NIHR Health Technology Assessment programme

NHS National Institute for Health Research

NETSCC, HTA

09 May 2012

The Health Technology Assessment programme is managed by NETSCC, HTA as part of the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton.

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National Institute for Health Research
Health Technology Assessment Programme
Commissioned Full Proposal

The HTA programme reserves the right to share, in confidence, details of your application with other research funding organisations in order to coordinate research activity in the UK.

Selection of funding body and workstream

Information

Proposal Type:	Full	Research Type:	Primary Research
Call name:	Screening intervals for diabetic retinopathy	Priority Area Reference (e.g. 10/1009):	10/66

Which funding stream are you applying to?	Health Technology Assessment
How did you hear about this call?	From a colleague

Full title of project (expand any abbreviations). If you have previously submitted this application as an Outline Proposal the title should remain the same.

Development of a cost-effectiveness model for optimization of the screening interval in diabetic retinopathy screening.

Number of applicants:	8

Start date:	1st May 2012	Proposed duration: (months)	24
Research grant:		Research grant inc. NHS costs:	

Is a Clinical Trials Unit (CTU) involved with this research proposal?	No

Does the CTU hold an UKCRC registration?	Please provide the UKCRC CTU Registration No:

Is the CTU receiving Clinical Evaluation and Trials support funding from NIHR / HTA?	

Section A: Applicant details

Lead Applicant details

Title:	Professor	Forename:	Peter
Middle Names:	Henry	Surname:	Scanlon

Post Held:	Programme Director, English National Screening Programme fo Diabetic Retinopathy
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Do you have an alternative contact address?	No

For HTA Use

Project reference: Date received:

HTA SAF / February 2011

Detailed project description

1. Project title:

10/66/01 - Development of a cost-effectiveness model for optimization of the screening interval in diabetic retinopathy screening.

2. How the project has changed since the outline proposal was submitted:

The project has changed since the outline application in two ways:

1. Extraction methodology for data from screening programmes with high ethnic minority groups

a) Coventry and Warwickshire - Since the outline application was submitted considerable progress has been made towards transfer of risk factor data (e.g. blood pressure and HbA1c) in the Department of Health sponsored National General Practice to Diabetic Retinopathy Screening (GP2DRS) project. Thus our original plan to use this approach for data extraction from the Gloucestershire service can be extended to the Coventry and Warwickshire Screening Service as they are an early adopter site for the GP2DRS project. They will be in a position to collect risk factor data in their service in the early roll out phase later in 2011. We have therefore increased the sample size in analysis phase 3 to include anonymised data from 2,000 people of Asian origin and 5,000 of Caucasian origin. We will validate the model from Phase 1 in the Gloucestershire data with literature derived weighting factors for ethnic minority groups.

b) The South London Diabetic Eye Complication Screening Service (DECS) are reconsidering whether they will be early adopters of GP2DRS. We plan to use this approach for data extraction to obtain the required data on a minimum of 2000 patients, of which 700 patients will be of African Caribbean origin. This method will also incur some support costs for the GP surgeries for the practice manager and practice nurse time involved in this data extraction exercise. The validation of the risk score and algorithm derived from the Gloucestershire data and the method of modifying it if needed will be the same in the different ethnic groups.

c) We have had a recent offer of data from Dr Tasso Gazis, Clinical Lead of the Nottingham Diabetic Retinopathy Screening service that is an early adopter site for GP2DRS which serves 28 000 people with diabetes, 12000 patients in Nottingham City PCT (ethnic mix 4.7% black, 8.0% Asian. 4.3 % DM) and 16000 patients in the southern half of Notts County PCT (ethnic mix. 1.0% black, 2.1% Asian. 4.6% DM). I have asked our data manager to assess the feasibility of including data from Nottingham within our study and we are assessing how this might enhance the study.

2. Quality of Life data - In order to simplify the design and conduct of this project we have decided not to carry out the study that would quantify quality of life in patients with DR. A targeted review of the literature was undertaken, and found that there were a number of well-conducted studies that could be used instead in the health economic modelling.

3. Planned investigation:

Research objectives

• Use demographic and routinely collected clinical information from 15000 patients in 85 Gloucestershire GP practices to develop a risk score for each patient and to identify patient groups whose risk of retinopathy progression is low and whose screening interval could potentially be safely extended (Analysis phase 1 - the Gloucestershire risk factor approach analysis will commence for a period of 6 months 1st May 2012 - 1st November 2012).

• Model what the influence of the grading classification error is on over referrals and under referrals and how that influence changes over time, taking into account sequential grading results and hospital outcome results, comparing screening intervals that vary according to risk score against current standard practice (annual screening intervals for all patients) and other fixed-interval approaches.
(Analysis phase 2 - the Oxford Monitoring interval approach will commence for a period of 6 months. 1st November 2012 - 1st May 2013).

• Extend our results to multi-ethnic populations using a dataset of 2000 Asians and 5000 Caucasians from Coventry and Warwickshire and a South London dataset of 2000 people with diabetes including 700 people of African Caribbean origin. Grading results can be made available from these datasets for at least a 3 year period. The risk score and algorithm will be tested against retinopathy grades in the two datasets where follow-up data is available. (Analysis phase 3 - Extension to an ethnically diverse population will commence for a period of 4 months - 1st May 2013 - 1st September 2013)

• Determine if assigning diabetic patients to differing diabetic retinopathy screening intervals using a risk estimation model is cost-effective when compared to current practice, which is annual screening of all eligible patients with diabetes; (Analysis phase 4 - the Health Economic modelling commences for a period of 18 months 1st July 2012 – 1st January 2014*)*.

• Estimate the economic benefits if personalised screening intervals were to be applied to the National Screening Programme in England. (Analysis phase 4 - the Health Economic modelling commences for a period of 18 months 1st July 2012– 1st January 2014*)*.

Existing research

Diabetes is one of the most common chronic diseases, having reached global epidemic proportions [12], placing a great economic burden to society due to increased healthcare expenditures and lost productivity [39]. Although the treatment of diabetes on its own is costly, its complications are the major contributors to healthcare costs [40, 41]. Amongst the main diabetes-related complications is diabetic retinopathy, which has been shown to be the leading cause of blindness in the working age population [2]. Diabetic retinopathy is treated effectively with laser photocoagulation, although this has only been found to be cost-effective if retinopathy is detected before irreversible damages take place [3, 5, 17]. Therefore, in order for diabetic retinopathy treatment to be cost-effective diagnosis has to be timely. Published evidence has shown that screening for sight-threatening diabetic retinopathy is highly cost-effective [18-21, 42]. In the UK, results from published studies also highlight the cost-effectiveness of screening for diabetic retinopathy [43], with James et al. (2000) showing that a screening programme using retinal photography was cost-effective when compared to opportunistic screening [6].

