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Simon Harding, Ayesh Alshukri, Duncan Appelbe, Deborah Broadbent, Philip Burgess, Paula Byrne, Christopher Cheyne, Antonio Eleuteri, Anthony Fisher, Marta García-Fiñana, Mark Gabbay, Marilyn James, James Lathe, Tracy Moitt, Mehrdad Mobayen Rahni, John Roberts, Christopher Sampson, Daniel Seddon, Irene Stratton, Clare Thetford, Pilar Vazquez-Arango, Jiten Vora, Amu Wang and Paula Williamson, The ISDR Study Group

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Individualised variable-interval risk-based screening in diabetic retinopathy: the ISDR research programme including RCT

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Abstract

Individualised variable-interval risk-based screening in diabetic retinopathy: the ISDR research programme including RCT

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Background: Systematic annual screening for sight-threatening diabetic retinopathy is established in several countries but is resource intensive. Personalised (individualised) medicine offers the opportunity to extend screening intervals for people at low risk of progression and to target high-risk groups. However, significant concern exists among all stakeholders around the safety of changing programmes. Evidence to guide decisions is limited, with, to the best of our knowledge, no randomised controlled trials to date.

Objectives: To develop an individualised approach to screening for sight-threatening diabetic retinopathy and test its acceptability, safety, efficacy and cost-effectiveness. To estimate the changing incidence of patient-centred outcomes.

Design: A risk calculation engine; a randomised controlled trial, including a within-trial cost-effectiveness study; a qualitative acceptability study; and an observational epidemiological cohort study were developed. A patient and public group was involved in design and interpretation.

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Setting: A screening programme in an English health district of around 450,000 people.

Participants: People with diabetes aged ≥ 12 years registered with primary care practices in Liverpool.

Interventions: The risk calculation engine estimated each participant's risk at each visit of progression to screen-positive diabetic retinopathy (individualised intervention group) and allocated their next appointment at 6, 12 or 24 months (high, medium or low risk, respectively).

Main outcome measures: The randomised controlled trial primary outcome was attendance at first follow-up assessing the safety of individualised compared with usual screening. Secondary outcomes were overall attendance, rates of screen-positive and sight-threatening diabetic retinopathy, and measures of visual impairment. Cost-effectiveness outcomes were cost/quality-adjusted life year and incremental cost savings. Cohort study outcomes were rates of screen-positive diabetic retinopathy and sight-threatening diabetic retinopathy.

Data sources: Local screening programme (retinopathy), primary care (demographic, clinical) and hospital outcomes.

Methods: A seven-person patient and public involvement group was recruited. Data were linked into a purpose-built dynamic data warehouse. In the risk assessment, the risk calculation engine used patient-embedded covariate data, a continuous Markov model, 5-year historical local population data, and most recent individual demographic, retina and clinical data to predict risk of future progression to screen-positive. The randomised controlled trial was a masked, two-arm, parallel assignment, equivalence randomised controlled trial, with an independent trials unit and 1 : 1 allocation to individualised screening (6, 12 or 24 months, determined by risk calculation engine at each visit) or annual screening (control). Cost-effectiveness was assessed using a within-trial analysis over a 2-year time horizon, including NHS and societal perspectives and costs directly observed within the randomised controlled trial. Acceptability was assessed by purposive sampling of 60 people with diabetes and 21 healthcare professionals with semistructured interviews analysed thematically; this was a constant comparative method until saturation. The cohort was an 11-year retrospective/prospective screening population data set.

Results: In the randomised controlled trial, 4534 participants were randomised: 2097 out of 2265 in the individualised arm (92.6%) and 2224 out of 2269 in the control arm (98.0%) remained after withdrawals. Attendance rates at first follow-up were equivalent (individualised 83.6%, control 84.7%) (difference −1.0%, 95% confidence interval −3.2% to 1.2%). Sight-threatening diabetic retinopathy detection rates were non-inferior: individualised 1.4%, control 1.7% (difference −0.3%, 95% confidence interval −1.1% to 0.5%). In the cost-effectiveness analysis, the mean differences in complete-case quality-adjusted life years (EuroQol-5 Dimensions, five-level version, and Health Utilities Index Mark 3) did not significantly differ from zero. Incremental cost savings per person not including treatment costs were from the NHS perspective £17.34 (confidence interval £17.02 to £17.67) and the societal perspective £23.11 (confidence interval £22.73 to £23.53). In the individualised arm, 43.2% fewer screening appointments were required. In terms of acceptability, changing to variable intervals was acceptable for the majority of people with diabetes and health-care professionals. Annual screening was perceived as unsustainable and an inefficient use of resources. Many people with diabetes and healthcare professionals expressed concerns that 2-year screening intervals may detect referable eye disease too late and might have a negative effect on perceptions about the importance of attendance and diabetes care. The 6-month interval was perceived positively. Among people with dementia, there was considerable misunderstanding about eye-related appointments and care. In the cohort study, the numbers of participants (total 28,384) rose over the 11 years (2006/7, *n* = 6637; 2016/17, *n* = 14,864). Annual incidences ranged as follows: screen-positive 4.4–10.6%, due to diabetic retinopathy 2.3–4.6% and sight-threatening diabetic retinopathy 1.3–2.2%. The proportions of screen-positive fell steadily but sight-threatening diabetic retinopathy rates remained stable.

Limitations: Our findings apply to a single city-wide established English screening programme of mostly white people with diabetes. The cost-effectiveness analysis was over a short timeline for a long-standing disease; the study, however, was designed to test the safety and effectiveness of the screening regimen, not the cost-effectiveness of screening compared with no screening. Cohort data collection was partly retrospective: data were unavailable on people who had developed sight-threatening diabetic retinopathy or died prior to 2013.

Conclusions: Our randomised controlled trial can reassure stakeholders involved in diabetes care that extended intervals and personalised screening is feasible, where data linkage is possible, and can be safely introduced in established screening programmes with potential cost savings compared with annual screening. Rates of screen-positive diabetic retinopathy and sight-threatening diabetic retinopathy are low and show consistent falls over time. Involvement of patients in research is crucial to success.

Future work: Future work could include external validation with other programmes followed by scale-up of individualised screening outside a research setting and economic modelling beyond the 2-year time horizon.

Trial registration: This trial is registered as ISRCTN87561257.

Funding: This project was funded by the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research programme and will be published in full in *Programme Grants for Applied Research*; Vol. 11, No. 6. See the NIHR Journals Library website for further project information.

