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Title of the project

What Works to **I**ncrease Attendance for **D**iab**e**tic **R**etinopathy Screening? An **E**vidence s**Y**nth**E**si**S**

Short title: WIDeR-EyeS

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1. BACKGROUND AND RATIONALE

1.1. UK diabetic retinopathy screening programme

The total number of people with diabetes is rising. The disease currently affects 4.5% of the UK population (approximately 3 million individuals); with type 2 diabetes being responsible for 90-95% of cases. [1] Diabetic retinopathy is the most common microvascular complication of diabetes and is one of the leading causes of legal blindness in people of working age in the UK and throughout the world.[2,3] Although effective treatments, such as pan-retinal photocoagulation and anti-vascular endothelial growth factor therapy (anti-VEGF), are available that can substantially reduce the likelihood of sight threatening complications,[4] the success of these treatments is dependent on early detection and timely referral. Systematic screening of the diabetic population with the aim of providing early diagnosis and enabling access to sight-saving treatment has been shown to be both clinically effective[5] and cost effective[6]. The UK was the first in the world to introduce a national population-based retinopathy screening scheme, based on annual digital fundus photography. This was initially introduced in England in 2003 as part of the National Service Framework for Diabetes[7] and by 2008 the scheme had become established throughout the UK. Retinal screening is overseen by the NHS Diabetic Eye Screening Programme (NDESP), which offers screening to all patients with diabetes over the age of 12 years from more than 80 local programmes. Screening services in Scotland, Wales and Northern Ireland are very similar but with slightly different operational procedures. If sight-threatening retinopathy is identified through the screening service, then referral to a specialist eye unit is arranged within a specified time frame for further assessment and treatment. An early indicator of the success of the NDESP, combined with incentives to primary care practitioners to improve the quality of diabetes care,[8] comes from a recent longitudinal analysis of the national database of blindness Certificates of Vision Impairment (CVIs)[3]. A comparison of blindness certifications attributable to diabetic retinopathy in England and Wales in working age adults (16-64 years) for two time periods a decade apart, showed a fall from 17.7% in 1999 to 2000 to 14% in 2009-2010.

1.2. Problem being addressed

1.2.1. Variation in attendance for diabetic retinopathy screening

People with diabetes are 25 times more likely than the general population to become blind, arising from the complications of diabetic retinopathy. It has been estimated that in England, eye screening potentially saves more than 400 people per year from significant sight loss.[9] Given the value of screening for reducing the risk of sight loss amongst people with diabetes, it is essential that screening programmes provide consistent and equitable access for the target population. Furthermore, an appropriate infrastructure needs to be in place to manage those testing positive with timely access to treatment for those who need it. To maximize screening coverage the diabetic population who would benefit from screening needs to be identified and receive annual retinopathy screening as part of their normal diabetic care. However attrition can occur at various points along the screening pathway (Figure 1). Following the initial screening appointment, systems need to be in place to ensure ongoing attendance and pathways need to be established to deal with those screening positive.

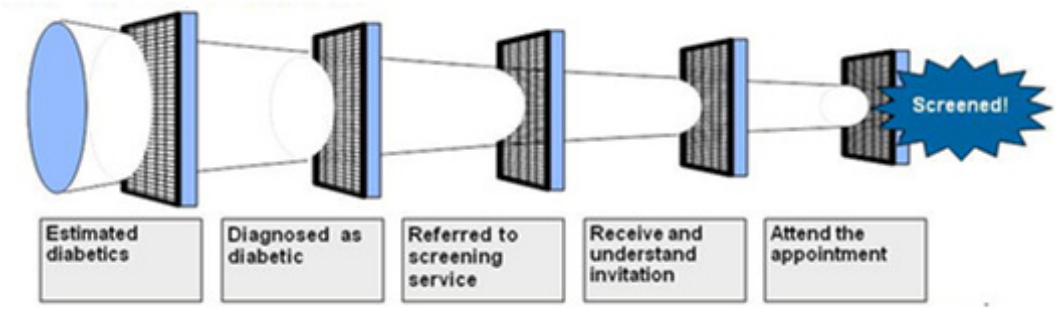

Figure 1. Patient pathway to screening

In the UK, there is an estimated 850,000 people with undiagnosed type 2 diabetes.[10] However, once the disease is diagnosed, not all eligible patients are referred into the eye screening service. Further barriers occur within the screening service itself; patients have to receive and understand the invitation to participate and then need to attend for their appointment. As an illustration of the scale of the problem, during the period April 2011 to March 2012, over 2.5 million eligible diabetics were identified from GP registers in England of which only 72.3% were screened.[11] Although a small proportion of the unscreened population are either excluded or suspended from the screening service, at least a third of those offered screening fail to attend. Wide geographical variation in screening uptake has been reported. Based on the most recently available data from former Primary Care Trusts (PCTs) in England (January to March 2013) (Figure 2) uptake varied from 66 to 95% of those referred into the screening service.[12]

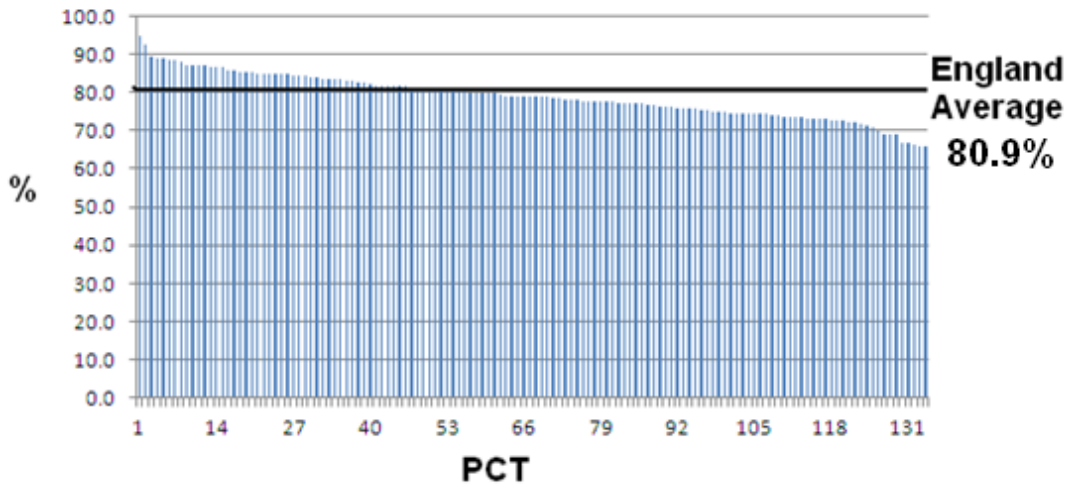

Figure 2. Percentage of the invited diabetic population receiving screening for diabetic retinopathy by PCT (January to March 2013)

In addition to the obvious impact on eye health, the high rates of non-attendance have major financial consequences. For example, from April 2012-April 2013, the Tower Hamlets Screening Programme invited 13,894 people to participate in retinal screening. Of those invited, 4,833 (34.7%) failed to attend for their appointment, without re-booking or cancelling. With each appointment costing £25, the total cost of non-attendance for that year was £120,825.[13]