In 2003 a national screening programme was introduced in England. The programme set out to provide advice, support and facilitation to NHS healthcare providers in implementing local systematic diabetic retinopathy screening programmes [44]. The English National Screening Programme recommended digital imaging as the preferred method of retinal photography for screening and mandated that local programmes respond to local needs with different models of care [45], with eye screening to be performed at time of diabetes diagnosis, and repeated annually thereafter. In England and Wales, annual diabetic retinopathy screening was also recommended for both Type 1 and Type 2 diabetes in clinical guidelines issued by the National Institute for Health and Clinical Excellence [7, 8]. In England quarterly returns from the DH [9] show that the number of people identified by GP practices in England has risen from 2.3 million in the third quarter of 2009 to over 2.4 million in the third quarter of 2010, a rise of over 120,000 in 12 months.

There are two recent studies [15, 16] that have shown that since 1985 people with diabetes have experienced lower rates of progression to proliferative DR and severe visual loss, probably reflecting improvements in diabetes care.

NICE recommendations exist but there is no evidence based consensus as to the optimal frequency of testing for diabetic retinopathy. Scottish Intercollegiate Guidelines Network (SIGN) [10] reported that patients with diabetes with no detected retinopathy could be screened every two years, with all others being screened at least annually. There have been a number of studies [22-25] that have modelled the possible effect of moving from annual to 2-3 year intervals in patients with Type 1 and Type 2 diabetes using incidence data from Icelandic, Liverpool, and Norwich Screening programmes. In 2007, Olafsdottir [26] reported the 10-year experience of biennial eye screening in patients with diabetes without retinopathy from Iceland concluding that this seems to be safe and effective.

An alternative modelling approach by Mehlsen [28] used clinical data from 5365 patients who had undergone 23,324 examinations at the Department of Ophthalmology, Arhus University Hospital and concluded that a subset of known risk factors for development and progression of diabetic retinopathy should be used to construct a decision model for optimising screening intervals for DR.

The current studies have not included factors such as the economic consequences of visual loss other than legal blindness, the effect in ethnic or racial minority groups (the studies had mostly been in patients of northern European extraction), and that long intervals between appointments may lead to difficulties in maintaining follow up with patients [29]. A study [11] in the Coventry area found that people with diabetes of South Asian ethnicity were diagnosed at a younger age had higher HbA1c, systolic and diastolic blood pressure, and total cholesterol and greater prevalence of diabetic retinopathy and maculopathy.

In Gloucestershire we have done preliminary analysis [46] of screening data and know that we can produce accurate and quality assured screening results from the system because data already transferred from GP practices has been of high quality. We have also been the pilot site for the National system development and roll out of software (GP2DRS) for transfer of demographic and risk factor from GP practices to screening software systems. It is vital that any modelling uses data that can be obtained easily from routine clinical care.

Grading of retinal photographs is not an exact measurement and hence intraobserver and interobserver variability occurs in the grading [47]. Screening and monitoring programmes for chronic conditions generate both "false positive" tests and "false negative" tests. In the retinal screening programme, "false positive" tests correspond to people detected by the retinopathy screening service as requiring referral to hospital, but who are subsequently found not to have retinopathy requiring treatment. "False negative" tests correspond to people with retinopathy who are missed by the screening service. False positive and false negative tests are an inevitable consequence of inexact measurement.

Glasziou et al. (2008) [48] showed that, even when there is no reference standard to determine which positive tests in a database are false positive, the proportion that are false positive can be estimated from a model of the variability of the test; similarly, so can the proportion of negative tests that are false negative. The model has been subsequently applied to blood pressure monitoring [49] and MaDOx have developed it further for monitoring HbA1c (paper under review) and microalbuminuria (HTA project in progress) in diabetes. In general the model needs to allow for variation between people, for average rate of change and variation in rate of change between people, and for the error rate in any individual test: we have recently published full details of the methodology [36]. These previous papers used a normal distribution model for the error structure, but we have conducted pilot methodological work showing that a logistic error structure can also be used successfully to model dichotomous outcomes (details available on request).

In addition, the evidence on the cost-effectiveness of different screening frequencies has been shown to be mixed [50]. A recent systematic review on the economic evidence of diabetic retinopathy screening found 3 studies addressing the issue of screening frequency [51], one performed in the US and two in the UK.

Vijan et al. (2000) examined the cost-effectiveness of differing diabetic retinopathy screening intervals for Type 2 diabetes patients in the USA [27]. The authors employed a Markov model using Quality Adjusted Life Years (QALYs) as the main outcome measure, with costs being assessed from a third-party payer perspective. Using the definition of $50,000 per QALY gained as a cost-effective intervention, the authors reported that annual retinal screening for all Type 2 diabetes patients was not warranted on the basis of cost-effectiveness.

A UK study by Brailsford et al. (2007) [52] also found similar results to that of Vijan et al. (2000). The study, which again used decision modelling techniques to assess the cost-effectiveness of screening intervals in diabetes patients (both Types 1 and 2), found that a 30-month screening interval was the most cost-effective option. However, in contrast to these two studies, another UK study by Davies et al. (2002) found that screening diabetic patients less than once a year would not be any more cost-effective than every year [53]. Davies et al. (2002) also based their study on a decision analytic model populated using results obtained from the published literature. A finding common in both UK studies was that screening of Type 1 diabetes patients was more cost-effective than screening Type 2 diabetes patients.

There were, however, important limitations with both of the UK studies. Both studies used sight years saved as their main outcome measure rather than a more generalisable health outcome, such as QALYs, that can be readily compared across interventions and disease areas, aiding the decision process [54]. In addition, the use of QALYs captures the full impact of the disease, in this case sight loss or blindness, on patients' lives. The two studies also failed to include in their models the additional costs to the healthcare service of patients losing sight or going blind. Finally, data in these two studies were derived from a wide range of sources and diabetic populations. As a result, numerous assumptions had to be made as to how best to synthesise the available data.

Relevant work prior to the development of this proposal

Gloucestershire was the Phase 1 Pilot site for the General Practice to Diabetic Retinopathy Screening (GP2DRS) project. This project is the primary phase of the GP2DRS Programme, the objective of which is to automate the transfer of relevant patient information between GP Practices and NHS diabetic retinopathy screening programmes. For the GP2DRS Phase 1 Pilot in Gloucestershire 14,919 patients from 54 GP Practices were identified on 17th April 2009 as within the criteria (C10 coded (Read code: Diabetes) and 12 years or over in age) for diabetic retinopathy screening. Within this group 712 patients were not known to the Gloucestershire DRSS. A detailed investigation was carried out into the reasons why these patients were not known to Gloucestershire DRSS. The project was written up as a project report [38] in 2009.

Over the subsequent 12 months, we sent out patient information leaflets to practices in Gloucestershire and, with a single letter after screening at a practice to ask them to provide a consent code update, we obtained risk factor data by September 2010 on 4220 people with diabetes. Irene Stratton undertook a preliminary analysis [46] of this data to check that it was of sufficient quality for this grant proposal. Irene has also been working over the last 24 months on all the outputs from the Electronic Annual Reporting system for the 91 screening programmes in England in order to try and improve data quality from English screening programmes. A full time administrator has been appointed in January 2011 in Gloucestershire in order to communicate with GP practices to encourage them to update the consent codes during 2011 so that we can achieve our target of 15000 people with both historic risk factor and retinopathy screening data by the end of 2011.

