Rapid Literature Review:

Would changing diabetic eye screening intervals from the current annual recommendation lead to changed clinical outcomes?

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Glossary of terms

Diabetic retinopathy	Disease of the retina of the eye caused by diabetes
Background retinopathy	Small blood vessel (capillary) disease on the retina with microaneurysms, leakage and lipid deposits.
Proliferative retinopathy	As *background retinopathy* with the addition of new blood vessel formation.
Diabetic Maculopathy	Retinal diseases, particularly capillary leakage, involving or near the macula (fovea)
Photocoagulation	Small retinal scars throughout the peripheral retina
HbA1c	Glycosylated haemoglobin
Monte Carlo Simulation	Modelling method – used to model the probability of patients moving from one state of health to another (e.g. from Background retinopathy to Proliferative retinopathy)
Discrete Event Simulation	A simulation model that changes with time and is used to predict the behavior within a complex system
Sight threatening diabetic retinopathy	Defined as moderate pre-proliferative retinopathy or worse, or clinically significant maculopathy in either or both eyes. (*if different definitions are used in identified studies, this is highlighted)*

Abbreviations

T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
STDR	Sight Threatening Diabetes Retinopathy
QALY	Quality-Adjusted Life Year
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
PROBAST	Prediction Study Risk of Bias Assessment Tool
CASP	Critical Appraisal Skills Programme
CRD	Centre for Reviews and Dissemination
ICER	Incremental Cost-Effectiveness Ratio
PSA	Probabilistic Sensitivity Analysis
GEE	Generalised Estimating Equations

EXECUTIVE SUMMARY

BACKGROUND

Current National Screening Committee guidelines recommend that patients above the age of 11 with diabetes are screened annually as part of the NHS Diabetic Eye Screening Programme. Screening programmes compared to no screening have been shown to be effective in reducing blindness from diabetes related eye conditions; however, opinions on the optimal interval between screens differ. There is a growing evidence base resulting from the experiences of a number of screening programmes, recent economic evaluations and risk stratification algorithms. All National Screening Committee policies are reviewed regularly, usually on a three year cycle. The 4 Nations Diabetic Retinopathy Study Group was tasked by the National Screening Committee to review the policy for Diabetic Eye Screening. This review was commissioned to inform that review. The question posed in this rapid literature review was the following: "would changing from the annual screening interval cause a change in clinical outcomes?"

METHODS

Major medical databases Medline (OVIDSP), 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 NHS Economic Evaluation Database were electronically searched. Search terms were deliberately broad, and combined terms referring to 'Diabetes' or' Diabetic Retinopathy', 'screening' and 'intervals', 'frequency', 'intervention' or 'policy'. The searches were not limited by date or language. Reference lists of identified papers were hand searched for additional relevant materials. Study eligibility criteria included; people (any age, both genders) with diabetes (type 1 and 2) at risk of retinopathy, studies relating to all forms of diabetic retinopathy screening regardless of screening tests and mode of delivery, any study design, with an outcome of the study providing evidence as to the effectiveness of diabetic retinopathy screening. Two independent reviewers screened all identified publications at title/abstract and full text levels using a pre-defined piloted study eligibility form as well as appraised all included studies using guidelines from the Critical Appraisal Skills Programme or CHEERS checklist for economic analyses.

RESULTS

12,063 titles/abstracts were identified and screened for potential inclusion. Of these 129 publications were evaluated at full text screen level, of which 25 fitted the inclusion criteria and were included in the review. The 25 studies were observational studies of existing screening programmes or participants in ongoing trials (n=10), economic analyses (n= 10), and studies describing the development/evaluation of risk stratification algorithms (n = 5). The majority of participants in the identified studies had T2DM and had no background diabetic retinopathy at baseline. Most of the observational studies of existing programmes reported clearly formulated objectives, population characteristics, main outcome measures, and descriptions of the screening programmes. Reportedly, the studies employed adequate methods of participant recruitment, exposure measurement (i.e., types of screening tests and between-test intervals), and outcome ascertainment. The completeness of follow up varied between studies; the lowest was 69% in two studies.

All the identified observational studies identified concluded that in low risk patients the screening interval could safely be extended to beyond one year, with a number of caveats. The definition of low risk patients varied, depending on factors measured and included controlled diabetes on dietary treatment, controlled blood pressure and duration of diabetes of less than 10 years. The evidence from cost-effectiveness studies was less clear, but generally supported the findings of observational studies for adopting longer screening intervals for low risk patients and suggested that biennial screening intervals could be adopted for those with no background retinopathy. Risk stratification algorithms showed potential for safely increasing the screening interval based on individual risk factors, but none were externally validated on a UK cohort.

CONCLUSIONS

The current evidence limited to observational studies supports extension of the current annual screening interval in people with T2DM who have no existing background retinopathy, who are not on insulin treatment and who have a duration of diabetes of less than 10 years. Consideration should also be given to other risk factors such as control of diabetes (HBA1c) and patients on oral therapy for T2DM. There was insufficient evidence on patients with T1DM. The majority of economic analyses also supported the extension of screening intervals to biennial screening in low risk patients. Risk stratification algorithms showed potential for safely increasing the screening interval based on individual risk factors, but none were externally validated on a UK cohort and require testing in real world situations. In general, cautious interpretation of the findings is warranted given the observational non-comparative nature of the evidence-base. The high or unclear attrition rates in several screening program studies may have underestimated the incidence

of diabetes related retinopathy progression or its complications. Furthermore, the majority of evidence available is from studies where people should have attended annual screening and instead have attended either more or less frequently than required. These people may not be typical of the whole screened population and therefore have differing risk factors for progression to sight threatening retinopathy. In future, well designed randomized or quasi-randomized comparative trials of screening programs using different screening intervals are needed to draw more definitive conclusions.

1. BACKGROUND

1.1 Introduction

Diabetic retinopathy is a major cause of vision loss and blindness. The NHS Diabetic Eye Screening Programme is a systematic population based screening programme that aims to offer annual screening for patients with diabetes aged 11 years and above. A number of studies have demonstrated the effectiveness of screening programmes for diabetic retinopathy in achieving the aims of reducing diabetes related blindness [1, 2].

The 4 Nations Study Group is tasked with conducting a review of the UK National Screening Committee's policy on the current Diabetic Eye Screening Programme. This Rapid Literature Review provides a synthesis of the available literature to provide evidence about whether changing screening intervals for diabetic eye screening from the currently recommended annual screening will lead to a change in clinical outcomes. The protocol for this review was approved by the 4 Nations Diabetic Retinopathy Steering Group.

1.2 The current situation

The prevalence of both type 1 (T1DM) and type 2 (T2DM) diabetes is increasing, with a projected doubling of new cases of T1DM in European children younger than 5 years and a rise in prevalent cases of 70% from 2005 to 2020 [3], this is alongside an expected 20% rise in cases of T2DM from 2000 to 2036 [4]. Together with the rising prevalence of diabetes, there has been a change in the profile of risk factors for retinopathy in the population potentially leading to a higher workload for screening programmes. A number of studies [5-8] have concluded that the interval between screening appointments could be increased for selected groups of people at lower risk of developing diabetic retinopathy. Such a scenario could enable resources for diabetes care to be more effectively distributed.

There are, however, arguments against longer intervals between screening appointments. From an economic perspective and patient satisfaction perspective there are potentially additional benefits from the eye examination beyond diabetic retinopathy identification, for example an opportunity to

reinforce health promotion messages, maintaining contact with patients and the discovery of other potentially blinding disorders, albeit beyond the current remit of the English programme. When considering clinical outcomes, there is a concern that longer screening intervals may affect the perception of risk in some individuals with diabetes, where an increased interval conveys an impression that visual loss is an unlikely event leading to lower uptake of screening. As many patients fail to comply strictly to the annual interval, there is concern that a biennial interval may cause delay beyond the two year mark and thus increase the number of cases of needless blindness [9].

Additionally, the practical issues of implementation – particularly around software and software interfaces are a cause of apprehension and concerns remain that a recommendation for biennial or other screening interval might influence patient behaviour, and have subsequent impact on the cost-effectiveness of screening programmes [10].

The decision for annual screening was based on consensus opinion [11, 12], and due to the nature of screening programmes, and the practical difficulties, randomised control trials have not been conducted.

1.3 A case for review

Nearly ten years ago there was a call for further research to demonstrate both effectiveness in achieving significant reduction in vision loss from diabetes using extended screening intervals for routine annual dilated eye examinations [13]. Demonstrating the effectiveness of non-annual screening intervals is practically difficult, with the majority of evidence available from cohorts where people should have attended annual screening and instead have attended either more or less frequently than required.

In other countries, different interval strategies have been used. In Sweden the interval for patients with diabetes type 2 and no retinopathy was increased from 2 to 3 years in 2010 [14]. Biennial screening intervals have been used for over 25 years in Iceland [15] and have been demonstrated as efficacious and safe [7]. These countries are known to have well-funded screening schemes and high uptake, and their validity in other countries has been questioned [16].

A number of seminal papers detail the progression of diabetic retinopathy [17, 18] and are highly relevant to the decision to alter or maintain current screening guidelines. However, as *Klein* [19] has highlighted in reference to the Epidemiologic Study of Diabetic Retinopathy (WESDR), these were not designed to evaluate the time period for the efficacy of different screening intervals. This rapid literature review aimed to identify, appraise, and synthesize the relevant evidence from studies from

observational studies, economic appraisals and risk algorithms which were designed to inform decisions on screening intervals, rather than capture the literature around the wider context of disease progression.

A literature review of which a sub-category was on screening intervals was published in 2009 [10] and summarised the economic evidence on diabetic retinopathy screening. One of the main concerns of this review raised was the failure of included economic modelling studies to evaluate and report an impact of screening interval on patient behaviour, compliance or reassurance.

2. AIMS AND OBJECTIVES

2.1 AIM

To determine if changes in screening intervals for diabetic eye screening from the currently recommended annual screening would lead to changed clinical outcomes.

2.2 OBJECTIVES

Objective 1: To perform systematic searches of the current literature.

Objective 2: To critically appraise the identified current literature.

Objective 3: To synthesise the findings of the literature search in a narrative format.

3. METHODS

3.1 Review Question

The structure of the review followed the suggested guidance from the Centre for Reviews and Dissemination (CRD). As suggested by the CRD guidelines [20], where only a few studies were likely to be found, the research question aims to be as inclusive as possible, with broad inclusion categories in terms of population, intervention, outcomes measured and type of study and answer defined aims and objectives. Thus, the *Population, Intervention, Comparator, Outcomes, Study Design (PICO)* criteria are broad.

As it is generally accepted that annual diabetic retinopathy screening has been effective at reducing the incidence of sight threatening diabetic retinopathy (STDR), those studies which demonstrate or provide information on systematic screening programmes other than the current, annual guidelines are included.

Population – People (any age, both genders) with diabetes (type 1 and 2) at risk of retinopathy.

Intervention – Studies relating to all forms of diabetic retinopathy screening regardless of screening tests and mode of delivery (e.g. automated grading of diabetic retinopathy).

Comparator / Control Group – Control or comparator groups as reported although absence of a control group does not preclude inclusion.

Outcomes – Evidence as to the effectiveness of diabetic retinopathy screening.

3.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were pre-determined and checked by the expert Four Nations Study Group.

Inclusion Criteria

- The publications provide information on the effectiveness of systematic diabetic retinopathy screening at intervals different to current National Screening Committee (NSC) guidelines of annual screening for people with diabetes aged 12 years or older.
- The publications explicitly specify screening interval duration, and provide some form of analysis or commentary on screening interval duration.
- Observational, cohort, case series, randomised control trial, systematic review, qualitative or health technology assessment.

Exclusion Criteria

- Publications in languages other than English
- Studies which investigate diabetic retinopathy but do not explicitly investigate screening intervals.

3.3 Search Strategy

Search terms were determined in conjunction with an Information Specialist. A systematic literature search was undertaken during July 2012. Medline (OVIDSP), 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 NHS Economic Evaluation Database were searched. Individual search strategies were used for each database. The electronic databases were searched using combination of Medical Subheadings (MeSH) and keywords or their respective alternatives in databases held on platforms other than OVID.

Searches were performed to identify literature pertaining to Diabetes or Diabetic Retinopathy, screening and intervals, frequency, intervention or policy. Searches were limited to Humans (in those databases where this was allowed). No other limits were set.

No date or language restrictions were applied and search terms were left deliberately broad. Full details of the search strategy can be found in Appendix B.

In those publications which were included, their references were hand-searched and publications which cited the included article were searched using the 'cited by' facility on PubMed Central.

All identified abstracts from each of the databases were merged together in *endnote v4*. Duplicates were removed from the publications identified using the search strategy using the 'remove duplicates' function of *endnote v4.*

3.4 Study Selection

A two stage selection procedure was undertaken to identify relevant studies. At stage one, two authors (DT and RL) independently completed an initial screening of titles and abstracts of all identified records using the inclusion/exclusion criteria by creating two shortlists. Following this process, shortlists were combined and duplicates were removed to compile a total shortlist of potentially relevant full text publications based on the information provided in their abstracts.

For the second stage, the available full publications were reviewed independently by two authors in accordance with the inclusion / exclusion criteria. Any differences in opinion were discussed and agreed with the input of a third adjudicator (AC) where required.

3.5 Data extraction strategy

Standardised data extraction sheets for the observational studies were developed in line with the requirements of the review question. The template forms were piloted and additional fields and themes included where relevant.

Data were extracted by two reviewers independently and any disagreements reconciled by a third party. The extracted data included the following: study characteristics (i.e., author, year, country, design, follow up length, sample size, information pertinent to reporting, methodological and risk of bias domains), population baseline characteristics (age, sex, diabetes type, comorbidity, duration of diabetes, other important risk factors for retinopathy), screening procedures as main intervention of focus (type of test, number of screens, length of interval between the screens), post-screening treatment details (% screened who received treatment, type of treatment), control – if applicable (type of test, number of screens, length of interval between the screens), outcome measures (type, timing of measurement, scale of measurement, measures of statistical uncertainty), and main conclusions.

Standardised data extraction sheets for the economic appraisals were developed in line with the requirements of the review question based on the findings from the CHEERS checklist [21]. Data were extracted by two reviewers independently and likewise any disagreements arising reconciled by a third party. The extracted data included bibliographic details, the type of economic evaluation,

population studied, comparators, methods (including study perspective, time horizon, and discount rate, outcomes, costs and sensitivity analyses), results and main conclusions.

All included studies were categorised by three methodological approaches:

- Screening program studies or screening undergone in the context of a trial (Assessment of clinical outcomes)
- Risk stratification models (Assessment of clinical outcomes)
- Economic appraisals (Assessment of cost-effectiveness)

3.6 Critical appraisal strategy

Screening program studies were assessed using the CASP appraisal tool [22] and checked by a second reviewer, any disagreements were discussed with a third reviewer to obtain resolution.

The risk prediction studies were not formally evaluated for quality using a checklist approach, because the most appropriate checklist for these study designs, the Prediction study risk of bias assessment tool (PROBAST) is yet to be published. The approach taken was that suggested by Steyerberg et al [23] in terms of focusing on the validation of the model rather than the development process, in particular external validation (on a separate dataset to that on which the model was developed) and impact on patient outcomes.

Economic appraisals identified in the literature search were assessed using the recently published checklist for economic evaluations: Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [21]. This new checklist has consolidated and updated previous checklists such as the Drummond and Jefferson (1996) [24] guidelines. In addition, if studies also reported an economic model, they were further assessed using the adapted checklist for critical appraisal for economic models by Phillips et al (2006) [25]

3.7 Data Synthesis and Qualitative Analysis

Initial scoping suggested that interventions, populations and outcome measures studied were heterogeneous, with the majority of data derived from cohort studies reporting different screening intervals or simulation models using data from non-compliant individuals arriving at different times for screening (i.e. people who were due to attend annually but attended at different intervals).

This heterogeneity prevented us from conducting a quantitative synthesis or direct comparison across study results, and restricted our ability to address some of the questions. We undertook a narrative synthesis in line with the CRD [20]framework (figure 1).

The themes were generated and considered in the context of the review's aims.

The included studies were categorised into three groups according to reported methodological approaches used: a) studies of screening programs (or screening in the context of trials) b) studies of risk stratification models, and c) studies of economic appraisals.

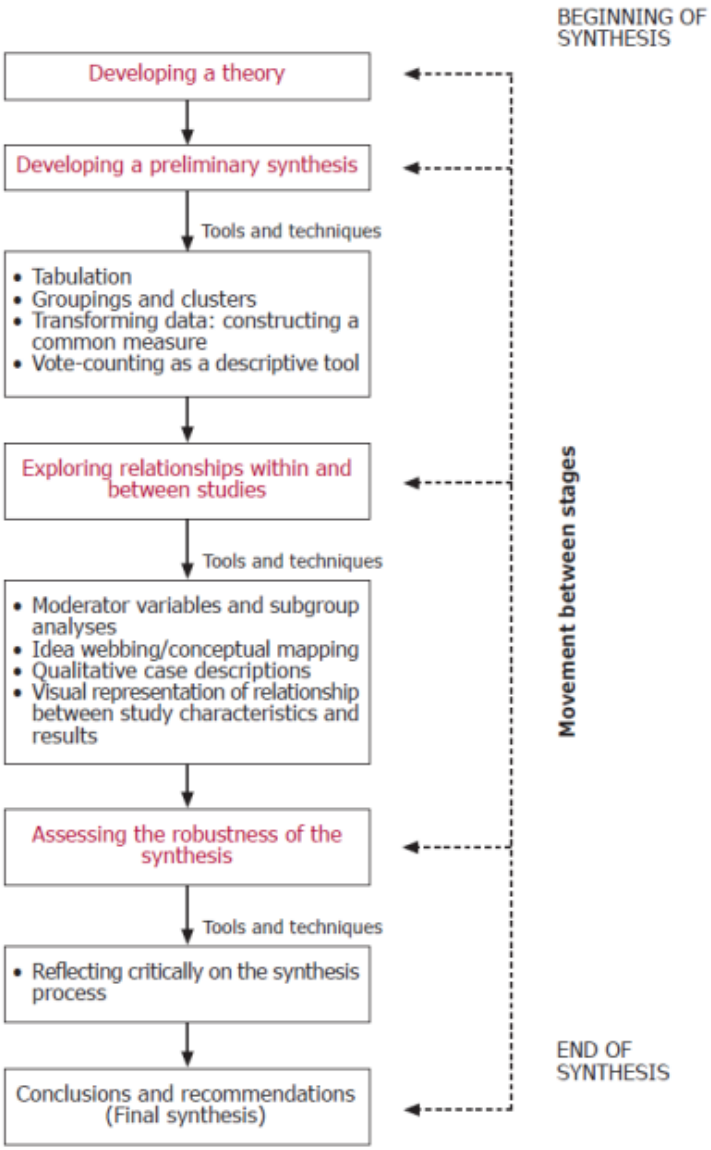

Figure 1: Method of Data Synthesis, as recommended by the CRD [26]

4. RESULTS

4.1 Results of literature search

A total of 16,197 records were identified, which yielded 12,060 publications after duplicates were removed; 3 further publications were identified through searching through references or reference made in the texts to other publications, and 6 additional publications were identified through contact with experts. Details of the number of publications identified from each bibliographic database can be found in appendix A.

At stage one, two authors (DT) and (RL) independently completed an initial screening of the 12,060 publications against the inclusion criteria based on the contents of the titles and abstracts creating two shortlists. Following this process, shortlists were combined and duplicates were removed to compile a total shortlist of 137 potential full publications based on the information provided in their abstracts.

An additional 2 publications were identified through hand-searching references of included publications, and 1 article identified through searching publications which cited the included article (this was published just after the completion of the database searches). Additional publications, including 6 papers not identified in the search were suggested by experts and were reviewed for inclusion or exclusion by the same methodology, providing a total of 141 publications for review. Of these, 129 full text publications were available. Four were not included as they were not published in English and 8, including a thesis, were unavailable in the time period afforded by this review. Figure 2 shows the PRISMA diagram [26] of information flow throughout the different stages of the systematic review.

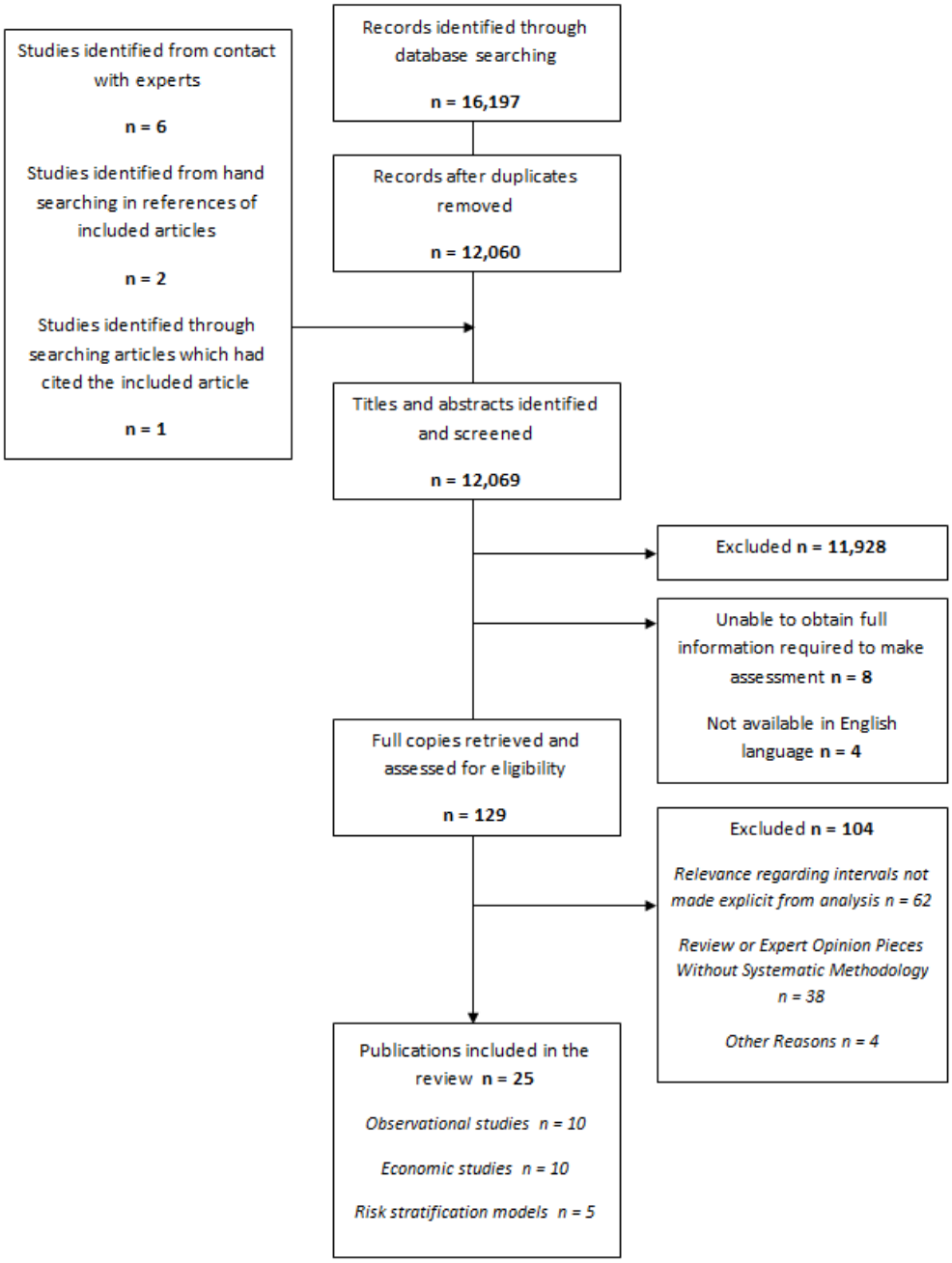

Figure 2: PRISMA flow chart describing information flow through the different phases of the systematic review [26]

4.1.1 Excluded studies

Of the 129 papers included at full text 104 were excluded. The titles of those papers that were screened but not included and the reason for exclusion are documented in appendix C. The most common reasons for exclusion were that publications did not relate to specifically to screening intervals (n = 62), or were a commentary or review papers without a systematic methodology (n = 38).