Further research is needed to explore individual and organisation barriers to diabetic retinopathy screening and to identify interventions and/or service models that have been shown to improve the uptake and performance of retinal screening. A systematic review of the literature will therefore provide a foundation on which to develop future quality improvement (QI) strategies. Although there have been previous systematic reviews on interventions to optimise adult screening programmes (including an HTA report[14]), it is likely that this evidence is not directly transferable to retinopathy screening. Screening for diabetic retinopathy differs from other forms of screening in that the target group already has significant contact with the healthcare system due to their underlying diabetes and screening has to be life-long (i.e. annual surveillance is necessary). Although the proposed review will inevitably have a UK focus, failure to perform diabetic retinopathy screening is a global public health problem and multiple interventions have been studied in a variety of populations and contexts; including private and publically-funded screening services. Therefore, given the complexity of the behavioural determinants of retinopathy screening and the multi-component nature of the interventions that have been used to increase screening attendance, the scope of the current review will be extended beyond a UK context.

1.2.1. Predictors of poor uptake of diabetic retinopathy screening and Quality Improvement (QI) interventions to improve screening attendance

A previous systematic review, that assessed the effectiveness of interventions to promote screening for diabetic retinopathy, was published in 2007,[15] and several systematic reviews of general strategies for improving the quality of diabetes care have included eye-screening outcomes.[16] There is evidence that a variety of interventions can be effective in improving screening attendance e.g. patient education and support, improving the healthcare system infrastructure and optimising administrative processes. However, it is likely that interventions containing a number of components will be required and these may need to be adapted and targeted to particular patient groups (i.e. based on socioeconomic factors, co-morbidities, rurality, etc).

Following the introduction of the UK Diabetic Eye Screening Programme, a series of published audits have reported significant inequity in screening uptake and outcomes. Living in areas of high social deprivation, younger age (<40 years) and a longer duration of diabetes have been found to be associated with lower rates of screening.[17-21] Ethnicity is also an important determinant of diabetic retinopathy screening uptake and outcomes. Black Minority and Ethnic (BME) groups with type 2 diabetes have a higher prevalence of diabetic retinopathy compared to white Europeans.[2] Furthermore, South Asians and African/Afro-Caribbean's are more likely to present with sight-threatening retinopathy and have higher rates of referral to ophthalmology following screening.[22,23] Despite the associated risk, there is evidence that these ethnic groups are less likely to attend for screening.[17]

In order to develop and evaluate QI interventions to improve retinopathy screening, it is important to understand the causal determinants of poor screening rates. There is overwhelming evidence that behaviour change plays an important role in people's health and health-related actions.[24] Interventions and/or screening models to improve screening

attendance are therefore likely to be more effective if they target the causal determinants of behaviour and behaviour change.[25,26]

1.3 Rationale for the proposed methodological approach

1.3.1. Systematic coding of interventions to improve screening attendance and behavioural determinants associated with participation

The majority of studies evaluating QI interventions for diabetes care (including interventions to improve retinopathy screening) involve multi-component interventions (i.e., consisted of more than one QI strategy) that attempted to change the behaviour of healthcare professionals (e.g., advising patients to attend diabetic retinopathy screening) and/or patients (e.g., actually attending).

As there is no consistent association between the number of intervention components and effectiveness of QI interventions,[27] the 'ideal' number of components in such programme is not known. Furthermore, given the complexity of interventions tested to date, it is not always clear which specific components are essential elements of these interventions (i.e. 'the active ingredients') to accomplish key outcomes.[24,28,29] Hence, the content of complex behaviour change interventions has been referred to as a 'black box'.[30,31] There is evidence that the more clearly the effective, core components of a complex intervention are known, the more readily the intervention may be delivered in an efficient, consistent and cost-effective manner.[29,32,33,34] Therefore, identification of effective interventions for increasing the uptake of diabetic retinopathy screening first requires clarity about intervention content and the functional relationship between components of interventions and outcomes.

Specifying the content of complex interventions:

Two recent methodological advances have resulted in a step-change in methods for specifying the active ingredients of behaviour change interventions. First, the development of a reliable taxonomy of 93 behaviour change techniques (BCTs),[35] has provided common, consistent terminology by which the component BCTs in complex interventions may be identified and described. BCTs are defined as the 'observable, replicable and irreducible components of an intervention that are designed to alter or redirect causal processes regulating behaviour (i.e. the proposed 'active ingredients').[35] Examples of BCTs include: 'goal-setting,' 'self-monitoring,' 'providing feedback on behaviour' and 'problem solving'. Inter-rater reliability assessments demonstrate that independent reviewers using the taxonomy as a coding framework can reliably identify the BCTs in intervention descriptions.[35] Taxonomies have therefore effectively been applied to systematically describe the components of behaviour change interventions.[36-39] Two members of the project team (Lorencatto and Francis) work at the forefront of this significant methodological development.

Identifying the 'active ingredients' in complex interventions:

Second, the common BCT labels and definitions provided in the taxonomy enable a systematic analysis of heterogeneity of intervention effects.[40] Several studies have employed this taxonomy specification approach in conjunction with statistical methods to explore

heterogeneity to assess whether the presence or absence of specific BCTs is associated with intervention effectiveness.[41-44] Members of the project team (Grimshaw, Ivers and Presseau) have already successfully piloted this approach on trials of QI interventions for diabetes care.

Identifying the theoretical determinants of screening behaviour:
This taxonomic approach to evidence synthesis is thus a key step towards clarifying what makes one intervention more effective than another. However, in addition to identifying the 'active ingredients' in complex interventions, evidence is also needed about how interventions 'work'. The need to design behaviour change interventions based on relevant theory is now well recognised[45]. The Medical Research Council guidance for developing and evaluating complex interventions advocates commencing with a 'theory phase' in which evidence is accumulated and a theoretical basis for the intervention is developed.[29] Theory provides a consistent, generalisable framework, alongside an integrated summary of the proposed causal processes involved in behaviour change.[46] There is also evidence that theory-based interventions are often more effective than those that are not.[25,26] Therefore, interventions that target diabetic retinopathy screening behaviour are more likely to be effective if they target the causal determinants of screening behaviour. However, the explanatory factors (constructs) from different theories often overlap, making it challenging to identify determinants.[47]

To address this, 128 explanatory constructs from 33 theories of behaviour change have been systematically synthesised into an integrated theoretical domains framework (TDF) comprising 12 'theoretical construct domains'. These domains are labelled: (1) knowledge, (2) skills, (3) social/professional role and identity; (4) beliefs about capabilities; (5) beliefs about consequences; (6) motivation and goals; (7) memory, attention, and decision processes; (8) environmental context and resources; (9) social influences; (10) emotion; (11) behavioural regulation; and (12) nature of the behaviours.[48] Each domain represents a range of related constructs that may mediate behaviour change. For example, the 'social influences' domain includes constructs such as social support, group norms and social comparison.[47] The TDF thus provides an accessible, theory-driven basis for understanding barriers and enablers of behaviour change, exploring implementation problems, designing implementation interventions to improve health care practice, and furthering our understanding of the processes of behaviour change. In addition, the TDF can be applied at the level of the individual, team or healthcare organisation to investigate barriers and enablers of behaviour change.[47]