The Coventry and Warwickshire Screening Service sites because they have registered as an early adopter site for the project and they are organising for their screening service to start sending out information about risk factor collection to the people with diabetes who are invited for screening in their programme. This will mean that they will be in a position to start to collect risk factor data in their service in the early roll out phase later in 2011. Although the South London Diabetic Eye Complication Screening Service (DECS) do not intend to be early adopters of GP2DRS and will not have data available through this route, we propose that we request ethics committee approval to follow a similar model that was agreed by the Patient Information Advisory Group (and subsequently the National Information Governance Board) for the National General Practice to Diabetic Retinopathy Screening (GP2DRS) project for this study but use the MiQuest data extraction tool for the risk factor data instead of the GP2DRS extraction tool.

Hence, the progress of the National GP2DRS project has been very important to this research and is summarised below:

In 2008 ENSPDR sought funding from Department of Health to develop a data transfer framework that would allow the electronic exchange of patient data between GP practices and screening programmes. This funding was approved and the GP2DRS ('General Practice to Diabetic Retinopathy Screening') programme was scoped and piloted.

It was anticipated that GP2DRS would address the current lack of provision and bridge the gap until NHS Connecting for Health's General Practice Extraction Service ('GPES') Solution could be adopted. Uncertainty over GPES scope and funding mean that GP2DRS is likely to provide the only feasible strategic solution for the next three years at least.

The aims of GP2DRS are to:
• provide a centrally endorsed and standardised solution to automate the sharing of data between GP practices and diabetic retinopathy screening programmes;
• provide an affordable and streamlined process through which as many programmes as possible can sign-up to receive up-to-date cohort information;
• cover all major GP systems and promote and incentivise improved GP involvement;
• operate effectively for at least a 3 year period; and
• integrate into the NHS Connecting for Health GPES solution when appropriate.

The system will enable the collation of demographic data and (optionally) key clinical risk factors on people aged 12 or over who have a diagnosis of diabetes recorded by their GP. Demographic data will be available to programmes once agreement has been obtained with each General Practice to activate the data extraction service. Clinical data will be transferred on the basis of consent implied by attendance for screening as approved by the National Patient Information Advisory Group and subsequently discussed with the National Information Governance Board.

The GP2DRS programme will be delivered in three phases:

• Phase 1 – automated download of patient information from participating GP systems and collation of this information within a central data repository;

• Phase 2 – interfacing of the central data repository with the Screening Management Software used by each participating screening programme, with associated processes to ensure that programme registers reflect the details held in GP systems; and

• Phase 3 – automatic return of consent data, retinopathy screening attendance records and screening results from the Screening Management Systems to each the relevant GP system (via the central repository).

A. Implementation progress

A pilot of GP2DRS has been operating with EMIS practices in Gloucestershire since 2007. The pilot has been highly successful and has demonstrated the disparity between GP records and the list of patients maintained by the local screening programme [38].

The central data repository has been procured and developed by Quicksilva, the supplier of ENSPDR's Electronic Annual Reporting System (EARS). Contracts for the extraction of data from GP systems have been signed with EMIS, In Practice Systems, iSOFT (formerly Torex) and Microtest. TPP is not formally engaged (contractual arrangements with NHS Connecting for Health do not allow their services to be procured under the same framework as other suppliers) but are working informally with Quicksilva to develop and test the system. In addition, contracts for the reconciliation of GP2DRS data with programme registers have been signed by Digital Healthcare, Orion Imaging and HISL.

• Phase 1: undergoing pilot. From spring 2011, early adopter programmes will be able to access data from the General Practices for which they are responsible from a central database. In particular, the central database will provide demographic updates when a new patient is registered with diabetes, when the contact details of a person with diabetes change, and when a patient should be removed from the screening programme's register. Initially this will be provided in a report format, so patient cohort changes will need to be manually updated within local programme databases.

The schedule below shows anticipated pilot and rollout timescales for the various GP system suppliers.

Microtest: Pilot completed Feb 2011; anticipated roll out to start in March 2011

In Practice Systems: Pilot anticipated completion May 2012; anticipated roll out to start in June 2012

EMIS: Pilot anticipated completion June 2012; anticipated roll out to start in July 2012

iSOFT: Pilot anticipated completion May 2011; anticipated roll out to start in June 2012

TPP: contract not yet signed: We are anticipating a pilot before the end of 2012.

Roll-out will be phased according to the capability of screening programmes to start using GP cohort data.

The early adopter sites for the GP2DRS project are Gloucestershire (also pilot sites for In Practice), Cornwall (also pilot sites for Microtest), Sutton & Merton (also pilot sites for iSOFT Premier), Wigan (also pilot sites for EMIS LV and PCS), Ealing and Hounslow, Hillingdon, Kingston, Bromley, Warwickshire, Nottinghamshire, North Yorkshire & York and Eastern & Coastal Kent.

• Phase 2: contracts signed; to be delivered from autumn 2012. Data can be sent automatically from the central database to local services' databases, with an automated tool to compare the data collated from GPs with the data stored in the local programme register. Queries and discrepancies will be flagged to programme users within their own software system for resolution. Programmes should be aware that the reconciliation between their existing records and the details derived from GP systems – essentially 'cleaning up' current registers – may be time consuming, and this process will be easier if efforts are made in advance to ensure that screening databases are as accurate as possible.

• Phase 3: from 2013 (this date has not yet been finalised), local services will be able to transfer consent records, screening attendance information and screening results to the patient's GP.

The risk factor data that will be collected from transfer of data from GP systems in the GP2DRS data transfer will include Age, Sex, Ethnicity, Duration of diabetes, Diabetes Type, Visual Acuity, Certified Severely Sight Impaired or Blind, Certified Sight Impaired or Partially Sighted, BMI, Systolic Blood Pressure, Diastolic Blood Pressure, HbA1c, Serum Creatinine, Urinary Albumin Level, Serum Cholesterol Level, Smoking Status and event date.

Research methods

The Health Technology being assessed is a variable screening interval based on risk of diabetic retinopathy (DR) assessed using two field digital photographs after pupil dilation as used in the English National Screening Programme (ENSPDR) and other clinical data available to the ENSPDR.

The target population (PR) is people with diabetes in England aged twelve years or above.
The setting of the study is anonymised data from patients screened as part of the ENSPDR in the Gloucestershire, Warwickshire and South London screening services.

The team has detailed knowledge of this area derived from an on-going literature search conducted by Dr Scanlon's team, which is described in the annual evidence update [55] that Dr Scanlon provides for NHS evidence.

The study design is primary research using routinely collected clinical data to model the clinical and cost-effectiveness of different screening intervals, informed by the development of an algorithm to identify those patients in whom eye screening may be safely extended.

