per eye - one macular centred and one nasal field	Non-mydriatic 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 3m Snellen chart		Retinal images transferred to a central reading centre for grading
Younis et.al 2003a	1% tropicamide with or without phenylepherine	Three overlapping non-stereoscopic 33mm transparency photographs of each eye	Either Canon CR4-45NM with 45 degree fields or a Topcon TRC 50 SX camera with 50 degree fields.	No information	Patients with ungradable images or STDR invited for slit lamp biomicroscopy by specialists in medical retinal disease.	STDR defined as moderate pre-proliferative 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, et al. 2003b	As Younis 2003b								

Appendix 4: Critical appraisal of the economic evaluation studies using the CHEERS checklist

CHEERS checklist (Husereau et al, 2013)	Brailsford et al (2007)	Chalk et al (2012)	Dasbach et al (1991)	Davies et al (2002)	Javitt et al (1990)	Javitt et al (1994)	Rein et al (2011)	Tung et al (2008)	Vijan et al (2000)
Title and abstract									
1 Title: Identify the study as an economic evaluation, or use more specific terms such as ``cost-effectiveness analysis``, and describe the interventions compared.	N	N	Y	N	N	Y	Y	Y	Y
2 Abstract: Provide a structured summary of objectives, methods including study design and inputs, results including base case and uncertainty analyses, and conclusions.	N	Y	N	Y	N	Y	Y	Y	Y
Introduction									
3 Background & objectives: Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Y	Y	Y	N	Y	Y	Y	Y	N
Methods									
4 Target Population and Subgroups: Describe characteristics of the base case population and subgroups analysed including why they were chosen.	Y	Y	Y	Y	Y	Y	Y	Y	Y
5 Setting and Location: State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Y	Y	Y	Y	Y	N	Y	Y	Y
6 Study perspective: Describe the perspective of the study and relate this to the costs being evaluated.	N	N	Y	N	Y	Y	Y	N	Y
7 Comparators: Describe the interventions or strategies being compared and state why they were chosen.	Y*	Y	Y	Y	Y	Y	Y	Y	Y*
8 Time Horizon: State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Y	Y	Y	Y	Y	Y	Y	Y	Y*
9 Discount Rate: Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Y	N	Y	N	Y	Y	Y	Y	Y
10 Choice of Health Outcomes: Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Y	Y	Y	Y	Y	Y	Y	Y	Y
11a Measurement of Effectiveness - Single Study-Based Estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	N/A	N/A	Y	N/A	N/A	N/A	N/A	Y	N/A
11b Measurement of Effectiveness - Synthesis-based Estimates: Describe fully the methods used for identification of included studies and clinical effectiveness data synthesis of clinical effectiveness data.	N	Y	N/A	Y	Y	Y	Y	N/A	Y
12 Measurement and Valuation of Preference-based Outcomes: If applicable, describe the population and methods used to elicit preferences for health outcomes.	N/A	N/A	N/A	N/A	N/A	N/A	Y*	Y	Y
13a Estimating Resources and Costs - Single Study-based Economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A	Y	Y	N/A	N/A	N/A	N/A	Y	N/A
13b Estimating Resources and Costs - Model-based Economic Evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe	Y	N/A	N/A	Y	Y	Y	Y	N/A	Y

primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.									
14 Currency, Price Date and Conversion: Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	N	N	Y	N	Y	Y	Y	Y	N
15 Choice of Model: Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.	Y	Y	Y	Y	Y	Y	Y	Y	Y
16 Assumptions: Describe all structural or other assumptions underpinning the decision-analytic model.	Y*	N	Y*	Y*	Y*	Y*	Y*	Y*	Y*
17 Analytic Methods: Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing or censored data, extrapolation methods, methods for pooling data, approaches to validate a model, & methods for handling population heterogeneity and uncertainty.	N	N	N	N	N	N	Y	N	N
Results									
18 Study parameters: Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. We strongly recommend the use of a table to show the input values.	N	N	Y	Y*	Y	Y	Y	Y*	Y
19. Incremental costs and outcomes: For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Y	N	N	N	N	N	Y	Y*	Y
20a Characterizing Uncertainty - Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness, parameters together with the impact of methodological assumptions.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
20b Characterizing Uncertainty - Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N	Y	Y	Y	Y	Y	Y	Y	Y
21 Characterizing Heterogeneity: If applicable, report differences in costs, outcomes or in cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Y	Y	Y	N	N	N	N	N	N
Discussion									
22 Study Findings, Limitations, Generalizability, and Current Knowledge: Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	Y*	Y	Y	Y*	Y*	Y	Y	Y*	Y
Other									
23 Source of Funding: Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other non-monetary sources of support.	N	Y	N	Y	N	Y	Y	Y	Y
24 Conflicts of Interest: Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations	N	Y	N	N	N	N	Y	N	N