4.1.2 Included Studies

Twenty five publications were included in the review. These included observational screening program evaluations (10 studies), risk stratification models (5 studies), economic appraisals (8 studies), and additional economic appraisals (2 studies). See Table 2

Table 1: Studies selected for inclusion based on the inclusion and exclusion criteria

Lead Author	Year	Title	Study design
Agardh and Tababat-Khani [6]	2011	Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy	screening program evaluation
Aspelund et al [27]	2011	Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy	Risk stratification model
Brailsford et.al [28]	2007	Combined discrete-event simulation and ant colony optimisation approach for selecting optimal screening policies for diabetic retinopathy	Economic appraisal
Chalk et al [29]	2012	Can the Retinal Screening Interval Be Safely Increased to 2 Years for Type 2 Diabetic Patients Without Retinopathy?	Economic appraisal
Dasbach et al [30]	1991	Cost-effectiveness of strategies for detecting diabetic retinopathy	Economic appraisal
Davies et al [31]	2002	The evaluation of screening policies for diabetic retinopathy using simulation	Economic appraisal
Javitt et al [32]	1994	Preventive eye care in people with diabetes is cost-saving to the federal government	Economic appraisal
Javitt et al [33]	1990	Detecting and treating retinopathy in patients with type I diabetes mellitus	Economic appraisal
Jones et.al [10]	2009	Diabetic retinopathy screening: a systematic review of the economic evidence	Economic appraisal – systematic review
Jones et al [34]	2012	Incidence and progression of diabetic retinopathy during 17 years of a population-based screening program in England	screening program evaluation
Kohner et al [35]	2001	Relationship between the severity of retinopathy and progression to photocoagulation in patients with Type 2 diabetes mellitus in the UKPDS (UKPDS 52)	Observational study in the context of another trial
Kristinsson et al [36]	1995	Screening for diabetic retinopathy - Initiation and frequency	screening program evaluation
Maguire et al [37]	2005	The Case for Biennial Retinopathy Screening in Children and Adolescents	screening program evaluation
Mellanby and Milne [38]	1999	Reducing the interval for diabetic retinal screening	Additional economic appraisal
Mehlsen et al [39]	2011	Identification of independent risk factors for the development of diabetic retinopathy requiring treatment	Risk stratification model
Mehlsen et al [40]	2012	Individualized optimization of the screening interval for diabetic retinopathy: a new model	Risk stratification model
Misra et al [5]	2009	Trends in yield and effects of screening intervals during 17 years of a large UK community-based diabetic retinopathy screening programme	screening program evaluation
Ólafsdóttir et al [7]	2007	Biennial eye screening in patients with diabetes without retinopathy: 10-year experience	screening program evaluation
Rein et al [41]	2011	The cost-effectiveness of three screening alternatives for people with diabetes with no or early diabetic retinopathy	Economic appraisal
Semeraro et al [42]	2011	Predicting the risk of diabetic retinopathy in type 2 diabetic patients	Risk stratification model
Thomas et al [43]	2012	Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis	screening program evaluation

Vijan et al [44]	2000	Cost Utility Analysis of Screening Intervals for Diabetic Retinopathy in Patients with type 2 Diabetes Mellitus	Economic appraisal
Younis et al [8]	2003b	Incidence of sight-threatening retinopathy in Type 1 diabetes in a systematic screening programme	Clinical effectiveness
Younis et al [45]	2003a	Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: A cohort study	Clinical effectiveness
Stratton et al [46]	2013	A Simple Risk Stratification for Time to Development of Sight-Threatening Diabetic Retinopathy	Risk stratification model

4.2. Assessment of Clinical Outcomes: Studies of screening programs and Risk Stratification

This section outlines the study characteristics, populations, screening strategies, and themes identified through data synthesis for the ten studies of screening programs. An assessment of the quality of studies of screening programs is also provided. Findings relating to clinical outcomes from the analysis of the five risk stratification studies are also included.

4.2.1 Description of Studies

There were no RCTs. The 10 observational studies comprised both adult and paediatric populations. For the adult studies, the number or participants varied and ranged from 81 [36] to 49,763 [43]. Tables detailing the characteristics of each of the included 10 studies are available in appendix E.

4.2.2 Description of Screening Strategies

Different screening strategies were employed amongst the studies, reflecting both the policy of the country delivering the screening, and/or technological improvements over the time period of the studies. In the study by Agardh et.al [6] red-free digital images of one central and one nasal 50° field per eye were obtained by fundus photography performed by specially trained ophthalmic nurses. The International Diabetic Retinopathy and Macula Edema Severity Scales were used for grading. In the study by Kohner et.al [35] four-field 30° retinal photographs were taken as stereo pairs at entry and 3 yearly thereafter, and were graded and allocated to a retinopathy severity level using the Early Treatment of Diabetic Retinopathy Study (ETDRS) final scale, modified for four standard fields. Seven fields were viewed with a Donaldson Stereoviewer and graded by an ophthalmologist and second grader independently in the paediatric study by Maguire et al [37]. In the two included studies by Younis et.al [8, 45] non-stereoscopic 3 field mydriatic photography and modified

Wisconsin grading. STDR defined as moderate pre-proliferative retinopathy or greater and/or significant maculopathy in any eye. In the studies by Misra [5] and Jones [34] two photographs of each eye were taken, one centred on the optic nerve and the other on the fovea. In their Icelandic study, Ólafsdóttir and colleagues [7] describe screening by an ophthalmologist using mydriasis and a slit lamp examination, with fundal photographs taken.

The majority of observational studies used scheduled annual screening [5, 8, 34, 37, 45], although the actual duration between screenings was variable. Two studies described screening every three years [6] [35] and one biennial screening programme [7].

4.2.3 Description of Populations Studied

The majority (8 studies) of the observational studies reported on adult populations, with 1 study [37] based on a paediatric population and one study including a paediatric population [36] alongside an adult population.

The study populations were made up predominantly of T2DM patients, with a total of 88,136 T2DM patients enrolled. Of these, the majority (73,784) had no background diabetic retinopathy at baseline. Of the total enrolled in all the studies, only 1,471 patients had T1DM. Five studies observed populations with solely T2DM [6, 35, 42, 43, 45] and one [6] of which solely T2DM patients without background diabetic retinopathy at baseline. Two studies [37,8] observed solely populations with T1DM, and four studies [5, 7, 34, 36] had mixed populations of T1DM and T2DM, although in the studies by Jones et.al [34] and Misra et.al [5] which use the same population, only a small proportion (n = 205) had T1DM. One study was conducted in the context of participants from a large trial rather than the general population [35].

The populations studied were relatively homogeneous from a geographical perspective; United Kingdom: seven studies [5, 8, 34, 35, 37, 43, 45], Iceland: two studies [7, 36], Australia: one study [37] and Sweden one study [6]. None of the observational studies provided information on the socio-economic make up of study participants.

4.2.4 Summary of Baseline Characteristics

The following outlines the baseline characteristics recorded for the participants in the observational studies.

4.2.4.1 Treatment at baseline

Only a small percentage of the participants who had T2DM were on insulin at the outset of the studies.

In the large study by Jones et.al [34] 4.8% of the patients with no retinopathy at baseline were on insulin (748), 70.8% (11,631) of the patients with no retinopathy were on oral agents and 24.4% of the patients were on diet only. In the study by Younis et.al [45] at the outset of those with no retinopathy, 1,879 (50%) were on diet only, 1,658 (44%) on oral agents and of those with no retinopathy 206 (6%) were on insulin. In the large study by Thomas et.al [43] 34.6% (17,236) of participants were on diet only, 58.4% (29,049) on oral agents and 5.4% (2,669) of participants on insulin.

4.2.4.2 Duration of diabetes at baseline

All but one of the studies [37] reported the duration of diabetes at baseline. Kohner [35] reported newly diagnosed patients with no duration of diabetes. Mean duration of diabetes ranged from 1 year [34] for patients with no retinopathy at baseline to a mean duration of 18 years in the study by Ólafsdóttir and colleagues [7].

Three of the observational studies record HbA1c at baseline. In the paper by Agardh et.al [6] this is recorded at 6.4 +-1.5% (in a population with a mean age at baseline of 55 +- 12 years), in the paediatric population of type 1 diabetics studied by Maguire et.al [37] in the <11 year group median HbA1c 8.5% range 8-9.2%) in the >= 11 year olds at first screening median HbA1c 8.7% range 8-9.7%). In the Icelandic study [7], the mean HbA1c at baseline is recorded at 8.0 (SD 1.6).

4.2.4.3 Methodologies employed

The observational studies shared a similar methodology analysing a cohort of individuals having undergone a screening process and provided some base line data on patient characteristics, although the statistical methods for dealing with results differed greatly. All but one study [35] observed 'real world' screening programmes. Kohner et.al [35] observed 3709 patients enrolled in the United Kingdom Prospective Diabetes Study until either the end of the study, when photocoagulation was required or where lost to follow up. Estimates of the survival function were calculated using the Kaplan-Meier method. Patients were screened every three years and the authors provided data up to 12 years from entry to study.

Life-table calculations were used in both studies by Younis et.al [8] [45]. Demographic differences at baseline were analysed using the Kruskal Wallis test for continuous data, or chi-squared for categorical data. The Life table method enabled cumulative incidence rates of STDR and grades of

retinopathy to be calculated for one year intervals which took into account varying intervals of follow up after the first screen visit. Life table calculations were performed for each baseline grade of retinopathy progressing to endpoint, and factors associated with progression to STDR were identified using the Cox proportional hazards model. In the study focussing on patients with T1DM, a cohort of all patients with T1DM enrolled with general practitioners were studied if retinopathy data was available at baseline and at least one further screening event. A similar methodology was employed for the study focussing on patients with T2DM. The cohort was followed between June 1991 and December 1999.

Thomas et.al [43] conducted a four year retrospective analysis on 57 199 people with T2DM, diagnosed at age 30 years or older and who had no evidence of diabetic retinopathy at their first screening event between January 2005 and November 2009 and had at least one further screening event within the study period. Chi-squared and t-test were used to explore differences between patients without any background or referable retinopathy, and parametric survival analysis with covariates was used to identify factors associated with referable retinopathy.

Two identified papers [5] [34] reported information from a large, dynamic cohort study design studying patients without proliferative diabetic retinopathy at baseline or sight threatening maculopathy from the Central Norfolk Diabetic Retinopathy Screening Service between January 1990 and December 2006. Life tables to estimate cumulative and annual incidence rates and Cox regression analysis to identify risk factors for progression were used in the most recent paper to be published [34]. The earlier paper to be published [5]had different aims (to describe trends in the characteristics of the patients screened and the results of screening over time, and to identify associations between patients' characteristics and screening results), and investigated associations between referable or STDR, screening interval and frequency of repeated screening whilst adjusting for age, duration and treatment of diabetes, hypertension treatment and period; for analyses of changes over time, continuous, binary and ordinal outcomes were analysed using linear, logistic and ordinal logistic regression models respectively.

Agardh and Tababat-Khani [6] examined a cohort of individuals having undergone an initial screen and observed the results of those which returned for screening three years later. They do, however, report high compliance, with only 9% of participants who were still alive having ignored or refused the follow up request. Olafsdottir et.al [7] employed a similar methodology, but observed a small cohort of 296 Icelandic patients with diabetes and no retinopathy over a period of 10 years and reported results at each biennial screen.

4.2.5 Quality Assessment: Clinical Effectiveness Studies

There is no validated tool specifically designed for the appraisal of internal validity (or methodological quality) of studies evaluating screening programs or natural history of diabetic retinopathy. Therefore, methodological and reporting quality of the 10 included cohort studies of screening programs was assessed using the CASP framework. This method of appraisal highlighted some significant key methodological issues which were common to the evidence base. Those limitations which emerged as a theme are detailed here. A summary of the CASP appraisals by individual criteria are located in appendix D.

The main limitation of the evidence-base was the lack of randomized trials comparing the effectiveness of screening programs utilizing different intervals between the screens (annual vs. biennial) with respect to the progression rate of retinopathy (e.g., from background to pre-proliferative or proliferative grade) and/or incidence of sight-threatening retinopathy/vision loss in subjects with diabetes. Moreover, none of the included studies was of comparative nature which would allow the direct comparison of progression to (or incidence) of sight-threatening retinopathy/vision loss between subjects with diabetes screened with different intervals. Rather the evidence base was comprised of single-cohort non-comparative studies reporting incidence or progression of diabetes-related retinopathy in relation to any given screening interval (e.g., two years between two screens). Given the above-mentioned limitations, specifically the lack of control/comparator data, the study findings warrant a cautious interpretation.

In general, all 10 studies asked clearly focussed questions, with population characteristics and the main outcome measures clearly documented, alongside thorough descriptions of the screening programmes (ophthalmoscopy, fundal photography). The majority of studies (90%) reported adequate methods of participant recruitment, exposure measurement (i.e., types of screening tests and between-test intervals), and outcome ascertainment. All studies measured and reported some important baseline risk factors or prognostic factors of retinopathy and its progression (e.g., age, sex, blood pressure, ethnicity, HbA1c, type of diabetes, duration of diabetes, diabetes treatment).

The completeness of follow up (i.e., sample attrition) varied across the studies reaching up to 31% in two studies [5, 45]. Three studies that had losses to follow up under 25% [6, 8, 36], reported that important baseline characteristics did not differ between the responders/completers and those lost to follow-up/dropped out. Although in one study [43] the rate of non-attendance for a repeat screen was relatively low (13%), the authors reported that non-attendees compared to attendees tended to

be older with a longer duration of diabetes. Due to poor reporting, the completeness of follow-up data could not be determined for four studies [7, 34, 35, 37]. In the study by Younis et al [45], only 77% of their invited cohort attended for baseline screening and 31% did not attend any follow up screening over the 6 year period. If non-participation in this study was associated with older age, longer duration of diabetes, non-compliance with other treatments for diabetes, and complications due to diabetes, the incidence rates of retinopathy and vision loss reported in this study may have been underestimated.

4.2.6 Recommendations Presented for Optimum Screening Intervals

The key conclusions from the observational studies are summarised in table 2 below.

Table 2. Key conclusions from observational studies

Study Author	Key Conclusion
Agardh et.al 2011 [6]	Three-year retinal screening intervals can be recommended in subjects with mild type 2 diabetes and no retinopathy.
Jones et.al 2012 [34]	Few patients without diabetic retinopathy at initial screening examination developed pre-proliferative retinopathy, diabetic retinopathy or sight threatening maculopathy after 5-10 years of follow-up. Screening intervals longer than 1 year may be appropriate for such patients.
Kohner et.al 2001 [35]	Few T2DM patients without retinopathy progress to photocoagulation in the following 3-6 years, while patients with more severe retinopathy lesions need to be closely monitored.
Kristinsson 1995 [36]	Diabetics without retinopathy did not develop retinopathy requiring treatment within 2 years of study.
Misra et.al 2009 [5]	It may be safe to increase screening intervals to 2 years, which would be safer for low-risk patients such as those well controlled on dietary treatment for diabetes with well controlled blood pressure and no retinopathy at initial screen. Increasing screening workload with a lower yield.
Maguire et.al 2005[37]	Adolescents in reasonable metabolic control could safely be screened biennially rather than current annual recommendations. Individuals with especially poor control need to be screened more frequently.
Ólafsdóttir et.al. 2007[7]	Every other year screening for diabetic eye disease seems to be safe and effective in diabetics without retinopathy.
Thomas et.al 2012 [43]	Supports the extension of the screening interval for people with type 2 diabetes mellitus beyond the currently recommended 12 months, with the possible exception of those with diabetes duration of 10 years or more and on insulin treatment.
Younis et.al 2003a [45]	A 3 year screening interval could be safely adopted for patients with T2DM and no retinopathy, but yearly or more frequent screening is needed for patients with higher grades of retinopathy.

Younis et.al 2003b [8]	Screening at 2-3 year intervals rather than annually for patients without retinopathy in T1DM is feasible because of the low risk of progression to STDR. Patients with higher grades of retinopathy may require screening at least annually or more frequent.

4.2.7 Risk Factors Relating to Clinical Outcomes

This section presents the key themes presented by the authors identified through the data synthesis process as risk factors that may affect clinical outcomes.

4.2.7.1 Retinopathy at baseline

The relationship between retinopathy at baseline and clinical outcomes is discussed in all cohort studies and links with the findings from the risk algorithm studies which report that patients with no retinopathy at baseline are unlikely to develop retinopathy over the various interval lengths observed in the studies. In contrast, patients with evidence of retinopathy at baseline screen were at higher risk of developing retinopathy or progressing further at follow up.

Jones et.al [34] found that patients with T2DM and no retinopathy at baseline are at low risk of developing retinopathy and very low risk of progressing to retinopathy requiring treatment even after 5 years of follow-up. However, patients with any level of retinopathy at baseline are at a much higher risk of clinical harm.

In the study by Thomas et.al [43] relating to people with T2DM with no evidence of diabetic retinopathy at the first screen, the annual incidence of any retinopathy per 1000 people was 124.94 (12.5%) in the first year, falling each year to 66.59 (6.7%) in the fourth year. The cumulative incidence at four years was 360.27 per 1000 people (36.0%). Importantly, the annual incidence of referable retinopathy per 1000 people was low at 2.02 (0.2%) in the first year, with a small increase to 3.54 (0.4%) in the fourth year; the cumulative incidence at four years was 11.64 (1.2%).

Kohner et.al [35] found that few patients without retinopathy developed a level of retinopathy that required photocoagulation within 3 to 6 years; however patients with evidence of retinopathy were more likely to need treatment by 3 years although still at low levels.

The authors of the Liverpool Diabetic Eye screening programme study of 20 570 screening events in patients with type 2 diabetes [45] demonstrate a yearly incidence of sight threatening diabetic retinopathy (STDR) in patients without retinopathy at baseline of 0.3% (95% CI 0.1-0.5) in the first year, rising to 1.8% (95% CI 1.2-2.5) in the fifth year. With background retinopathy at baseline this incidence rate rose to 5.0% in year 1 (95% CI 3.5-6.5). Interestingly, for a 95% probability of

remaining free of sight-threatening diabetic retinopathy, mean screening intervals by baseline status were; no retinopathy 5.4 years (95% CI 4.7 – 6.3), background 1.0 years (95% CI 0.7-1.3) and mild preproliferative 0.3 years (95 % CI 0.2-0.5).

Importantly, supplementary data from the well conducted, long study by Jones et.al [34] show that cumulative incidence (%) of non-proliferative retinopathy in patients with T2DM and no retinopathy at baseline (regardless of other risk factors) is a relatively rare event (1.5%) one year from entry to study, rising to 12.2% in year two of the study. The cumulative incidence of preproliferative retinopathy is very low (0.1%) in year one, rising to 0.8% in year two. The cumulative incidence of sight threatening maculopathy is 0.01% in year one, rising to 0.11% in year two, and cumulative incidence of proliferative retinopathy 0.01% in year one and 0.13% in year two. In the study by Younis et.al [45], cumulative incidence of any retinopathy in patients with T2DM is 10.9 % (95%CI 9.8-11.8) in the second year of study, reducing to 1% (95% CI 0.7-1.3) for development of mild preproliferative retinopathy, 0.6% (95% CI 0.3-0.9) for sight threatening maculopathy and 0.8% (0.5-1.1) cumulative incidence for STDR in the second year. In the large study by Thomas et.al [43] cumulative incidence of any retinopathy 2 years since first screen is reported as 216.81 per 1000 people (95% CI 211.5 to 220.04), with cumulative incidence of referable retinopathy very low in the second year since last negative screen much lower at 4.85 (95% CI 4.85 to 5.43) per 1000 people.

Agardh et.al [6], Ólafsdóttir et.al [7] and Kristinsson et.al [36] only consider patients with no retinopathy at baseline in their studies. Agardh et.al [6] reported that over 70% of individuals were entirely without any retinopathy at the three year follow up with any identified retinopathy of the remaining patients being low level and the incidence of referable STDR as 0.19% of eyes (5 out of 2,644 eyes) at three year follow up.

Ólafsdóttir [7] reported that no patients went from no retinopathy to STDR over a 2 year period, and over the full 10 year observation period, 172 of the 296 individuals still did not develop diabetic retinopathy with the remaining 96 patients developing mild non-proliferative retinopathy, 6 developing clinically significant diabetic macular oedema, 23 having developed preproliferative retinopathy, and four having developed proliferative diabetic retinopathy.

Kristinnsson et al [36] examined screening frequency and outcome in a small group of diabetics diagnosed before age 30 without retinopathy over a two year observation period. The study found that for 87 patients with T1DM, 77% still had no retinopathy after 2 years while 21% had background retinopathy and 2% had preproliferative diabetic retinopathy. No patients were considered to need any eye treatments. For 118 patients with T2DM, 84% had no retinopathy after 2 years while 14% had background retinopathy and 2% had preproliferative diabetic retinopathy.

Stratton et.al [46] developed a risk prediction model based on data from one English screening centre. (See section 4.2.8 for description of risk prediction models). This model predicted that 0.7% of patients with no retinopathy at their first two screens were expected to progress to STDR within 1 year, compared to 2.2% to 12% of those who had background retinopathy at their first two screens (variable risk dependent on extent of background retinopathy). Mehlson et al [40] also found the log of the number of retinal haemorrhages to be a significant risk factor for progression to STDR in patients with T1DM (OR=2.7, 95% CI 1.8-3.9) and T2DM (OR 2.4, 95% CI 1.8-3.1). Aspelund et.al. [27] also included presence of nonproliferative retinopathy as a risk factor in their model, from published data from the UK prospective diabetes study and the Wisconsin epidemiological study, risk ratios varied from 1.8 to 3.3 dependent on gender and type 1 or 2 diabetes. Full details of these studies are in section 4.2.8.3.

4.2.7.2 Duration of diabetes

Four cohort studies considered the relationship between duration of diabetes and clinical outcomes [5, 8, 43, 45].

Misra et.al [5] found that a longer duration of diabetes at baseline was related to increased severity of retinopathy and maculopathy at follow up. Thomas et.al [43] reported that duration of diabetes was independently associated with incidence of retinopathy and went on to recommend that patients with a diabetes duration over 10 years should continue to be screened annually.

The two Liverpool Diabetic Eye screening programme papers [8, 45] reported that diabetic retinopathy incidence was associated with diabetes duration for both T1DM and T2DM. For T1DM, Younis et al [45] found that T2DM patients with no background retinopathy at initial screen, but with the longest duration of diabetes were most likely to progress to sight threatening diabetic retinopathy over the 6 year observation period with patients with a diabetes duration over 20 years reporting a 3 year cumulative incidence of STDR of 13.5% (8.5 – 18.5) compared to 0.7% (0.4 – 1.0) in patients with a diabetes duration lower than 10 years. Similar differences are also observed in patients with low level retinopathy at baseline. For patients with T1DM, Younis et.al [8] also found that longer duration of diabetes was associated with greater progression of STDR.

Duration of diabetes was also a risk factor in the risk prediction algorithms developed by Semeraro et al. [42] using an Italian cohort of Caucasian T2DM patients (Hazard Ratio 1.06 95% CI 1.05-1.08 for 1 year increase in duration) and by Mehlsen et al. [39] in a Danish cohort of patients with T1DM

(Odds Ratio 1.04 95% CI 1.01-1.07 for 1 year increase in duration). However in the same Danish cohort duration of diabetes was not a significant risk factor for T2DM but age at diagnosis was a significant factor. The authors attribute this to inaccuracy in measurements of disease duration in T2DM patients, see section 4.2.8.3.

4.2.7.3 Insulin

Four cohort studies considered the impact of insulin use on clinical outcomes [5, 8, 10, 42, 43] Perhaps unsurprisingly, insulin use was also associated with a longer duration of diabetes [43].