Sample size - Phase 1: The GDRSS dataset will contain 15,000 patients by May2012 with up to 8 years of graded photographs. We expect 750 patients per annum with events in the training data (~10% of 7,500). We nominally require 20 events per fitted covariate. Phase 2: GDRSS data and the outcome data (e.g. laser treatments) on those referred to hospital on the electronic record. Phase 3 will include 2000 Asians and 5000 Caucasians from Coventry and 700 patients of Afro-Caribbean origin within a 2000 patient dataset from South London.

Data extraction - the data sets will be extracted from screening service software and from GP computer systems. The ENSPDR has procured a central database as part of the GP2DRS project from which the risk factor data items can be extracted by screening services and linked to the grading results from diabetic retinopathy screening. All data for this research will be anonymised. The full list of risk factor data specified in the GP2DRS data transfer is listed above in the section entitled '*Relevant work prior to the development of this proposal'*. For the health economic evaluation we will collect economic data from a number of sources including targeted literature reviews, work conducted as part of Phase 2 of this project, and data from different screening services providing differing screening models (i.e. mobile screening units, fixed location screening using optometrists and fixed location screening using technicians)

Data analysis - there are 4 project phases:
Phase 1: GDRSS risk factor approach - We will use a data-splitting approach, non-randomly selecting 50% of patients to derive the model ('training data') and 50% to validate the model ('validation data'). Multivariate modelling on the training data will develop a risk score for retinopathy/maculopathy with an outcome of referable R2 pre-proliferative DR, R3 proliferative DR or M1 diabetic maculopathy.
Exposures: a) biometric and biochemical measurements and grading results from previous retinal screening episodes.
Analysis: Cox survival model treating missed visits as interval-censoring with stepwise selection of covariates. From phase 1 a risk score threshold below which patients can safely be screened less often will be developed.
Phase 2: Monitoring interval approach – existing Oxford statistical methods [36] will be extended to categorical data by replacing the 'normal distribution' model for error with a categorical misclassification approach. This will allow classification error in retinopathy grades. An evidence-base for the existing annual monitoring interval or a recommended alternative will be developed.
Phase 3: The best available relative risk estimate from existing literature for an ethnicity effect on progression of DR will be used to modify the risk score and algorithm developed above. Both versions of the risk score and algorithm will then be tested against retinopathy grades in the two datasets with higher ethnic minority populations.

Phase 4: This phase will extend the work from phase 2 by assessing the health outcomes and costs associated with each of the screening intervals identified in phase 2. For this, a Markov model [37] simulating screening annually or at individualized intervals will assess the impact of screening frequency on healthcare costs and health-related quality of life (QoL). A cost-effectiveness and cost-utility analysis will be conducted, in which the outcome measures will be years of sight saved and Quality-Adjusted Life Years (QALYs) gained. Data to populate the model (treatment effectiveness, screening uptake rates, life expectancy etc…) will be obtained from the GDRSS dataset with QoL data from recent studies assessing QoL in DR patients with different visual acuity levels. Costs of screening will be assessed from 3 English programmes using different screening modalities (i.e. mobile screening units, fixed location screening using optometrists and fixed location screening using technicians).

Health Economic Model
We propose constructing a decision analytic model for the simulation of diabetic retinopathy screening annually or every other year for Type 1 and Type 2 diabetes patients assessing the impact of screening on healthcare costs and health-related quality of life. For this purpose a decision analytic Markov model will be used, using a National Health Service (NHS) and social services perspective. We also plan to conduct a cost-effectiveness and cost-utility analysis, in which the main outcome measures will be years of sight saved and Quality-Adjusted Life Years (QALYs) gained.

Model input parameters
In order to inform the development of the model, a systematic review of existing natural history and decision analytic models of diabetic retinopathy screening will be conducted using the Cochrane and NHS EED databases, MEDLINE and EMBASE. Other important model input parameters will include:

- Screening uptake rates. This information will be obtained from data available from the Gloucestershire Diabetic Retinopathy Screening Service (GDRSS);
- Characteristics of the retinopathy screening test, such as sensitivity and specificity. Again, this information will be obtained from the GDRSS and further analyses of this dataset as part of the application;
- Effectiveness of retinopathy treatment, which will be obtained from analysis of the GDRSS dataset and estimates from the literature, identified through targeted reviews of the Cochrane database, MEDLINE and EMBASE;
- Costs of diabetic retinopathy screening. There are currently 91 screening programmes in England, each with different models of care [44]. As a result, local programmes can use either mobile services or fixed locations (high street optometrist, health centre or hospital), and employ either technicians or optometrists. As model of care will have an impact on the costs of screening, the costs of screening using 3 different models of care (mobile screening units, fixed location screening using optometrists and fixed location screening using technicians) from 3 screening programmes will be assessed. Costs assessed will include: administration; staff time; equipment; IT connections to upload, download and grade images; grading of images; and referrals to ophthalmology hospital services. These costs will be assessed from the 3 programmes using a structured questionnaire.
- Health-related quality of life (QoL). We plan to obtain this information from the literature, in particular using the results from the study by Clarke et al. (2006) [56] that ascertained quality of life and utility values associated with visual acuity in type 2 diabetes. .
- Health and social care costs associated with care of diabetic retinopathy and diabetes. Cost information will be identified through targeted reviews of the Cochrane database, MEDLINE and EMBASE. In addition, for Type 2 diabetes patients we will obtain long-term costs of diabetes, based on patients' risk factors, by applying individual patient risk factor data available from the GDRSS into the UK Prospective Diabetes Study (UKPDS) model[41];
- Life expectancy. As the model will evaluate costs and outcomes over the lifetime of the patient, long-term estimates of survival will be required. Due to the wealth of data and long-term follow-up of patients in the GDRSS dataset, survival information will be obtained from this dataset.

As costs and outcomes will be generated over the lifetime of the patient, future costs and outcomes will be discounted using an annual rate of 3.5% as recommended by NICE [54].

Planned inclusion/exclusion criteria
The inclusion criteria is all people with diabetes in England aged twelve years or above who have been screened by the English National Diabetic Retinopathy Screening Programme
The exclusion criteria are the same as the exclusion criteria set by the English National Screening Programme for Diabetic Retinopathy [57], which includes those people with the following conditions:

1. No perception of light in each eye
2. Terminal illness
3. A small number with physical disabilities making photographic screening impossible
4. A small number with learning or mental disability
5. Patients who are currently under the care of an ophthalmologist and a report on retinal status has been provided to the screening service.
6. A person who has chosen to opt out of screening

Approval by ethics committees

It has been agreed that risk factor data should be collected in the Department of Health sponsored General Practice to Diabetic Retinopathy Screening (GP2DRS) project by screening services in the English National Screening Programme and a National consent model has been agreed by the National Patient Information Advisory Group and subsequently by the National Information Governance Board. However, although the data will be anonymised for the purposes of this research, the patients have not given specific permission for use of their anonymised data in this way and research ethics committee approval will therefore be required.
The Gloucestershire and the Coventry and Warwickshire Screening Service sites have registered as early adopter sites for the project. Gloucestershire have been sending out information to the patients about the transfer of risk factor data since the pilot project in 2009 which has resulted in their service having over 23,000 patients eligible for the transfer of risk factor data, with screening results available on the screening database. The Coventry and Warwickshire Screening Service are currently organising for their screening service to start sending out information about risk factor collection to the people with diabetes who are invited for screening in their programme. This will mean that they will be in a position to start to collect risk factor data in their service in the early roll out phase later in 2011. They currently screen 30,000 patients in their screening service every year but will need GP practices to provide a consent code update once individual patients are eligible for this transfer.