Key: Y = yes, No = no, N/A = not applicable and * = partially completed

Appendix 5: Critical appraisal of the economic models using an adapted Phillips checklist

	Philips et al (2006)	Brailsford et al (2007)	Chalk et al (2012)	Dasbach et al (1991)	Davies et al (2002)	Javitt et al (1990)	Javitt et al (1994)	Rein et al (2011)	Tung et al (2008)	Vijan et al (2000)
STRUCTURE										
1	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Is the objective of the model evaluation and model specified and consistent with the stated decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Is the primary decision maker specified?	Y	N	N	N	Y	Y	N	N	N
4	Is the perspective of the model stated clearly?	N	N	Y	N	Y	Y	Y	N	Y
5	Are the model inputs consistent with the stated perspective?	UN	UN	Y*	UN	Y	Y	Y	UN	Y
6	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	Y	Y	Y	N	Y	Y	Y
7	Are the sources of the data used to develop the structure of the model specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y*	N	Y*	Y*	Y*	Y*	Y*	Y*	Y*
9	Is there a clear definition of the options under evaluation?	Y*	Y	Y	Y	Y	Y	Y	Y	Y*
10	Have all feasible and practical options been evaluated?	Y	Y	Y	Y	Y	Y	Y	Y	UN
11	Is there justification for the exclusion of feasible options?	UN	UN	UN	UN	UN	N	UN	UN	UN
12	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	Y	Y	Y	Y	Y	Y	Y
13	Is the time horizon of the model sufficient to reflect all important differences between the options?	Y	Y	Y	Y	Y	Y	Y	Y	Y*
14	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	UN	Y	N	Y	Y	N	Y	Y	Y
15	Is the cycle length defined and justified in terms of the natural history of disease?	N	N	Y	N	Y	Y	N	N	N
DATA										
16	Are the data identification methods transparent and appropriate given the objectives of the model?	Y	UN	Y	Y	Y	UN	Y	Y	Y
17	Where choices have been made between data sources are these justified appropriately?	UN	UN	UN	Y	Y	UN	Y	Y	Y
18	Where expert opinion has been used are the methods described and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
19	Is the choice of baseline data described and justified?	UN	UN	UN	N	N	N	UN	UN	UN
20	Are transition probabilities calculated appropriately?	UN	Y	Y	Y	UN	UN	Y	Y	UN
21	Has a half-cycle correction been applied to both costs and outcomes?	N	N	N	N	N	N	N	N	N
22	If not, has the omission been justified?	N	N	N	N	N	N	N	N	N

23	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y
24	Are the costs incorporated into the model justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y
25	Has the source for all costs been described?	Y	Y	Y	Y	Y	Y	Y	Y	Y
26	Have discount rates been described and justified given the target decision maker?	Y	N	Y	N	Y	Y	Y	Y	Y
27	Are the utilities incorporated into the model appropriate?	N/A	N/A	N/A	N/A	N/A	N/A	Y	Y	Y
28	Is the source of utility weights referenced?	N/A	N/A	N/A	N/A	N/A	N/A	Y*	Y*	Y
29	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	N/A	N/A	N/A	N	N/A	N/A	Y	N	N
30	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	N	N	N	N	N	N	Y	Y*	Y
31	Has heterogeneity been dealt with by running the model separately for different sub-groups?	Y	Y	Y	N	N	N	N	N	N
32	Have the results been compared with those of previous models and any differences in results explained?	Y	Y	Y	Y	Y	Y	Y	Y	Y

Key: Y = yes, No = no, UN = unclear, N/A = not applicable and * = partially completed