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List of supplementary material

Supplementary Material 1 Stages of PPI involvement in ISDR

Supplementary Material 2 ISDR data warehouse data fields, sources and input schema

Supplementary Material 3 Topic guides for qualitative interviews in the ISDR programme

Supplementary Material 4 ISDR end of programme symposium

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List of abbreviations

ADA	American Diabetes Association
AICc	corrected Akaike's information criterion
ARVO	Association for Research in Vision and Ophthalmology
BI	business intelligence
BMJ	British Medical Journal
BP	blood pressure
CI	chief investigator
CRF	case record form
CTRC	clinical trials research centre
DR	diabetic retinopathy
DW	data warehouse
EASD	European Association for the Study of Diabetes
EASDec	European Association for the Study of Diabetes eye complications study group
EMIS	Egton Medical Information Systems
EQ-5D-5L	EuroQol five dimension five level instrument
GP	general practitioner
HbA1c	glycated haemoglobin
HCP	healthcare professional
HDL	high-density lipoprotein
HES	hospital eye service
HUI3	Health Utilities Index Mark 3
ICER	incremental cost-effectiveness ratio
INMB	incremental net monetary benefit
IP	intellectual property
ISDR	individualised screening for diabetic retinopathy
ITT	intention-to-treat
LCCG	Liverpool Clinical Commissioning Group
LDESP	Liverpool Diabetes Eye Screening Programme
logMAR	logarithm of the minimum angle of resolution
NDESP	National Diabetic Eye Screening Programme
NIHR	National Institute for Health Research
PENS	patient electronic notes system
PGfAR	Programme Grant for Applied Research
PP	per-protocol
PPI	patient and public involvement
PWD	people with diabetes
QALY	quality-adjusted life year
RCE	risk calculation engine
RCT	randomised controlled trial
RLBUHT	Royal Liverpool and Broadgreen University Hospital Trust
SQL	structured query language
STDR	sight-threatening diabetic retinopathy
STM	sight-threatening maculopathy
STR	sight-threatening retinopathy
VA	visual acuity
VI	visual impairment
WHO	World Health Organization
WP	work package

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Plain language summary

Diabetic retinopathy remains a leading cause of vision loss for people with diabetes. Annual photographic screening allows early detection and prompt treatment in many countries. A new approach is to vary how often this is undertaken at each visit, after calculating each person's risk of progression; we have called this 'individualised' screening.

We tested this variable-interval risk-based approach against annual screening in a randomised controlled trial of 4534 people in Liverpool. Six-, 12- or 24-month intervals represented high, medium and low risks, respectively, of becoming screen-positive by the next appointment. With our patient and public involvement group, we designed a computer-based risk-calculation system using personal information from screening, general practitioners and hospitals.

Attendance rates at the next screening appointment were similar in the individualised (84%) and annual (control) (85%) groups. Similar amounts of sight-threatening diabetic retinopathy were detected in the two arms (1.4% individualised, 1.7% control), with 43% fewer visits. In this study in a single geographical region, savings estimated to accrue to the NHS per person over 2 years were £17.34 and £23.11 for wider society, but estimates did not include treatment costs.

During interviews, 60 people with diabetes and 21 healthcare professionals said that individualised screening would be acceptable because of increasing rates of diabetes and the chance to target high-risk people. Patients had anxieties about the reliability of the risk-calculation and restricting access, requesting opportunities for earlier screening if risks changed.

Varying screening intervals based on a person's own risk of progression appears feasible and safe. Low-risk people would be spared unnecessary appointments. Introducing an individualised approach could now move to wider testing and validation in other UK and international settings. The trial only ran for 2 years and was in a long-established programme with low rates of disease, so monitoring of attendance and retinopathy rates should be included as part of wider testing.

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Scientific summary

Background

Diabetic retinopathy remains the most common cause of visual impairment in working populations worldwide. Systematic annual screening to detect and treat sight-threatening diabetic retinopathy (STDR) is established in several countries including the United Kingdom (UK) and has greatly improved the detection of treatable disease. With the rapid increase in the prevalence of diabetes, new approaches to screening are required. Risk stratification, personalised (individualised) medicine, and clinical bioinformatics offer opportunities to extend the screening interval for people at low risk of progression and to target those at high risk. However there is significant concern among people with diabetes, healthcare professionals and health commissioners in the UK around the safety and acceptability of changing an established and successful programme. To ensure that health care is available for all it is imperative that it is not only efficacious but cost-efficient, that is, it delivers care at an affordable cost for commissioners. Evidence to guide these decisions is very limited and there are no randomised controlled trials (RCTs).

Much of the data on prevalence and incidence of diabetic retinopathy and progression to more severe stages of disease come from the 1980s to 1990s and before the introduction of systematic screening and improvements in diabetes and blood pressure control. Data on the current progression rates in screening populations are limited and are reported variably.

We conducted a programme of quantitative and qualitative research to develop and test the acceptability, safety, efficacy and cost-effectiveness of an individualised approach to screening for STDR.

To provide data for future planning of early detection programmes and the design of future research studies we designed a longitudinal observational cohort study of the population of people with diabetes in Liverpool. We aimed to investigate the prevalence and incidence of the stages in the natural history of diabetic retinopathy, namely screen-positive, sight-threatening and treatable disease, and visual impairment, all key patient-centred outcomes in the disease.

Changes to the programme and their implications

A number of changes to the programme occurred in the early years. A systematic review was published at around the time of the programme start. We used these data to design aspects of the study and conducted a literature review instead. Data for the cohort study proved not to be available on people who had died prior to programme start. We adopted a mixed retrospective and prospective analysis but this added some difficulty in interpreting the findings.

In 2016 resources were repurposed from the cohort study to support recruitment of the RCT, which was behind schedule. The scope of the cohort study was narrowed to focus only on the data available from the screening programme, meaning that we were unable to complete data collection on the patient-centred outcomes after sight-threatening retinopathy had been confirmed, namely treatment and visual impairment. Recruitment of non-attenders proved beyond the resources available and was abandoned. Further research is needed to address these unanswered questions.

Methods

The programme included the development of a bespoke data warehouse, the development of a risk-calculation engine, a RCT, a within-trial cost-effectiveness study, a qualitative study of acceptability, and an observational cohort study. We recruited and fully embedded a seven-person patient and public involvement group which was maintained throughout the programme.

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The setting was the screening programme of a single English health district (clinical commissioning group). All people with diabetes aged 12 years and over registered with general practices in the Liverpool city area were invited by letter to participate in the research programme. Consent was through an opt-out process.

A purpose-built dynamic data warehouse was developed to support all aspects of the programme including bespoke processes addressing inconsistency in routinely collected data, multiple data platforms and lack of technical manuals. Data on eligible participants were sourced from primary care (demographic, clinical), Liverpool Diabetes Eye Screening Programme (retinopathy) and hospital outcomes (true screen-positive, STDR). Data were cross referenced against opt-out records before further use within the programme.

A risk-calculation engine was developed for the assessment of individual risk of progressing to screen-positive using patient-focused covariate selection, a continuous-time Markov model, 5-year historical local population data, and the most recent individual demographic, retina and clinical data. The risk-calculation engine was linked to the data warehouse. The Patient and Public Involvement group determined the risk criterion of < 2.5% and screening intervals of 6, 12 and 24 months. These were set as high-, medium- and low-risk for progression to screen-positive respectively.

We conducted a masked, two-arm, parallel assignment, equivalence, RCT with design input, monitoring and analysis by an independent trial unit. Recruitment took place at screening clinics with invitations given to all attenders. After informed (opt-in) consent, participants were allocated 1 : 1 to either annual (control) or variable-interval risk-based screening (individualised, intervention arm) at 6, 12 or 24 months determined by the risk-calculation engine. At each visit the risk was recalculated and the interval reassigned.