The South London Diabetic Eye Complication Screening Service (DECS) are reconsidering whether they will be early adopters of GP2DRS. We plan to use this approach for data extraction to obtain the required data on a minimum of 2000 patients, of which 700 patients will be of African Caribbean origin

For Primary Research only - give further details under the following subheadings a as appropriate:

Risks and anticipated benefits for trial participants and society, including how benefits justify risks.

The National Screening Programme for Diabetic Retinopathy ("NSC DR") approached the Patient Information Advisory Group (PIAG) for advice as to whether or not it was necessary to make a full application for s.60 support. A decision was taken in December 2004 by PIAG and has been minuted as follows:
"**Diabetic Retinopathy Screening**
PIAG considered a request from the national retinopathy screening programme for clarification about whether Section 60 support was required for the programme as information would need to be shared across several PCTs, hospital clinics and general practices. There had been reluctance on the part of some data controllers to release patient information to the screening programme because of confusion about this. The Advisory Group agreed that call and recall for retinopathy screening was part of the care pathway. As such, consent to sharing relevant data could be implied from information about how patient information is used by the retinopathy screening programme, being provided to patients, and by making it clear patients had the right to opt out. There was therefore no requirement to apply for Section 60 support."
The Patient Information Advisory Group (PIAG) were also asked for their views on a consent model for the transfer of risk factor data within the GP2DRS project, a National project of electronic transfer of demographic and risk factor data between General Practices and Screening Services in England.
PIAG agreed that if patients had the following letter sent to them prior to screening attendance, there would be implied consent if they turned up for screening for risk factor data transfer, assuming that they did not inform the programme staff or GP staff that they did not want this data to be transferred. No transfer would be considered if a patient did not attend for screening.
The data used in this study will not identify individual patients. It will be pseudo-anonymised so that grading data can be matched with risk factor data and then the analysis will be anonymised to analytical staff.

What sort of information about me is held by the NHS DR Screening programme?

The only information that the programme will have about you at the beginning will be your name, date of birth, contact details, NHS number, details of your GP, information to help establish your preferred language and contact method and whether you might need large print documents and the fact that you have been diagnosed as having Type 1 or Type 2 diabetes.

Once you agree to have your eyes screened then it will be necessary to be able to check on the results on any previous screening event. It might be that the programme would like to have further information about your medical history relating to your diabetes (such as your blood sugar levels, blood pressure, foot checks, smoking history etc, but not sensitive information such as erectile dysfunction) so that those who are assessing you have a more complete picture about what is happening. When you confirm or attend your screening appointment it will be taken that you are consenting for that sort of data to be given to those involved in screening and assessment both in the programme and in the acute trust. However if you do not wish this further information to pass to the programme then you should let the programme staff or your GP know. This will not prevent your eyes being screened but would mean that staff are less able to assess your case as carefully. You can change your mind about this at any time.

Who will see information about me?

Those involved in the **administration** of the programme (normally based in a Primary Care Trust or a hospital): the details can be found on the letter accompanying this document.

Those who are carrying out the **screening process** (including putting in the eye drops, checking vision, taking your history, taking photographs of your eyes and grading the photographs). These are either staff employed by the PCT, acute trust or other NHS body OR are optometrists, self-employed ophthalmologists or staff employed by independent companies. The programme will provide you with a list of non-NHS personnel and companies if you are concerned in any way about who will see information about you and you should let the programme staff know if you have any particular concerns about any particular individual or company.

If your case is referred to the **hospital** for further assessment the information about you will be forwarded to the hospital so that those who will be looking after your case can have as much information about your history as possible.

In order to make sure that the programme is operating effectively from time to time its work is assessed by **clinical auditors** and others involved in **quality assurance**. They may need to have access to your data. In addition efforts will be made nationally to carry out research using fully anonymised data to try and identify as precisely as possible how best diabetes should be managed in the long term (some examples may be how many people have diabetic retinopathy in any area or how quickly it progresses in different groups of people). Any efforts to use any identifiable information would result in us working with the Patient Information Advisory Group to make sure that all necessary agreements are obtained.

Occasionally problems may occur in the software which is necessary to support the programme. Normally the software supplier will not need to see any information that is identified to a specific individual, but occasionally it may become necessary to supply basic information to ensure that the correct information is maintained by the programme securely. Software suppliers who work with the NHS are bound by requirements of confidentiality and should be supervised by NHS staff if they need to look at information that is linked to a named individual.

Your results and screening information will be sent to your GP.

Proposed time period for retention of relevant trial documentation.

The National Diabetic Retinopathy Screening Programme recommends that all images and data relating to those images should be kept for a minimum of 8 years and until the age of 25 years (for children) even after grading, so that reference can be made to this original image in the future if required. The original data will remain with the screening service because it is needed for clinical purposes.
The data from this study is pseudo-anonymised and will be kept for 8 years. It is likely that if any data is required after that time, a new extraction would be required.

Proposed sample size

Sample size - Phase 1: The GDRSS dataset will contain 15,000 patients by 1st May 2012 with up to 8 years of graded photographs. We expect 750 patients per annum with events in the training data (~10% of 7,500). We nominally require 20 events per fitted covariate. Phase 2: GDRSS data and the outcome data (e.g. laser treatments) on those referred to hospital on the electronic record. Phase 3 will include 2000 Asians and 5000 Caucasians from Coventry and 700 patients of Afro-Caribbean origin within a 2000 patient dataset from South London. Phase 4: the health economic modelling work will use information from the above datasets, in addition to other published studies, and cost information from three screening service providers.

Statistical analysis

Phase 1: Risk factor approach

1a. Rationale

Rates of incidence and progression of retinopathy are greater in people with longer duration of diabetes and in those with poor glycaemic control (higher HbA1c) and may also vary with other factors such as blood pressure and type of diabetes. It is possible to identify those at higher absolute risk of sight-threatening DR and this suggests it may be possible to identify subgroups of those with diabetes in whom the screening interval can be extended without risk of sight-threatening diabetic retinopathy developing before the next screening visit.