For instance, the application of the TDF may involve developing interview questions and questionnaire items to assess the barriers and enablers to behaviour change in numerous clinical contexts (http://www.implementationscience.com/series/TDF). The TDF has also been applied in secondary data analysis as a coding framework to guide the data synthesis of existing qualitative and quantitative findings, as part of systematic reviews (e.g., aiming to identify barriers and facilitators to guideline implementation for weight management).[49,50] In the context of diabetes, the TDF has been applied as part of a survey examining the barriers and enablers to translating gestational diabetes guidelines into clinical practice.[50] The

domains of knowledge, beliefs about consequences, motivation and goals, social/professional role/identity, social influences, memory attention and decision processes, and environmental context and resources emerged as barriers to guideline implementation in this context.[50] The TDF is thus an appropriate theoretical framework for scoping and synthesising evidence on barriers to diabetic retinopathy screening, from the published and grey literature.

Organisational level behaviour change:
Furthermore, it is possible that barriers and enablers could operate at multiple levels in the healthcare system. Ferlie and Shortell 2001[51] propose four distinct levels of change that should be considered in order to maximise likely effectiveness: individual, group or team, overall organization and wider system or environment. The Consolidated Framework for Implementation Research (CFIR)[52] extends upon this idea by providing an integrated framework of domains to guide the identification of potential barriers and facilitators to behaviour change across these different organizational levels. Members of the project team (Lorencatto, Francis and Grimshaw) are involved in NIHR-funded research that applies the TDF in conjunction with the CFIR to identify behavioural determinants of healthcare professionals' behaviour, with a view to designing complex behaviour change interventions to improve clinical practice. [53]

Integrating BCTs and Theory to design interventions:
Application of these frameworks therefore provides a replicable, multi-level approach to identifying barriers and enablers of retinopathy screening behaviour. However, the frameworks provide limited guidance on how to target these barriers/enablers. Additional research has been conducted to map BCTs to domains from the TDF,[47,54] thereby linking BCTs directly to the hypothesized causal processes of behaviour change and enabling theory to be used more effectively in designing interventions. [41] As a simplistic example, if patients do not attend for screening due to forgetting (the domain, 'attention, memory and decision processes'), the mapping process[54] identifies that the BCT 'prompts/cues' will likely be effective in increasing attendance. Such prompts or cues could be delivered in a variety of ways, e.g., as reminder notes stuck to the mirror or as text reminders.

Based on these considerations, the proposed study will integrate and apply these theoretical frameworks (i.e. BCT Taxonomy; TDF; CFIR) and analytical approaches (i.e. meta-regression) to systematically examine the barriers and enablers relating to attendance for diabetic retinopathy screening.

1.3.2. Application of novel methods for exploring heterogeneity

A previous systematic review, of QI interventions for diabetic care (co-written by two members of the current project team)[55] identified substantial heterogeneity in effect size in 23 trials reporting outcomes for retinopathy screening (I^2 >80%). Heterogeneity is to be expected given that QI programmes are applied in different contexts and typically involve multiple components that can interact synergistically or antagonistically. Consequently, a traditional meta-analytical approach, which estimates the 'mean effect', may not be particularly informative since it averages over potentially interesting data patterns. We

therefore propose to explore heterogeneity within the review dataset to attempt to determine the effectiveness of each component and to test for possible effect modifiers. Members of the project team (Grimshaw and Ivers) are working at the forefront of research into the development of innovative methods for exploring heterogeneity in systematic reviews of complex interventions. Therefore, in addition to standard methods such as sub-group analysis and univariate meta-regression we will apply novel exploratory methods to identify interactions between components. For example hierarchical multivariate meta-analysis models will allow for greater utilisation of the available data by specifying models that evaluate within-study and between-study variability. Similarly, all subsets combinational meta-analysis[56] performs separate meta-analyses on all possible subsets of studies in a meta-analysis and then the summary effect sizes and other statistics produced by the meta-analyses are used to generate graphs to visualise heterogeneity, identify influential studies, and explore subgroup effects. For example we could explore the degree to which studies evaluating an intervention with a specific BCT component appear to be homogeneous with each other.

1.4. Scoping literature search

1.4.1. Published literature

Scoping searches were conducted to estimate the potential size of the literature relevant to this project. For the current review we plan to use a modified version of the search strategy used by Tricco et al in their review of QI interventions for diabetes care.[55] For this review, searches were conducted in Medline from July, 2003 to July, 2010 and the Cochrane Effective Practice and Organisation of Care (EPOC) database (July, 2003, to July, 2010). A total of 5592 titles and abstracts were identified, yielding 23 trials reporting outcomes on diabetic retinopathy. Since studies assessing the effect of QI interventions aimed solely at the patient (i.e., with no associated health systems or professional change) were excluded, we would anticipate a higher yield of trials for the current review. We have independently identified a further 12 trials and estimate that approximately 50 trials (RCTs and cluster RCTs) will be available for data analysis.

To identify the size of the published literature on determinants of screening uptake (barriers and facilitators), a scoping Medline search using the terms ‘semi structured interview* OR questionnaire* OR focus group* OR qualitative research AND screening AND diabetic retinopathy’ identified 294 references. Based on an analysis of a sample of 100 records approximately 10% were relevant to the scope of the review.

1.4.2. Grey Literature

It is difficult to estimate the number of studies that will need to be screened and extracted from the grey literature. We have conducted a series of searches of relevant literature sources using the terms "diabetic retinopathy" AND screening AND barrier*. The results are shown in the Table below:

Source	Number of result
Open Grey	61
PsychExtra	264
Google	286,000*

** Google's proprietary algorithm PageRank will ensure that the majority of relevant articles will be in the first few hundred results*

For identification of relevant high quality sources of unpublished literature we will also use personal communication with our stakeholder advisory group, other experts in the field and organisers of local screening programmes.