The authors of the Liverpool Diabetic Eye screening programme paper reported that diabetic retinopathy incidence was associated with insulin treatment in their study of patients with T2DM. Younis et al [45] reported that T2DM patients with higher levels of baseline retinopathy had a higher frequency of insulin use at baseline. For patients with no retinopathy, 6% used insulin (n=206), this rose to 14% of patients displaying background retinopathy (n=112) and 21% of patients with mild preproliferative retinopathy (n=45). Younis et al [45] also found that the highest rates of progression to STDR were in T2DM patients given insulin at baseline.

Younis et al [45] further examined the relationship between taking insulin, oral hypoglycaemics or dietary interventions with progression of retinopathy amongst patients with T2DM and no retinopathy at baseline. They found that the five year incidence of retinopathy was 23.3% (11.7 – 34.9) for those on insulin, 4.4% (2.4 – 6.4) for those taking oral hypoglycaemics and 1.4% (0.4 – 2.4) for those using dietary interventions (p=0.0004). Similar trends were found in patients with mild preproliferative retinopathy at baseline. These results demonstrate that patients using dietary interventions only have a lower incidence of retinopathy and STDR compared to those using insulin or oral hypoglycaemics.

The Welsh study [43] included an analysis of a subgroup of T2DM patients where incidence of referable retinopathy was associated with use of insulin treatment. For participants needing insulin treatment with a duration of diabetes of 10 years or more, cumulative incidence of referable retinopathy at one, two and three years was 9.61 and 17.10 and 24.24 per 1,000 people, respectively – almost triple what was observed in patients not using insulin with a duration of diabetes more than 10 years who had an incidence of 2.24, 5.86 and 10.33 per 1,000 people respectively. Although Thomas et al [43] supports the extension of the screening interval for people with T2DM beyond the currently recommended 12 months, they state that patients on insulin treatment with a history of diabetes of 10 years or more should be screened annually

The study by Jones et.al [10] also investigates the relationship between baseline characteristics and time to preproliferative retinopathy or maculopathy; among patients with nonproliferative retinopathy or without retinopathy at baseline the adjusted hazard ratio is 2.17 (95% CI 1.68-2.81).

Use of insulin was a strong predictor in the model developed by Semeraro et.al [42] on an Italian cohort of patients with T2DM (Hazard Ratio 6.8 95% CI 2.9-16.0), as is use of oral hypoglycaemic agents (Hazard Ratio 3.9 95% CI 1.7-8.8), see section 4.2.8.3 for full details.

4.2.7.4 HbA1c

Two cohort studies considered the impact of HbA1c percentages on clinical outcomes [7, 37] and two risk prediction algorithms included HbA1c as a risk factor to progression to STDR.

Maguire et.al [37] found in the study of children and adolescents that in the group with HbA1c of 10% or above recorded at any visit, the risk of retinopathy increased significantly after 2 years ($p = 0.001$). The risk of retinopathy did not increase until 3 years in the group whose HbA1c was always below 10% ($p = 0.003$).

The small cohort of patients (n = 296) in the Icelandic study [7] reported, on average, a reasonable metabolic control for their study cohort as a whole (mean HbA1C 8.0%). Although they did not report specifically on their findings relating to risk factors, they did provide results that detailed those patients with preproliferative diabetic retinopathy (n=23) had a higher mean HbA1c percentage at 8.4% (6.7-10.1) than those with mild retinopathy (8.1% (6.8-9.4)) or no retinopathy (7.8% (6.2-9.2)).

HbA1c was also a risk factor in the risk prediction algorithms developed by Semeraro et al [42] using an Italian cohort of Caucasian T2DM patients (Hazard Ratio 1.2 95% CI 1.09-1.25 for a 1% increase in HbA1c), and by Mehlsen et al.[39] in a Danish cohort (T1DM Odds Ratio=1.5 95% CI 1.2-1.9, T2DM odds ratio = 1.2 95% CI 1.1-1.3 for 1% increase). The Aspelund [27] model also includes HbA1c as a risk factor for progression to STDR using published data from the UK prospective diabetes study (Odds ratio = 1.2 95% CI 1.16-1.25) see section 4.2.8.3.

The results of the study by Kohner et.al [35] imply that adoption of less than annual screening is safe, however, this must be considered in the context of the UKPDS trial where blood pressure was monitored every three months so the recommendation presupposes controlled blood pressure and glycaemia.

4.2.7.5 Type 1 diabetes

There is less data available for patients with T1DM as most studies focus on the larger cohorts of patients with T2DM, however Younis [8] report on only T1DM patients in a study that matches the design of their T1DM cohort. Olfasdottir et.al [7] also report separately on a T1DM sub-cohort.

Younis [8] found that after one year, the incidence of retinopathy in patients with no retinopathy at baseline was the same (0.3%) as the incidence they reported for their T2DM cohort [45]. However, lower precision relating to the smaller cohort of T1DM patients must be appreciated when considering these findings, and used their findings to recommend optimum screening intervals for each of their cohorts. They recommend that T1DM patients with no retinopathy at baseline could be screened every 5.7 years and those with T1DM with background retinopathy should screened every 1.3 years. There recommendations are similar to those made for their T2DM cohort where they recommend intervals of 5.4 years for patients with no retinopathy at baseline and shorter intervals (1 year) for those with background retinopathy.

Ólafsdóttir et.al [7] studied a small number of both T1DM and T2DM. Of the 172 patients who did not develop any level of retinopathy over the 10 year period they found that 46 had T1DM and 126 had T2DM. Of the original cohort of 97 patients with T1DM and 199 patients with T2DM, this represents 44.6% of patients with T1DM and 63.3% of patients with T2DM.

The risk prediction papers do not make direct comparisons between risk of progression to STDR for patients with T1DM or T2DM. Instead they present separate hazard ratios for each of the other factors dependent on whether the patient has type 1 or type 2 diabetes. However, internal validation of the Danish model [39] showed that in patients from the same screening centre the screening interval could be prolonged by average 2.9 times for patients with T1DM and 1.2 times for patients with T2DM whilst maintaining the same risk levels for STDM .

4.2.7.6 Children and adolescents

Maguire [37] focussed on outcomes and screening intervals specifically for paediatric populations studying a group of Australian 668 children and adolescents with T1DM aged under 11 or aged 11 – 19 at first screening. Kristinsson et.al [36] also studied a small group of 81 Icelandic children aged under 15 at recruitment but did not report on their findings past their baseline characteristics.

At baseline, the Maguire et al [37] study found the prevalence of retinopathy at baseline screening to be 16% (<11 age group) and 22% (>11 age group), with 3 out of the total 668 children displaying

moderately severe nonproliferative retinopathy in accordance to level 41 of the Airlie House classification of diabetic retinopathy. At follow up, one to two years later, in the <11 age group, retinopathy regressed in 80% but progressed in none. In the >11 age group retinopathy regressed in 36% and progressed in 13%. The three patients displaying moderately severe nonproliferative retinopathy at baseline had regression of retinopathy at the follow up screen. At follow up, none of the 668 patients had proliferative retinopathy and no patients were considered to need any eye treatments.

Maguire et al [37] then used generalised estimating equations (GEEs) to compare risk of retinopathy at yearly intervals for 6 years and found that after the second eye assessment retinopathy did not increase significantly until 3 years later in the >11 age group (p=0.028) and until 6 years later in the <11 age group (p=0.014). Patients with higher HbA1c (indicative of poorer metabolic control) or >10 years diabetes duration (>10% recorded at any visit) were deemed to be at greater risk. In the group with higher HbA1c >10%, retinopathy increased significantly after 2 years (p=0.001), while patients with HbA1c always <10% increase was not seen until after 3 years (p=0.003). Patients with diabetes duration >10 years had no significant increase of retinopathy after 1 year; however they were less likely to have an improvement in retinopathy. Maguire et al (2005) use their findings to conclude that adolescents with reasonable metabolic control (HbA1c levels <10%) could safely be screened biennially rather than current annual recommendations. Although, individuals with especially poor control should to be screened more frequently.

4.2.7.7 Other risk factors

Younis et al [45] did not identify any significant relationship between retinopathy incidence or progression with sex. However the Aspelund model [27] using published risk factors uses separate risk ratios for males and females concerning the presence of nonproliferative diabetic retinopathy. For example for T2DM the risk ratio associated with presence of nonproliferative diabetic retinopathy is 1.8 for women and 3.3 for men.

Systolic blood pressure is also a risk factor identified in the models by Aspelund et al. [27] (T1DM Hazard Ratio =1.08, 95% CI 1.04-1.12, T2DM Hazard Ratio=1.5 95% CI=1.1-2.3 per 10mmHg), and by Semeraro et al. Hazard Ratio =1.014 95% CI 1.008-1.020 per mmHg).

Jones et.al [34] performed a Cox regression analysis which showed that age (<40), treatment of diabetes (oral drugs; Odds Ratio 2.01 (1.71-2.37) risk independently associated with referable retinopathy) and people not on hypertension treatment (Odds Ratio 0.81 (0.73-0.90) independently associated with referable retinopathy) were independent risk factors for retinopathy progression, which is in keeping with earlier work on the same cohort by Misra et.al [5].

Thomas et.al [43] examined the role of oral hypoglycaemic agents; for participants on diet treatment with a duration of diabetes of less than five years, the cumulative incidence of referable diabetic retinopathy at one, two and three years was 1.83, 3.66 and 5.45 per 1000 people respectively. The corresponding values for participants using insulin treatment with duration of diabetes of more than 10 years were 9.61, 17.10 and 24.26 per 1000 people respectively, an approximately five fold increase. For participants not using insulin with a duration of diabetes of more than 10 years, the corresponding values were 2.24, 5.86 and 10.33 per 1000 people, and 0.71, 3.80 and 10.10 per 1000 people respectively, for those using insulin treatment with a duration of diabetes of less than 10 years.

Table A shows the relationship between putative risk factors and the risks of patients developing diabetic retinopathy [43] or time to preproliferative retinopathy, PDR or maculopathy [34], taken from two key observational studies [34,43], showing significantly raised risk of either any retinopathy [43] or time to preproliferative retinopathy, PDR, or maculopathy with type of treatment and duration of diabetes. Non-proliferative retinopathy at baseline is clearly the biggest risk factor identified in the study by Jones et.al.

Table 3: Putative risk factors from two key studies

Risk factors from two key observation studies [34,43]		
Risk Factors	Relationship between baseline characteristics and time to preproliferative retinopathy, PDR, or maculopathy (1,264 cases) among patients with nonproliferative retinopathy or without retinopathy at baseline: Cox regression analysis model from Jones et.al [34] (Adjusted Hazard Ratio)	Parametric survival analysis with covariates in participants who developed diabetic retinopathy, according to grading category (any retinopathy). Adjusted Hazard Ratios from Thomas et.al. [43] All factors significant at p<0.001
Nonproliferative retinopathy at baseline		
N	1	-
Y	4.97 (4.41-5.60)	-
Years since diabetes diagnosis		
<5	-	1
5-9	-	1.39 (1.34-1.45)
>10	-	1.92 (1.72-1.93)
<10	1	-
10 to <20	1.21 (1.01-1.44)	-
>20	0.93 (0.68-1.26)	-
Treatment for diabetes mellitus		
Diet	1	1
Oral Hypoglycaemic Agents	1.77	1.41 (1.36-1.47)
Insulin	2.17	2.03 (1.89-2.18)

4.2.8 Risk Algorithm Studies

Five of the papers [27, 39, 40, 42, 46] describe four risk stratification models to determine the most effective screening interval based on identified risk factors. The four models identified were developed using data from the English screening programme [46], the Italian screening programme for T2DM [42], the Danish screening programme [39], and using published risk factors [27].

The Stratton model [46] is based on data from the English breast screening service and uses diabetic retinopathy grade over two screening rounds to predict risk of sight threatening diabetic retinopathy over set time periods. This model identifies previous screening results as a strong predictor of time to a sight threatening diabetic retinopathy, but the other studies show this calculation would be more accurate with the addition of other key risk factors. The Semeraro et al [42] study is based on 6 monthly screening data over eleven years in Italy, and includes the risk factors of gender, time from diagnosis of diabetes, HbA1c, systolic blood pressure, albuminuria, and taking therapy for diabetes such as oral hypoglycaemic agents and insulin. The Mehlsen et al model [39] from the Danish

screening programme contains factors such as disease type (1 or 2), duration, number of retinal haemorrhages, HbA1c and blood pressure. This study found that using the risk prediction algorithm at a level to match current rates of STDR prolonged the screening interval by average 2.9 times for patients with T1DM and 1.2 times for patients with T2DM. The current Danish screening system has screening intervals which are already dependent on risk factors, and so there are some difficulties in translating the findings to a UK system with its universal screening interval currently. The Aspelund risk prediction algorithm [27] is based on data largely from the UK prospective diabetes study and includes the following predictors: disease type (1 or 2), HbA1c, systolic blood pressure, gender and presence of nonproliferative diabetic retinopathy. When tested on the same Danish dataset as described by Mehlson et.al [40] the authors project that use of the algorithm could result in 59% fewer visits at the same risk level. This does not directly translate to the UK context.

4.2.8.1 Description of study designs

The models were developed using either Cox's proportional hazards or regression approaches. This review focuses on evaluation of model performance rather than development.

None of the models have been externally validated on a UK dataset. One model [46] was internally validated on data from one screening centre in England. One model [27] was externally validated on a Danish database, and two further models were internally validated on an Italian database [42] and a Danish database [39]. Internal validation tends to overestimate performance in comparison to external validation due to statistical overfitting, and potential lack of generalizability to patient cohorts in different locations [47].

4.2.8.2 Description of models and populations

The four models identified were developed using data from the English screening programme [46], the Italian screening programme for T2DM [42], the Danish screening programme [39], and using published risk factors [27].

Each of the four models is described in further detail here. Stratton et al. [46] followed 39,329 patients on the screening register at one centre in the English diabetic eye screening service over a 5 year period, including people with type 1 and 2 diabetes aged 12 years or over. The first two screening rounds were used as a baseline to predict future risk over a mean follow up of 2.7 years. A Cox's proportional hazard model was used to calculate the hazard ratios for progression to STDR dependent on the outcome of the baseline screens. A log logistic model was fitted to predict the proportion having STDR at 1, 2, 3, 5, and 10 years after the baseline screens. This model extrapolates several years beyond the data. In first two rounds used as the baseline 14,554 patients had only mild

nonproliferative DR or no DR. Of these 7,246 had no DR at either screening, 1,778 had no diabetic retinopathy in either eye at first screen and in one eye at second screen, and 1,159 had background DR in both eyes at both screenings. The log logistic model showed that these three groups progressed to STDR at a rate equivalent to 0.7%, 1.9%, and 11% in the first year respectively. The full results for all nine potential outcomes from the first 2 screens are shown in table 3. This is a large study on the population screened in England which demonstrates that results over two screening rounds are a very strong predictor of probability of progressing to STDR over a short time period. However, even in the population with no DR in either eye for either of the two baseline screens, the model based on these data indicates that around 0.7% develop STDR within 1 year, 1.2% within 2 years, 1.9% within 3 years and 3.0% by 5 years. This lowest risk category makes up around half of the eligible patients in the dataset. Further risk stratification would be possible by the addition of other risk factors.

The model shows that patients with some retinopathy at both screens have a risk of between 2.2% and 12% of a STDR within one year, and so extension of the screening interval beyond one year in this group would be difficult to justify. Table 3 is from Stratton et.al [46] and shows time to development of referable retinopathy by results of patients first two screening appointment.

Table 3: Demographic Characteristics and Outcomes in Baseline Categories (reproduced from Stratton et.al [46])

Group	A	B	C	D	E	F	G	H	I
First screen	R0 both eyes	R1 one eye	R1 both eyes	R0 both eyes	R1 one eye	R1 both eyes	R0 both eyes	R1 one eye	R1 both eyes
Second screen	R0 both eyes	R0 both eyes	R0 both eyes	R1 one eye	R1 one eye	R1 one eye	R1 both eyes	R1 both eyes	R1 both eyes
n	7,246	1,266	343	1,778	897	356	853	656	1,159
Progressed to STDR	120	30	12	80	49	23	82	108	299
Referable grade, *n* (%)									
R1M1	104 (86.7)	23 (76.7)	11 (91.7)	73 (91.3)	45 (91.8)	16 (69.6)	56 (68.3)	67 (62.0)	159 (53.2)
R2M0	9 (7.5)	4 (13.3)	1 (8.3)	4 (5.0)	2 (4.1)	5 (21.7)	13 (15.9)	28 (26.0)	100 (33.4)
R2M1	5 (4.2)	3 (10.0)	0	1 (1.3)	1 (2.0)	1 (4.4)	10 (12.2)	12 (11.1)	34 (11.4)
R3M0	1 (0.8)	0	0	1 (1.3)	1 (2.0)	1 (4.4)	2 (2.4)	1 (0.9)	4 (1.3)
R3M1	1 (0.8)	0	0	4 (1.3)	0	0	1 (1.2)	0	2 (0.7)
Hazard ratio (95% CI)	1.0	1.5 (1.0-2.3)	2.6 (1.4-4.7)	2.9 (2.2-3.8)	3.6 (2.6–5.1)	4.8 (3.0-7.4)	6.0 (4.5-7.9)	10.0(7.7-13.0)	18.2 (14.7-22.5)
Expected proportion with referable DR from time of second nonreferable screening episode (from log logistic model) (%)									
By 1 year	0.7	1.0	1.5	1.8	2.2	2.8	3.8	6.7	12.0
By 2 years	1.2	1.9	3.0	3.5	4.4	5.5	7.3	12.4	21.4
By 3 years	1.9	2.8	4.4	5.1	6.4	8.0	10.6	17.5	29.0
By 5 years	3.0	4.5	7.1	8.2	10.1	12.7	16.4	26.1	40.4
By 10 years	5.9	8.6	13.2	15.2	18.3	22.4	28.1	41.2	57.5

M0, no photographic markers of maculopathy; M1 photographic markers of maculopathy; R0, no DR; R1, mild NPDR (approximate ETDRS level 20-35); R2, approximate level ETDRS level ≥43a; R3, approximate ETDRS level ≥61a

Semeraro et al [42] identified 3,327 Caucasian T2DM patients without diabetic retinopathy at study outset at an Italian clinic. These patients were followed up every 6 months between 1996 and 2007, and these data were used to create a Cox's proportional hazards model of risk of diabetic retinopathy. A further 1,707 patients meeting the same criteria were used to test the model. Diabetic retinopathy was assessed using slit lamp biomicroscopy by an ophthalmologist, but no

indication was given of the type or severity, or whether the patient went on to have treatment. Predictors of diabetic retinopathy in the final model are in table 4. The area under the ROC curve for one year without retinopathy was 0.825. The authors present the model results in the format of a nomogram, which can be used to calculate the risk of a diabetic retinopathy in a set time period. There is no calculation of the benefits of introducing this model at a set level of risk to determine different screening intervals for different patients. Instead they present a classification tree showing percentage of patients reaching between 1 and 10 years without diabetic retinopathy based on single thresholds for each significant risk factor.

In summary low risk is defined as: patients with systolic blood pressure lower than 135mmHg, who have had diabetes for less than 6 years and who are on no diabetes medication, and high risk is defined as: patients with longer duration of diabetes, high HbA1c, and albuminuria higher than 101mg/day. This model is based on data from a screening population with set screening interval, and so avoids the complications associated with the test developed using Danish data where screening interval is based on risk [39].

Table 4. Cox's model of the risk factors for development of diabetic retinopathy by Semeraro et al [41]

	Hazard Ratio (95% CI)	**p**
Male gender	1.307 (1.052–1.625)	<.02
Time from diagnosis of diabetes (years)	1.062 (1.045–1.079)	<.001
HbA1c (%)	1,163 (1.086–1.246)	<.001
Therapy for DM (vs. diet):		
Oral hypoglycaemic agents	3.900 (1.726–8.814)	.001
Hypoglycaemic agents and insulin	8.859 (3.543–20.677)	<.001
Insulin	6.794 (2.891–15.968)	<.001
Creatinine clearance (ml/min)	0,997 (0.993–1.001)	.095
Albuminuria (mg/day)	1.001 (1.001–1.001)	<.001
Systolic blood pressure. (mm Hg)	1.014 (1.008–1.020)	<.001

Mehlsen et al. 2011 [39] describe an investigation to determine the risk factors affecting progression to diabetic retinopathy which requires treatment. They followed 5,311 patients (of whom 1,385 had T1DM) at a screening centre in Denmark between 1994 and 2007. None of the patients received treatment for retinopathy at their first screening visit. Each patient had an average 4.3 appointments over the study period. At this screening centre there was not a uniform screening interval for all; interval varied from 3 months to 60 months. For T1DM patients with <10 years diabetes duration, the interval was 60 months, for T2DM patients above the age of 60 years with no retinopathy the interval was 48 months, for T2DM patients with four or fewer micro aneurysms/haemorrhages the

interval was 24 months, if there was mild diabetic retinopathy the interval was 12 months, and in the presence of more serious symptoms the interval was 3 or 6 months. A logistic regression analysis was used to determine the risk factors affecting the probability of a patient requiring treatment during each interval. The occurrence of patients requiring treatment in all screening datasets is interval censored, because when diabetic retinopathy requiring treatment is detected at screening the patient would have developed this at some point during the interval since the previous screen. However, there are additional complications in this dataset because the interval duration is dependent on risk factors. The authors apply inverse probability of treatment weighting to account for this; they suggest that if there are no unmeasured confounders this approach would produce unbiased estimates.

There is a strong probability of unmeasured confounders, and this complication makes the results more difficult to interpret in the UK context. As would be expected the recommended screening interval is a strong predictor for risk of treatment. For T1DM patients the predictors of requiring treatment during the interval were: disease duration in years (OR 1.04 95% CI 1.01-1.07), the log of the number of retinal haemorrhages (OR 2.68, 95% CI 1.83-3.91), deviation from the recommended screening interval in months (OR 1.04, 95% CI 1.01-1.06), and mean HbA1c in percentage units (OR 1.49, 95% CI 1.17-1.90). For T2DM patients the predictors of requiring treatment during the interval were: age at diagnosis in years (OR 1.02, 95% CI 1.01-1.03), the log of the number of retinal haemorrhages (OR 2.37, 95% CI 1.84-3.06), deviation from the recommended screening interval in months (OR 1.03, 95% CI 1.02-1.05), mean HbA1c in percentage units (OR 1.22, 95% CI 1.12-1.33), and diastolic blood pressure (OR 1.03, 95% CI 1.00-1.05).

Disease duration may have been a significant factor for T1DM and not T2DM because it is less accurately measured for T2DM; the authors cite diagnosis of T2DM is typically 7-8 years after onset. Age of onset is a predictor for T2DM but not T1DM, perhaps because it simply doesn't vary enough in T1DM. This study used separate models for T1DM and T2DM because there are different protocols for determining screening interval for the two types in Denmark. Whilst risk factors do appear to differ between the two types, the method of defining patients as type 1 or type 2 may not be the same in the UK. In this study the patient was defined as having T1DM if the age of onset was below 30 years, or if the age of onset was between 30 and 40 years, insulin treatment was commenced within one year of diagnosis of diabetes and the body mass index was below 25.

Mehlsen et al. [40], use the same data and regression model from 5,311 diabetes patients in Denmark to test alternative risk weighting strategies. The model was tested on a set of 1,372 patients (500 of which had T1DM) from the same centre who attended screening in 2000, using a set

risk of reaching a treatment end point between screens of 0.1, 0.5, 1.0, 5.0, and 10.0. At risk level 0.5% none of the 1,372 would have reached a treatment end point before the next screening round, and the screening interval was prolonged by average 2.9 times for patients with T1DM and 1.2 times for patients with T2DM. This is an improvement on the current Danish system of risk weighted intervals, but we do not know how that may translate to a change from the current UK screening interval of one year. The model was unable to make a prediction for some patients, at risk 0.5% the model was unable to make a prediction for 109/451 patients with T1DM and 102/649 patients with T2DM, the authors suggest that this was due to difficulties in making predictions for high risk low screening interval patients.