1b. Dataset

The Gloucestershire Diabetic Retinopathy Screening Service (GDRSS) includes 27,000 people with diabetes aged over 12 who are eligible for annual screening. Our database includes

- Longitudinal data on annual photographs from 1998 to the present
    - Digital photographs on two fields, with mydriasis (eyes dilated) to maximise image quality
    - Consistent grading team
    - Quality control including repeat grading and external quality assurance
- Risk factor data through separately funded "GP2DRS" project
    - Risk factor data was available from GP electronic records (EMIS) on 4,400 screened patients by September 2010. Further risk factor data transfer on the remaining 9,800 patients has continued since then when individual patient consent codes have been updated in General Practice.
    - Data capture from In Practice Systems (supplies approximately 33 Gloucestershire practices) practices scheduled to begin April 2011
    - By the end of April 2012, we estimate that we will have screening and risk factor data available on over 15,000 patients

Since this dataset is much larger than needed for this project, we will use a data-splitting approach, non-randomly selecting 50% of patients for the model derivation dataset ('training data') and reserving the other 50% for model validation purposes ('validation data').

1c. Methods

Phase one: multivariate modelling with the following parameters

- Outcome: either of
    - diabetic retinopathy (grade 2, referable, or grade 3, sight-threatening)
    - diabetic maculopathy
- Exposures:

  - age, sex, smoking, BMI,
  - previous retinal photographs
  - duration of diagnosed diabetes, type of diabetes
  - HbA1c, blood pressure, urine albumin, lipid measurements
- Analysis:
  - Cox survival model treating occasional missed visits as interval-censoring
  - Stepwise selection

will be used to develop a risk score for retinopathy/maculopathy at subsequent visits.

Phase two: seek a threshold on the risk score below which patients can safely be screened less often. This will be set on the training data and evaluated in the validation data, stratifying outcomes by severity (referable retinopathy, sight-threatening retinopathy, maculopathy). See also phase 3 below.

This project will be carried out by IMS and colleagues in Gloucestershire.

1d. Expected outcome
A candidate algorithm for use in recalling patients for screening; after project 3 (below) the candidate algorithm will become a validated algorithm for use nationally.

Phase 2: Monitoring interval approach

2a. Rationale

The reasons for the current annual monitoring interval are unclear and may be more historical than evidence-based. In recent years a statistical methodology has been developed for studying the time intervals in monitoring and screening programmes, and their consequences for patients and service providers. In this phase we will extend that methodology to diabetic retinopathy screening to confirm (or otherwise) the appropriateness of annual screening as the default for retinal photography.

2b. Dataset
GDRSS data. The following features, in addition to those described above, are relevant here:

- Second grading, with adjudication, on all images showing disease and a ≥10% subset of other images
- Sub-study of patients referred to hospital, with adjudication on discrepancies between screening service and hospital assessment

2c. Methods
The existing statistical methods were developed by members of our team and collaborators [36, 48]. We will extend them to categorical data, as generated by retinopathy screening, by replacing the 'normal distribution' model for continuous error with a categorical misclassification approach. This phase advances on phase 1 by allowing classification error in retinopathy grades. The risk score of phase 1 will be considered as a potential explanatory variable.

Retinal screening gives a composite categorical measure (retinopathy grade and presence or absence of maculopathy). We will convert this into a dichotomous measure (eye disease requiring referral, defined by retinopathy grade 2 or higher or maculopathy grade 1) and apply the modelling methods referred to above with a logistic error structure. We will calibrate the rates of false positive tests estimated by the model against the rates of observed false positive tests in our data, defined by patients referred to hospital for further assessment but not found to require treatment. Rates of false negative tests will be available from simulation modelling only.

We will estimate rates of true and false positive and negative tests under the following scenarios:
- Annual testing (base case)
- Other fixed intervals including 6 monthly, biennial and others as indicated by early results
- Screening intervals stratified by the risk score (developed in phase 1)

The impact of varying levels of non-attendance will be considered based on estimated attendance rates from our data and, in sensitivity analyses, from the literature. Simulations will be cross-checked against other calculation methods, and further checked against the observed data to verify internal validity of the model.
This work will be carried out by RJS and colleagues in Oxford, with expert input from IMS, PHS and PG.

2d. Expected outcome

An evidence-base for the existing annual monitoring interval *or* a recommended alternative to annual monitoring as the default.

Phase 3: Extension to an ethnically diverse population

3a. Rationale
It is good practice to verify statistical modelling results in external data, especially since the Gloucestershire data is atypically high quality and collected on an ethnically homogenous population. In this phase we will verify the results of phases 1 and 2 in an external dataset of greater diversity.

3b. Data

- Data from the Coventry and Warwickshire Screening Service including risk factors and retinal photographs from 2000 UK Asians and 5000 comparators (non-Asian)
- Data from the South London (DECS) Screening Service including risk factors and retinal photographs from 700 people of African Caribbean origin and 1300 comparators (non African)

We will review the existing literature for evidence of an ethnicity effect on progression of diabetic microvascular disease and use the best available relative risk estimate to modify the risk score developed in phase 1 and the algorithm developed in phase 2. We will then test unmodified and modified versions of the risk score and algorithm against retinopathy grades in the two datasets.

3c. Expected outcome

A validated algorithm for recalling patients of white, Asian ethnicity or African Caribbean ethnicity for retinopathy screening, for use by the National Diabetic Retinopathy Screening Programme and the 91 individual screening programmes across England.

3e. Potential limitations
Gloucestershire data is not typical in that its graders are arguably the most consistent (source: EQA test-set data), but this limitation is mitigated by the forthcoming national roll-out of (a) City and Guilds training scheme and (b) Training and Test Set programme to other services, as well as by the provision of independent data in phase 3.

Gloucestershire has a low ethnic minority population The main ethnic minority groups in Gloucestershire are Indian/British Indian (0.7%), and black/black British (0.8%) although the percentage of people from an ethnic minority group in the population with diabetes in Gloucestershire is nearer 5% because of the higher prevalence of diabetes in these groups. However, the data from Coventry and Warwickshire and South London will use confirmed data sources that include a higher ethnic minority population from UK Asian and African Caribbean groups.

Phase 4. Health Economic Analysis
Uncertainty in each model input parameter will be propagated through the model and quantified in the resulting costs and effects. This probabilistic sensitivity analysis allows for a comprehensive and consistent way of representing uncertainty for making decisions and guiding future research [58]. Cost and effect results will be reported as means with standard errors and differences with 95% credible intervals. Incremental cost-effectiveness (i.e. additional cost per year of sight saved) and incremental cost-utility (i.e. additional cost per QALY gained) will be calculated by dividing the difference in costs by the difference in effects. Using results from the probabilistic sensitivity analysis, the value of information approach will be used to identify key model inputs for which there would be gain from reducing uncertainty by collecting more data in a subsequent study. This information will then be useful in the future to help inform the design of future clinical trials in the area.

As previous studies evaluating diabetic retinopathy screening have found differing cost-effectiveness results when screening different groups of diabetic patients [52, 53], i.e. Type 1 vs. Type 2 diabetes, three different scenarios will be tested:

1) Assigning Type 1 diabetic patients to differing diabetic retinopathy screening intervals using risk estimation;
2) Assigning Type 2 diabetic patients differing diabetic retinopathy screening intervals using risk estimation; and
3) Assigning all diabetic patients to differing diabetic retinopathy screening intervals using risk estimation.