2. AIMS AND OBJECTIVES

The aim is to determine the most effective components of interventions that seek to increase screening rates for diabetic retinopathy in people with type 1 or type 2 diabetes and to identify predictors of poor uptake and ongoing attendance screening

The specific objectives are to:

1. Systematically review the evidence for the effectiveness of quality improvement interventions that seek to increase attendance for diabetic retinopathy screening.
2. Enrich the dataset by contacting authors of included studies to obtain information on missing data elements on the content of the intervention and/or context.
3. Code the descriptions of the interventions used in the included studies in terms of behaviour change techniques (BCTs) (with BCTs being the 'active components' of interventions that aim to improve screening attendance).
4. Explore heterogeneity in effect size using conventional and innovative meta-analytic methods to identify factors associated with improved effectiveness.
5. Systematically identify the published and grey literature reporting barriers and facilitators associated with diabetic retinopathy screening.
6. Code barriers and facilitators identified in objective 5 according to Theoretical Domains Framework of behaviour change and The Consolidated Framework for Implementation (with domains being explanatory factors that are proposed to mediate change).
7. Assess BCTs (from objective 3) and barriers and facilitators (identified from objective 6) in terms of their coherence (i.e., do the intervention components target the proposed mediators?).
8. Use data from 1-7 above to estimate potential cost-consequence and cost-utility of interventions increase attendance at retinopathy screening.
9. Integrate the findings (objectives 1-8), with input from stakeholders end users, to make recommendations on the design of future interventions aiming to improve the attendance for diabetic retinopathy screening in areas or population subgroups with low uptake.

3. RESEARCH PLAN

The study will be conducted in three phases with stakeholder input and PI throughout.

At each stage of the review process we will adhere to accepted guidance for the conduct and reporting of systematic reviews.[57,58] We will register the protocols for the reviews *a priori* on PROSPERO (http://www.crd.york.ac.uk/prospero/) and publish them as appropriate in the Cochrane Library or *Systematic Reviews* journal.

3.1. Stakeholder Advisory Group

We have established a representative stakeholder reference group to capture the views of end users of the outputs from this project. The group includes experts in diabetes care, representatives of the four nations screening programme, patients, practitioners, professional organisations and policy makers. The following individuals are involved:

- Prof. Peter Scanlon (Clinical Director, Diabetic Retinopathy Screening Programme, England)
- Dr Deborah Broadbent (Director of Diabetic Eye Screening, Liverpool)
- Mr Andrew Crowder (Head of Diabetic Retinopathy Screening Wales)
- Dr Caroline Styles (Lead Clinician for Diabetic retinopathy screening Scotland)
- Mr Raymond Curran (Assistant Director, Directorate of Integrated Care, Health & Social Care Board, Northern Ireland)
- Grant Duncan (British Association of Retinal Screeners)
- Simon O'Neil (Diabetes UK)
- Helen Lee (RNIB)
- Chigozie Joe Adigwe (Eye Health Equalities Officer RNIB Scotland).

An early meeting of the stakeholder group (which will also include the Chair of the Patients and the Public (PPI) panel, see section 10) will be used seek their input on key review decisions and to advise the review team on potential sources of evidence (for reviews in phases 1 and 2). At the end of the project the stakeholder group will take part in a formal knowledge exchange event (see section 4.2) to discuss the outputs from the evidence synthesis and their implications for policy/research (phase 3).

3.2. Health technologies being assessed:

Quality improvement (QI) interventions seeking to increase the uptake and ongoing attendance for diabetic retinopathy screening:

- *Types of intervention:* Interventions may be targeted at individuals, healthcare professionals or the healthcare system (e.g. organisational change or change in the screening model).
- *Controls/comparators* will be those eligible for screening who do not receive the trial intervention or receive standard care.

3.3. Design and theoretical/conceptual framework

Evidence synthesis of the published and grey literature to identify the effectiveness of quality improvement (QI) interventions for improving the attendance for diabetic retinopathy screening and to explore barriers and facilitators relating to participation in retinopathy screening. The study design will incorporate:

- Use of validated taxonomies of behaviour change techniques[35] (BCTs) and theoretical frameworks[48,52,] to specify the components of the interventions and theoretical determinants of screening behaviour.

- Exploration of within and between study heterogeneity using conventional and novel meta-analytic techniques.
- Mapping of the coherence between intervention components and barriers/facilitators associated with poor attendance for diabetic retinopathy screening
- Estimation of the relative cost-effectiveness of potential BCTs to increase screening attendance using cost-consequence analysis and decision-modelling.
- Formal process of 'knowledge exchange' with end users to discuss interpretation and application of project findings.

The advantage of this strategy over conventional systematic review methodologies is that it explicitly uses theoretical constructs to conceptualise the determinants of screening behaviour and the content of successful or unsuccessful interventions. Given the complexity of QI interventions it is not always clear which specific components are the essential elements (i.e. 'the active ingredients') of these interventions or which contribute to key outcomes. By identifying these elements this novel approach to evidence synthesis will facilitate the development and delivery of future theoretically-informed interventions to improve diabetic retinopathy screening.

3.4. Detailed methods

3.4.1. Phase 1: Systematic review of the effectiveness of interventions to increase attendance for diabetic retinopathy screening (Objectives 1-4)

The aim of phase 1 will be a systematic review of quality improvement (QI) programmes for diabetic care that seek to improve the attendance for of retinopathy screening. The review will be conducted in line with Cochrane methodology under the umbrella of the Cochrane Eyes and Vision Group (CEVG), who will oversee the development of the searches. Additional methodological support will be provided by the Cochrane Effective Practice and Organisation of Care (EPOC) group.

Inclusion criteria:

- *Population:* Participants with type 1 and type 2 diabetes, healthcare professionals responsible for diabetic care.
- *Types of study:* We will include randomised controlled trials (RCTs); both individually randomised and cluster RCTs.
- *Types of intervention:* Interventions may be targeted at individuals, healthcare professionals or the healthcare system (e.g. organisational change or change in the screening model).
- *Controls/comparators* will be those eligible for screening who do not receive the trial intervention or receive standard care.
- *Outcomes:* The Primary outcome will be uptake of diabetic retinopathy screening (collected by researcher based on self-reports or health record audit (hospital, GP or screening administration system record). If data are available we will also analyse adherence to screening and attendance for treatment/ongoing monitoring following initial screening. Secondary outcomes will be any of the mediating factors that may explain the pathway of change (for example, attitude, intention, motivation, self-

efficacy, etc). If measured and reported, any such mediators will be codable into theoretical domains and the findings will be used in Phase 3 (integration phase). Other secondary outcomes may be proposed mediators operating at the level of the individual (socioeconomic factors, ethnicity), healthcare profession or organisation.

Setting/context:
There will be no restrictions on location of care (primary or secondary), healthcare system or screening model used as interventions delivered in a different context will have elements that could work in a UK setting (see section 1.1.)

Search strategy for identification of studies:
We will search the following bibliographic databases and trials registers to identify *published, unpublished and on-going studies*: CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE, EMBASE, CINAHL PsycINFO, Latin American and Caribbean Literature on Health Sciences (LILACS), and for ongoing studies the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en) and the EU Clinical Trials Register (www.clinicaltrialsregister.eu). Two members of the project team (Grimshaw and Ivers) were co-authors on a systematic review of 12 QI interventions for diabetes that included eye screening as an outcome[55]. Their search strategy will be adapted for this review (see Appendix 1 for details) and will be developed in conjunction with an experienced information scientist at the Cochrane Eyes and Vision Group (CEVG).