Our primary hypothesis was that attendance rates at first follow-up (primary outcome) would be equivalent in the two arms with a 5% equivalence margin. We allowed up to 90 days for attendance after invitation. The estimated minimum sample size was 4460 for 90% statistical power, a 2.5% one-sided type 1 error, assuming the same attendance rate in both arms and allowing for 6% per annum loss over 24 months. Our secondary hypothesis was that detection of STDR was non-inferior in the individualised arm at a prespecified margin of 1.5%. Our analyses followed a per-protocol approach supported by secondary intention-to-treat and multiple imputation analyses. Other secondary outcomes measured efficacy (rates of screen-positive and STDR) and cost-effectiveness [cost/quality-adjusted life year (QALY), incremental cost savings].

A sample (n = 868) of the first participants enrolled into the RCT completed a set of health economics questionnaires. These included a detailed health resource use questionnaire and quality-of-life measures (EQ5D-5L and HUI3). We measured the current cost of screening and the cost of non-attendance using a detailed micro-costing approach to establish the NHS cost of diabetic retinopathy screening. The analysis was within the trial. Clinic costs were observed for each service delivery setting across a sample of clinics. Costs were also directly measured from the patient-based trial case record forms (CRF) and detailed NHS and hospital costs for areas such as photography and grading. As such this was a mixed-methods approach to obtain an accurate picture of screening costs. We developed a bespoke questionnaire to measure participant and companion costs and undertook a detailed workplace analysis to measure resources and staff time. We estimated the additional costs of running the risk-calculation engine using a screen population size of 22,000 (Liverpool).

The within-trial cost-effectiveness of the options was investigated over a 2-year time horizon assessed as cost per QALY for NHS and societal costs using the EQ5D-5L and HUI3 instruments at baseline and follow-up visits including ingredient-based costing and patient resource-use data. Incremental cost savings per person screened were calculated. Multiple imputation was conducted with chained equations using available case data.

For the qualitative study, semi-structured interviews were used with 60 people with diabetes (30 before and 30 after introduction of individualised screening) and 21 healthcare professional participants involved in eye screening identified using purposive sampling. Recruitment was by specific letter and included an additional ‘opt-in’ consent process. Interview data were analysed thematically using the constant comparative method until saturation.

The observational cohort study was conducted on data in the data warehouse listed above after exclusion of people who opted out. The values for time-dependent variables closest to the screening episode were used. Incidences of screen-positive, screen-positive due to diabetic retinopathy and STDR in the population undergoing active screening were estimated. STDR was determined from hospital records of slit lamp examinations within 90 days of the screening episode. Data were corrected for the effects of censoring prior to the commencement of the programme in 2013 and recruitment to the individualised arm of the RCT.

Reporting followed CONSORT 2016 guidelines for non-inferiority and equivalence trials, and CHEERS, COREQ and STROBE guidelines.

Results

Data warehouse: Accessing data from multiple platforms was challenging due to poor or absent documentation. Quality of data entry was highly variable, requiring bespoke solutions. Data were available by the end of the programme (January 2020) on 28,384 individuals with 318,053,075 data items.

RCT: 4534 participants were randomised: 2097/2265 (individualised arm) and 2224/2269 (control arm) remained after withdrawals. Attendance rates at first follow-up were equivalent (control 84.7%, individualised 83.6%) (difference −1.0, 95% confidence interval −3.2 to 1.2). Within the individualised arm equivalence was found for the low-risk group [control 85.7%, individualised 85.1%, difference −0.6% (−2.9 to 1.7)]. For the medium-risk group the difference in attendance was small but equivalence was not confirmed due to the relatively wide confidence interval. In the high-risk group attendance was lower in the individualised group [control 77.3%, individualised 72.3%, difference 5.0% (−13.6 to 3.5)]. STDR detection rates were non-inferior: individualised 1.4%, control 1.7% (−0.3, −1.1 to 0.5). Sensitivity analyses confirmed these findings.

No clinically significant worsening of diabetes control was detected and no effect on rates of visual acuity or visual impairment. 43.2% fewer screening appointments were required in the individualised arm. Within the individualised arm the high-risk group had the highest screen-positive rate [high 10.72% (34/317), medium 6.02% (15/249), low 3.7% (53/1442)]. The risk-calculation engine and data warehouse were stable.

Cost-effectiveness study: Summary costs (2019/2020 values) associated with the screening programme to the NHS were £28.73 per attendance and £12.73 per non-attendance, while additional productivity losses and out-of-pocket payments by the patient accounted for £9.00. There was dominance of individualised screening in terms of QALYs gained (non-significant) and cost savings. Mean differences in complete case QALYs did not significantly differ from zero. Incremental cost savings per person (not including treatment costs) were: £17.34 (17.02 to 17.67), NHS perspective; £23.11 (22.73 to 23.53), societal perspective.

Qualitative study: For the majority of both people with diabetes and healthcare professionals changing to variable intervals was perceived as acceptable. Annual screening was perceived as unsustainable against the increasing diabetes prevalence and to be an inefficient use of resources. Many people with diabetes and healthcare professionals expressed concerns that 2-year screening intervals might detect referable disease too late and would have a negative effect upon perceptions about the importance of attendance and diabetes care. The 6-month interval for the high-risk group was perceived positively as medical reassurance. Among people with diabetes, there was considerable conflation and misunderstanding about different eye-related appointments and care.

Observational cohort study: Numbers of participants rose from 6637 (2006/7) to 14,796 (2016/17). After exclusions/ineligibility (opt-out was 7.1% over the programme) data from 28,384 PWD were available for analysis. Annual incidences (%) in the screened population were: screen-positive [4.4–10.6, due to diabetic retinopathy (2.3–4.6)], STDR (1.3–2.2). Rates of screen-positive and screen-positive from diabetic retinopathy dropped over the 11 years. STDR remained stable with 53.8% being true-positive.

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Rates were higher in people with diabetes attending screening for the first time but only 28.1% of these were true-positive.

Conclusions

Evidence from our RCT, the largest ophthalmic RCT in individualised diabetic retinopathy screening to date, can reassure all parties involved in diabetes care that extended and personalised screening intervals can be safely introduced in established screening programmes. There are potential improvements in cost-effectiveness by moving to individualised screening without harming people currently receiving annual screening. Our findings support the scale-up of individualised screening through whole programmes in the UK outside a research setting. However, evidence of repeatable results and validation of the risk engine in at least one other screening programme are needed.

There are a number of limitations in the findings of the programme. We had low rates of retinopathy and sight-threatening retinopathy in our 24-month group and overall. This is not unexpected in a long-established systematic screening programme like ours. Findings may not be generaliseable across other programmes in the UK; our data are from a single programme with predominantly white ethnicity. More widely, our findings should be treated with caution in populations with a higher prevalence, poorer control of diabetes or wider ethnic mix, or in programmes during the set-up process.