Aspelund et al. [27] describe the development and testing of a risk prediction algorithm called the risk medical solutions calculator (available at www.risk.is). The risk calculator is based on prevalence data from the Icelandic eye screening database and published risk factors. The risk factors included in the model are type 1 or 2 diabetes, HbA1c, systolic blood pressure, gender, and whether non-proliferative diabetic retinopathy is present. The coefficients used are from the UK Prospective diabetes study [18, 35], and the Wisconsin Epidemiologic study of diabetic retinopathy [17].

Table 5. Risk ratios used by Aspelund et al. [26] to develop their risk calculation algorithm

Variable	Risk ratio [95% CI]	Reference
Type 1 diabetes		
HbA1c (%)	1.20 [1.16, 1.25]	[17]
Systolic BP (10 mmHg)	1.08 [1.04, 1.12]	[17]
Nonproliferative diabetic retinopathy		
Female	2.74	[17] [35]
Male	3.30	[17] , [35]
Type 2 diabetes		
HbA1c (%)	1.46 [1.05, 2.02]	[48]
Systolic BP (10 mmHg)	1.54 [1.06, 2.27]	[49]
Nonproliferative diabetic retinopathy		
Female	1.78	[18, 35]
Male	3.30	[18, 35]

The algorithm was tested on the same diabetes patients in Denmark as in the two studies by Mehlsen et al. [39, 40], although in this paper there are 5,199 patients which is 112 fewer than cited in the other publication. The information gathered at each patient's first visit to the screening

programme was entered into the model, which was used to calculate a suggested screening interval for each individual. The risk level set in the model was such that the number of individuals with sight threatening retinopathy at their next screening visit was equal to that for fixed annual screening. To calculate this they used the Danish data that 2.9% or 149/5,199 developed sight threatening retinopathy in their first year in the screening programme. This may not be the optimal way to set the risk level, because in the Danish programme lower risk patients are not rescreened within 1 year so sight threatening retinopathy may not have the opportunity to be detected, and patients first year in the screening programme may not be typical of other years in the screening programme. A floor of 6 months and ceiling of 60 months was applied to constrain the intervals suggested by the model. Recommended intervals covered the full range from 6 to 60 months, with a mean of 29 months. This represented 59% fewer visits for diabetic retinopathy screening than annual screening. Receiver operating characteristic (ROC) analysis provides the opportunity to explore performance over a range of risk thresholds. The area under the ROC curve was 0.76, so the authors conclude that there is a 76% probability that a randomly selected patient who develops sight threatening retinopathy will be given a higher risk score than a randomly selected patient who does not develop sight threatening retinopathy. However the authors do not state the time period over which they are considering the risk of developing sight threatening retinopathy here. There was missing data in the test set (systolic blood pressure was missing for 67% of patients and HbA1c was missing for 22% of patients) which may have inhibited the performance of the algorithm, and therefore the area under the ROC curve calculated may be improved if more complete data for each individual screened were available. In these cases HbA1c was set at 8% and blood pressure at 130mmHg. The authors' state that the model fit was worse at higher risk levels, similar to the findings of Mehlson et. al. [39].

4.2.8.3 Key findings from risk algorithm studies

Risk stratification algorithms show potential for efficient reallocation of resources to screening at time periods appropriate to the individual's risk. Internal validation of a Danish model showed that in patients from the same screening centre the screening interval could be prolonged by an average of 2.9 for patients with T1DM and 1.2 for patients with T2DM whilst maintaining the same risk levels for STDM. This is an improvement on the current Danish system of risk weighted intervals, but we do not know how that may translate to a change from the current UK screening interval of one year, or whether this improvement would be maintained in an external validation of the model on another dataset. Finally, the model did not work for all patients (particularly at higher risks). The Aspelund model [27] was based mostly on published data, largely from the UK prospective Diabetes study, and in an external validation on a Danish data set found that 59% fewer visits could be achieved at the same risk levels. However this validation was on a Danish dataset where the screening interval is

already variable based on risks, and so it is unclear how this may translate to a UK context. The Stratton model [46] based on UK data demonstrates that presence of retinopathy is a very strong predictor of faster progression to STDR, but does not include any other risk factors. The Semeraro model [42] is internally validated on Italian data to measure area under the ROC curve, and identifies some strong predictors of progression to STDR, but does not report the outcomes of most clinical interest and is not externally validated. An external validation study investigating the comparative performance of all available models on historical UK screening data would be necessary to inform any choice of system. Furthermore consideration of the measurement accuracy of the predictors used is necessary, whether these data are available in the UK diabetic retinopathy screening programme, and the cost of calculating and adjusting individual risks. In particular are the criteria for defining which patients are types 1 and 2 in UK screening the same as those used in creating the algorithms, and with what level of accuracy and reliability can we measure HbA1c, systolic blood pressure, and time of onset of diabetes?

4.3 Assessment of Cost-Effectiveness: Results

This section outlines the description of the populations included in the economic appraisals, the models used, an appraisal of study quality and the key findings.

4.3.1 Description of Studies

The search found eight papers which assessed the cost-effectiveness of interval screening for diabetic retinopathy [28] [29] [30] [31] [33] [32] [41] [44] . In addition, the search also identified two other important publications: 1) a report compiled by the Wessex Institute looking at the implications of reducing the interval for diabetic retinal screening from two years to one year [38]; and 2) a systematic review looking at the economic evidence for diabetic retinopathy screening [10].

4.3.1.1 Models and comparators

Each of the eight papers used various types of simulation models to estimate the cost-effectiveness of the different intervals for screening for diabetic retinopathy. Most of the studies were conducted on hypothetical cohorts of patients with diabetes and used data from existing datasets and literature, to build and populate the model. The models produced results in terms of costs and outcomes for an individual patient or a cohort of patients. Three of the eight models used the patient-orientated simulation technique (POST) to simulate the retinopathy progression and screening of individual diabetic patients throughout the specified time period. With this model patients' experiences over time are divided into events and each event determines the time of

subsequent events [28] [29] [31]. Two models used a network simulation program known as the 'PROspective Population Health Event Tabulation' (PROPHET). This modelling system is designed for modelling the progression of chronic irreversible diseases which includes features from various other models including decision trees, Markov processes and Monte Carlo simulations; the system is used to model events and costs for each patient as a separate individual over the predicted lifetime of the cohort [33] [32]. The descriptive characteristics and key economic variables from each of the studies are summarised in Table 1.

Brailsford et.al [28] estimated the cost-effectiveness of different screening strategies compared with no screening (baseline) using a discrete event simulation (DES) which was embedded in an ant colony optimisation model for patients with type 2 diabetes. This complex model aimed to find the most optimal screening policy using the least amount of simulations. The screening process was carried out in two stages (first stage in a community setting and second stage in a hospital setting) and two tests were conducted (the first test is cheaper and less accurate than the second). Under policy 1, patients are screened by the same test in both stages, although possibly at more frequent intervals once background retinopathy has been detected. Under policy 2, patients are always screened in hospital using the second test after the detection of background retinopathy. Chalk and colleagues [29] developed a new, retinopathy screening simulation model (ReSS) which builds upon POST to assess the cost-effectiveness of a retinal screening test used every two years compared with annual (or six-monthly screening) for patients with type 2 diabetes without diabetic retinopathy. Using existing data from the Royal Devon and Exeter NHS Trust on incidence and progression rates, the model simulates the progression of disease and screening of individual diabetic patients and each patient has a specific health 'state' that shows you how far their retinopathy has progressed, whether they have lost their vision or whether they have died. Similarly, Dasbach et al [30] assessed the cost-effectiveness of screening for diabetic retinopathy comparing biannual and annual screening programmes for three different modes (community office-based health care professional using an ophthalmoscope, nonmydriatic camera screening, and mydriatic camera screening) using two simulation models which were developed using a Markov process. The first model simulated the natural disease progression for diabetic retinopathy and the second model adds to the first by introducing the effects of ophthalmologic care (detection and treatment of retinopathy) on the natural disease progression. Davies et al [31] developed a DES model to determine the cost-effectiveness of varying the screening method and the screening intervals. Each different screening scenario was compared to no screening. Screening intervals were varied: 1 year and 2 years before background or advanced retinopathy was detected and 6 months or 1 year afterwards. Under policy 1, optometrist screening, diabetologist ophthalmoscopy and GP screening was at intervals of 12

months and a 6-month interval between visits once diabetic retinopathy had been detected. Under policy 2, people were screened by the different methods every 12 months, even after the detection of background retinopathy, until treatable retinopathy is detected when visits where scheduled every 6 months. Mydriatic seven-field photography by an ophthalmologist was assumed to be the 'gold' standard and this consisted of screening every 6 months, with visits every 3 months after diabetic retinopathy had been detected.

Javitt and colleagues [33] aimed to estimate the cost implications of alternative screening strategies for detecting diabetic retinopathy in patients with type 1 diabetes using the simulation program PROPHET. Five different screening strategies were evaluated: 1) dilated ophthalmoscopy every 2 years for all patients; 2) dilated ophthalmoscopy annually for all patients; 3) dilated ophthalmoscopy annually for patients with no retinopathy and examination every 6 months for those with retinopathy; 4) dilated ophthalmoscopy with full fundus photographs annually; and 5) dilated ophthalmoscopy with full fundus photographs annually for patients with no retinopathy and examination every 6 months for those with retinopathy. The authors [32] in their follow-up work, aimed to estimate the cost savings resulting from screening and treatment of retinopathy for type 2 diabetes patients. The authors again used the PROPHET modelling system and proposed eight screening strategies: in strategies 1 and 2, all patients would be seen by an ophthalmologist every 2 years (those with background or more advanced retinopathy will be seen either semi-annually under strategy 1 or annually under strategy 2); for strategies 3, 4, and 5 the initial interval is increased to 3 years (those with background retinopathy screened every 6, 12, or 18 months, respectively); and for strategies 6, 7, and 8 the initial screening interval is increased to every 4 years (for those with background retinopathy screened every 6, 12, or 24 months, respectively). Rein et al [41] wanted to determine whether biennial eye evaluation or telemedicine screening are cost-effective alternatives to current recommendations for people with diabetes but no or minimal diabetic retinopathy. Their model used Monte Carlo simulations and looked at four methods of interval screening: patient self-referral following visual symptoms (current practice), annual eye evaluation, biennial eye evaluation, and annual telemedicine screening in primary care settings. Finally, Vijan et al [44] wanted to examine the cost-effectiveness of various screening intervals (annual vs. less frequent) for eye disease in patients with type 2 diabetes. The model adopted was a Markov model using Monte Carlo simulations looking at the incidence of developing and progressing through the stages of non-proliferative retinopathy.

4.3.1.2 Study perspective and time horizon

In terms of the analysis, study perspective is crucial to the economic evaluation as it will determine whether the appropriate resource use and costs have been collected, calculated and reported. Study perspective was not stated in three studies [28] [29] [31] ; Javitt et al [33] and Javitt et al [32] used a government perspective; Dasbach et al [30] and Rein et al [41] used a societal perspective; and Vijan et al [44] in the base-case analysis used a third party payer perspective and in the sensitivity analysis they used both government and societal viewpoints.

All studies choose to have different time horizons for their simulation models ranging from 10 years to the lifetime of the patient cohort. The time horizon should be sufficiently long enough to capture all the benefits that would accrue from these different screening programmes [50]. Dasbach et al [30] choose to run their model for two time periods, one for 10 years and another for 60 years; Chalk et al [29] simulated each scenario in their model for 15 years and this was replicated for 10 times and the results obtained were averaged over these replications; Davies et al [31] chose a 25 time horizon; Brailsford et al [28] ran their complex model for a 100 years; whilst the other four studies choose a lifetime horizon, although this was not explicitly stated in the study by Vijan and colleagues [32] [33, 41, 44]. Only three of the studies explicitly stated the cycle length for their models which ranged from 2-monthly cycles [32] [33] to a 1-yearly cycle [30] .

4.3.1.3 Health outcomes

The various studies all used different measures of health outcomes for the simulation models, the most common being sight years saved or gained [28] [30] [31] [32] [33]. Chalk et al [29] used the proportion of type 2 diabetes patients who lost their vision (diabetes associated vision loss) as a measure of effectiveness and both Rein et al [41] and Vijan et al [44] used quality-adjusted life years (QALYs) as an outcome measure. QALYs are the recommended measure of health effects in England and Wales, as they take into account both the quality and quantity of life lived [50]. Brailsford et al [28] acknowledged that they haven't attempted to estimate the cost of blindness or to calculate QALYs which would have enabled a cost-utility analysis.

The different measures of effectiveness for the simulation models came from various data sources. Chalk et al [29] used existing data from the Royal Devon and Exeter NHS Trust on incidence and progression rates, which was supplemented by literature, and Dasbach et al [30] used data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) which was a population-based study looking at the incidence and prevalence of diabetic retinopathy. Four studies used effectiveness data to populate their models from published literature and trial results, in addition to their own assumptions [31] [33] [32] [44]. Rein et al [41] used literature sources in addition to

various other sources including the United Kingdom Prospective Diabetes Study and the National Health and Nutrition Examination Survey; whereas Brailsford et al [28] didn't state the source(s) for their effectiveness data.

4.3.1.4 Resource use, costs and discounting

In terms of resource use and costs which were used in the simulation models, Brailsford et al [28] obtained costs of screening and treatment and outpatient visits from the NHS National Screening Committee website (Diabetic Retinopathy Screening); Chalk et al [29] included the costs of the screening test, an ophthalmology visit and laser photocoagulation treatment; some of these unit costs were provided directly by the NHS Trust; Dasbach et al [30] included a comprehensive account of the direct costs to the health service which were included in the model. These were the different modes of screening, clinic visits and treatment and rehabilitation; the unit costs were obtained from the University of Wisconsin apart from the indirect annual costs of blindness which was obtained from literature; Javitt et al [33] and Javitt et al [32] included the costs of screening and treatment which were derived from the average Medicare charges in 1986 and 1990, respectively and the costs of a year of blindness for a working-age American was estimated [32]; Rein et al [41] included intervention costs (including telemedicine costs for the telemedicine arm), treatment and follow-up costs and also productivity losses; Vijan et al [44] included costs for ophthalmology visits including eye examinations, laser photocoagulation and angiogram and costs were standardised using average Medicare reimbursement rates; and Davies et al [31] reported costs for the primary screener, ophthalmology outpatient visits, courses of treatment, and use of the mobile camera where applicable (including set-up costs and quality assurance costs. Again like Brailsford et al [28] study, the unit costs were obtained from the NHS National Screening Committee website.

Half of the studies reported the currency and price year[30] [33] [32] [41]; whereas, the other four studies only reported the currency and no price year [28] [29] [31] [44]. For those studies where no price year is reported, researchers cannot use these unit costs for their own studies or do cost comparison with their own or other studies.

All studies except two [29] [31], reported that discounting had been performed, using the same discount rate for both costs and outcomes (range: 3% to 5%). Although, Davies et al [31] acknowledged that further cost-effectiveness analyses needed to be undertaken using discounting. Discounting is important in cost-effectiveness analyses as it is a method which converts future costs into present values, thereby allowing comparisons between costs and benefits that occur at different times. This is especially important for screening programmes where costs occur in the current time period, whilst benefits are usually not evident until some point in the future. Brailsford

et al [28] used two discount rates for their base-case analysis (3% and 5%); Dasbach et al [30], Javitt et al [33], and Javitt et al [32] used a 5% discount rate and also reported the different ranges over which the discount rate was varied in the sensitivity analysis. Rein et al [41] and Vijan et al [44] used a 3% discount rate.

4.3.1.5 Presentation of results and sensitivity analyses

All studies reported both costs and outcomes in a disaggregate form; however, four of these studies did not report an incremental cost-effectiveness ratio (ICER) [29] [30] [33] [32]. An ICER is important as it helps decision makers to compare against different screening programmes if the same outcome measure is used or against other health interventions (including screening programmes) if a common outcome is used such as QALYs; the ICER here would be an incremental cost per QALY gained. The study by Rein and colleagues [41] also reported results in terms incremental net benefits. The incremental net benefit ratio is useful, in addition to the ICER, because it is easier to determine which screening strategy is best compared with the next most costly strategy.

Sensitivity analyses are important in economic analyses as they deal with uncertainty around key parameters and assumptions made in the model and help confirm the robustness of the results. Brailsford et al [28] did not report any sensitivity analyses. One-way and multi-way sensitivity analyses were conducted for six studies [29] [30] [31] [33] [32] [44]. Rein et al [41] used probabilistic sensitivity analyses (PSA), this is where probability distributions, which are based on a large number of Monte Carlo simulations, are applied to specific ranges for key parameters and samples are drawn at random from these distributions to generate distributions of the cost-effectiveness ratio. Using the results from the PSA, results were presented as cost-effectiveness acceptability curves; these curves show the probability that a screening strategy is cost-effective for different amounts the decision maker is willing to pay. The authors also calculated the expected value of perfect information for parameters included in the probabilistic sensitivity analyses. The expected value of perfect information shows the additional cost of research in reducing uncertainty in the model.

4.3.2 Quality Assessment: Economic Appraisals

Overall, evaluation using the 27 point CHEERS checklist indicated that target population and subgroups, choice of health outcomes, and choice of model were well reported by the 8 economic analyses (see Appendix H). Two publications did not describe all the comparators fully [28] [44]; in addition Vijan et al [44] did not report the time horizon clearly. The article by Rein and colleagues [41] was the most comprehensively completed in terms of economic analysis using the CHEERS

checklist: 20 of the 27 statements (74.1%) were a 'yes', 3 statements (11.1%) were partially completed, one statement (3.7%) was not completed and three statements (11.1%) did not apply. Both Dasbach et al [30] and Javitt et al [32] indicated a 'yes' to 17 statements (63.0%), 1 was partially completed (3.7%), five statements were not completed (18.5%) and four statements (14.8%) did not apply. The least comprehensive article in terms of the economic analysis was the article by Brailsford et al [28] in which their study resulted in 'yes' to 10 of the 27 statements (37.0%), 3 statements were partially completed (11.1%), 10 statements were not completed (37.0%) and 4 statements did not apply (14.8%).

Using the adapted Phillips et al [25] 32-point checklist to critical appraise the economic models, demonstrated that overall the 8 publications adequately reported a clear statement of the decision problem, the objective of the model evaluation, the sources of data used to develop the structure of the model, the type of model for the decision problem, the methods and assumptions to extrapolate short-term results into final outcomes, the costs including sources used in the model, and compared results with previous models (see Appendix I). The models did not provide clear justification if any feasible options were excluded, none of the methods used expert opinion. None of the models applied a half-cycle correction and in none was its omission justified. Again, the article by Rein et al [41] was the most comprehensive economic analysis when using the Phillips et al [25] checklist to critique the article: 22 of the 32 statements (68.8%) were a 'yes', 2 statements (6.3%) were partially completed, five statements (15.6%) were not completed, two statements were unclear (6.3%) and one statement (3.1%) did not apply. The article by Chalk et al [29] was not as comprehensively completed in terms of the economic model: only 14 of the 32 statements were a 'yes' (43.8%), 9 statements were not completed (28.1%), five statements were unclear (15.6%) and four statements did not apply (12.5%).

4.3.3 Identification of other key economic appraisals

In additional to the 8 papers we identified a systematic review from Jones et al [10]and a report published in 1999 by the Wessex Institute looking at the implications of reducing the interval for diabetic retinal screening from two years to one year [38]. The Wessex Institute report identified no primary research studies investigating differences in screening intervals for diabetic retinal screening; however, four studies using complex simulation models were identified [30] [32] [51] [52]. Two of these four studies were identified in our search [30] [32]. The study by Javitt et al [52] was a companion study to one we have included [33]; the main differences were that this study did

not explicitly address the issue of screening intervals and also sight benefit was not discounted, whereas the study included in our search results did discount sight benefit. Davies et al [51], compared screening taking place annually or biennially until background retinopathy develops, with patients then examined six-monthly or more frequently. The study only looked at benefits in terms of sight years saved and no costs were estimated; hence, this was a partial economic evaluation and was therefore not included in our cost-effectiveness search results. The report recommended supporting annual screening as opposed to a two-year screening, as there would be a net gain in the number of sight years saved and as a result fewer patients would go blind.

The systematic review by Jones et.al [10] used the Drummond Checklist [53] to review quality along with additional two questions concerning validity. The Jones review included Vijan et.al [44], Davies et.al [31] and Brailsford et.al [28] but does not include the earlier cost-effectiveness analyses by Dasbach et.al [30] or Javitt et al [32], Javitt et al [33] or the later papers by Rein et.al [41] or Chalk et.al [29]. The authors found various factors of uncertainty in the issue of optimal screening intervals such as: 'variation in compliance rates, age of onset of diabetes, glycaemic control and screening sensitivities'. They argued that there is controversy in relation to the economic evidence on optimal screening intervals, as some of this is consistent with evidence from cohort studies which conclude that longer screening intervals are cost-effective for patients with no retinopathy; however, further research was needed to determine the optimal screening interval.

4.3.4 Key Findings from Economic Appraisal studies

Brailsford et al [28] found that the most cost-effective screening policy was to start screening at age 35 (no discounting) or age 30 (with discounting) and to stop screening at age 60. If there was no discounting, incremental costs were £166,591 and the incremental number of years of sight saved was 180, resulting in an incremental cost per year of sight saved of £928. Using a 3% and a 5% discount rate, when comparing screening with no screening, the incremental costs per year of sight saved were £1,119 and £1,262, respectively. With no discounting and screening start age of 30 and end age of 60, the most cost-effective option was that the two screening tests should be carried out at 30 month intervals with an incremental cost per year of sight saved at £899 (policy 2). Chalk et al [29] found that with either screening strategies: every two years or annual (or six-monthly screening) found that 1.9% of type 2 diabetes patients would be predicted to lose their vision and that there would be a reduction of 11,050 appointments over the 15 years. The costs for the proposed screening every two years were £1.36 million compared with £1.83 million for the annual

screening, which represented a reduction of approximately 25% in screening costs. Dasbach and colleagues [30] found in terms of benefits, 273 sight years gained per 1,000 invitations and costs were dominated by the cost of rehabilitation and associated savings for annual screening. The results showed that for the 60-year time horizon, an annual examination with mydriatic fundus photography was the most effective for the younger onset diabetes population, as the programme might save from 303 to 319 sight years over the lifetime of the cohort; whereas this program will save from 58 to 62 sight years in an older onset diabetes cohort who are taking insulin, and only from 19 to 21 sight years in the older onset diabetes population not taking insulin. Davies et al [31] found for both type 1 and type 2 patients together, the mobile camera (policy 2) had the lowest costs at £449,200 per year and a cost per sight year saved of £2,842. For type 1 diabetic patients, the costs per year of sight saved were £2,143 if policy 1 was implemented by optometrist fundoscopy, £1,399 if policy 2 was implemented by the mobile camera, and £4,122 if the 'gold' standard was used as the screening strategy. For type 2 diabetic patients, the costs per year of sight saved were £4,700, £3,349, and £11,263 respectively. The authors concluded if the mobile camera screening was reduced to once every 2 years before detection of retinopathy; there would be an 8% reduction in the cost per sight year saved. If the sight years saved are to be kept above 85% of the gold standard, then the recall interval, once retinopathy is detected should be 6 months.