Additional studies will be identified by searching the reference lists of included studies, and contacting experts in the field and searching conference abstracts of national and international ophthalmology and diabetes conferences (e.g. Association of Research in Vision and Ophthalmology (ARVO), American Academy of Ophthalmology, Diabetes UK and World Diabetes Congress).

Study selection and data extraction:
Two review authors will independently screen the titles and abstracts identified in the electronic searches, complete manuscripts will sought in the case of uncertainty and any differences of opinion will be resolved by consensus. Conference abstracts will be included if they provide sufficient data.

Data from included studies will be extracted using a modified version of the Cochrane Effective Practice and Organisation of Care (EPOC) group data collection checklist. This incorporates information on study design, type and duration of interventions, participants, setting, methods, outcomes, and results. Uptake and adherence to screening will be treated as dichotomous outcomes. The number in each treatment arm who underwent retinopathy screening prior to the intervention and the number assessed at the end of the study will be extracted in order to calculate a risk ratio and 95% confidence interval (CI). Data extraction

will be carried out by one reviewer and checked by another. Discrepancies between reviewers will be resolved by discussion.

BCT coding of intervention content:

Published descriptions of included interventions will be coded into component BCTs using an established taxonomy of 93 BCTs[35] as a coding framework. BCTs will be coded as 'present' or 'absent' in each intervention description. Data on the frequency with which BCTs are identified within each intervention will also be extracted in order to examine the 'dose' with which BCTs feature in interventions; for example, an intervention that features the BCT 'goal-setting' three times, and 'feedback' only once, has a stronger dose of the BCT 'goal-setting'. Frequency of BCT identification will also be compared across interventions. There is also increasing evidence that the content of complex behaviour change interventions is often poorly described in published reports, rendering it more difficult to clearly specify the content of interventions on this basis alone and increasing the risk of misclassification. [37,59] Therefore in the case of insufficient information being available to adequately specify the content of the included interventions, we will supplement this analysis by contacting the authors of included studies with a request for additional materials or information that provides further detail on the content of the intervention (i.e. a trial protocol). Initial examinations of papers identified via the scoping searches indicate this step is likely to be necessary. Received materials will be coded using the taxonomy in the same manner as the corresponding published reports. Members of the project team (Grimshaw and Ivers) have successfully developed and tested an online platform to request relevant data from authors.
Data extraction and BCT coding will be carried out independently by two reviewers. Inter-rater reliability will be assessed using Cohen's Kappa.[60] Discrepancies will be resolved through discussion.

Assessment of risk of bias:

Study quality will be assessed independent by two authors using the Cochrane Effective Practice and Organisation of Care (EPOC) group criteria for assessing risk of bias as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*. [57] The EPOC criteria uses 9 standard criteria are used for appraising RCTs.

- Was the allocation sequence adequately generated?
- Was the allocation adequately concealed?
- Were baseline outcome measurements similar?
- Were baseline characteristics similar?
- Were incomplete outcome data adequately addressed?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Was the study adequately protected against contamination?
- Was the study free from selective outcome reporting?
- Was the study free from other risks of bias?

The risk of bias tool will be applied independently by two reviewers and any differences resolved by discussion. Studies will not be excluded on the basis of poor quality but a

sensitivity analysis will be performed to compare studies of high versus low risk of bias if data are sufficient.

Data analysis:

A meta-analysis will be performed using the random effects inverse variance method (DerSimonian and Laird) to estimate the pooled risk ratio's across studies.[57] It is anticipated that a large number of included studies will use a cluster RCT design. Data from cluster RCT will be included in meta-analyses directly where the sample size has been adjusted for clustering. However, if outcomes are presented at patient level (i.e. a unit-of analysis error) we will use established methods to adjust for clustering by calculating an effective sample size by dividing the original sample size by the design effect which can be calculated from the average cluster size and the intra-class correlation coefficient (ICC).[57] Where the ICC is unknown, this will be estimated from similar trials.

Exploring heterogeneity:

The consistency of the results from each study will be assessed by a forest plot and the degree of heterogeneity will be determined using the χ^2 test and the I^2 statistic. Based on a scoping exercise we expect a high heterogeneity within the included studies and we plan to perform a variety of traditional and innovative methods to explore sources of variability. Sub-group analysis and meta-regression will initially be performed to investigate whether the presence or absence of particular covariates explains variation in the study results. The choice of co-variants for the sub-group analysis and meta-regressions will be determined *a priori* in consultation with the stakeholder advisory group. However, it is likely that subgroup analyses will investigate whether the effectiveness of the QI intervention is affected by baseline uptake of retinopathy screening, geographical location, patient group or if there is an association between individual BCTs and intervention effectiveness. To be included in the analysis, each BCT is required to be evaluated by at least four separate studies.[41]

Innovative meta-analytical approaches will be used to further explore potential interactions between component interventions and effect modifiers. For example, we will conduct all-subsets combinatorial meta-analysis on the updated dataset to identify the most effective QI interventions and to determine the impact of key effect modifiers. We use the summary effect sizes produced by the all-subsets meta-analyses to generate graphs that can be used to investigate heterogeneity, identify influential studies, and explore subgroup effects.[56] Multivariate meta-analysis methods will be used to evaluate the effect of QI components (or other arm-level factors) on screening effectiveness within each arm of the trial (within study) and then model between-study variability to account for unexplained heterogeneity (between-studies). The resulting multivariate meta-regressions will potentially allow for the exploration of interactions between component interventions and effect modifiers.

5.4.2 Phase 2: Identification of barriers and facilitators associated with attendance for diabetic retinopathy screening (Objectives 5 and 6).

We will review the published and unpublished ('grey' literature) to identify the determinants of retinopathy screening uptake. We plan to use the TDF and CIFR as coding frameworks to identify the behavioural determinants associated with screening uptake, as described below.

We will use an integrated approach consisting of the following stages;

- Searching of bibliographic databases for published papers on barriers and facilitators in the context of diabetic retinopathy screening
- Personal communication with the stakeholder group to identify sources of grey literature
- Searching for additional grey literature
- Selection and assessment of validity of published and unpublished literature
- TDF coding of included studies/reports
- Research synthesis

Inclusion criteria:

- *Population:* Participants with type 1 and type 2 diabetes, healthcare professionals responsible for diabetic care
- *Types of studies:* Studies/reports will be included if they focussed on barriers, facilitators or predictors of uptake of retinopathy screening. If studies are available we will also include barriers to attendance for treatment/ongoing monitoring following initial screening. There will be no restriction on study design, although it is likely that the majority of included studies will incorporate qualitative or mixed methods.
- *Outcomes:* All factors thought to influence the uptake of screening e.g. socioeconomic, behavioural, social, economic or institutional.
- *Search strategy:* An internet search will conducted using the search engine Google (terms: "diabetic retinopathy" AND screening AND barrier* OR facilitate* OR health behaviour) as well as a search of established sources of grey literature (e.g. conference abstracts, OpenGrey, PsycEXTRA, OpenSIGLE, The Healthcare Management Information Consortium (HMIC) database). Methodological filters optimised for qualitative research[61,62]will be applied to the search strategy. The search strategy for the database searches will be reviewed by the review team and the external stakeholder group. The reference lists of all studies or reports that meet the inclusion criteria will be searched for any additional literature not identified in the database searches. The stakeholder group will also advise the team on sources of grey literature relevant to the review aim.