Our trial had a 2-year time horizon, which is short in the context of a life-long condition. However, moves to extend to 2 years for people at low risk of progression are gathering pace and so our findings are relevant to this question. Most disease was detected in the high- and medium-risk groups [sight-threatening retinopathy by 24 months: high-risk group 37 (12.2%), medium-risk group 12 (3.6%), low-risk group 14 (0.4%)]. There were potential cost savings with moving to variable-interval screening which are unlikely to be lost over a longer time horizon. However, further modelling to include lifetime costs of treatment and care would be beneficial.

A switch to variable-interval risk-based screening appears to be acceptable to people with diabetes and healthcare professionals. However, there were important caveats. For individualised screening programmes to be successfully implemented clear safeguards will be needed to allay user anxiety. Changing the message to people with diabetes from the importance of regular, annual check-ups to one of varying the time between screening episodes is unlikely to be easy or straightforward. Further qualitative research should address acceptable safeguards and monitoring, investigate the reasons for non-attendance and develop approaches to improve understanding of eye disease in diabetes.

Cohort data collection was partly retrospective and around 5% of the screening population died or moved away. However, our findings show that rates of screen-positive diabetic retinopathy and STDR are low and show a consistent fall over time. Higher rates of disease are seen in new screenees in spite of 80% of screen-positives being due to media opacity or other significant eye disease. Further research on visual impairment in people with diabetes attending hospital will give a clearer picture of the impact of diabetes on vision.

Involvement of patients in research is crucial to success. A research connector is required in structured well-supported Patient and Public Involvement meetings, with participation of the chief investigator.

Trial registration

This trial is registered as ISRCTN87561257.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research programme and will be published in full in *Programme Grants for Applied Research*; Vol. 11, No. 6. See the NIHR Journals Library website for further project information.

Synopsis

Background

A recent report by the World Health Organization (WHO) shows that diabetic retinopathy (DR) remains one of the most common causes of visual loss in adults worldwide.[1] Screening for DR aims to detect sight-threatening DR (STDR) and refer people with diabetes (PWD) to the hospital eye service (HES) for timely treatment. Systematic programmes of screening are universally recognised to be important in preventing visual impairment (VI).[2]

In England, annual eye screening for STDR for PWD over the age of 12 years commenced in the early 1990s and developed into the National Diabetic Eye Screening Programme (NDESP), with complete coverage achieved by 2008.[3]

As in many other countries, the programme screening interval was set at 12 months in England and Wales for all PWD,[4] while in the HES follow-up intervals are variable. Evidence to support the delivery of the pathway is limited to screening research cohorts and with minimal input from users.

There has been a rapid increase in the prevalence of diabetes, increasing faster in low- and middle-income countries than high-income countries,[5] and resources are stretched. Much evidence supporting extended intervals suggests that it is safe to screen low-risk people at longer intervals[6–8] and this has been introduced in some countries. However, the underpinning evidence for this change comes from observational studies in areas with low incidence rates[6,9–11] and from modelling studies,[12–14] and is not conclusive. In England and Wales, extended intervals have not been adopted, largely because of safety concerns highlighted by a recent systematic review calling for a randomised controlled trial (RCT) and cost-effectiveness data,[8] and recent problems in cancer screening programmes.[15]

The emerging technologies of digital data linkage and risk prediction offer opportunities to personalise the approach to screening. By varying the frequency of screening depending on a person's own risk of progression, an individualised approach can be developed with further potential improvements in effectiveness and cost-effectiveness.

There are potential opportunities for reallocation of resources within the NHS by varying the screen interval, but no cost-effectiveness research data other than from limited modelling. The safety and acceptability of extending the screen interval in low-risk groups have not been investigated.

Estimates of the incidence and prevalence of DR are important in designing screening programmes and clinical services. The landmark epidemiological studies on DR that have provided these data are over 30 years old.[16,17] Since then, there have been changes in diagnostic criteria for diabetes,[18,19] and diabetes and blood pressure (BP) control have improved in some populations.[20] At the time of the design of this programme, there were few data on incidence and prevalence in screening populations, mainly those from our own work in the 1990s.[6] As systematic programmes have been introduced and detected early disease, incidence in screened populations has changed, characterised as the 'first pass effect'. Clinical studies of interventions aimed at early disease utilise cohorts, such as those undergoing systematic screening, and require prevalence and incidence data for study design and comparison.

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Aims and objectives of the ISDR programme of applied research

Our aim in this National Institute for Health and Care Research (NIHR) Programme Grant for Applied Research (PGfAR) on individualised screening for DR (ISDR) was to conduct a mixed quantitative and qualitative programme of research to strengthen the evidence base for DR screening in the United Kingdom (UK) and beyond. We structured the programme in work packages, reordered here to aid the narrative in our report. A very active patient and public involvement (PPI) group was involved throughout, so we describe their involvement first, with additional detail in *Supplementary Material 1*.

Data warehouse (work package B1)

The aim of work package B1 was to collate, link and store patient data from routinely collected sources in a study data warehouse (DW) to support the development of a risk-calculation engine (RCE), the RCT and epidemiological, qualitative and cost-effectiveness studies.

The Liverpool Risk Calculation Engine (work package C)

The aim of work package C was to develop an individualised (personalised) method of calculating screen intervals using a RCE based on individual risk factors (see Eleuteri *et al.*[21]).

RCT to evaluate the safety, efficacy and cost-effectiveness of individualised variable-interval risk-based screening (work package E)

The aim of work package E was to investigate the safety, efficacy and cost-effectiveness of longer screening intervals in low-risk PWD and shorter intervals in high-risk PWD (see Broadbent *et al.*[22,23]).

Health economics (work package D)

The aim of work package D was to estimate the likelihood that individualised screening is more cost-effective than current practice (see Broadbent *et al.*[23]).

Qualitative study with patients and healthcare professionals on changing screening intervals (work package F)

The aim of work package F was to explore the underlying perceptions of screening and early detection, and to test the acceptability of our new method of screening to PWD and healthcare professionals (HCPs) (see Byrne *et al.*[24]).

Observational cohort study in people attending DR screening (work package B2)

The aim of work package B2 was to conduct a whole-population longitudinal observational cohort study to estimate up-to-date rates of incidence of DR and STDR in PWD in Liverpool (see Cheyne *et al.*[25]).

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Knowledge transfer and preparation for implementation (work package G)

To disseminate the research findings to clinical and academic beneficiaries, develop an NHS implementation plan through a dissemination event and develop any intellectual property (IP).

Figure 1 shows the stages and development of the work packages, how the work packages interconnect and the contribution of each work package (WP) to the whole programme.