In addition, we will undertake a series of one-way sensitivity analyses by varying key parameters in the model over plausible ranges. For example, screening uptake rates will be varied to assess whether these have any impact on cost-effectiveness and on the model's results.

Proposed outcome measures

A risk-based algorithm for screening interval; cost-effectiveness; adverse events.
Other outcomes: Key recommendations for further research.

Research Governance

The Nominated Sponsor of this research application is Gloucestershire Hospitals NHS Foundation Trust.

A Project Advisory Group will be formed to oversee the progress of the research, which will meet every 2 months and will include an independent Chair, the lead researcher, the co-applicants, two lay representatives, and the R&D Lead for the host trust GHNHSFT.

The lead researcher will prepare the first draft of the ethics committee application which will then receive input from other members of the research team.

A full time project manager will be appointed to handle the day-to-day management of this project. Their responsibilities will be:

• Organising and co-ordinating meetings of the project advisory group
• Making sure that the views of the patient representatives and lay groups are taken into account throughout the duration of the project.
• Identifying and reporting any potential problems arising in the project to the chair and to the project advisory group
• Establishing good operating practice for financial management and co-ordinating financial audits to comply with necessary local and national regulations
• Establishing and operating a robust knowledge management system to ensure rapid and effective online document handling and version control as well as data protection in accordance with legislation

The project manager will have support provided from a data manager contractor who has experience of the different screening software used by screening services in England to assist with data management. This contractor has also assisted Gloucestershire with data management in both the first and current pilot GP2DRS project in Gloucestershire.

The full time project manager will also be responsible for:

• liaising with the three screening services, and
• for organising regular meetings between the data manager contractor and the Coventry and Warwickshire and the South London Screening services to make sure that any technical difficulties are overcome.

4. Project timetable and milestones:

Work pre-project commencement:

August 2011 - hear the outcome
1st January 2012 - recruiting a project manager/project support by 1st May 2012
1st January 2012 - data extraction will have been completed in Gloucestershire
1st January 2012 – clarify that ethics committee approval is not required for use of the psudo-anonymised data in Gloucestershire, Coventry and Warwickshire and South London data.

Project commencement 1st May 2012

1st May 2012 - Analysis phase 1 - the Gloucestershire risk factor approach analysis will commence for a period of 6 months.
1st May 2012 – 1st October – risk factor data extraction will be collected in Coventry and Warwickshire
1st May 2012 – 1st October – risk factor data extraction will be collected in South London
1st July 2012 - Analysis phase 4 - the Health Economic modelling commences for a period of 18 months.
1st October 2012 - Analysis phase 2 - the Oxford Monitoring interval approach commences for a period of 6 months.
1st May 2013 - Analysis phase 3 - Extension to an ethnically diverse population will commence for a period of 4 months.
1st January 2014 - the final phase of the project, completing the project reports and dissemination commences for 4 months.
1st May 2014 - Project finishing date.
Duration - 24 months

5. Expertise:

Peter Scanlon submitted an R & D Project Grant report (R/21/01.98/Scanlon/R) in 2001 which provided an evidence base for the methods used in the UK National DR Screening Programmes. In 2003 he was appointed as Programme Director for the English National Screening Programme for Diabetic Retinopathy (ENSPDR) with 91 screening programmes across England offering screening to over two million people with diabetes. He has 14 related publications.
Irene Stratton is a senior medical statistician and was the manuscript reviewer for all United Kingdom Prospective Diabetes Study papers published between 1988 and 2008. She is a co-author of over 100 papers.
Andrew Farmer is one of the lead investigators on the NIHR grant that created the Oxford Centre for Monitoring and Diagnosis (MaDOx). The success of this programme has led to a number of spin-off grants including HTA funding for research into monitoring of albumin-creatinine ratio for early detection of diabetic nephropathy in T1D and T2D, and NHS Diabetes funding for research into the best monitoring and treatment strategies for glycaemic control in T2D.
Richard Stevens is a senior statistician working in the Department of Primary Health Care as part of MaDOx since 2008. His research interests include clinical prediction rules, arising from his work on the UK Prospective Diabetes Study Risk Engine for calculating cardiovascular risk in people with diabetes. He project manages the HTA project 08/67/03 on monitoring kidney disease in diabetes and an NHS-funded project on monitoring glycaemic control with HbA1c, as well as co-leading the methodological research on monitoring chronic diseases
Jose Leal has been involved in the development of several cost-effectiveness decision analytic models across a wide range of disease areas, particularly in screening decision models, working in projects evaluating the cost-effectiveness indifferent disease areas. He also has considerable experience working with the UKPDS Outcomes model, which is a computer simulation model particularly suited to facilitate economic evaluations.
Ramon Luengo-Fernandez has been involved in the analysis of costs and outcomes (life-expectancy, quality of life and disability) using patient level data from a large population-based cohort study (the Oxford Vascular Study). His work has been funded over the last 5 years from fellowships from the NIHR and MRC.
Paul O'Hare is a consultant diabetologist and lead investigator for the United Kingdom Asian Diabetes Study.
Sobha Sivaprasad is a consultant ophthalmologist and investigator for the DECS Programme in South East London.

6. Service users/public involvement

A lay member of the Diabetes Research Network (DRN), 'Screening for Diabetic Retinopathy' Mike Whatmore was involved in the original discussions on both reasons for non-attendance in diabetic retinopathy screening and in discussions over screening intervals for diabetic retinopathy. Mike Whatmore has Type 2 diabetes and is a co-applicant on the Research for Patient Benefit (RfPB) grant 'Understanding factors leading to low uptake of diabetic retinopathy screening in Primary Care' which is a qualitative study that addresses questions about the facilitators and disablers to screening uptake as experienced by people with diabetes and the effect of extending the screening interval. Another Gloucestershire Lay Member, Mike Larkin, has read and commented on this application. Mike Larkin has had Type 1 diabetes since 1977 and has had retinopathy since 1988. He is currently a member of a professional/lay group within Diabetes UK that is the main group in setting research strategy for the Charity for the next 5 years. Mike Whatmore and Mike Larkin have influenced the design of this

research application and feedback has also been obtained from the Thames Valley Diabetes Local Research Network Patient and Lay Involvement Group during the development of the application.