Javitt and colleagues [33] found all strategies resulted in net annual savings ranging from $62.1 (strategy 5) to $108.6 million (strategy 2) for type 1 diabetes patients. Strategy 3 which consisted of the dilated ophthalmoscopy annually for patients with no retinopathy and examination every 6 months for those with retinopathy saved more sight than did less frequent examination and was nearly as cost saving, whereas strategy 4 which consisted of dilated ophthalmoscopy with full fundus photographs annually was not as effective or cost saving as more frequent examination without photography. In their latter study, Javitt et al [32] found screening and treatment for type 2 diabetes patients generates annual savings of $248 million and 53,986 person-years of sight in total, even at current suboptimal (60%) levels of care. Changing the frequency of screening for patients with no or mild background retinopathy from one to two years, even though costs were reduced, this had no detrimental effect on years of sight saved. For persons with background retinopathy, a one year compared to a two year screening interval saves an extra 8,960 years of sight over the life of the cohort. A 6-month screening interval for patients with background retinopathy can save about 3,360 person-years of sight over the life of the cohort compared with a 12-month screening interval, and 12,320 person-years of sight over the life of the cohort compared with a 24-month screening interval. Once patients developed moderate or more advanced retinopathy, savings in sight-years are sensitive to the screening interval. Rein et al [41] found self-referral offered the

lowest costs and QALYs, followed by telemedicine, biennial evaluation, and annual evaluation. The different methods compared to self-referral produced the following ICERS: for annual telemedicine assessments was US$ 55,000 per QALY gained; biennial examination was US$ 38,000 per QALY gained and annual evaluation was US$ 46,000 per QALY gained. The different methods of screening were more likely to be cost-effective at different willingness to pay (WTP) values: self-referral between US$0 and US$37,500 per QALY gained; biennial evaluation between US$37,500 and US$150,000 per QALY gained, and annual evaluation at US$150,000 per QALY gained. A direct comparison found biennial eye evaluation to be more cost-effective than telemedicine or annual eye evaluation. Finally, Vijan et al [44] concluded that for patients with type 2 diabetes, increasing screening from every other year to screening annually the marginal costs are $107,510 per QALY gained, while screening every other year versus every third year costs $49,760 per QALY gained. Using a threshold of $50 000 per QALY as a cost-effective intervention, the authors suggest screening every other year as the most cost-effective choice, with the option of tailoring screening to the needs of different individuals. So for example, those patients with the poorest glycaemic control would be screened more often and those with good glycaemic control and no retinopathy would be screened every year or every third year.

5. DISCUSSION

This section presents the findings from the assessment of the potential impact of different screening interval lengths on clinical outcomes. The key limitations of the review and uncertainties are also presented.

5.1 Principal Findings

Analysis of the available evidence suggests that altering screening intervals for some groups of patients will not adversely affect clinical outcomes. However, risk factors have been identified through observational studies and through risk stratification models that suggest that caveats should be in place for certain patient groups.

5.1.1 Safety of altering screening interval

All of the identified literature from the included observational studies supported the adoption of at least biennial screening for patients with T2DM and are low risk patients, such as those with well controlled diabetes on dietary treatment, with well controlled blood pressure and do not have background retinopathy. One key paper [5] concludes that biennial screening would be acceptable in low risk patients without background retinopathy, but intervals of more than 24 months lead to an increased risk.

Several studies identified factors that increase the risk of developing retinopathy during an interval period and subgroups of patients at higher risk of developing diabetic retinopathy. The principal findings relating to each risk factor are outlined in this section.

5.1.1.1 Background retinopathy

All of the observational studies identified in this literature review conclude that screening intervals of longer than one year may be appropriate in lower risk patients without background diabetic retinopathy for patients with T1DM and T2DM.

The data on cumulative incidence from a number of well conducted studies [34, 45, 43] would suggest that a move to biennial screening would be associated with some increased risk of progression in the mid interval period to some forms of referable retinopathy. However, this risk level is reported in the studies as low, but perception of this risk would be for decision makers to decide and measure against alternative use of resources.

The authors of the Liverpool Diabetic Eye screening programme paper [45] demonstrated a low cumulative incidence rate of sight threatening diabetic retinopathy (STDR) in patients with T2DM without retinopathy at baseline resulting in a recommendation for adoption of 3 yearly screening intervals in patients without background diabetic retinopathy. For patients with T1DM [8] they described the risk of developing STDR as being associated with more advanced retinopathy at baseline and went on to recommend that intervals of 2-3 years for patients with no retinopathy, 1 year for patients with background and 3-6 months for patients with mild pre-proliferative retinopathy would provide a minimum 95% certainty of remaining free of STDR.

Triennial screening has been adopted in Sweden. Here Agardh et.al [6], in a study of 1,322 patients with T2DM with no background diabetic retinopathy, found that no patients had developed severe non-proliferative diabetic retinopathy during the three year interval. The authors concluded that triennial screening is safe and effective. One patient did, however, need laser treatment for macular oedema. These findings are supported by the findings of Kohner et.al [35], where out of the 2,316 patients with T2DM and no diabetic retinopathy, only 0.2% needed photocoagulation at 3 years.

Screening intervals longer than one year have been demonstrated to be safe in people without diabetic retinopathy at initial screening in the Icelandic cohort [7] of 296 patients followed for 10 years with biennial screening, where no patients went from no diabetic retinopathy to STDR in less than two years. Patients who developed STDR were placed on an annual screening interval.

The data from the Norfolk cohort [5, 34] also supports the adoption of screening intervals of between 19-24 months, with cumulative incidence of proliferative diabetic retinopathy of 0.13% (95% CI 0.7-.22) and STM of 0.11% (0.3-0.19) at 5 years amongst patients with T2DM and no background diabetic retinopathy. Importantly, screening intervals of more than 2 years were associated with an increased risk of referable retinopathy, with an OR of 1.56 (95% CI 1.41-1.75).

5.1.1.2 Additional Risk factors

The studies that recommend increasing screening intervals for low risk patients include caveats that high risk patients should still be able to access screening at more regular intervals than the general population of low risk people with well controlled T2DM and no background retinopathy. Risk factors linked with increased risk of developing or progressing retinopathy included duration of diabetes, insulin use, blood pressure treatment and HbA1c levels.

Patients who are recorded as using insulin were observed to be at greater risk of developing diabetic retinopathy. Patients with a longer duration of diabetes are also more likely to use insulin. The large observational study by Thomas et.al. [43] reported incidence of retinopathy to be independently

associated with age at diagnosis, use of insulin treatment and duration of diabetes, leading the authors to conclude that the results support the extension for screening interval for people with T2DM beyond the currently recommended 12 months, with the exception of those with duration of 10 or more years or on insulin treatment who should continue to be screened annually.

Patients with a higher HbA1c percentage recorded at any time were found to be at higher risk of developing retinopathy. A higher level of HbA1c is indicative of less well controlled diabetes. Higher levels HbA1c percentages recorded at any visit were found to be associated with a higher risk of retinopathy in the populations studied by Maguire [37] and Olfasdottir [7] suggesting that patients with poorly controlled indicated by elevated HbA1c levels recorded at any visit may be at higher risk of developing retinopathy during a longer screening interval. Monitoring risk relating to elevated HbA1c level would also require regular assessment in the screened population.

Of course, an individual's ability to maintain good control over their diabetes can vary over time with increasing age, disease progression or through different periods of an individual's life. Safeguards would have to be employed to ensure that if patients entered a risk group at any time during their normal screening interval, they would change to a new and appropriate schedule for their needs.

Alongside recommendations for patients with T1DM presented by Younis et.al [8], data from the paediatric population studied by Maguire et.al [37] supports biannual screening in adolescents with T1DM and reasonable metabolic control, although no definition of 'reasonable' is provided.

These findings indicate that individuals that display any of these risk factors may experience poorer clinical outcomes if they were to be screened less often than annually.

The key observational studies by Jones et.al [34] highlight the importance of hypertension treatment as a risk factor, as well as the increased risk of progression in patients on oral hypoglycaemic medications, which was also found in the study by Thomas et.al [43], and Semerero et.al [42]. However, as the authors of Thomas et.al [43] highlight, the risk incidence of referable diabetic retinopathy is low in people with type 2 diabetes mellitus without evidence of retinopathy at initial screen, with the exception patients with a longer duration of diabetes than 10 years and on insulin treatment. This is also in the context of the other studies identified in this paper, which have led the authors of this review to a similar conclusion.

5.1.2 Cost-Effectiveness of Altering Screening Intervals

Evidence for cost-effectiveness supports the findings of observational studies for adopting longer screening intervals for low risk patients and suggests that biennial screening intervals could be adopted for those with no background retinopathy.

As with recommendations from some of the observational studies, two of the cost-effectiveness analyses support the notion that those at higher risk should be screened more frequently [28] [44]. They conclude that changing screening from annually to biennially would save resources and costs in health care such as screening visits, which could then be spent in other health areas where the need for financial resources is much greater. This is in contrast to Davies et al [31] who concluded that annual screening remains most cost-effective and they recognised the trade-off between compliance, intervals, and sensitivity, and they also acknowledged that a change in interval may have knock on effects for changes in compliance and attendance. This concern is investigated further in the supplementary review in Appendix J. Davies et al [31] found that the main difference between their results and those of Vijan et al [44] was that as Vijan and colleagues did not incorporate compliance levels of less than 100%, their costs of screening were higher and the use of QALYs rather than sight years saved. Rein et al [41] concluded that annual evaluation was costly per QALY gained compared with biennial evaluation and that biennial eye evaluation was the most cost-effective treatment option when the ability to detect other eye conditions was included in the model; similarly Chalk et al [29] concluded that the model implementing a 2-year screening interval does not increase their risk of vision loss for type 2 diabetes patients without diabetic retinopathy, and could reduce screening costs by approximately 25%.

5.2 Strengths and Limitations of the Evidence Base

5.2.1 Strengths of the Evidence Base

The majority of large scale observational studies are based on UK data [5, 8, 34, 35, 37, 43, 45] and thus the results are largely valid for a UK audience and particularly relevant to the decision makers in these countries.

The identified observational studies, were, largely, well conducted, with clearly focused questions with population characteristics and the main outcome measures clearly documented, alongside thorough descriptions of the screening programmes. The majority of studies (90%) reported

adequate methods of participant recruitment, exposure measurement (i.e., types of screening tests and between-test intervals), and outcome ascertainment. All studies measured and reported some important baseline risk factors or prognostic factors of retinopathy and its progression (e.g., age, sex, blood pressure, ethnicity, HbA1c, type of diabetes, duration of diabetes, diabetes treatment). Some studies were particularly large [43], or covered large timescales [5,34]. Some of the studies were large [43, 34,5,45,8] and over long time periods.

Overall, the 8 economic analyses publications as evaluated by the 27 point CHEERS checklist found that the reporting of the target population and subgroups, the choice of health outcomes, and the choice of model were well reported (see Appendix H).

The authors of this review did not formally assess the quality of the risk algorithm, this would be appropriate in the future when there are risk prediction algorithms relevant to the UK population and the PROBAST tool is published. However, these studies were reasonably well described, both in terms of the methodologies used and the underlying data used to build the models.

5.2.2 Limitations of the Evidence Base

The studies from Sweden and Iceland [6, 7] document the experience of triennial and biennial screening programmes in low risk patients respectively. The validity and applicability to a UK based population has however, been questioned – these countries have particularly well-funded schemes, high compliance and comparatively small populations [16]. Levels of compliance have not always been as well documented in all areas of the UK.

A limitation to the evidence base from observational studies of screened populations is the inability of researchers to account for high attrition or dropout rates – for example 12% of participants who were eligible did not attend a second screening session in the largest study of its kind [43], and in the Norfolk cohort [34] only 14,360 of 20,686 patients were screened twice. There remains the possibility there are systematic differences in the non-attendees, or that attendances and referral to ophthalmologist care are not captured.

The majority of the large studies also focus largely on T2DM patients (88,136 T2DM patients versus 1,471 patients with T1DM), with the majority of the T1DM patients being paediatric (52%). Thus the applicability of conclusions as a whole cannot be applied necessarily to patients with T1DM. Also, the bulk of T2DM patients in the identified studies had in the majority (83%) no background DR at the start of studies.

The studies included in this rapid review span a 21 year period ranging from 1990 to 2012, or rely on data from older studies such as the UKPDS, which may no longer be as applicable. The epidemiology, treatment and patterns of care for diabetes have changed in recent years; a systematic review and meta-analysis carried out by Wong et al [54] in 2009 describes the rates of progression in diabetic retinopathy during different time periods and concludes that these "changing patterns of care for diabetes, including earlier identification and initiation of care along with attention to appropriate management of diabetic may have led to substantially lower rates of diabetic retinopathy progression and incident visual loss over time".

None of the studies identified describe in detail the ethnicity of the study group, nor do studies describe the socio-economic makeup of trial participants.

None of the risk stratification algorithms identified were externally validated on a UK cohort. Only one risk prediction tool was (internally) validated on a UK dataset and this only included one predictor: previous retinopathy results. Only one risk prediction algorithm was externally validated at all and this was on a Danish dataset where there was a large amount of missing data, and where screening intervals are already stratified by risk so not directly comparable to the UK system.

In terms of the economic appraisals, the study by Vijan and colleagues [44] highlighted some of the limitations with its study such as: utility scores were not assigned to differing degrees of sight loss, assumption of 100% compliance, no account for benefits of detecting other eye disorders, and the use of a high utility value for vision loss. In addition, the retinopathy progression data is based on UK Prospective Diabetes Study (UKPDS) progression data, and has been criticised for underestimating progression rates in the US but remains valid for the UK national screening committee audience, and due to medical advances, the UKPDS is thought to overestimate this concern [55]. The paper by Davies et al [31] in contrast does account for compliance, but does not discount costs and benefits. The latter paper by Rein et al [41] was a well conducted economic analysis by addressing some of these issues: by not assuming 100% compliance, and accounting for the benefits of detecting other eye disease; however, they still reach the same conclusion as Vijan et al [44]. The earlier papers by Javitt et al [33], Javitt et al [32] and Dasbach et al [30] are now over 20 years old, and – although robust papers – must be considered in the light of advances in medical advances, changing prevalence and changing costs.

None of the risk stratification algorithms identified were externally validated on a UK cohort. Only one risk prediction tool was (internally) validated on a UK dataset and this only included one

predictor: previous retinopathy results. Only one risk prediction algorithm was externally validated at all and this was on a Danish dataset where there was a large amount of missing data, and where screening intervals are already stratified by risk so not directly comparable to the UK system.

The main methodological issue with cost-effectiveness analyses is addressed by Jones and Edwards [10] and remains an issue with the papers which have been published since; it remains uncertain if patient behaviour and compliance would be negatively affected by recommendations for a biennial screening interval. Also, individual patient characteristics potentially determine optimal screening interval, and the practicalities of providing individualised screening intervals have been questioned. Finally, we were also unable to find evidence from real world data for cost-effectiveness of interval screening, as all studies relied on hypothetical simulation models.

5.3 Strengths and Limitations of This Review

5.3.1 Strengths

The main strength of this review is a systematic approach and an a priori determined methodology that was applied to the research question formulation (including PICO domains), inclusion/exclusion criteria, identification, selection, data extraction, study quality appraisals, and synthesis of relevant evidence. The purpose of such systematic approach was to minimize the risk of bias at all stages of the review process. For example, the searches were not limited by language or time of publication and covered multiple major electronic databases and alternative sources (e.g., hand search, relevant websites). The study selection, data extraction, and quality appraisal were performed by independent reviewers using a priori developed and piloted forms to minimize errors or inaccuracies in data. Inclusion criteria was sufficiently broad (in terms of study design and populations) to ensure that all research questions are addressed comprehensively. The results, where possible, were stratified by important baseline characteristics such as type of diabetes, duration of diabetes, age, and sex.

5.3.2 Limitations

The main limitation of this review rests upon the evidence itself. Although the findings of included cohort studies were more or less consistent suggesting safe increase of screening intervals compared to annual, this evidence warrants a cautious interpretation. Specifically, there were no

randomized controlled trials of the effectiveness of screening programs comparing different screening intervals (annual vs. biennial) for the progression rate of retinopathy and/or incidence of sight-threatening retinopathy/vision loss in subjects with diabetes. Moreover, none of the included studies was of comparative nature (no control/comparator data), which would allow the direct comparison of progression to (or incidence) of sight-threatening retinopathy/vision loss between subjects with diabetes screened with different intervals. Rather, the identified cohort studies were non-comparative cohorts that reported incidence or progression of diabetes-related retinopathy for given screening interval. Furthermore, for some cohort studies attrition rates could not be determined and several other studies reported high attrition rates (incomplete follow-up data) without any additional information on those who were lost to follow-up. Possible systematic differences between attendees and non-attendees in these studies may have underestimated incidence rates of retinopathy and other diabetes related complications such as vision loss.

Other limitations of this review include inability to pool quantitative study results and to assess the extent of publication bias which may have been present due to the exclusion of grey literature and non-English language publications. Moreover, given the heterogeneous and non-comparative nature of the evidence (i.e., absence of effect estimates for the main outcomes), the overall quality of the evidence could not be graded. This review may also be limited in terms of applicability of its findings to adults with diabetes type 1.

The risk stratification algorithms were not assessed using a formal checklist approach, instead they were reviewed and a narrative summary developed. In this process we focused on the validation of the model rather than the development process, in particular external validation (on a separate dataset to that upon which the model was developed) and impact on patient outcomes as described by Steyerberg et al [23] . A formal checklist approach would not have resulted in a different conclusion here because there were no risk stratification algorithms externally validated on a UK dataset. There is some work underway to develop models based on UK data, and therefore another review when these results have been published, and when the Prediction study risk of bias assessment tool (PROBAST) tools is also published would be valuable, as initial indications suggest that risk prediction algorithms may have the potential to be safely decrease the overall number of screening appointments required.

Searches were undertaken one year ago, athough we are not aware of major subsequent studies which would alter the finding of this review.

6. CONCLUSIONS

The current evidence limited to observational studies supports extension of the current annual screening interval in people with T2DM who have no existing background retinopathy, who are not on insulin treatment and who have a duration of diabetes of less than 10 years. Consideration should also be given to other risk factors such as control of diabetes (HBA1c) and patients on oral therapy for T2DM. There was insufficient evidence on patients with T1DM. The majority of economic analyses also supported the extension of screening intervals to biennial screening in low risk patients. Risk stratification algorithms showed potential for safely increasing the screening interval based on individual risk factors, but none were externally validated on a UK cohort and require testing in real world situations. In general, cautious interpretation of the findings is warranted given the observational non-comparative nature of the evidence-base. The high or unclear attrition rates in several screening program studies may have underestimated the incidence of diabetes related retinopathy progression or its complications. Furthermore, the majority of evidence available is from studies where people should have attended annual screening and instead have attended either more or less frequently than required. These people may not be typical of the whole screened population and therefore have differing risk factors for progression to sight threatening retinopathy. In future, well designed randomized or quasi-randomized comparative trials of screening programs using different screening intervals are needed to draw more definitive conclusions.

The majority of economic analyses also support the extension of screening intervals to biennial screening. Recently developed risk stratification algorithms show a degree of promise, but require testing in real world situations. The evidence base is limited in that the methodologies employed do not address concerns that changed intervals would impact behaviour and consequently uptake.

All observational studies conclude that either biennial or triennial screening is safe in low risk patients with diabetes mellitus and no background diabetic retinopathy. One UK based study [5] concludes that biennial screening is safe in low risk T2DM patients, but screening intervals of more than 24 months are associated with an increased risk of retinopathy.

The majority of evidence has been gathered in patients with T2DM. Only a small number of studies looked at solely patients with T1DM and sub-sets of patients with T1DM were small.

7. Acknowledgements

Author Contributions

Dr Daniel Todkill produced the initial draft, performed the searches and search strategy, and contributed to writing the final version.

Rachael Leslie produced the final version, performed the searches and search strategy.

Dr Hema Mistry evaluated, summarised and appraised the economic studies; and contributed to writing the draft and final versions of the review.

Dr Sian Taylor-Phillips evaluated and summarised the risk prediction algorithms, and contributed to writing the draft and final versions of the review.

Dr Alexander Tsertsvadze supported the quality assessment of the cohort studies and contributed to the final version.

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8. Appendices

Appendix A: Number of publications identified from each bibliographic database

Database	Number of Abstracts
Medline (OVID)	4574
EMBASE 1980 onwards	7901
SCOPUS	1883
ProQuest	0
Cochrane Database of Systematic Reviews	14
Cochrane Other Reviews (Database of Abstracts of Reviews of Effects)	27
Cochrane Central Register of Trials	1560
Cochrane Methods Studies	0
HTA Database (Cochrane Technology Assessments)	29
NHS EED (Cochrane Economic Evaluations)	26
Cochrane Groups	0
Other Sources	10

Appendix B: 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 C: Full publications screened but not included with justification

Study No	Lead Author	Year	Title	Reasons for exclusion
DR1	Aamir, A. H. and S. Jan	2012	Frequency of diabetic retinopathy in a tertiary care hospital using digital retinal imaging technology.	Relevance regarding intervals not made explicit from analysis
DR4	Agarwal, S. et al	2006	Diabetic retinopathy in type II diabetics detected by targeted screening versus newly diagnosed in general practice.	Relevance regarding intervals not made explicit from analysis
DR6	Arun, C. S., D. Young, et al.	2006	Establishing on-going quality assurance in a retinal screening programme.	Relevance regarding intervals not made explicit from analysis
DR7	Arun, C. S., N. Ngugi, et al.	2003	Effectiveness of screening in preventing blindness due to diabetic retinopathy	Relevance regarding intervals not made explicit from analysis
DR9	Barry, H.	2003	What is a reasonable interval for screening patients with diabetes for retinopathy?	Review or Expert Opinion Pieces Without Systematic Methodology
DR10	Begg, I. S.	1993	Screening for diabetic retinopathy: changes in direction?	Relevance regarding intervals not made explicit from analysis
DR13	Bloomgarden Z. T,	2007	Screening for and managing diabetic retinopathy: Current approaches	Review or Expert Opinion Pieces Without Systematic Methodology
DR14	Boucher M and Desroches	2009	Diabetic Retinopathy Screening	Review or Expert Opinion Pieces Without Systematic Methodology
DR15	Brailsford, S. C., et al.	1998	Evaluating screening policies for the early detection of retinopathy in patients with non-insulin dependent diabetes.	Relevance regarding intervals not made explicit from analysis
DR17	Brannigan, L.	2009	Encouraging annual dilated eye exams: a preventative strategy for diabetic retinopathy	Relevance regarding intervals not made explicit from analysis
DR18	Bresnick, G. H., et al.	2000	A screening approach to the surveillance of patients with diabetes for the presence of vision-threatening retinopathy.	Relevance regarding intervals not made explicit from analysis
DR19	Brown, D. M. and E. A. Orzeck	1996	Diabetic retinopathy: How and when to screen.	Relevance regarding intervals not made explicit from analysis
DR20	Brown, G. C., et al	2000	How often should patients with diabetes be screened for retinopathy?	Review or Expert Opinion Pieces Without Systematic Methodology
DR21	Broadbent, D. M., J. A. Scott, et al.	1999	Prevalence of diabetic eye disease in an inner city population: the Liverpool Diabetic Eye Study	Relevance regarding intervals not made explicit from analysis
DR22	Bounaccorso KM	1999	Diabetic retinopathy screening: A clinical quality improvement project	Relevance regarding intervals not made explicit from analysis
DR23	Casey, P., et al.	1996	Outcome measures in diabetic retinopathy screening	Review or Expert Opinion Pieces Without Systematic Methodology
DR24	Cathelineau, G. and B. V. Cathelineau	1991	Diabetic retinopathy: Methodologies in practice	Relevance regarding intervals not made explicit from analysis
DR26	Chew, S. J., et al.	1990	Ophthalmic screening for diabetics: the importance of physician-ophthalmologist collaboration in the prevention of blindness	Relevance regarding intervals not made explicit from analysis
DR27	Cotton, P.	1990	Advances in diabetic retinopathy could save sight with more frequent eye exams.	Review or Expert Opinion Pieces Without Systematic Methodology
DR30	Davies, R., et al.	1996	Simulation of diabetic eye disease to compare screening policies.	Relevance regarding intervals not made explicit from analysis
DR32	Davies R et al	2000	Using Simulation Modelling for Evaluating Screening Services for Diabetic Retinopathy	Not about intervals - simulation model of patient flows through a diabetes centre.
DR33	Deb, N., G. Thuret, et al.	2004	Screening for diabetic retinopathy in France.	Relevance regarding intervals not made explicit from analysis
DR35	Fendrick, A. M., et al.	1992	Cost-effectiveness of the screening and treatment of diabetic retinopathy: What are the costs of underutilization?	Relevance regarding intervals not made explicit from analysis
DR36	Fong, D. S.	2002	Changing times for the management of diabetic retinopathy	Relevance regarding intervals not made explicit from analysis
DR37	Fong, D. S., et al.	2001	Understanding the value of diabetic retinopathy screening	Review or Expert Opinion Pieces Without Systematic Methodology
DR39	Freudenstein, U. and J. Verne	2001	A national screening programme for diabetic retinopathy	Review or Expert Opinion Pieces Without Systematic Methodology
DR40	Garvican, L	2007	Issues regarding quality assurance in the English national screening programme for sight-threatening diabetic retinopathy: Response	Review or Expert Opinion Pieces Without Systematic Methodology
DR41	Garvican, L and P H Scanlon	2004	Pilot quality assurance scheme for diabetic retinopathy risk reduction programmes	Relevance regarding intervals not made explicit from analysis
DR43	Gillibrand, W, et al	2004	The English national risk-reduction programme for preservation of sight in diabetes	Review or Expert Opinion Pieces Without Systematic Methodology