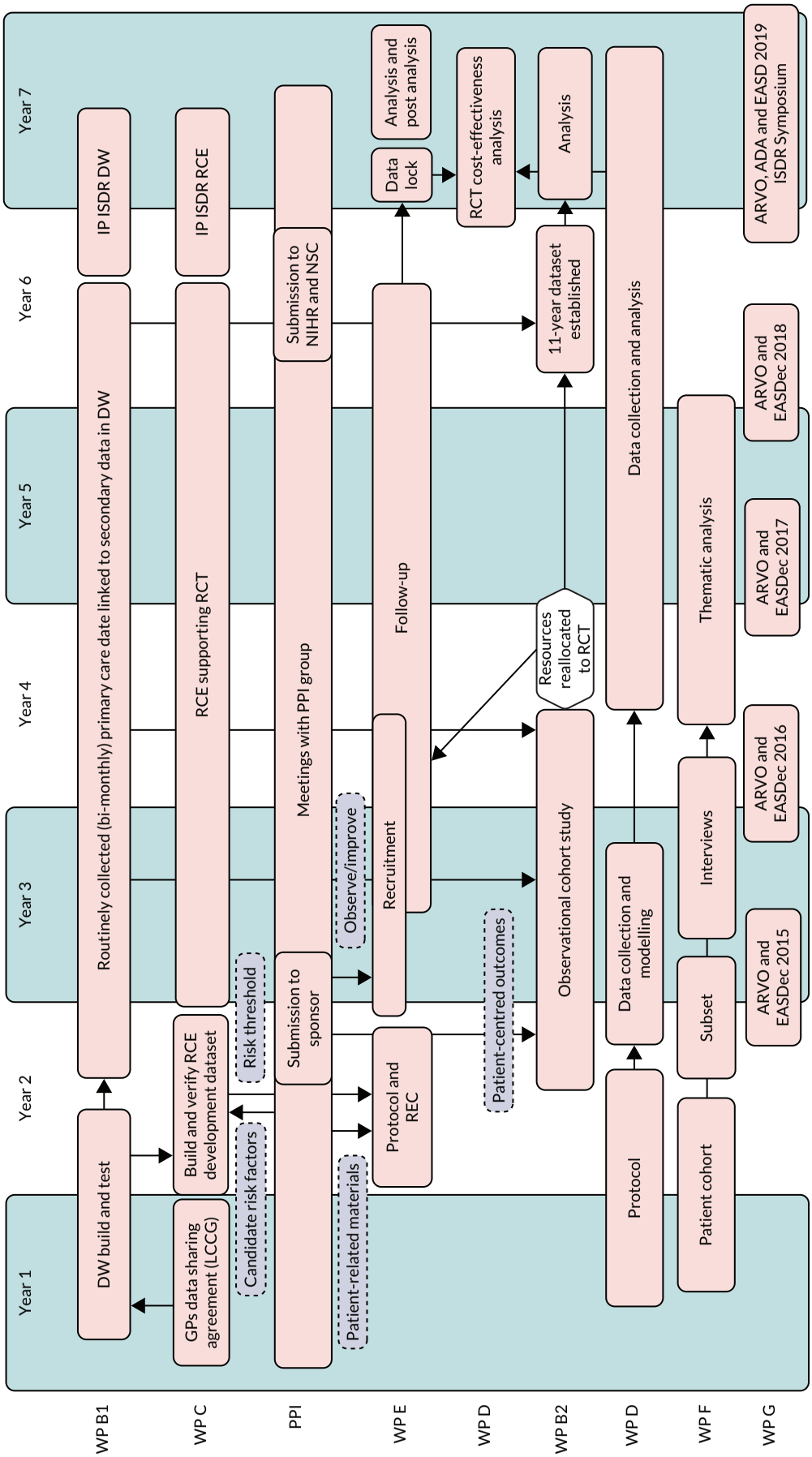


FIGURE 1 Pathway diagram showing the work flow in the ISDR Programme Grant for Applied Research, the work packages and their interrelationships. WP B1 DW development; WP C RCE; PPI (involvement shown in dashed boxes); WP E RCT; WP D Health economics; WP B2 Observational cohort study; WP F Qualitative study; WP G Dissemination. Resources were reallocated to the RCT from the cohort study in year 4 to support delayed recruitment (white hexagon and arrow). Arrows indicate input into specific item(s) of a WP. ADA, American Diabetes Association; ARVO, Association for Research in Vision and Ophthalmology; EASD, European Association for the Study of Diabetes; EASDec, European Association for the Study of Diabetes eye complications study group; LCCG, Liverpool Clinical Commissioning Group; NSC, National Screening Committee.

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Changes to the programme

A number of changes to the planned programme of work occurred in the early years of the programme:

- We planned to conduct a systematic review (WP A in the grant application). However, a systematic review in this area by Taylor-Phillips *et al.*[8] was published early in the programme in 2016. To replicate this was inefficient and, therefore, we conducted a literature review instead. Taylor-Phillips *et al.*[8] concluded that there was insufficient evidence to recommend a move to extended interval screening and mixed and poorly designed cost-effectiveness studies. They provided further confirmation of the need for a RCT with a robust economic analysis.
- A decision was made by the NIHR PGfAR team in May 2016 to move resources from the cohort study to support the RCT (WP E), which was behind with recruitment. This meant that the cohort study needed to be scaled back. We were able to report findings in an 11-year cohort of PWD being screened in Liverpool, but not the people attending the HES.
- The observational cohort study (WP B2) utilised data prospectively collected from 2005. However, we were unable to obtain data on people who had died prior to the start of the programme. This resulted in the cohort needing to be considered as partly retrospective, making analysis more difficult to interpret.
- We were unable to recruit non-attenders in the screening programme, a secondary aim in our qualitative study (WP F), despite multiple attempts in an identified cohort.
- We had intended to interview participants longitudinally in the qualitative study. However, insufficient participants responded to our invitation, so we revised our sample to reach 60 single interviews.

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Patient and public involvement in the ISDR programme

Public engagement is considered a key element in healthcare research by UK and international funders to ensure that research is relevant. Effective engagement empowers patients, ensures research is fit for purpose and develops patient-centred outcomes. NIHR describes involvement of the public in research under its 'INVOLVE' guidance.[26]

Aims

We set out to involve members of the public in all aspects of our programme, the RCT in particular, and to support the research team to make the research relevant, attainable and applicable to patients and HCPs.

Methods

Seven PWD were recruited to the programme with the help of local and national service-user groups. Some members were recruited during the development phase of the programme, with all of the current group retaining membership during the course of the research grant.

The methods developed for the PPI group within ISDR are listed below:

- We held regular meetings preceded by lunch in a venue located within the university campus. The location helped to create a relaxed and social atmosphere.
- We sent the agenda prior to meetings, and any information related to agenda items with items signposted for discussion with and decisions by the group.
- We made significant efforts to 'translate' any scientific or medical information.
- Our discussions of items often created more questions from our PPI members and a need for other information. We realised early on in the meetings that we often needed at least two (and sometimes three) sessions to discuss agenda items and arrive at a considered position. Much of the information that we gave was technical, scientific or medical and there was often an associated high amount of material. We were asking our PPI group to make significant research decisions, such as the level of risk for the RCE, that would affect other PWD.
- We worked with the PPI group in their decision-making to ensure that they were able to arrive at decisions without any doubts around their understanding or favouring a decision. This involved the following:
    - The chief investigator (CI) of the programme attended every PPI meeting and gave an update on the RCT.
    - We created a 'research translator', a member of the team who checked on the PPI group's understanding and expectations.
    - We invited experts from the ISDR research team to give presentations and answer any queries from members of the PPI group.
    - We fed back at every meeting the progress of the PPI group's decisions on every aspect of the RCT.