Data collection:

Two review authors will independently screen the titles and abstracts (if available) of all the references generated from the searches to determine if the complete study/report should be retrieved. Any differences of opinion regarding relevance will be resolved by consensus. Retrieved reports will be independently appraised by two reviewers. The first level of screening will place the report into one of the following categories:

- judged to have sufficient relevance and quality to be included in the next stage of the selection process
- judged to provide background or contextual information
- judged not to be relevant to this review

Reports that are selected for possible inclusion will be further screened by the two reviewers that involve detailed reading and appraisal of the reports to assess whether they should be included in the review.

Data extraction and quality assessment:

Standard data extraction templates will be developed that are suitable for qualitative and survey research incorporating details of context, design, participants, data analysis methods and main findings. Data extraction and quality assessment will be carried out by two reviewers independently and any discrepancies resolved by discussion. Depending on the nature of the included study/report, standard quality appraisal templates will be used e.g. AACODS (Authority, Accuracy, Coverage, Objectivity, Date, and Significance) checklist for grey literature and for the assessment of qualitative studies, instruments recommended by the Cochrane Qualitative Research Methods Group will be used[63] e.g. the Critical Appraisal Skills Programme (CASP) quality assessment tool for qualitative studies.

Data analysis (TDF/CFIR coding):

A coding framework will be developed a priori that encompasses the domains from the TDF[48] and CFIR frameworks.[52] Two versions of the TDF have been published, referred to in the field as TDF1[48] and TDF2[64], which differ primarily in terms of the profile of expertise of the independent panels involved in the development of both versions. There is substantial overlap between TDF1 and TDF2 in terms of the domain labels and content, representing robust evidence of validity. There is informal consensus in the field that selection of which TDF version to apply in any particular study should be based on the level of fit between the framework and context of study. In some contexts, the nature of the behaviour itself is potentially a key barrier to change, or may not be sufficiently understood and warrants further exploration. For example, adopting a complex pattern of new actions that is substantially different from a current habit would be more difficult to achieve than a minor adaptation of current behaviour that is not habitual. These factors may be explored using TDF1, which features the domain 'Nature of the Behaviours;' this domain is absent in TDF2. In general, attending a health screening program has been recognized as a "complex" behaviour, involving a sequence of multiple, different sub-behaviours, from making an appointment (i.e. an intention-related behaviour) through to attending the appointment (i.e. enactment behaviour).[63] It is plausible that these sub-behaviours may each interact with some patient characteristics. This complexity is likely to also apply for diabetic retinopathy screening. Therefore, we have chosen to apply TDF1 for the proposed analysis, in order to examine the nature of the behaviours involved in attending diabetic retinopathy screening.

All extracted findings and raw data from included studies will be coded following a framework synthesis approach, utilising the developed coding framework. Such data may include, for instance, participant quotations in qualitative studies, statistical analyses from questionnaire and survey studies, alongside interpretive descriptions and summaries of

results in the published report. The frequency with which domains from the TDF and CFIR are identified within and across included studies will be assessed and tabulated.

Coding will be conducted independently by two reviewers. Inter-rater reliability will be calculated for all domains and studies using Cohen's Kappa to assess whether both reviewers assigned the same domain labels to the same data point. A minimum kappa value of 0.75 will be taken to represent high agreement. All discrepancies will be resolved through discussion until consensus is reached.

From the TDF and CFIR coding of existing data, specific themes regarding the barriers and facilitators to screening uptake will be identified. Themes provide detail regarding the importance and role of each domain in influencing behaviour. For example, if it emerged that lack of an understanding of the purpose of retinopathy screening was associated with lack of uptake or lower intention to attend screening; this would be identified as a barrier under the 'knowledge' domain of the TDF. Key themes influencing screening uptake will be identified by concurrently considering three factors: the frequency with which beliefs emerge across included studies; the presence of conflicting beliefs; and the perceived strength of the themes impacting screening uptake. [64]

3.4.3. Phase 3: Assess BCTs (from objective 3) and barriers and facilitators (identified from objective 6) in terms of their coherence (i.e., do the intervention components target the proposed mediators? (Objective 7).

Mapping of coherence of BCT coding of interventions and identified behavioural determinants

A methodologically innovative aspect of this study is that the final phase of the study will integrate findings from the reviews conducted in phases 1 and 2, by evaluating, in terms of coherence, the intervention components (i.e. BCTs) identified as effective in meta-regression analyses in phase 1 against the theoretical domains identified as key barriers and facilitators to screening uptake in phase 2. For example, coherence would be demonstrated if the BCT 'providing information on the health consequences' of screening uptake was identified as effective in Phase 1, and 'knowledge' was also identified as a key barrier to screening uptake Phase 2; in this instance, interventions including this BCT would coherently address the relevant theoretical, causal determinant of the target behaviour. Conversely, incoherence would be displayed if findings from Phase 1 identified numerous BCTs related to social support as being significantly associated with screening uptake, but 'social influence' was not identified as a key domain in Phase 2 (or vice versa).

Hence, the findings from phase 3 will inform a clear set of recommendations for future research in terms of evidence-based intervention components (that are likely to be effective) and trial design features (e.g. process variables that should be assessed).

3.4.4. Phase 3: Economic evaluation (Objective 8)

Using interventions to improve the uptake of diabetic retinopathy screening will not be without cost and it will be important to determine whether the benefits that these interventions provide will be worth these costs. This issue will be addressed in the economic evaluation. Diabetic retinopathy has, however, already been judged cost-effective and

numerous economic evaluations on the value of diabetic retinopathy have been conducted. Therefore, we do not propose to develop a detailed economic evaluation model but rather we will conduct an initial cost-consequence analysis (CCA) which will describe the costs and outcomes for a hypothetical cohort representative of the eligible UK population. The data on the effectiveness of interventions will come from the systematic review described in Section 3.4.1. This approach will allow us to consider how costs and consequences might vary by those key effect modifiers (derived from the exploration of heterogeneity conducted as part of the systematic review) that describe the characteristics of individuals within the cohort (location, type of diabetes, ethnicity, etc).

For the CCA information on the cost of interventions will be based on the description of the intervention within included studies and advice from the whole study team to identify resources required to deliver these interventions. These data will be combined with unit costs from routine sources and study specific estimates to estimate a cost for each intervention. Within the CCA the main perspective for costs will be the NHS but cost falling on other groups (e.g. those being invited for screening) will also be included. With respect to people eligible for screening we will estimate their costs using data collected that has been collected within recent RCTs on the time and travel cost of accessing and using different types of care provided in different locations (community, primary, secondary, tertiary care). We have access to a large number of trials (many of which have been funded by NIHR HTA) that have collected these data for a very large range of services.