DR44	Gonzalez Villalpando, C, et al	1997	A diabetic retinopathy screening program as a strategy for blindness prevention	Relevance regarding intervals not made explicit from analysis
DR45	Grant and Mames	1991	Eye care guidelines for patients with diabetes mellitus	Relevance regarding intervals not made explicit from analysis
DR46	Gudmundsdottir, A, et al	2011	Individual Risk Assessment and Information technology to control screening for diabetic retinopathy	Poster presenting Olafdottir study
DR47	Hansen and Andersen	2004	Screening for diabetic retinopathy in Denmark: the current status	Relevance regarding intervals not made explicit from analysis
DR48	Hansen, et al	2005	Model simulation of the patient flow through a screening centre for diabetic retinopathy	Relevance regarding intervals not made explicit from analysis
DR49	Harper, et al	1995	Early detection of diabetic retinopathy	Relevance regarding intervals not made explicit from analysis
DR50	Harper, et al	1996	Screening for diabetic retinopathy	Review or Expert Opinion Pieces Without Systematic Methodology
DR51	Hart and Harding	1999	Is it time for a national screening programme for sight-threatening diabetic retinopathy?	Relevance regarding intervals not made explicit from analysis
DR52	Hartstra WW and Holleman	2007	Screening for diabetic retinopathy	Review or Expert Opinion Pieces Without Systematic Methodology
DR53	Harvey, et al	2006	Towards comprehensive population-based screening for diabetic retinopathy: Operation of the North Wales diabetic retinopathy screening programme using a central patient register and various screening methods	Relevance regarding intervals not made explicit from analysis
DR54	Hayat, H, et al	2009	Risk factors for visual impairment registration due to diabetic retinopathy in Leeds, 2002-2005	Relevance regarding intervals not made explicit from analysis
DR55	Hazin, R, et al	2011	Revisiting diabetes 2000: Challenges in establishing nationwide diabetic retinopathy prevention programs	Relevance regarding intervals not made explicit from analysis
DR56	Henricsson, M, et al	1996	Incidence of blindness and visual impairment in diabetic patients participating in an ophthalmological control and screening programme	Relevance regarding intervals not made explicit from analysis
DR57	Hutchinson, A, et al	2000	Effectiveness of screening and monitoring tests for diabetic retinopathy - A systematic review	Relevance regarding intervals not made explicit from analysis
DR58	Jackson, W	2002	Improving diabetic retinopathy screening	Review or Expert Opinion Pieces Without Systematic Methodology
DR59	James, M, et al	2000	Cost effectiveness analysis of screening for sight threatening diabetic eye disease	Relevance regarding intervals not made explicit from analysis
DR60	Javitt, J C and L P Aiello	1996	Cost-effectiveness of detecting and treating diabetic retinopathy	Relevance regarding intervals not made explicit from analysis
DR62	Javitt, J C, et al	2000	How often should patients with diabetes be screened for retinopathy?	Review or Expert Opinion Pieces Without Systematic Methodology
DR66	Karma A and Gummerus	1987	Predicting diabetic retinopathy	Relevance regarding intervals not made explicit from analysis
DR67	Khandekar, R.	2012	Screening and public health strategies for diabetic retinopathy in the Eastern Mediterranean Region	Relevance regarding intervals not made explicit from analysis
DR68	Klein, R.	1999	Guidelines for screening for diabetic retinopathy revisited	Review or Expert Opinion Pieces Without Systematic Methodology
DR69	Klein, R.	2003	Screening interval for retinopathy in type 2 diabetes.	Review or Expert Opinion Pieces Without Systematic Methodology
DR70	Klein, R. and B. E. K. Klein	2002	Screening for diabetic retinopathy, revisited	Review or Expert Opinion Pieces Without Systematic Methodology
DR71	Klein, R., B. E. K. Klein, et al.	1990	The Wisconsin epidemiologic study of diabetic retinopathy: An update	Relevance regarding intervals not made explicit from analysis
DR73	Kohner EM	1991	Detecting diabetic retinopathy VI	Review or Expert Opinion Pieces Without Systematic Methodology
DR74	Kohner, E. M. and M. Porta	1991	A protocol for screening diabetic retinopathy in Europe.	Relevance regarding intervals not made explicit from analysis
DR75	Kohner, E. M. and M. Porta	1991	Diabetic retinopathy: Preventing blindness in the 1990's [2].	Review or Expert Opinion Pieces Without Systematic Methodology
DR76	Kohner, E. M. and M. Porta	1991	Protocols for screening and treatment of diabetic retinopathy in Europe.	Review or Expert Opinion Pieces Without Systematic Methodology
DR77	Kohner EM	1993	Fortnightly Review: Diabetic Retinopathy	Review or Expert Opinion Pieces Without Systematic Methodology
DR78	Kristinsson et.al	1997	Diabetic retinopathy. Screening and prevention of blindness	Review or Expert Opinion Pieces Without Systematic Methodology
DR78b	Kristinsson et.al	1998	Active Prevention in diabetic eye disease	Relevance regarding intervals not made explicit from analysis
DR80	Kristinsson & Stefansson et al	1994	Screening for eye disease in type 2 diabetes mellitus	Relevance regarding intervals not made explicit from analysis
DR81	Lee, S., et al.	2004	Early detection of disease and scheduling of screening examinations.	Relevance regarding intervals not made explicit from analysis

DR82	Looker et al	2012	Diabetic Retinopathy at diagnosis of type 2 diabetes in Scotland's	Relevance regarding intervals not made explicit from analysis
DR83	Lueder G T, Silverstein, J.	2005	Risk of retinopathy in children with type 1 diabetes mellitus before 2 years of age	Review or Expert Opinion Pieces Without Systematic Methodology
DR85	Matz, H., et al.	1996	Cost-benefit analysis of diabetic eye disease.	Relevance regarding intervals not made explicit from analysis
DR86	McGhee, Harding, Wong, D	2012	Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy	Review or Expert Opinion Pieces Without Systematic Methodology
DR91	Miller, S. and E. J. Lindbloom	2003	What is a reasonable interval for retinopathy screening in patients with diabetes?	Review or Expert Opinion Pieces Without Systematic Methodology
DR92	Mirsky S	2003	Screening for diabetic retinopathy	Review or Expert Opinion Pieces Without Systematic Methodology
DR94	Morris, A., et al.	2003	Current status of screening for diabetic retinopathy in the UK	Review or Expert Opinion Pieces Without Systematic Methodology
DR95	Muller, A., H. T. Vu, et al.	2006	Rapid and cost-effective method to assess vision disorders in a population	Relevance regarding intervals not made explicit from analysis
DR96	Murphy, C. and W. Newton	2000	How frequently should patients with type 2 diabetes mellitus be screened for retinopathy?	Summary of data from an included study which does not represent a reanalysis
DR98	Owens, D. K.	1996	Screening and treatment of diabetic retinopathy was cost-effective	Review or Expert Opinion Pieces Without Systematic Methodology
DR99b	Owens et al	2000	Diabetic Retinopathy Screening	Review or Expert Opinion Pieces Without Systematic Methodology
DR100	Palmberg, P.	2001	Screening for diabetic retinopathy.	Review or Expert Opinion Pieces Without Systematic Methodology
DR101	Peto, T. and C. Tadros	2012	Screening for Diabetic Retinopathy and Diabetic Macular Edema in the UK	Relevance regarding intervals not made explicit from analysis
DR102	Phillipov G and Alimat et al	1995	Screening for Diabetic Retinopathy	Relevance regarding intervals not made explicit from analysis
DR103	Porta M and Allione	2004	Diabetic Retinopathy and its relevance to paediatric age. An update	Relevance regarding intervals not made explicit from analysis
DR105	Raikou M and McGuire	2003	The economics of screening and treatment in type 2 diabetes mellitus	Review or Expert Opinion Pieces Without Systematic Methodology
DR106	Rodriguez, N. and B. Cote	2008	Screening for diabetic retinopathy in Quebec	Relevance regarding intervals not made explicit from analysis
DR107	Rowe, S., et al.	2004	Preventing visual loss from chronic eye disease in primary care: scientific review	Review or Expert Opinion Pieces Without Systematic Methodology
DR108	Sackett, C. S. and F. L. Ferris	1982	Screening for diabetic retinopathy in a diabetic management clinic.	Relevance regarding intervals not made explicit from analysis
DR109	Saldanha, M. J. and U. Meyer-Bothling	2006	Outcome of implementing the national services framework guidelines for diabetic retinopathy screening: Results of an audit in a primary care trust	Relevance regarding intervals not made explicit from analysis
DR110	Salman, R.	2004	Screening of Diabetic Retinopathy in Primary Care	Relevance regarding intervals not made explicit from analysis
DR111	Scanlon, P. H	2008	The English national screening programme for sight-threatening diabetic retinopathy	Review or Expert Opinion Pieces Without Systematic Methodology
DR112	Scanlon, P. H	2010	Diabetic Retinopathy	Relevance regarding intervals not made explicit from analysis
DR113	Shotliff, K.	2002	Erratum: Screening for diabetic retinopathy	Correction for a diagram reported in another study
DR114	Shotliff, K. P. and G. Duncan	2006	Diabetic retinopathy screening programmes and reducing ophthalmologists workload	Review or Expert Opinion Pieces Without Systematic Methodology
DR116	Singer, D. E., D. M. Nathan, et al	1992	Screening for diabetic retinopathy	Relevance regarding intervals not made explicit from analysis
DR119	Stefànsson, Kristinsson, et al	1997	Prevention of diabetic blindness	Review or Expert Opinion Pieces Without Systematic Methodology
DR121	Sutton BS	2003	A Cost-Effectiveness and Probabilistic Sensitivity Analysis of Opportunistic Screening Versus Systematic Screening for Sight-Threatening Diabetic Eye Disease.	Relevance regarding intervals not made explicit from analysis
DR122	Tapp, R. J., et al.	2004	Diabetes care in an Australian population: Frequency of screening examinations for eye and foot complications of diabetes	Relevance regarding intervals not made explicit from analysis
DR123	Taylor R	2003	Screening for diabetic retinopathy	Review or Expert Opinion Pieces Without Systematic Methodology
DR125	Tubbs, C. G., et al.	2004	Do routine eye exams reduce occurrence of blindness from type 2 diabetes?	Relevance regarding intervals not made explicit from analysis
DR127	Vigen S and Hoogendoorn	2006	Cost effectiveness analysis of preventative interventions in type 2 diabetes mellitus: A systematic literature review	Relevance regarding intervals not made explicit from analysis
DR128	Wareham, N. J.	1993	Cost-effectiveness of alternative methods for diabetic retinopathy screening	Review or Expert Opinion Pieces Without Systematic Methodology
DR129	Waugh, N. R., et al.	1986	Screening for diabetic retinopathy: Options and cost effectiveness	Review or Expert Opinion Pieces Without Systematic Methodology
DR134	Wong et al	2009	Rates of Progression in Diabetic Retinopathy During Different Time Periods A systematic review and meta-analysis	Relevance regarding intervals not made explicit from analysis

DR130	Younis, N., et al.	2002	Prevalence of diabetic eye disease in patients entering a systematic primary care-based eye screening programme	Relevance regarding intervals not made explicit from analysis
DR133	Zoorob, R. J. and M. D. Hagen	1997	Guidelines on the care of diabetic nephropathy, retinopathy and foot disease	Relevance regarding intervals not made explicit from analysis
DR136	Klein	1995	Retinal Microaneurysm Counts and 10-Year Progression of Diabetic Retinopathy	Relevance regarding intervals not made explicit from analysis
DR137	Chen	2010	Microaneurysm number and distribution in the macula of Chinese type 2 diabetics with early diabetic retinopathy: population-based study in Kinmen, Taiwan	Relevance regarding intervals not made explicit from analysis
DR138	Hutchins	2012	Diabetic retinopathy screening in New Zealand requires improvement: results from a multi-centre audit	Relevance regarding intervals not made explicit from analysis
DR139	Yau	2012	Global Prevalence and Major RiskFactors of Diabetic Retinopathy	Relevance regarding intervals not made explicit from analysis
DR140	Kohner	1999	Microaneurysms in the development of diabetic retinopathy (UKPDS 42)	Relevance regarding intervals not made explicit from analysis

Study No	Lead Author	Year	Title	Reasons for exclusion
DR3	Agardh et.al	1998	Eye complications in diabetes. According to new criteria patients with diabetes should have ophthalmological examination at the time of diagnosis	Not available in English Language
DR5	Aldington, S. J., et al.	2012	Progression of diabetic retinopathy to referable or sight threatening retinopathy? Does it matter whether there is background retinopathy in either or both eyes?	Not available
DR11	Bischoff, P.	1989	Ophthalmologic study in diabetic retinopathy	Not available in English Language
DR12	Bischoff, P.	1993	Frequency of ophthalmological examination in diabetic retinopathy [German]	Not available in English Language
DR28	Crijns, H., et al.	1995	Prospective need of ophthalmic care for diabetic patients - A cost-effectiveness analysis. [Dutch]	Not available in English Language
DR34	Evans, A. T. and J. A. Kylstra	1992	Screening for diabetic retinopathy: A review.	Not available
DR38	Foulds, W. S., et al.	1983	Diabetic retinopathy in the West of Scotland: its detection and prevalence, and the cost-effectiveness of a proposed screening programme	Not available
DR42	Gillibrand, W	2003	A national screening programme for sight-threatening diabetic retinopathy in England	Not available
DR99	Owen DR and Farrel	2000	Screening for Diabetic Retinopathy in young insulin dependent diabetics (type 1)	Not available
DR117	Singer and Schachat	1992	Screening guidelines for diabetic retinopathy	Not available
DR118	Singh K and Mehta	2000	Diabetes and retinopathy	Not available
DR120	Stefánsson, E., et al.	2000	Screening and prevention of diabetic blindness	Not available

Appendix D: Results from CASP appraisals

		Agardh (2011)	Jones (2012)	Kohner (2001)	Thomas (2012)	Kristinsson (1995)
	Study design	Prospective cohort study	Dynamic cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
1	**Did the study address a clearly focused issue?**	Study aims to record the incidence of sight threatening retinopathy in T2DM patients without retinopathy over a 3 year period.	Study focusses on estimating retinopathy incidence and progression rates of the cohort of mostly T2DM patients and compares the rate of progression of retinopathy between subgroups of level of retinopathy at first examination.	Study aims to establish the relationship between severity of retinopathy and the progress to photocoagulation for a group of T2DM patients	Study aims to determine the incidence of referable retinopathy in a cohort of people with T2DM over a 4 year period.	The study addressed two questions. 1. Whether diabetic children under 12 years old could initiate screening at age 12 2. Whether biennial examinations suffice for T1DM and T2DM patients without retinopathy.
2	**Was the cohort recruited in an acceptable way?**	Clear criteria for recruitment - study recruited cohort of all T2DM patients at one hospital that fit criteria.	Norfolk dataset (as Misra, 2009). Large cohort (n=20,788) of all people with T2DM screened by Norfolk Service between 1990 and 2006 identified through GP diabetes registered. Patients who already had STDR were excluded. Dynamic cohort design means that individuals enter and leave the cohort at different times. A smaller group of T1DM patients were also recruited.	Large cohort of 3,709 patients with T2DM were selected as having good quality retinal photographs from the wider UKPDS cohort. UKPDS participants were recruited in line with a robust criteria. Only patients with good images and follow up images at 3 and 6 years were included.	Large cohort of 57,199 representing every Welsh patient aged over 12 and registered with a GP with T2DM that fit a clear criteria for age and no retinopathy at baseline between 2005 and 2009. Exclusion criteria based on medical grounds or diagnosis of T1DM.	Two Cohorts followed for comparison. 1. Small cohort of 81 Icelandic children aged under 15 at recruitment. 2. Small cohort of 185 Icelandic patients with T1DM and T2DM and no retinopathy.

3	**Was the exposure accurately measured to minimise bias?**	All patients who were available for follow up were 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.	(As Misra 2009) All patients were invited for screening annually. It is not clear if non attendees were followed up or whether actually attendance was at sooner or later than the 12 month mark.	Participants of UKPDS underwent a full medical examination, including retinal examination yearly.	Patients screened yearly under a standard procedure. Patient data was anonymised.	Intervals of group 2. Described as 'at least annually'. Intervals were not reported for group 1. (children)
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.	(As Misra 2012) Some measurement bias is possible over the period of the study. All patients were screened at their own GP practices with the same mobile retinal camera operated by the same trained retinal screeners. The same protocol was used for all patients. Imaging and grading changed after 2000 when instead of printed images being graded by a diabetologist with special interest; digital images were introduced and were graded by a team of different professionals. Two different verified grading systems (scales) were used over the period of the study although the authors describe than as virtually identical and the protocol for primary, secondary and arbitrary grading changed after 2006.	The same protocol for screening and grading was used for the cohort. All images were graded by physicians at the Retinopathy Grading Centre.	Standard protocol for screening and grading used for all patients. Patient data was anonymised.	Standardised examination and reporting method used across both patient groups.

5	**Have the authors identified all important confounding factors?**	The authors measured HbA1c at base line and follow up and concluded that percentage did not significantly differ at baseline between attendees and non-attendees. Age at diagnosis, duration of diabetes and diabetes treatment method was also recorded. Other confounders not reported could include adherence to treatment and whether other screens had occurred during the interval.	The authors also record and analyse other prognostic characteristics recording their relationship with the time taken to develop retinopathy or move between grades. Age, duration of diabetes, type of diabetes treatment and hypertension treatment were all measured at baseline. The authors state that smoking history, blood glucose, blood pressure, sex and ethnicity were not recorded as part of the screening programme.	The study did not consider other confounders such as HbA1c or therapy allocation in the context of this study, however, they do state that in the wider UKPDS study no difference in outcome was recorded for treatment allocation but better glycaemic and blood pressure control were associated with less occurrences of retinopathy.	Patient characteristics were recorded at baseline and included age at diabetes diagnosis, duration of diabetes, diabetes treatment and sex. HbA1c percentage was not used in the study.	For children (group 1) onset of puberty was considered. Age at onset and duration of disease were reported for group 2. HbA1c was not reported or analysed in either group.
6	**Was the follow up of the subjects complete enough?**	1,691 participants were recruited and 1,322 were followed up. Of the 22% who did not participate in the follow up, 6% had died and 9% rejected or did not attend a follow up. Recording of patient characteristics was not complete, although it was high at baseline (4% for HbA1c) and lower at follow up (7% for HbA1c). The authors state that patient characteristics and HbA1c levels did not differ in those with and without follow up data.	As the cohort was a dynamic design, it is not clear from the information provided what length of follow up was observed across the group, for example, patients recruited at year one could be followed for up to 17 years, whereas follow up period would be shorter for those recruited later. Misra et al (2009) provide a more comprehensive account of follow up for the same cohort.	The study followed a 6 year follow up period. The study only included patients who had all the required follow up images and data.	Of the 57,199 individuals recruited with no retinopathy at baseline, 7,436 (13%) did not attend a further screening. Of the 7,436, 449 were not eligible for a second screen (recruited less than 12 months from the end of the study). The authors are unable to provide information as to why the remaining 6,987 patients did not attend as records were anonymised, however, they do state that the non-attendees were more likely to be older and have a longer duration of diabetes.	Adults were studies over a 2 year observation period to identify incidence retinopathy. This is a short period than other studies included in this review. 10 patients who did not attend for a second screen were excluded and are not included in the retrospective cohort of 185 participants.

7	**What are the results of this study?**	At follow up >70% of individuals were without any retinopathy. Sight threatening retinopathy was detected in 0.19% of eyes (5 out of 2644 eyes). The study concludes that 3 year intervals are safe and will not lead to clinical harm at a high level.	The study found that patients with T2DM and no retinopathy at baseline are at low risk of developing retinopathy and very low risk of progressing to retinopathy requiring treatment even after 5 years of follow-up. Patients with any level of retinopathy at baseline are at a much higher risk of clinical harm.	The study found that few patients without retinopathy developed a level of retinopathy that required photocoagulation within 3 to 6 years; however patients with evidence of retinopathy were more likely to need treatment by 3 years although still at low levels.	Overall, the study reported incidence of retinopathy in different groups and found that intervals could be extended beyond 12 months for patients with no evidence of retinopathy at baseline. The study found that incidence of retinopathy was independently associated with several of the risk factors identified including age at diagnosis and insulin use and that patients on insulin treatment or duration of diabetes over 10 years should continue to be screened annually.	For group 1. The authors use their findings to recommend that age 12 should be used as a universal initiation point for regular eye examinations unless it is known that puberty has onset before that age with puberty considered to be a related to an increase in retinopathy prevalence. For group 2. The authors report no patients have STDR over the 2 year study period.
8	**How precise are the results?**	Statistical calculations were performed to compare differences in diabetes treatment method in the overall cohort from baseline to follow up. P values were reported that indicated that changes from less intensive treatments such as diet treatment had reduced and more intensive treatment such as taking oral treatments or antihypertensive treatment had increased.	Cumulative and annual incidence rates are estimated using life tables. Risk factors measured at baseline are analysed using Cox regression analysis. For incidence, the percentage of individuals with each retinopathy status at 5 years is recorded. Annual incidence for patients with no retinopathy at baseline and nonproliferative retinopathy at baseline is provided at each year of follow up with 95% confidence intervals. Confidence intervals are wider for nonproliferative retinopathy as numbers are smaller, particularly as time progresses. Confidence intervals are narrow for up to 4 years for patients with no retinopathy at baseline.	The proportion of patients requiring photocoagulation was reported at entry, 3 years and 6 years for patients with no retinopathy, micro aneurysms in one or both eyes and severe retinopathy. Confidence intervals were provided for each of the patient groups. Intervals are wider for patients with severe retinopathy, probably due to smaller numbers and as time progresses.	The study uses t tests and chi squared tests to explore the differences between patient characteristics. Incidence from 1 to 4 years by presence of retinopathy is provided with confidence intervals. As the cohort is large, confidence intervals are narrow.	Only proportions of outcomes are reported for both groups. No further analysis to statistical analysis is provided.

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.	Data for patients with no retinopathy at baseline is very precise and based on large numbers, making it believable. 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 an increased non-compliance to diabetes treatment that may make progression to retinopathy more rapid.	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. As patients were recruited to an official study that included intense monitoring for some groups of patients, their adherence to treatment may be better than the general population.	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.	For both groups, the study population is small. The lack of precision and short follow up periods would make the findings difficult to rely on their own, however considered in the wider context of the review the findings are in line with other studies.
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 is of a large population in the UK, making application to the rest of England acceptable.	Study uses a sample of patients form the wider UKPDS making the findings applicable to the rest of England acceptable.	Study uses a Welsh population and is applicable to an English population.	The study uses a small Icelandic population which makes the findings less applicable to the English population as characteristics such as screening compliance and diabetes control can vary.
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 find incidence of retinopathy in patients with no retinopathy at first screen was low over a 5-10 year follow up period and their conclusions are similar to other studies when recommending that intervals longer than one year may be appropriate for this group of people.	As with other studies, the authors found that retinopathy incidence was low in patients without retinopathy over a 3 - 6 year period.	Similarly to other studies, the authors recommend longer intervals for patients with no retinopathy at baseline. Risk factors for higher risk groups are similar to other studies and include age, insulin use and duration of diabetes and the recommendation for annual screening matches the recommendations from other studies.	The findings for the adult population cohort are broadly in line with the findings of other studies in that incidence of retinopathy in a group of people with no retinopathy is very low. The findings for children are more stand alone as other studies do not address the same question, although Maguire (2005) do address intervals for children.