- Members of the PPI group were also on the Programme Steering Committee, Programme Investigators Committee and Trial Steering Committee and had a macro view of the research process. Before each of these meetings, a pre meeting took place between the PPI member and one of the investigators.
- Operational, logistical or political issues were discussed with the group for potential strategies.

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Results: summary of patient and public involvement contributions to the ISDR programme

We met with our PPI group 19 times between 2013 and 2019, as detailed in *Supplementary Material 1*. In summary, they:

1. contributed to the programme development grant and research and programme grant application
2. developed with the research team candidate risk factors associated with progression of DR (WP C)
3. prioritised research questions by identifying the most important patient-centred outcomes (WP B2)
4. were heavily involved in setting the acceptable risk threshold in the RCE to be tested in the RCT (WPs C and E)
5. assisted in the preparation of patient-related materials, such as consent forms and patient information booklets (WP E)
6. suggested measures to improve study recruitment by observing screening clinics and the ISDR RCT consent process (WP E)
7. made suggestions to the clinical director of the Liverpool Diabetic Eye Screening Programme (LDESP) to improve screening attendance
8. served on oversight committees and helped to resolve issues during the lifetime of the grant
9. participated in cost-effectiveness analyses and suggested ways in which savings could be used to improve future services (WP D)
10. commented on this report and draft papers from the RCT and a paper on the acceptability of variable-interval risk-based screening to HCPs and PWD (WP F)
11. were involved in a PPI session in the dissemination conference (WP G).

Discussion: reflections/critical perspective

Members of our PPI group had a very positive impact on all aspects of the programme and strongly supported the research team. Their activities have been wide-ranging, not only in the technical details of the RCT, but also in their lobbying for variable-interval screening. As PWD, they were primarily concerned about the safety of the trial and improving the health of others, and mindful of the potential consequences of making the wrong decision and its impact on others' lives. Our key lessons on successful PPI are set out in *Box 1*.

BOX 1 Lessons from the ISDR programme on PPI in research

How to develop a successful PPI group:

- Co-investigators and preferably the CI to attend all PPI meetings.
- Identify a 'research translator' or 'research connector' with sufficient knowledge of the research objectives and empowered to constructively challenge the research team.
- Identify critical decisions in the research design to be taken by the group and develop a process to reach a clear conclusion. Needs to extend beyond reviewing patient information sheets and consent forms.
- Avoid overload – plan to address two to three topics at each meeting and develop over a series of meetings.
- Go slowly – give time for PPI members to express their opinions.
- Assess levels of knowledge at all stages.
- Hold regular meetings in a relaxed environment.
- Ensure an appropriate spread of ages, experience and, where relevant, disease type.
- Work hard at maintaining engagement over the duration of the research.
- Ensure adequate funding is available.

What can be achieved?

- Patients and members of the public can become 'patient experts'.
- Complex nuanced decisions can be reached.
- Patient-centred outcomes can change research questions.
- Well-argued patient opinions that are much more powerful than views of academics.
- A research team with greatly improved communication skills and a clearer insight of the potential impact of their research.

Over the extended duration of our research programme, our PPI members developed wide expertise and became 'patient experts'. Further work to develop systems to retain and build on this expertise could provide a useful resource for funding bodies and policy-makers.

Interrelation to other work packages and overall aims of the programme

The PPI group members supported most work packages of the programme, including B2 (observational cohort study), C (RCE), D (health economics), E (RCT) and F (qualitative study).

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The ISDR study data warehouse

Research aims

To design and develop a purpose-built DW to support the development of the RCE, the delivery of the RCT, and the economic, qualitative and cohort studies.

Methods

Using Structured System Analysis and Design Methodology,[27] the ISDR business intelligence (BI) team designed and built the ISDR DW and supporting architecture. The DW centralises data into a single Microsoft SQL (structured query language) server data repository hosted on a secure private local area network within the Department of Medical Physics and Clinical Engineering at the Royal Liverpool and Broadgreen University Hospital Trust (RLBUHT). All incoming and outgoing file transfers were carried out using secure networks and encryption methods, and received local information governance approvals (Privacy Impact Assessment, Data Governance Committee, Caldicott Guardian).

The following data sources interacted with the ISDR DW:

- Demographic and systemic risk factor data from general practices (GPs) via the Liverpool Clinical Commissioning Group (LCCG) (Egton Medical Information Systems, EMIS Web, EMIS Health; www.emishealth.com).
- Demographic, retinopathy grading and visual acuity (VA) data from –
    - the LDESP, collected in the Orion/Digital healthcare database between 1995 and 2013 and in OptoMize from 2013
    - HES-based screen-positive assessment clinics, collected in a bespoke Microsoft Access database (Diabolos) (1991–2015) and the hospital patient electronic notes system (PENS) (from 2016).
- Appointment and treatment records from the hospital's integrated patient-management system.
- An 'opt-out register'. PWD who were registered with GPs in Liverpool were informed of the project in a letter addressed from the screening programme. Their consent for inclusion in the DW was obtained via an 'opt-out' method and a record of those patients who opted out was kept in a register.

The flow of data in the programme is illustrated in *Figure 2*.

The DW received all relevant data from PWD streamed from primary and secondary care. The RCE was fed directly from the DW. Risk factors included were demographic (e.g. age, deprivation and ethnicity), ocular (e.g. previous and current retinopathy severity, previous treatment and VA) and systemic (e.g. diabetes control and duration, BP, and lipids). The data fields are listed in more detail in *Supplementary Material 2*, *Table 1*.

To ensure the credibility of data coming from multiple sources, which contained data with varying quality, covariates in the source data were examined for outliers and distribution inconsistencies. Credibility limits were developed using a statistical methodology. This set of scripts cleansed and validated incoming data for the DW. Input and output schemas (see *Supplementary Material 2*, *Table 2*) were developed for each data transfer element, as indicated by the arrows in *Figure 2*.

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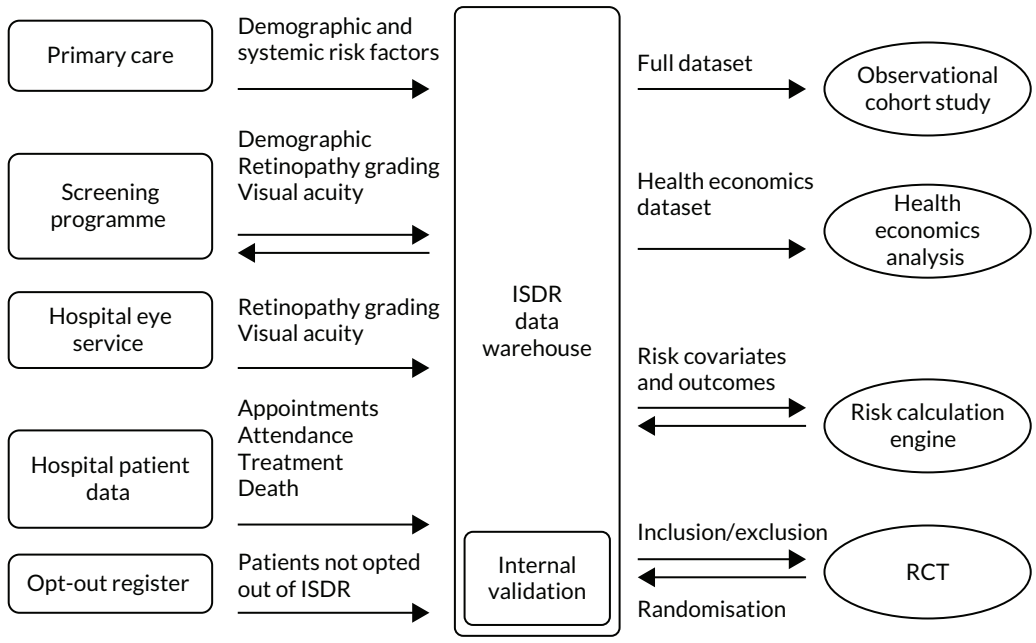


FIGURE 2 Diagrammatic representation of ISDR DW data flows.