The work conducted as part of Phase 2 (Section 3.4.2) will identify combinations of BCTs that have not as yet been subject to evaluation but may be used as an intervention to increase the uptake of screening. Working with the rest of the study team we produce vignettes of the resources required to deliver interventions comprising these BCTs. Using the approach outlined above the cost of these will be estimated and these cost data will be used to estimate the implied additional value of a more costly intervention compared to a less costly one. This approach is based on the conditions required for an efficient allocation of resources and will allow us to say how much more effective a more costly intervention would need to be to be considered efficient and was used in a recent NIHR HTA funded evidence synthesis project. [65]

In addition we will develop a simple decision analytic model to compare identified and potential interventions to increase the uptake of screening for diabetic retinopathy. In this decision model we will assign individuals who are screened or not screened estimates of costs and quality adjusted life years (QALYs) taken from a recent NIHR funded study. [66] This will allow us to estimate cost-effectiveness against the same criteria normally considered by decision-makers such as NICE.[67] As part of this work we will also explore the trade-off between cost of an intervention and its effectiveness in terms of uptake of screening. This will define the combination of costs and uptake rates that would provide an incremental cost per QALY of at least no more than £20,000 – a threshold usually considered as relevant in the UK [67].

For all analyses we will consider the impact of key uncertainties using both deterministic and probabilistic sensitivity analyses. These data along with the implied value data will help us form judgements on best candidates of interventions to be taken forward to future research.

3.4.5. Phase 3: Integration of the findings of the evidence synthesis from phases 1 and 2, and health economic analysis, augmented by a stakeholder knowledge exchange event to consider the implications for current services and the development of future research recommendations (objective 9)

Knowledge exchange event

The main outcome from this project will be the identification of evidence on the effectiveness of targeted interventions to increase uptake and ongoing attendance for diabetic retinopathy screening and the identity of the behavioural determinants of poor attendance. Although stakeholder input will be sought at all stages of the project through the stakeholder advisory group, we plan to host a formal one-day knowledge exchange event to present the results of the study and explore the service implications of the findings. The event will be hosted by City University and a summary of the results (including a lay summary) will be distributed in advance. The event will be attended by patient groups, leading charities (Diabetes UK, RNIB), screening providers, professional bodies (Royal College of Ophthalmologists, Royal College of General Practitioners, College of Optometrists) and representatives of the four nations screening programmes. All participants will receive a summary of the results in advance of the meeting. The discussion will centre on the implications of the findings for the UK diabetic retinopathy screening programme and identify directions for future research.

4. DISSEMINATION AND PROJECTED OUTPUTS

4.1. Scholarly outputs

The results of the project in the form of the HTA monograph will be disseminated through the HTA Journal Series and through the databases and publications of the Centre for Reviews and Dissemination (CRD). The systematic review on the effectiveness of interventions to increase the uptake of diabetic retinopathy screening will be published in *The Cochrane Library* and disseminated through the Cochrane Collaboration. Dissemination activities, which are co-ordinated through the Cochrane Editorial Unit, include press releases and the use of social media. In addition, each Cochrane Review Group (CEVG and the EPOC group) has their own targeted dissemination activities. The protocol for the review on barriers and facilitators to retinopathy screening will be published on PROSPERO (the International prospective register of systematic reviews) and in the Journal *Systematic Reviews.*. The completed review will be submitted to an open access journal for publication concurrent with publication in Cochrane and HTA and will conform to reporting guidelines outlined in the PRISMA statement. All scholarly outputs will include a programme funding statement and disclaimer.

4.2. Knowledge translation

Study results will be widely disseminated to those involved in the organisation and delivery of diabetic retinopathy screening. The UK eye care and diabetes communities will be targeted through presentations at conferences (e.g., Diabetes UK, the British Retinal Screeners Association and the annual conferences of the College of Optometrists and Royal College of Ophthalmologists). The planned knowledge exchange event (see section 3.4.5), which includes service users and representatives from the four UK nations, will also be used as a means of knowledge translation. The project stakeholder group will also advise on how best to communicate project findings to the target audience.

5. PLAN OF INVESTIGATION AND TIMETABLE

A detailed project timetable is shown in Figure 4. Funding starts; 1st September 2015. Months 0-4; Writing protocols for phase 1 and phase 2 systematic reviews; Months 3-6; Developing and running searches; Months 4-14; Screening, data extraction, quality assessment coding and meta-analysis; Months 5-11; Grey literature searches; Months 11-15; Exploration of study heterogeneity using traditional and novel methods: 14-17; Main economic modelling activity (although this work runs through the project); Months 16-17: Engagement with stakeholders (Knowledge exchange): Months 13-18; Report writing. Final report submission on 28th February 2017.

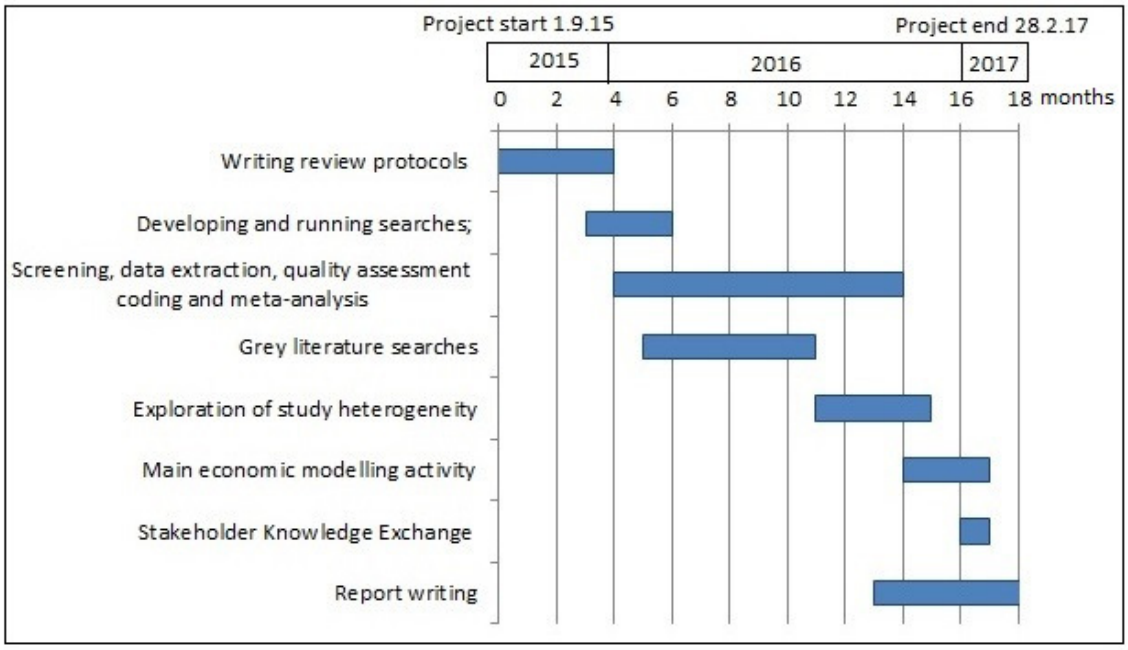

Figure 4: Project timetable

6. PROJECT MANAGEMENT

Lawrenson will take lead responsibility for the management of the project supported by Burr (co-lead). They will meet fortnightly (either by Skype or face-to-face) to monitor progress and achievement of project milestones and will report to the project management team (PMT), consisting of all grant holders, every 3 months for the duration of the project. Lawrenson and Lorencatto will be responsible for the day-to-day supervision of the City-

based RA. Bunce will supervise the Moorfields-based statistician (employed on the grant during months 14-17). Francis and Lorencatto will co-ordinate the BCT coding of the data. Consultation between the Patient and Public Involvement (PPI) working group and Stakeholder Group (SG) will take place as required at all stages of the project. The SG will formally meet early in the project time line (month 2) and towards the end (month 17). Both meetings (Chaired by Lawrenson) will be attended by our co-applicants (Grimshaw and Ivers).