		Olafsdottir (2007)	Misra (2009)	Maguire (2005)	Younis (2003a)	Younis (2003b)
	Study design	Retrospective cohort study	Dynamic cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
1	**Did the study address a clearly focused issue?**	Study aims to examine the incidence of retinopathy over a 10 year period following a change in screening protocol from annual to biennial.	Study has three focus areas, aiming to describe the changes in patient characteristics over a 16 year period, estimate the prevalence of retinopathy over time and investigate the relationships between patient characteristics and retinopathy risk.	Study aimed to identify the optimum screening frequency for children and adolescents with T1DM	Study aimed to investigate yearly and cumulative incidence of different levels of retinopathy in patients with T2DM and calculate optimum screening intervals	Study aimed to investigate cumulative incidence of different levels of retinopathy in patients with T1DM and calculate optimum screening intervals.
2	**Was the cohort recruited in an acceptable way?**	Cohort of 296 patients with T1DM and T2DM with no retinopathy at baseline. It is not clear whether this represents the total population of eligible participants in Iceland or a sample or what the selection process may be, although they do state that a smaller proportion of T2DM patients are included in the study.	Norfolk dataset (as Jones 2012). Large cohort (n=20,788) of all people with T2DM screened by Norfolk Service between 1990 and 2006 identified through GP diabetes registered. Patients who already had STDR were excluded. Dynamic cohort design means that individuals enter and leave the cohort at different times. A smaller group of T1DM patients were also recruited.	Cohort of 668 children and adolescents recruited from a hospital in Australia. All patients who had a baseline and at least one follow up screen performed before age 20 were included in the cohort. The cohort was spilt into a younger group (aged under 11 at first screen) and older group (aged 11 or over at first screen).	Liverpool Diabetic Eye Study dataset. Large cohort of all patients with T2DM registered with GPs and first screened between 1991 and 1999 who had retinopathy data available at baseline and at least one further screening. Cohort represented 4770 patients and 20,570 screening events, although baseline findings were reported and analysed for 7615 patients.	Liverpool Diabetic Eye Study dataset. Large cohort of all patients with T1DM registered with GPs and first screened between 1991 and 2000 who had retinopathy data available at baseline and at least one further screening. Cohort represented 501 patients and 2745 screening events.
3	**Was the exposure accurately measured to minimise bias?**	The screening protocol for the cohort was screening every other year, which would move to annual if retinopathy was identified or based on clinical judgement.	(As Jones 2012) All patients were invited for screening annually, although people who were clinically indicated or those with questionable images or technical problems were rescreened at 6 months.	Patients were followed longitudinally and different screening frequencies were observed. Interval lengths were recorded and patients were grouped by interval length for analysis.	Patients with no retinopathy or background retinopathy were screened yearly. Patients with retinopathy without sight threatening maculopathy were followed up every 6 months.	Patients with no retinopathy or background retinopathy were screened yearly. Patients with retinopathy without sight threatening maculopathy were followed up every 6 months.

4	**Was the outcome accurately measured to minimise bias?**	Standard protocol used for screening patients. Screening undertaken using the same method and graded by an ophthalmologist. Retinopathy reported for each patient based on the worst eye.	As Jones (2012) Some measurement bias is possible over the period of the study. All patients were screened at their own GP practices with the same mobile retinal camera operated by the same trained retinal screeners. The same protocol was used for all patients. Imaging and grading changed after 2000 when instead of printed images being graded by a diabetologist with special interest; digital images were introduced and were graded by a team of different professionals. Two different verified grading systems (scales) were used over the period of the study.	A protocol was used for screening the cohort. Outcomes were verified by a proportion of photographs being graded independently by a second grader for quality control and 'good agreement' was found between the graders. A standardised Airlie classification was used.	Standardised protocol for screening, reviewing, grading (Wisconsin algorithm) and reporting retinopathy for all patients included in the study. Provision for rescreening or validating results in place.	Standardised protocol for screening, reviewing, grading (Wisconsin algorithm) and reporting retinopathy for all patients included in the study. Provision for rescreening or validating results in place.
5	**Have the authors identified all important confounding factors?**	Authors document a range of patient characteristics, including gender, diabetes duration, blood glucose and HbA1c. The authors state that T1DM patients are over represented as a smaller proportion of T2DM patients are included.	The authors investigate the relationship between patient characteristics and risk of retinopathy. They include factors that have been recorded as part of the study group which includes age, duration of diabetes, months since last screened, type of diabetes treatment and hypertension treatment were all measured at each screening episode.	At each eye examination, height, weight, pubertal staging, blood pressure and HbA1c were recorded. Diabetes duration was also used in the study for analysis. Further potential confounding factors such as diabetes treatment not recorded.	The authors consider a comprehensive set of confounding factors, including age, duration of diabetes, age at diagnosis, follow up duration, number of screening visits, sex and treatment at baseline.	The authors consider age, diabetes duration, age at diagnosis, follow up duration and sex.

6	**Was the follow up of the subjects complete enough?**	The study followed the cohort over a 10 year period. The retrospective study only included patients who were still alive at the end of the 10 year period. There is not information provided about patients who may have died during the period of the study whose outcomes may have been different to the outcomes in the overall group.	Overall, 14,360 (69%) of patients were screened at least twice, and 4337 (21%) were screened 5 or more times. Patients recruited at year one could be followed for up to 17 years, whereas follow up period would be shorter for those recruited later. 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	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.	A large proportion of patients (31%, n=2388) had not undergone a repeat screening by the end of the study period and were not eligible to be considered in the cohort that has a baseline plus one other screen. However, of these, only 681 were recorded as did not attend, others had died, been referred to an ophthalmologist or were not due a second screen. It is important to consider that the patients who chose not to attend a second appointment may differ from those that did attend a second appointment in crucial areas such as adherence to treatment, which could affect onset of retinopathy. The time period for the study enabled follow up of up to 9 years.	Population coverage was lower in the study of T1DM patient from the Liverpool cohort. Of the 1050 eligible patients, only 79% (n=831) accepted an invitation for a baseline screen, and of those, 501 participated in a follow up screen. Many of those that did not take part in a further screen had required referral at baseline screen. The authors report that there was no significant variation in baseline demographic characteristics of those that dropped out of the programme and those that completed 6 years of follow up, although numbers are smaller at the later stages of the study.

7	**What are the results of this study?**	No patients went from no retinopathy to STDR over a 2 year period. The study reports that the majority of participants did not develop any retinopathy during the 10 year period and patients that did develop macular oedema or proliferative retinopathy had been identified and changed to an annual screening protocol.	Additional to the findings reported by Jones (2012), the authors found that risk factors such as age, treatment type and duration of diabetes were associated with increasing severity of retinopathy and maculopathy.	The authors found that after one year, retinopathy prevalence had not increase in any group (age or risk factor), however retinopathy increased significantly after 2 years in the over 11 age group, and in the group of people with a HbA1c level measured above 10% at any screen.	The authors reported that yearly incidence of STDR in patients without retinopathy at baseline was very low after 1 year (0.3%). Incidence at 5 years was 1.8%, with cumulative incidence reported as 3.9%. Findings for rates of progression were incremental with patients with higher level baseline retinopathy resulting in higher incidence of STDR. The authors also consider baseline retinopathy in light of patient characteristics and report that patients with higher levels of baseline retinopathy had a longer duration of diabetes and a higher frequency of oral hypoglycaemic use. Five year incidence of retinopathy was higher in patients using insulin.	The study found that after 1 year, incidence of STDR in patients without baseline retinopathy was 0.3%; this had increased to a cumulative incidence of 3.9% at 5 years. Rates of progression were higher in those with background or preproliferative retinopathy, reported as 3.6% and 13.5% after one year respectively. Longer duration of diabetes was associated with greater progression of STDR.
8	**How precise are the results?**	The authors report the proportion of patients with different outcomes after 10 years. They also present the mean values and ranges for each of the recorded patient characteristics and later present patient groups by outcome comparing the mean HbA1c and diabetes type by group. Further statistical analysis is not provided for the results of this study.	The authors provide 95% confidence intervals and p values in their regression analysis of risk factors. Grade of retinopathy and risk factors are also presented as percentages. The study is large meaning that reported results and confidence intervals are precise.	The authors used General Estimating 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 are used to indicate significance of findings when comparing incidence of retinopathy between patient groups. The numbers studies are small, particularly when divided into subgroups by age and risk factor, which would affect the precision of the results.	Confidence intervals are reported for all findings and the large study group means that reported result have high precision. Analysis of heterogeneity of the cohort is undertaken and the group is divided by retinopathy status at baseline for analysis.	Confidence intervals and p values were reported for all findings, although as this was a smaller group, confidence intervals were wider meaning that results were less precise, particularly for the group of patients with mild preproliferative retinopathy at baseline.

9	**Do you believe the results?**	The cohort for the study is small although it does cover a long time period. There is some discrepancy amongst the numbers reported (e.g. The patients listed by outcome do not add up to the total cohort) and there is little information provided around the limitations of the study (e.g. how the cohort was recruited and the implications of not included patients who were not alive after the 10 years.	The large cohort and robust analysis of risk factors and description of limitations makes the findings believable.	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.	A large cohort with a robust methodology for screening and a thorough analysis of results makes the results believable.	The study has a robust methodology and analysis of results and the authors acknowledge the limitations of the smaller sample size and the impact of the non-participants on the findings reported. Overall, the results are believable particularly for the larger group of patients with no retinopathy at baseline, although more caution should be applied for the findings for the group with mild preproliferative retinopathy at baseline.
10	**Can the results be applied to the population of England?**	Compliance to screening and glycaemic and blood pressure control has been reported to be 'reasonably good' in Iceland, compliance may be lower in some areas of England.	Study is of a large population in the UK, making application to the rest of England acceptable.	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. However, these findings are specific to a child or adult population.	Study is of a large population in Liverpool, UK making application to the rest of England applicable.	Study is of a large population in Liverpool, UK making application to the rest of England applicable.

11	**Do the results fit with other evidence?**	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 that a screening interval of 18 -24 months is safe for lower risk individuals. Annual screening was still recommended for higher risk patients, which in this study included patients using insulin, those with poorly controlled diabetes, patients with a longer duration of diabetes and those aged under 40.	This study focusses on children, although results are similar in recommending that STDR is unlikely to occur within an interval of 2 years in patients with no baseline retinopathy; however individuals with risk factors such as poor glycaemic control or a long diabetes duration should continue to be screened annually. As with other studies, the authors recommend that upon detection of retinopathy, frequency should change to annual.	Optimum screening intervals are calculated for each of the baseline groups for a 95% probability of remaining free of STDR. Overall they present a similar pattern of longer screening intervals (5.4 years) for patients with no retinopathy at baseline and shorter intervals (1 year) for those with background retinopathy although the 5.4 year interval for those with baseline retinopathy is longer than recommendations from other studies.	This study uniquely focusses on patients with T1DM and provides useful information that generally fits with the other studies that include a small cohort of T1DM patients. As with the Younis 2003a study, the authors calculate an optimum screening interval for a 95% likelihood of remaining free of STDR by baseline status and report that patients with no retinopathy at baseline could be screened every 5.7 years - much longer than the intervals recommended by other studies. Those with background retinopathy are recommended to be screened every 1.3 years, which is more in line with recommendations from other studies.

Appendix E: Descriptive Characteristics of Cohort Studies

Study	Design	Number of participants analysed	Number of participants without background diabetic retinopathy	Population Studied	Methodology	Primary Results	Conclusions
Agardh et.al 2011 [6]	Cohort	1322	1322	Swedish population with T2DM with no diabetic retinopathy in two 50 degree red free fundus photographs. Invited to baseline screen and follow up 3 years later. At baseline, HBA1C 6.4 +/- 1.5%. 74% were on oral agents +/- insulin. Diabetes duration 6 +/- 6 yrs.. Age 55 +/- 12yrs at diagnosis, 60 +/- 12yrs at baseline.	Baseline fundal photography and scheduled follow up 3 years later. Red-free digital images of one central and one nasal 50° field per eye were obtained by fundus photography. The International Diabetic Retinopathy and Macula Edema Severity Scales were used for grading.	Of the 1,322 subjects available for follow up, 73% were without diabetic retinopathy, 28% (362) mild or moderate, none severe non-proliferative diabetic retinopathy. 3 Subjects had developed macular oedema, two in both eyes, one in one eye. Only of the five eyes required laser treatment and acuity was restored. Thus sight threatening retinopathy occurred in 5 of 2644 eyes, but affected visual acuity in only one.	Three-year retinal screening intervals can be recommended in subjects with mild type 2 diabetes and no retinopathy.
Jones et.al 2012 [34]	Cohort	20,686, of all patients screened, 14,360 were screened at least twice	16,444	UK population (Norfolk), patients registered with GPs and invited to annual screening. Majority of patients enrolled had T2DM except 205 younger probably T1DM patients. Of the patients with no retinopathy at baseline: mean age 66.7 (58-74.5), T2DM, UK based, Norfolk, 70.8% on oral hypoglycaemics only, 62.7% on hypertension treatment. Age at diagnosis = 63.9 (55.1-71.9)	Dynamic Cohort study. Cumulative and annual incidence rates were estimated using life tables and risk factors for progression were identified using Cox regression analysis. Retinal screening done using fundal photography at GP practices using trained retinal screeners. NSC grading used from 2006.	Among patients with no retinopathy at baseline, after 5 yrs of follow up their cumulative incidence of non-proliferative retinopathy was 36%, pre-proliferative. 4.0%, maculopathy 0.59% and diabetic retinopathy .68%. At 2 yrs 12.2% (11.6-12.8), 0.8%(0.7-1), STM 0.11% (0.36-0.19) and proliferative diabetic retinopathy 0.13% (.07-.22) Insulin treatment at baseline had an adjusted HR of 2.17 * see comment	Few patients without diabetic retinopathy at initial screening examination developed pre-proliferative retinopathy, Diabetic retinopathy or STM after 5-10 yrs of follow-up. Screening intervals longer than 1 year may be appropriate for low risk patients
Misra et.al 2009 [5]	Cohort	20,686	16,444	As per Jones et.al (above)	A population of predominantly Type 2 diabetic patients, managed in general practice,	Compared with screening intervals of 12-18 months, screening intervals of 19-24 months were not	Screening intervals of up to 24 months should be considered for

					and screened between 1990 and 2006, with up to 17 years' follow-up and up to 14 screening episodes each. Associations between referable or sight-threatening diabetic retinopathy (STDR), screening interval and frequency of repeated screening, whilst adjusting for age, duration and treatment of diabetes, hypertension treatment and period	associated with increased risk of referable retinopathy (adjusted OR 0.93, 95%CI 0.82-1.05, but screening intervals of more than 24 months were associated with increased risk (OR 1.56, 95% CI 1.41-1.75). Screening intervals of < 12 months were associated with high risks of referable retinopathy and STDR.	lower risk patients
Kohner et.al 2001 [35]	Cohort	3709	2316	UK based population enrolled in UKPDS. Type 2 Diabetics	Patients followed up until end of study / received photocoagulation / lost to FU. Retinopathy severity categorized as no retinopathy, MA only in one eye, MA in both eyes and more severe retinopathy features. Risk of photocoagulation assessed in relation to severity of retinopathy at baseline, 3 and 6 yrs. .	Of the 2316 with no retinopathy, 0.2% needed photocoagulation at 3 years, 1.1% at 6 years and 2.6% at 9 years. Those with MA in one eye only (n=708) were similar, with 0%, 1.99% and 4.7% needing photocoagulation at 3,6 and 9 years respectively.. Amongst those who had more retinopathy features at entry (n=509), 15.3% required photocoagulation by 3 years, and 31.9% by 9 years.	Few T2DM patients without retinopathy progress to photocoagulation in the following 3-6 years, while patients with more severe retinopathy lesions need to be closely monitored
Maguire et.al 2005 [37]	Cohort	668	532	UK based paediatric population with T1DM attending annual screening. Patients divided into 2 age groups <11 years at first retinopathy screening (n = 50, median HbA1c 8.5%, range 8.0–9.2%) and > or =11 years at first retinopathy screening (n 618, median HbA1c 8.7%, range 8.0 – 9.5%). The prevalence of retinopathy at baseline screening was 16% (11-year-old group) and 22% (11- year-old group).	Generalized estimating equations used to compare risk of retinopathy with baselines at yearly intervals, in older and younger groups, in higher risk groups (diabetes duration 10 years or HbA1c _10% at any screening), and after stratification, < or = to 10 and more than 10 years in duration. Fundal photography and retinal screener used.	After 1 year, retinopathy did not increase significantly in the older group (n= 618, median HbA1c 8.7%, range 8.0 –9.5), younger group (n = 50, median HbA1c 8.5%, range 8.0 –9.2), or the higher-risk groups. Retinopathy increased significantly after 2 years in the older group (P 0.003) but not until 6 years in the younger group (P 0.01). In the group with HbA1c 10% recorded at any visit, retinopathy increased significantly after 2 years (P 0.001). but not until 3 years in the group whose HbA1c was always 10% (P 0.003). After the second eye assessment, retinopathy did not increase significantly until 3 and 6 years	Adolescents in reasonable metabolic control could safely be screened biannually rather than current annual recommendations. Individuals with especially poor control need to be screened more frequently.

						later in the older and younger groups, respectively (P 0.028 and 0.014).	
Ólafsdóttir et.al. 2007 [7]	Cohort	296	296	Icelandic adult population with no diabetic retinopathy attending screening in 1996/1997 and followed with biennial screens for 10 years. 296 patients with DM, 97 had T1DM, 199 had T2DM, 120 of group were female. Average age of women 62 (range 19-90), average age men 58 (range 16-87). Average duration of DM = 18 years. * see comment	The 296 patients were followed with biennial eye examinations until they had developed retinopathy or for 10 years.	No patient went from no retinopathy to STDR in < 2 years. All patients who developed STDR had been diagnosed before that happened, and were placed on at least an annual examination schedule.	Every other year screening for diabetic eye disease seems to be safe and effective in diabetics without retinopathy. Such an approach would reduce the number of screening visits more than 25%.
Kristinsson (1995) [36]	Cohort	81 children 185 adults	81 children 185 adults	Two cohorts – 1. Icelandic children aged under 15 at recruitment, 185 Icelandic adults with T2DM or T1DM	Adult group screened "at least annually"	No patients developed STDR over the 2 year study period	Aged 12 should be used as a universal initiation point for regular eye examinations.
Younis et.al [8]	Cohort	501	305	All patients with T1DM enrolled with GPs located within boundaries of Liverpool Health Authority. Majority Caucasian in Liverpool Health Authority and excluded those under care of an ophthalmologist. Of those without retinopathy, median age was 30.2 (21.5-39.8), median years of diabetes duration was 7.8 (3-13). 52.5% males.	All patients with T1DM registered with enrolled GP, excluding only those attending an ophthalmologist, were studied if retinopathy data was available at baseline and at least one further screening event. STDR used as key endpoint – stage at which ophthalmic follow up is needed.	Cumulative incidence of STDR in patients without baseline retinopathy was 0.3% (95% CI 0.0-0.9) at 1 year, rising to 3.9% (1.4-1.5) at 5 years. Rates of progression to STDR in patients with background and mild pre-proliferative retinopathy at 1 year were 3.6% (0.5-6.6) and 13.5% (4.2-22.7) respectively. Progression to STDR was greater in patients with a higher grade of baseline retinopathy (p = 0.001) or a longer disease duration (p =0.003). 95% likelihood of remaining free of STDR, mean screening intervals by baseline status were: no retinopathy: 5.7 (95% CI 3.5-7.6) years, background 1.3 (0.4-2.0)	Screening at 2-3 year intervals rather than annually for patients without retinopathy in T1DM is feasible because of the low risk of progression to STDR. Patients with higher grades of retinopathy may require screening at least annually or more frequent.

						and mild pre-proliferative 0.4 (0-0.8) years.	
Younis et.al 2003 [45]	Cohort	4770[43]	3743	All T2DM enrolled with GPs located within boundaries of Liverpool Health Authority who had retinopathy data and at least one subsequent visit. T2DM defined as age at dx of diabetes of 30 yrs or older or age at dx of younger than 30 in absence of insulin dependence. Those with no retinopathy; age median = 63.4 (56.1-69.8), average duration of diabetes median 3 years (0.8-4.0), age of diagnosis median = 59 (51-66.1), median 4 screening visits 4 (2-9), 50% diet only, 44% oral hypoglycaemics, 6% insulin. 55% male.	Cumulative and yearly incidence rates of STDR and grades of retinopathy were calculated for 1 year intervals by life table method, which accounted for varying intervals of FU after first screening visit. Patients who did not develop STDR contributed to person yrs up until last screening visit, year of death or end of study.	Yearly incidence of STDR in patients without retinopathy at baseline was 0.3% (95%CI 0.1-0.5) in the first year, rising to 1.8% (1.2-2.5) in the fifth year. Rates of progression to sight threatening diabetic retinopathy in year 1 by baseline status were: background 5% (3.5-6.5) and mild preproliferative 15% (10.2 - 19.8). For a 95% probability of remaining free of STDR, mean screening intervals by baseline status were; no retinopathy 5.4 years (95%CI 4.7-6.3), background 1 years (0.7-1.3) and mild pre-proliferative 0.3 years (0.2-0.5). In the 326 (9%) of 3532 patients with no retinopathy, who were using diet treatments or oral hypo-glycaemics at baseline, and who subsequently needed insulin, 5-year incidence of sight-threatening diabetic retinopathy was 7·0% (2·3–11·7).	A 3 year screening interval could be safely adopted for patients with T2DM and no retinopathy, but yearly or more frequent screening is needed for patients with higher grades of retinopathy.
Thomas et.al [43]	Cohort (retrospective)	49 763	49 763	People with T2DM aged over 30, registered with a GP in Wales and referred to Diabetic Retinopathy Service, with T2DM who attended screening between January 2005 and November 2009 and attended more than once. Digital retinal images and review by trained retinal screeners.	Descriptive analyses used to characterise the study population and patterns of diabetic retinopathy, and used *t* tests and $\chi 2$ tests to explore differences between patients without any retinopathy and those who developed any, background, or referable retinopathy. Parametric survival analysis with covariates identified those factors associated with the development of	Cumulative incidence of any and referable retinopathy at four years was 360.27 and 11.64 per 1000 people, respectively. From the first to fourth year, the annual incidence of any retinopathy fell from 124.94 to 66.59 per 1000 people, compared with referable retinopathy, which increased slightly from 2.02 to 3.54 per 1000 people. Incidence of referable retinopathy was independently associated with known duration of diabetes, age at diagnosis, and	Supports the extension of the screening interval for people with type 2 diabetes mellitus beyond the currently recommended 12 months, with the possible exception of those with diabetes duration of 10 years or more and on insulin treatment.

					referable retinopathy. English National Screening Protocol used. Referable retinopathy defined as preproliferative or proliferative maculopathy or maculopathy with background retinopathy.	use of insulin treatment. For participants needing insulin treatment with a duration of diabetes of 10 years or more, cumulative incidence of referable retinopathy at one and four years was 9.61 and 30.99 per 1000 people, respectively.	