Results

The ISDR DW held data from 2009 on 28,556 participants as of January 2020 (end of the programme) over 11 screening cycles. Data linkage was achieved for all participants. The ISDR DW received test and preliminary data sets from early 2013. One of the main data sets was the 'ISDR Cohort Study Dataset', which supported WP B2. This contained data for 28,384 participants in October 2017, equivalent to 318,053,075 data points; a data point is a discrete unit of information,[28] an example being a single recording of weight for a patient.

Discussion: challenges in the DW

The ISDR programme collated and linked large-scale routinely collected clinical data across different domains in a single repository. It successfully supported all aspects of the programme and routine patient management in the local screening programme. The DW is dynamic in that it updates on a regular basis. It demonstrated resilience and the potential to be developed into a routine health informatics tool in the NHS for personalised medicine.

We faced a number of challenges. No existing 'off the shelf' databases existed. The data were complex and came from multiple data sources. The Liverpool CCG had to set up and run a set of manual processes throughout the lifetime of the project to link the various domains within primary care. There was variability in data quality, which required bespoke processing and the development and application of credibility limits before the data could be considered adequate for a clinical application. Systems were of widely differing design: some were commercial (OptoMize) and some were developed in house (Diabolos, PENS). Systems had to be 'cracked' before the relevant data could be extracted. Data labels had to be investigated and tested. Several clinical system upgrades took place during the lifetime of the programme, which tended to occur unannounced, resulting in some lengthy delays and wasted effort.

The multidisciplinary nature of the programme meant that several members of the team had very little understanding of the requirements of database development and engineering, and similarly the database team struggled with adequate engagement with the clinical teams. There appears to be a lack of

bioinformatic expertise to act as a bridge between the technical BI and computer science teams on the one hand and the clinical/research end-users on the other. This needs urgently addressing.

We learnt several important lessons. Establishing a real-time data repository within an NHS environment to underpin personalised medicine requires:

- sufficient time for interdisciplinary team working on data sanity checks, outlier/credibility handling protocols, logic rule development and imputation strategies
- investment in developing cross-disciplinary bioinformatics expertise to link technical teams and clinical/research end-users.

Interrelation to other work packages and overall aims of the programme

In addition to the underpinning role of the DW across much of the programme, it has led to development of new IP covered in WP G. Imputation strategies needed to be developed in several WPs to deal with missing data.

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The Liverpool Risk-Calculation Engine

A peer-reviewed publication[21] reports additional information on the continuous Markov process, imputation, covariate selection, threshold setting and model checking.

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Research aims

To develop and internally validate a RCE to estimate the risk of progression to screen-positive or referable DR and assign individualised screening intervals (WP C).

Methods

Data set

Data from established screening and primary care systems were combined in the ISDR DW. A set of candidate covariates was selected for the model in partnership with our PPI group. A review of the literature around the known risk factors was presented by the research team, and additional candidate covariates were proposed by the PPI team to create a 'long list'. The ISDR DW was explored with this set of candidates in mind, and a RCE development data set was extracted containing covariates with ≥ 80% completeness in PWD who were screen-negative at the first of at least two episodes that occurred in a 5-year sample period.

Model

We selected a continuous-time Markov process to allow for a set of individuals to transition among states over time.[29] The state at each time point was defined by the level of retinopathy, including separation by one or both eyes (*Figure 3*):[30] state 1 – no DR detected; state 2 – non-referable DR in one eye only; state 3 – non-referable DR in both eyes; and state 4 – referable DR (screen-positive for at least one eye).

Only one baseline screening event was used. The risks or intensities for each of six transitions between these states were entered into the model within a probability matrix. The interval censoring seen in screening data required special methodology. Missing clinical data were handled using multiple imputation.

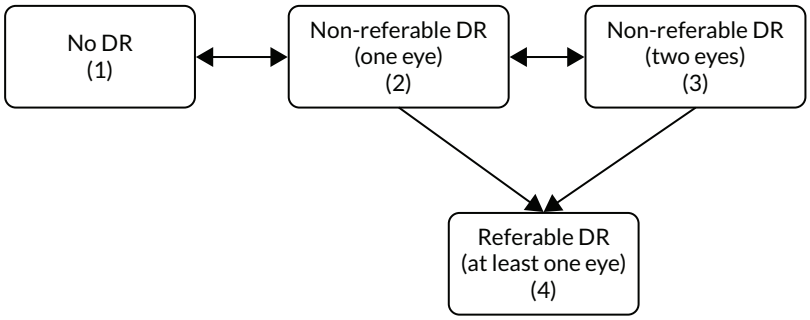


FIGURE 3 States and transitions in the continuous-time Markov process in the Liverpool Risk-Calculation Engine.

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Ten covariates met the entry criteria and were ranked using Wald statistics. A set of nested models were built to estimate corrected Akaike's information criterion (AICc). The model with the smallest AICc was chosen to give the best fit to the data.

We checked the RCE development data set using random samples of event vectors. The model was checked for the influence of outliers, regression and distributional assumptions; Pearson-type goodness of fit and corrected C-index were calculated. Bootstrapping and fourfold cross-validation were used for internal validation. Further internal validation was conducted using a geographical split based on deprivation index.[31]

Implementation

The effect of a set of risk thresholds (5%, 2.5%, 1%) on screening interval allocation was investigated and a final threshold was selected in discussion with the PPI group.

A small sample of cases assigned by the RCE to 6-, 12- and 24-month intervals were independently checked against patient records for clinical credibility.

After design and testing, the RCE was implemented within the Liverpool Clinical Trials Centre for testing within the RCT (see *Randomised controlled trial to evaluate the safety and cost-effectiveness of individualised variable-interval risk-based screening*). Data were received from the DW electronically on a daily basis.

Results

Data extracted into the RCE development data set were from 11,806 PWD attending the LDESP between 20 February 2009 and 4 February 2014.

Covariates meeting the selection criteria are listed in *Table 1*. Those that gave the best fit and were included in the final model were disease duration, glycated haemoglobin (HbA_{1c}), age at diagnosis, systolic BP and total cholesterol. Although the retinopathy stage is not technically a covariate, it is included in the table to show the improvement in predictive power when covariates are added to the model.