7. APPROVAL BY ETHICS COMMITTEES

NHS Research Ethics Approvals will not be required the study does not involve primary research in the NHS. The study will be sponsored by City University, London. Prior to any stakeholder involvement approval for the study will be sought from the University Ethics committee.

8. PATIENT AND PUBLIC INVOLVEMENT

Patients and the Public will be involved (PPI) throughout the study in several ways. We have contacted Diabetes UK, RNIB and the NHS Diabetic Retinopathy Screening programme who have all expressed a willingness to be involved in the study. We will convene a working group, with a membership drawn from these organisations, to review the study protocols to ensure that we are seeking to identify the most relevant studies and to ensure that all important outcomes, relevant to the study question are collated in the review. We will include a representative of this group as a member of stakeholder advisory group. The whole group and a wider network as advised by the group will be invited to the Knowledge Exchange event (see section 4.2)

9. EXPERTISE AND JUSTIFICATION OF SUPPORT REQUIRED

We have assembled a strong multidisciplinary team for this project consisting of experienced systematic reviewers, subject matter experts and researchers with specific expertise in intervention science, health psychology and statistics. Lawrenson (Professor, City University London) is an optometrist with previous experience in diabetic retinopathy screening, conducting systematic reviews and evaluating complex healthcare interventions. Lawrenson will act as overall project lead and supervise the City-based systematic reviewer RA. Burr (Reader, University of St Andrews) is an ophthalmologist, experienced Health Services Researcher and co-editor of the Cochrane Eyes and Vision Group (CEVG). She is a co-applicant on several HTA projects, both evidence synthesis and randomised controlled trials. She has led NIHR HTA projects on clinical and cost-effectiveness of glaucoma screening and an evidence synthesis and economic evaluation of surveillance for ocular hypertension. Burr will act as co-lead on the project. Locencatto (Research Fellow, City University London) and Francis (Professor, City University London) will provide expertise on the behaviour change techniques and identifying the behavioural determinants of screening uptake. Peto (Medical retinal specialist and Head of Reading Centre Moorfields Eye hospital, lead of the Tower Hamlets, Diabetic Retinopathy Screening Programme) has played a leading role in developing and evaluating retinopathy screening services and will support the project leads

in providing expert advice on retinopathy screening throughout the project. Bunce (Principal Statistician, NIHR Biomedical Research Centre, Moorfields Eye Hospital and statistical editor for the CEVG) will act as statistical advisor on the project and will supervise the statistician employed to conduct the meta-analysis and statistical exploration of heterogeneity. Vale (Health Foundation Chair in Health Economics; Editor Cochrane Effective Practice and Organization of Care (EPOC) Group) is an international expert in economic evaluation and health economics. He has and continues to work extensively on evidence synthesis and trials in the area of ophthalmology including several involving members of the research team. He will lead on the economic evaluation component. Grimshaw (Professor, University of Ottawa and coordinating Editor of the Cochrane Effective Practice and Organization of Care (EPOC) Group) and Ivers (Family Physician, University of Toronto) have previously conducted systematic reviews on quality improvement interventions in diabetes care (including uptake of retinopathy screening) will provide methodological advice and will provide specific input on the use of novel methods for exploring and explaining heterogeneity in systematic reviews of complex interventions. Justin Presseau (working with Grimshaw and Ivers) has been using the BCT taxonomy to identify active ingredients within trials of implementation interventions for diabetes care and has agreed to collaborate on the current project. http://www.implementationscience.com/content/pdf/1748-5908-7-35.pdf

10. FLOW DIAGRAM

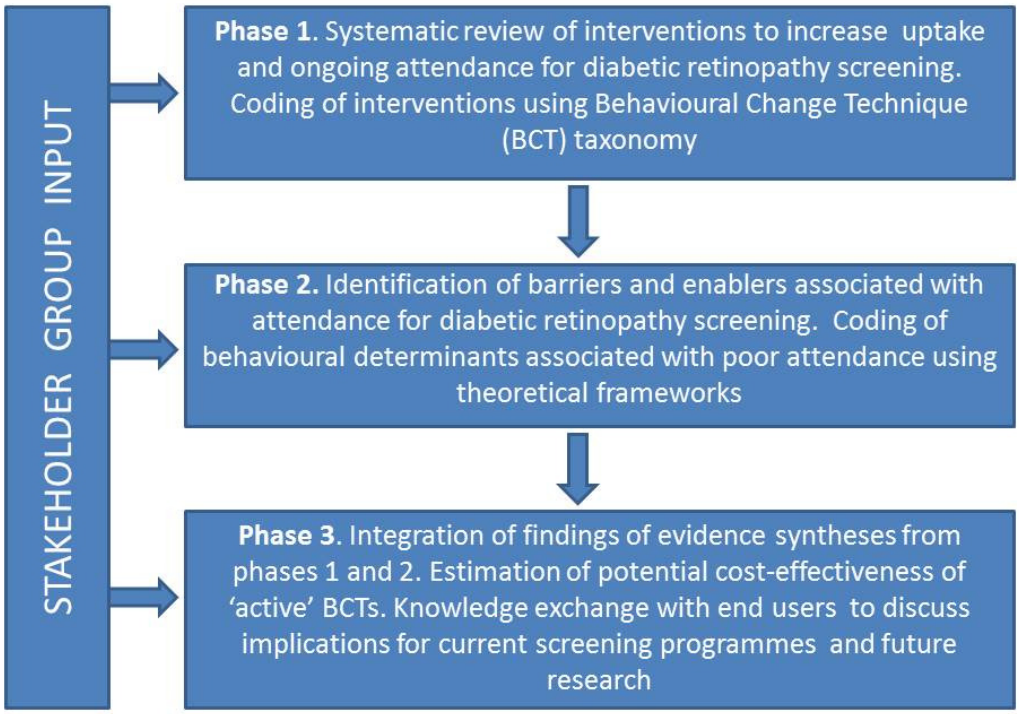

Figure 5: Study Flow Diagram

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