T2DM = Diabetes Mellitus Type 2, STM = Sight Threatening Maculopathy, diabetic retinopathy = Diabetic Maculopathy

Appendix F: Descriptive Characteristics of Risk Stratification Algorithm Studies

Study	Data Set	Number of patients for development	Number of patients for testing	Methodology	Primary Results	Conclusions
Aspelund et.al [27]	Published risk factors and prevalence data from the Icelandic screening programme	N/A	5,199	A risk algorithm was created based on published epidemiological data on risk factors for diabetic retinopathy. The algorithm uses information on diabetes type, HbA1c, systolic blood pressure, gender and presence on nonproliferative retinopathy. The Aarhus database was used to test efficacy of algorithm against 20 yrs of data for 5,199 pts.	In the Danish diabetes database, the algorithm recommends screening intervals ranging from 6 to 60 months with a mean of 29 months. This is 59% fewer visits than annual screening. This amounts to 41 annual visits per 100 patients.	The algorithm has the potential to save on resources by reducing the number of screening visits for an ever increasing diabetic population.
Mehlsen et.al 2011 [39]	Aarhus Database, Denmark. Dataset comprises data from 11970 patients representing 39559 screening examinations which were cleansed due to unknown migration, parts or disease history missing, which left 5311 pts.	5311 pts, 1385 pts with T1DM, 3926 with T2DM		Logistic regression was used to identify associations between selected risk factors from database and treatment events for diabetic retinopathy. The model is based on data from the Danish screening database where screening interval is already based on risk factors.	The risk of reaching a treatment end point was in both diabetes types independently affected by retinopathy grade and HbA1c. In type 1 diabetic patients the risk of reaching a treatment end point was independently affected by disease duration. In type 2 diabetes this risk was affected by increasing age of diagnosis of the disease.	Only a subset of known risk factors for development and progression of diabetic retinopathy should be used to construct a decision model for optimizing screening intervals for diabetic retinopathy
Mehlsen et.al 2012 [40]	Sub-Set of Aarhus Database, Denmark. All patients screened during year 2000.		1372 (500 of which had T1DM)	Model from Mehlsen et al 2011 tested on 1372 patients screened during year 2000.	When the probability of reaching a treatment requiring event was set to 0.5%, none of the patients reached a treatment end-point in a validation of the model, and the screening interval was prolonged on average 2.9 times in patients with type 1 diabetes and 1.2 times in those with type 2 diabetes.	A model for optimizing the examination interval during screening for diabetic retinopathy in low-risk patients was constructed. The model can potentially be improved by identifying unknown or unmeasured confounders.
Semeraro et.al 2011 [42]	T2DM patients at an Italian clinic	3327	1707	Factors associated with the occurrence of diabetic retinopathy were assessed by Cox's proportional hazard model.	Results presented in the form of a nomogram which could potentially be used to stratify risk and individualise screening intervals. Model performance: area under the ROC curve for one year without retinopathy was 0.825.	Duration of diabetes, HbA1c, systolic blood pressure, male gender, albuminuria and diabetes therapy other than diet were all significantly associated with diabetic retinopathy.

Appendix G: Descriptive characteristics and key economic variables of the included economics studies

Author (Year)	Aim	Economic evaluation type	Population studied	Comparators	Methods	Results and main conclusions
Brailsford et al, 2007	To identify the most cost-effective diabetic retinopathy screening programme and to maximise the number of years of sight saved (regardless of cost)	Cost-effectiveness analysis using discrete event simulation embedded in an ant colony optimisation model. Simulation uses an approach called Patient Orientated Simulation Technique (POST).	Hypothetical population (general population including ethnic minorities) of 100,000 people aged 20 and above with type 2 diabetes in England and Wales in 1991. Subgroup analyses: All white population with no ethnic minorities	Different screening scenarios (2 policies) vs. no screening (baseline). The different screening methods used for the two policies were: optometrist fundoscopy, diabetologist ophthalmoscopy, GP ophthalmoscopy, mobile camera and mydriatic 7 field photography reported by ophthalmologist (gold standard).	Study perspective: Not stated Time horizon: 100 years Discount rate: 0, 3 & 5% 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 Currency/price year: UK £ - year not stated Sensitivity analyses: Not stated	Most cost-effective screening policy is to start screening at age 35 (no discounting) or age 30 (with discounting) and to stop screening at age 60. This is policy 2 where the optometrist carries out both screens (1 and 2 – 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	To assess whether diabetic retinopathy screening every two years rather than annually was more cost-effective	Cost-effectiveness analysis using a simulation model. The simulation model uses POST.	Hypothetical population of 5,000 people with lower risk of type 2 diabetes without diabetic retinopathy in a Devon and Exeter NHS trust. Subgroup analyses: Patients who develop maculopathy	Annual (or six-monthly) screening programme (usual care) vs. a two year screening programme (proposed care)	Study perspective: Not stated Time horizon: 15 years Discount rate: Not stated Outcomes: Proportion of diabetes patients with vision loss Costs: Screening test, ophthalmology visits and laser treatment ICER: None stated Currency/price year: UK £ - year not stated Sensitivity analyses: One-way	The costs were £1,360,516 for the proposed screening every two years and £1,834,060 for the annual screening, which represents a 25.8% reduction in screening costs. A retinal screening test every two years was a safe and cost-effective strategy.
Dasbach et al, 1991	To assess the cost-effectiveness of screening for diabetic	Cost-effectiveness analysis using a simulation model using	Three hypothetical groups of a 1,000 patients: 1) patients < 30 years old with	Seven different screening strategies were compared: 1) natural disease progression (no care); 2 and 3) annual	Study perspective: Societal Time horizon: 10 and 60 years	60-year results: annual examination with mydriatic fundus photography for group 1, group 2 and group 3

	retinopathy comparing biennial and annual screening programs	a Markov process.	onset diabetes of >=5 years duration; 2) patients >=30 years old with onset diabetes, taking insulin; and 3) patients >=30 years old with onset diabetes, not taking insulin	or biennial visits to a community health care professional using an ophthalmoscope; 4 and 5) annual or biennial non-mydriatic camera screening; 6) and 7) annual or biennial mydriatic camera screening	Discount rate: 5% (varied between 0 and 10%) Outcomes: Sight years saved Costs: Screening and clinic visits, treatments and rehabilitation ICER: None stated Currency/price year: US$ in 1989 prices Sensitivity analyses: One-way	might save from 303 to 319, from 58 to 62 and from 19 to 21 sight years over the lifetime of the cohort, respectively.
Davies et al, 2002	To determine the cost-effectiveness of varying the screening method and the screening interval	Cost-effectiveness analysis using discrete event simulation. The simulation model uses POST.	Hypothetical population of 500,000 people with type 1 or type 2 diabetes in England and Wales who could develop diabetic retinopathy	Screening can be either by a mobile camera, diabetologist, optometrist, GP, or any other method. Each screening scenario was compared to no screening. Under policy 1, optometrist, diabetologist and GP screening intervals of 12 months and a 6-month interval between visits once diabetic retinopathy had been detected. Under policy 2, people continue to be screened by the chosen method 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 (assumed 'gold' standard) consisted of screening every 6 months, with visits every 3 months after retinopathy had been detected.	Study perspective: Not stated Time horizon: 25 years Discount rate: Not undertaken Outcomes: Average years of sight saved Costs: Screener, ophthalmology outpatient visits, treatment and use of the mobile camera (including set-up costs and quality assurance costs). ICER: Costs per year of sight saved Currency/price year: UK £ - year not stated 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 £2,842. For Type 1 diabetic patients, the costs per year of sight saved were £2,143 (policy 1) and £1,399 (policy 2) and £4,122 if the 'gold' standard screening was used. For Type 2 diabetic patients, the costs per year of sight saved were £4,700 (policy 1), £3,349 (policy 2), and £11,263 if the 'gold' standard screening was used. Policy 2 was more cost-effective than policy 1 as long as the screening sensitivity and compliance were relatively high.
Javitt et al, 1990	To estimate the economic implications of alternative screening strategies for detecting retinopathy in a diabetic population	Cost-effectiveness analysis using a simulation model. The simulation model used the PROspective Population Health Event Tabulation (PROPHET) modelling system. PROPHET uses Monte Carlo	A cohort of type 1 diabetes patients (screening begins 5 years after onset of diabetes)	5 different screening strategies all strategies have dilated ophthalmoscopy: 1) every 2 years for all patients; 2) annually for all patients; 3) annually for patients with no retinopathy and examination every 6 months for those with retinopathy; 4) with full fundus photographs annually; 5) with full fundus photographs	Study perspective: Government Time horizon: Lifetime Discount rate: 5% Outcomes: Person years of sight saved Costs: Screening (eye examination, angiography) and treatment (laser	All strategies resulted in savings: net annual savings of $62.1 (strategy 5) to $108.6 million (strategy 2). Between 71,474 (strategy 1) and 85,315 (strategy 5) years of sight can be saved. Strategy 3 saved more sight than did less frequent examination and was nearly as cost saving. Strategy 4

		simulations to model each patient as a separate individual.		annually for patients with no retinopathy and examination every 6 months for those with retinopathy.	panretinal or focal) ICER: None stated Currency/price year: US$ in 1986 prices Sensitivity analyses: One-way	was not as effective or cost saving as more frequent examination without photography. Strategy 5 saved only 1% more sight than strategy 3 without photography and was far less cost saving. The model predicts a clear economic advantage in adding semi-annual visits under strategy 3. Although it was slightly less cost saving than annual examination alone, 4200 (6%) more years of sight are saved in each annual cohort.
Javitt et al, 1994	To estimate the cost savings resulting from screening and treatment in diabetes patients	Cost-effectiveness analysis using a simulation model. The simulation model used PROPHET modelling system.	A cohort of type 2 diabetes patients with diabetic retinopathy	8 different screening strategies: Strategies 1 and 2, all patients will have an eye examination by an ophthalmologist every 2 years. Patients with background or more advanced retinopathy will be seen either semi-annually under strategy 1 or annually under strategy 2. Strategies 3, 4, and 5 increase the initial examination interval to 3 years, with the follow-up screenings for those with background retinopathy scheduled every 6, 12, or 18 months, respectively. Strategies 6, 7, and 8 further increase the initial screening intervals to every 4 years and the screening for those with background retinopathy to every 6, 12, or 24 months, respectively.	Study perspective: Government Time horizon: Lifetime Discount rate: 5% (varied between 2.5 and 10%) Outcomes: Person years of sight saved Costs: Screening and treatment and cost of blindness ICER: None stated Currency/price year: US$ in 1990 prices Sensitivity analyses: One-way	Changing the frequency of screening for patients with no or mild background retinopathy from 1 to 2 years has no detrimental effect on years of sight saved while reducing costs. Once patients develop moderate nonproliferative or more advanced retinopathy, savings in sight-years are sensitive to the screening interval. A 6-month screening interval for patients with background retinopathy can save about 3,360 person-years of sight over the life of the cohort compared with a 12-month screening interval and 12,320 person-years of sight over the life of the cohort compared with a 24-month screening interval.
Rein et al, 2011	To determine whether biennial eye evaluation or telemedicine screening are cost-effective alternatives to current recommendations for people with diabetes but no or minimal	Cost-utility analysis using Monte Carlo simulation.	Hypothetical 10 million type 2 diabetes patients with no or early diabetic retinopathy aged 30 to 84 years	Four screening methods: patient self-referral following visual symptoms (current practice), annual eye evaluation, biennial eye evaluation, and annual telemedicine screening in primary care settings	Study perspective: Societal Time horizon: Lifetime Discount rate: 3% Outcomes: Quality-adjusted life years (QALYs) Costs: Intervention (including telemedicine) and treatment costs	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. Self-referral was most likely to be cost-effective at a WTP between US$0 and US$37,500 per QALY gained. Biennial evaluation was

	diabetic retinopathy				and productivity losses ICER: Cost per QALY gained Currency/price year: US$ in 2010 prices Sensitivity analyses: Probabilistic	most likely to be cost-effective at a WTP between US$37,500 and US$150,000 per QALY gained, and annual evaluation was most likely to be cost-effective at WTP values US$150,000 per QALY gained. The EVPI suggested that an additional US$ 709 million was needed to reduce uncertainty.
Vijan et al, 2000	To examine the cost-effectiveness of various screening intervals (annual vs. less frequent) for eye disease in patients with diabetes	Cost-utility analysis using a non-stationary Markov model.	Hypothetical type 2 diabetes patients based on the US population of 40 years and older from the Third National Health and Nutrition Examination Survey	Various screening intervals (annual vs. less frequent)	Study perspective: Third party payer (government and societal used in sensitivity analyses) Time horizon: Lifetime Discount rate: 3% Outcomes: QALYs Costs: Screening, ophthalmology visits, laser treatment and angiogram ICER: Cost per QALY gained Currency/price year: US$ - year not stated Sensitivity analyses: One-way & multivariate	The marginal cost-effectiveness of screening annually vs. every other year also varies; patients in the high risk group cost an additional $40,530 per QALY gained, while those in the low risk group cost an additional $211,570 per QALY gained. Screening annually costs $107,510 per QALY gained, while screening every other year vs. every third year costs $49,760 per QALY gained.

POST = Patient Orientated Simulation Technique; PROPHET = PROspective Population Health Event Tabulation; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; EVPI = expected value of perfect information.

Appendix H: 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)	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
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
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	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
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
6 Study perspective: Describe the perspective of the study and relate this to the costs being evaluated.	N	N	Y	N	Y	Y	Y	Y
7 Comparators: Describe the interventions or strategies being compared and state why they were chosen.	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*
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
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
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	N/A	N/A	Y	N/A	N/A	N/A	N/A	N/A

data.								
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	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
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	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 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.	Y	N/A	N/A	Y	Y	Y	Y	Y
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	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
16 Assumptions: Describe all structural or other assumptions underpinning the decision-analytic model.	Y*	N	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, and methods for handling population heterogeneity and uncertainty.	N	N	N	N	N	N	Y	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
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

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
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
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
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
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
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

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

Appendix I: 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)	Vijan et al (2000)
STRUCTURE									
1	Is there a clear statement of the decision problem?	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
3	Is the primary decision maker specified?	Y	N	N	N	Y	Y	N	N
4	Is the perspective of the model stated clearly?	N	N	Y	N	Y	Y	Y	Y
5	Are the model inputs consistent with the stated perspective?	UN	UN	Y*	UN	Y	Y	Y	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
7	Are the sources of the data used to develop the structure of the model specified?	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*
9	Is there a clear definition of the options under evaluation?	Y*	Y	Y	Y	Y	Y	Y	Y*
10	Have all feasible and practical options been evaluated?	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
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
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*
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

15	Is the cycle length defined and justified in terms of the natural history of disease?	N	N	Y	N	Y	Y	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
17	Where choices have been made between data sources are these justified appropriately?	UN	UN	UN	Y	Y	UN	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
19	Is the choice of baseline data described and justified?	UN	UN	UN	N	N	N	UN	UN
20	Are transition probabilities calculated appropriately?	UN	Y	Y	Y	UN	UN	Y	UN
21	Has a half-cycle correction been applied to both costs and outcomes?	N	N	N	N	N	N	N	N
22	If not, has the omission been justified?	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
24	Are the costs incorporated into the model justified?	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
26	Have discount rates been described and justified given the target decision maker?	Y	N	Y	N	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
28	Is the source of utility weights referenced?	N/A	N/A	N/A	N/A	N/A	N/A	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
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
31	Has heterogeneity been dealt with by running the model separately for different sub-groups?	Y	Y	Y	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

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

Appendix J: Supplementary Review

Please find the supplementary review in the supporting document:

Supplementary Review: Rapid Literature Review: Does a change in screening interval lead to a subsequent change in uptake?

References

1. Scanlon, P.H., *The English national screening programme for sight-threatening diabetic retinopathy.* Journal of Medical Screening, 2008. **15**(1): p. 1-4.
2. Agardh, E., C.D. Agardh, and C. Hansson-Lundblad, *The five-year incidence of blindness after introducing a screening programme for early detection of treatable diabetic retinopathy.* Diabetic Medicine, 1993. **10**(6): p. 555-559.
3. Patterson, C.C., et al., *Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study.* The Lancet, 2009. **373**(9680): p. 2027-2033.
4. Bagust, A., et al., *The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060.* Diabetic Medicine, 2002. **19**(s4): p. 1-5.
5. Misra, A., et al., *Trends in yield and effects of screening intervals during 17 years of a large UK community-based diabetic retinopathy screening programme.* Diabetic Medicine, 2009. **26**(10): p. 1040-1047.
6. Agardh, E. and P. Tababat-Khani, *Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy.* Diabetes Care, 2011. **34**(6): p. 1318-9.
7. Olafsdottir, E. and E. Stefánsson, *Biennial eye screening in patients with diabetes without retinopathy: 10-year experience.* British Journal of Ophthalmology, 2007. **91**(12): p. 1599-1601.
8. Younis, N., et al., *Incidence of sight-threatening retinopathy in Type 1 diabetes in a systematic screening programme.* Diabetic Medicine, 2003. **20**(9): p. 758-65.
9. Javitt, J.C., *How often should patients with diabetes be screened for retinopathy?* JAMA: the journal of the American Medical Association, 2000. **284**(4): p. 437-439.
10. Jones, S. and R. Edwards, *Diabetic retinopathy screening: a systematic review of the economic evidence.* Diabetic Medicine, 2009. **27**(3): p. 249-256.
11. Ophthalmologists, T.R.C.o., *Guidelines for Diabetic*

Retinopathy. London: The Royal College of Ophthalmologists 1997.

12. Association, A.D., *Diabetic retinopathy.* Diabetic retinopathy, 1998. **21: 157–159**.
13. Klein, R., *Screening interval for retinopathy in type 2 diabetes.* Lancet, 2003. **361**(9353): p. 190-1.
14. Socialstyrelsen, *National guidelines for diabetes. Stockholm, Sweden, Socialstyrelsen.* Available online at http://www.socialstyrelsen.se. Last Accessed May 2011, 2010.
15. Stefánsson, E., *Diabetic retinopathy screening [1].* Pediatrics, 2006. **117**(2): p. 586.

16. McGhee, S., S.P. Harding, and D. Wong, *Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy by Aspelund et al.(2011) Diabetologia 54: 2525–2532.* Graefe's Archive for Clinical and Experimental Ophthalmology, 2012: p. 1-2.

17. Klein, R., et al., *The Wisconsin epidemiologic study of diabetic retinopathy: XVII: The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes11Proprietary interest: none.* Ophthalmology, 1998. **105**(10): p. 1801-1815.

18. Stratton, I., et al., *UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis.* Diabetologia, 2001. **44**(2): p. 156-163.

19. Klein, R., *Guidelines for screening for diabetic retinopathy revisited.* Ophthalmic Epidemiology, 1999. **6**(1): p. 1-4.

20. CentreforReviewsandDissemination, *Systematic Reviews: CRD's guidance for undertaking reviews in health care.* Available at: http://www.york.ac.uk/inst/crd/index_guidance.htm 2011;Last visited 08/06/12, 2011.

21. Husereau, D., et al., *Consolidated health economic evaluation reporting standards (CHEERS) statement.* BMC medicine, 2013. **11**(1): p. 80.

22. Unit, P.H.R., *The Critical Skills Appraisal Programme: making sense of evidence* Public Health Resource Unit, England, 2006. **Retrieved from: http://www.casp-uk.net/**.

23. Steyerberg, E.W., et al., *Prognosis research strategy (PROGRESS) 3: prognostic model research.* PLoS medicine, 2013. **10**(2): p. e1001381.

24. Drummond, M. and T. Jefferson, *Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party.* BMJ: British Medical Journal, 1996. **313**(7052): p. 275.

25. Philips, Z., et al., *Good practice guidelines for decision-analytic modelling in health technology assessment.* Pharmacoeconomics, 2006. **24**(4): p. 355-371.

26. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* PLoS medicine, 2009. **6**(7): p. e1000097.

27. Aspelund, T., et al., *Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy.* Diabetologia, 2011. **54**(10): p. 2525-32.

28. Brailsford, S.C., et al., *Combined discrete-event simulation and ant colony optimisation approach for selecting optimal screening policies for diabetic retinopathy.* Computational Management Science, 2007. **4**(1): p. 59-83.

29. Chalk, D., et al., *Can the Retinal Screening Interval Be Safely Increased to 2 Years for Type 2 Diabetic Patients Without Retinopathy?* Diabetes Care, 2012. **35**(8): p. 1663-1668.

30. Dasbach, E.J., et al. (1991) *Cost-effectiveness of strategies for detecting diabetic retinopathy (Structured abstract)*. Medical Care, 20-39.

31. Davies, R., et al., *The evaluation of screening policies for diabetic retinopathy using simulation.* Diabetic Medicine, 2002. **19**(9): p. 762-770.

32. Javitt, J.C., 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**(8): p. 909-917.

33. Javitt, J., et al., *Detecting and treating retinopathy in patients with type I diabetes mellitus. A health policy model.* Ophthalmology, 1990. **97**(4): p. 483-94; discussion 494-5.

34. Jones, C.D., et al., *Incidence and Progression of Diabetic Retinopathy During 17 Years of a Population-Based Screening Program in England.* Diabetes Care, 2012. **35**(3): p. 592-596.

35. Kohner, E.M., et al., *Relationship between the severity of retinopathy and progression to photocoagulation in patients with Type 2 diabetes mellitus in the UKPDS (UKPDS 52).* Diabetic Medicine, 2001. **18**(3): p. 178-184.

36. Kristinsson, J.K., et al., *Screening for diabetic retinopathy. Initiation and frequency.* Acta Ophthalmologica Scandinavica, 1995. **73**(6): p. 525-8.

37. Maguire, A., et al., *The case for biennial retinopathy screening in children and adolescents.* Diabetes Care, 2005. **28**(3): p. 509-513.

38. Mellanby, A., et al., *Reducing the interval for diabetic retinal screening*. 1999: Wessex Institute for Health Research and Development.

39. Mehlsen, J., et al., *Identification of independent risk factors for the development of diabetic retinopathy requiring treatment.* Acta Opthalmologica, 2011. **89**(6): p. 515-21.

40. Mehlsen, J., et al., *Individualized optimization of the screening interval for diabetic retinopathy: A new model.* Acta Ophthalmologica, 2012. **90**(2): p. 109-114.

41. Rein, D.B., et al., *The cost-effectiveness of three screening alternatives for people with diabetes with no or early diabetic retinopathy.* Health Services Research, 2011. **46**(5): p. 1534-1561.

42. Semeraro, F., et al., *Predicting the risk of diabetic retinopathy in type 2 diabetic patients.* Journal of Diabetes & its Complications, 2011. **25**(5): p. 292-7.

43. Thomas, R.L., et al., *Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis.* BMJ: British Medical Journal (Overseas & Retired Doctors Edition), 2012. **344**(7848): p. 18-18.

44. Vijan, S., T.P. Hofer, and R.A. Hayward, *Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus.* JAMA, 2000. **283**(7): p. 889-96.

45. Younis, N., 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**(9353): p. 195-200.

46. Stratton, I.M., et al., *A Simple Risk Stratification for Time to Development of Sight-Threatening Diabetic Retinopathy.* Diabetes care, 2013. **36**(3): p. 580-585.

47. Vickers, A.J. and A.M. Cronin, *Everything you always wanted to know about evaluating prediction models (but were too afraid to ask).* Urology, 2010. **76**(6): p. 1298.

48. Turner, R., et al., *Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).* lancet, 1998. **352**(9131): p. 837-853.

49. Group, U.P.D.S., *Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38.* BMJ: British Medical Journal, 1998: p. 703-713.

50. NICE, *National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London: NICE, 2008 [online]. Available from URL: http://www.nice.org.uk/media/ B52/A7/TAMethodsGuideUpdatedJune2008.pdf* 2008.

51. Davies, R., P. Sullivan, and C. Canning, *Simulation of diabetic eye disease to compare screening policies.* British journal of ophthalmology, 1996. **80**(11): p. 945-950.

52. Javitt, J.C., et al., *Detecting and treating retinopathy in patients with type I diabetes mellitus: savings associated with improved implementation of current guidelines. Discussion.* Ophthalmology, 1991. **98**(10): p. 1565-1574.

53. Drummond, M.F., et al., *Methods for the economic evaluation of health care programmes*. 2005: Oxford University Press, USA.

54. Wong, T.Y., et al., *Rates of progression in diabetic retinopathy during different time periods a systematic review and meta-analysis.* Diabetes care, 2009. **32**(12): p. 2307-2313.

55. Klein, R. and B.E.K. Klein, *Are individuals with diabetes seeing better? A long-term epidemiological perspective.* Diabetes, 2010. **59**(8): p. 1853-1860.