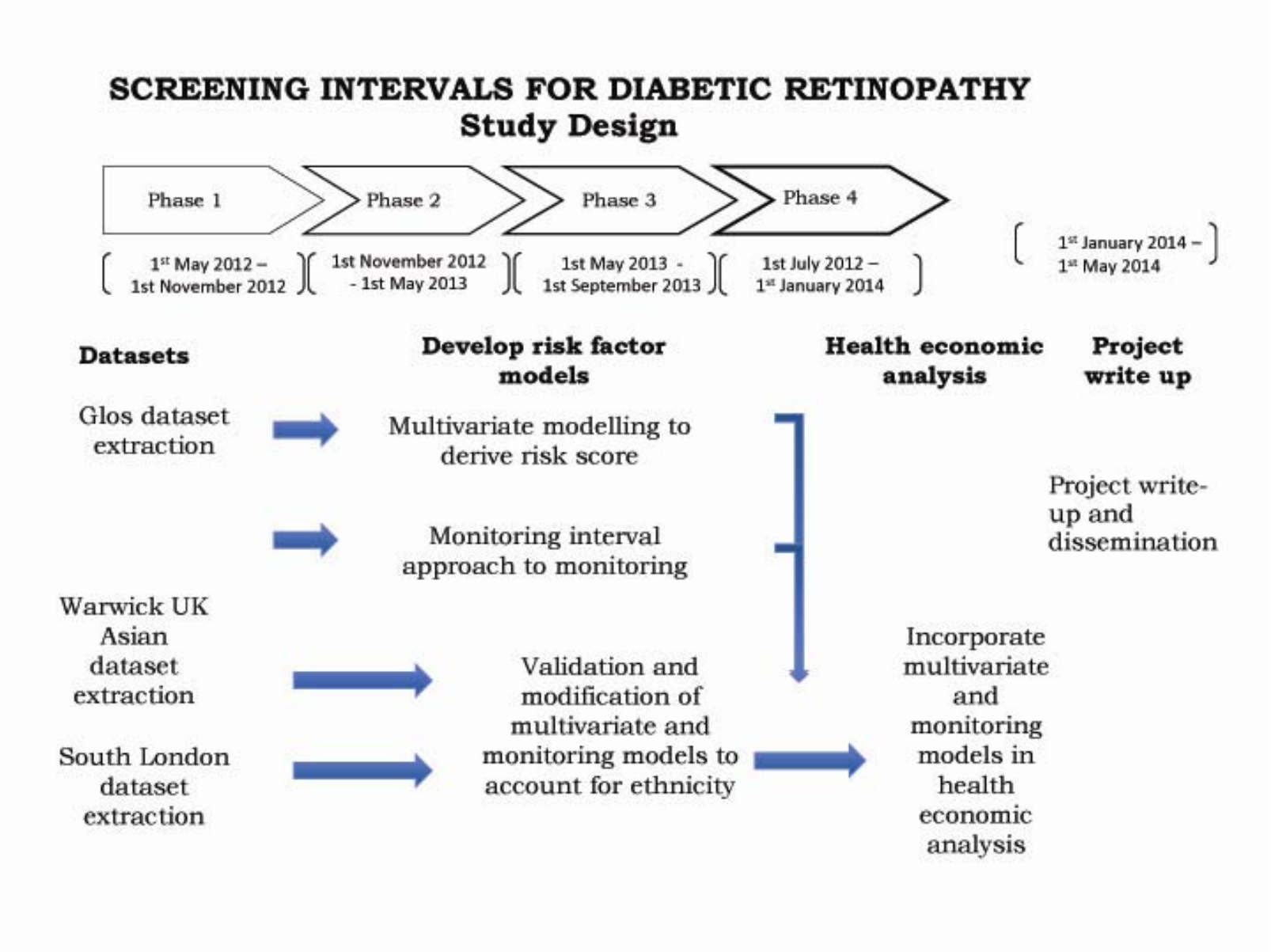
Mike Whatmore will be on the steering group overseeing the project and Mike Larkin one other Gloucestershire lay member, have offered to meet regularly with the Lead researcher to discuss the project at the different stages. The Thames Valley Diabetes Local Research Network Patient and Lay Involvement Group members will also be involved in early feedback of any analyses so that their views are taken into account in all phases of the project.

The Research for Patient Benefit study entitled 'Understanding factors leading to low uptake of diabetic retinopathy screening in primary care' was developed with the collaboration of members of the Warwick Diabetes Research & Education User Group (WDREUG), who have reviewed the research questions, the interview schedule questions and the sampling processes. The interview schedule does include asking people with diabetes how they would feel about differing screening intervals. The WDREUG group consists of approximately 10 people with diabetes have been meeting bi-monthly since 2001 to consult with the diabetes research team on the development, execution, analysis and dissemination of the research projects and they have been acknowledged in 8 previous publications and contribute to INVOLVE activities. A further 10 members are involved via email. This group will be consulted during the current HTA study so that their views are taken into account in all phases of the project.

Lay members will also be contributing to the study report and with the dissemination of results both formally and in their multiple contacts with health professionals, Diabetes UK members and newsletters.

The reason for involving the lay members in the research is to make sure that any recommendations made are acceptable to a patient group who have to live with the condition. It may, for example, present practical problems for patients and their medical advisers if longer intervals are recommended which lead to difficulties in maintaining follow up. It might lead to worse control of the diabetes if an individual is informed that they are in a 'lower risk group' and all of these practical difficulties need to be considered.

The contributions from these lay groups will be coordinated by the project manager.


SCREENING INTERVALS FOR DIABETIC RETINOPATHY
Study Design
Phase 1
Phase 2
Phase 3
Phase 4
1st May 2012 – 1st November 2012
1st November 2012 - 1st May 2013
1st May 2013 - 1st September 2013
1st July 2012 – 1st January 2014
1st January 2014 – 1st May 2014
Datasets
Develop risk factor models
Health economic analysis
Project write up
Glos dataset extraction
Multivariate modelling to derive risk score
Monitoring interval approach to monitoring
Project write-up and dissemination
Warwick UK Asian dataset extraction
South London dataset extraction
Validation and modification of multivariate and monitoring models to account for ethnicity
Incorporate multivariate and monitoring models in health economic analysis

Key:

Timeline

Work commencing pre-project start date

PS: Peter Scanlon
IS: Irene Stratton
POH: Paul O'Hare
SS: Sobha Sivraprasad
AF: Andrew Farmer
RS: Richard Stevens
RLF: Ramon Luengo-Fernandez
JS: Jose Leal

ACTION	OWNER	PRE-START				YEAR 1												YEAR 2											
-	-	Mnth -4	Mnth -3	Mnth -2	Mnth -1	Mnth 1	Mnth 2	Mnth 3	Mnth 4	Mnth 5	Mnth 6	Mnth 7	Mnth 8	Mnth 9	Mnth 10	Mnth 11	Mnth 12	Mnth 13	Mnth 14	Mnth 15	Mnth 16	Mnth 17	Mnth 18	Mnth 19	Mnth 20	Mnth 21	Mnth 22	Mnth 23	Mnth 24
-	-	Jan-12	Feb-12	Mar-12	Apr-12	May-12	Jun-12	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14
Screening and risk factor data collection in Gloucestershire	PS																												
Appoint project manager / support	PS																												
R&D approval for Glos and Warwickshire data collection	PS / POH																												
R & D Approval for South London data collection	SS																												
Gloucestershire risk factor approach analysis	IS																												
Data collection in Warwickshire	POH																												
Oxford Health Economic Analysis	RLF / JS																												
Data collection in South London	SS																												
Oxford monitoring interval statistical approach	AF/RS																												
Extension of analysis to ethnically diverse populations	RS																												
Complete project reports and dissemination	PS																												

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