TABLE 1 Ten covariates included in the initial model with corresponding Wald statistics, rescaled AICc and proportions of explained likelihood. Covariates above the double line were included in the final model

Covariates	Wald statistic	Rescaled AICc	Explained likelihood (%)
Retinopathy (baseline)		893.65	–
+ Disease duration (years)	293.4	423.23	48
+ HbA_{1c} (mmol/mol)	201.2	68.61	85
+ Age at diagnosis (years)	44.2	10.85	92
+ Systolic BP (mmHg)	18.9	6.61	94
+ Total cholesterol (mmol/l)	18.7	0	96
+ Disease type	15.2	0.99	97.5
+ Diastolic BP (mmHg)	8.2	5.61	98.6
+ eGFR (ml/min^{-1} 1.73 m$^{2\ -1}$)	5.4	13.63	99.4
+ Sex	5.1	24.95	99.9
+ HDL cholesterol (mmol/l)	0.73	40.99	–

AICc, Akaike's information criterion; HDL, high-density lipoprotein.

The risk model is summarised in three equations. The first gives the hazard rates (or intensities or 'risks') of going from one state to another for each transition:

$$\log \lambda_{ij} = \beta_{ij}^{0} + \beta_{ij}^{AgeD} AgeD + \beta_{ij}^{DiseaseD} DiseaseD + \cdots + \beta_{ij}^{SP} SBP, \quad (1)$$

where $i, j = \{1, 2, 3, 4\}$ and β^{C}_{ij} is the model parameter for covariate C (or baseline intensity when C = 0); *AgeD* is age at diagnosis and *DiseaseD* is disease duration. From this equation, a transition intensity matrix is derived for the four states described above:

$$Q = \begin{pmatrix} -\lambda_{11}\lambda_{12} & 0 & 0 \\ \lambda_{21} & -\lambda_{21} - \lambda_{23} - \lambda_{24}\lambda_{23} & \lambda_{24} \\ 0 & \lambda_{32} & -\lambda_{32} - \lambda_{34}\lambda_{34} \\ 0 & 0 & 0 \end{pmatrix} \quad (2)$$

Probabilities of transition occurring at a specific time are obtained by using the third equation:

$$P(t) = \exp(Qt^{0.9}) \quad (3)$$

Tables 2 and *3* show the estimated baseline hazard ratios and probabilities of each transition state. Further details are available elsewhere.[30]

Data and model checking

Homogeneity in the RCE was checked by smoothed summary residuals compared with follow-up time with 95% CI. The calibration curves for the Cox–Snell residuals were close to the theoretical optimal calibration. The Pearson-type statistic denoted not enough evidence to reject the null hypothesis of good fit. Cross validation showed that the training and test performance measures were essentially the same. Fitting the model to the most deprived subjects produced only very small changes in risk allocation of the non-deprived group.

Setting the risk threshold

The PPI group identified acceptable screen intervals of 6, 12 and 24 months, and risks of 1% and 2.5% of missing screen-positive disease at any future screen episode. Exploration of the effect of different risk thresholds on allocation to the three different screen intervals showed that, as the threshold decreased, the proportion of incorrect allocations decreased for screen-positives (overestimation) and increased for negatives (underestimation). For all three, there was a reduction in the overall number of screening episodes required. The research team and PPI group considered that a 2.5% criterion showed a satisfactory distribution across the three screening intervals and a reasonable reduction in episodes, and this was selected for implementation.

Discussion

We have developed and tested a RCE in which an individual's risk can be predicted from routinely collected clinical data, referenced to the clinical histories of the local population, and using covariates of local relevance. The risk can be reassessed at each screening episode as new clinical information is acquired.

Strengths of our model include the strongly embedded PPI group, which allowed us to develop an appropriate preliminary covariate list, acceptable screen intervals and risk threshold. The model internally handles interval censoring, inherent to retinopathy data in screening.[29] It predicts the

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TABLE 2 Baseline hazard ratios for each transition, with 95% CIs

	HR for transition (95% CI)				
Transition	**Age at diagnosis**	**Disease duration**	**HbA_{1c}**	**Cholesterol**	**SBP**
1 to > 2	1.00450 (1.00115 to 1.00787)	1.0280 (1.0213 to 1.0348)	1.0101 (1.00743 to 1.0128)	0.963 [0.923 to 1.00521]	1.00409 (1.00104 to 0.0073)
2 to > 1	1.00580 (1.00237 to 1.00919)	0.983 (0.975 to 0.992)	0.998 (0.995 to 1.00140)	1.0153 [0.973 to 1.0592]	0.999 (0.996 to 1.00244)
2 to > 3	0.989 (0.984 to 0.994)	1.0261 (1.0173 to 1.0350)	1.00621 (1.00221 to 1.0102)	0.965 [0.901 to 1.0333]	0.998 (0.993 to 1.00255)
2 to > 4	1.0245 (0.990 to 1.0605)	0.989 (0.931 to 1.0510)	1.00554 (0.983 to 1.0285)	1.0231 [–0.27 to 0.37]	1.00342 (0.977 to 1.0310)
3 to > 2	1.00839 (1.00329 to 1.0135)	0.959 (0.949 to 0.968)	0.990 (0.985 to 0.994)	1.0836 [1.0147 to 1.157]	0.997 (0.993 to 1.00126)
3 to > 4	0.986 (0.977 to 0.995)	1.00420 (0.989 to 1.0200)	1.0164 (1.00888 to 1.0239)	1.0346 [0.918 to 1.166]	1.00501 (0.996 to 1.0141)

SBP, systolic BP.

TABLE 3 Baseline probabilities of state transition at 1 year, with 95% CIs

Transition	Probability (95% CI)
1 to > 2	0.114 (0.111 to 0.118)
2 to > 1	0.552 (0.541 to 0.565)
2 to > 3	0.141 (0.134 to 0.148)
2 to > 4	0.0163 (0.0139 to 0.0202)
3 to > 2	0.283 (0.272 to 0.294)
3 to > 4	0.0574 (0.0485 to 0.0678)

probabilities of transition for all patient states and embeds a model for multiple imputation of missing covariates.

Potential limitations include not adjusting for misclassification of retinopathy during grading. This could be addressed by adding a misclassification model but at the cost of substantially more observations and computational complexity. Some potentially useful covariates were not informative in the Liverpool setting: ethnic diversity and prevalence of abnormal estimated glomerular filtration rate levels were low, and 'type of diabetes' may not have been accurately recorded. We used the date of the first HbA_{1c} test to improve data on 'duration of diabetes'. This was helpful in people with long durations but less reliable since the introduction of HbA_{1c} as a primary screening test.

The model consistently showed good levels of prediction for the 2.5% risk threshold. The numbers of screen-positive cases with overestimated screening dates and screen-negative cases with underestimated screening dates were smaller. The majority of people were correctly allocated (78% of screen-positives, 80% of screen-negatives), with a reasonable allocation across the 6-, 12- and 24-month intervals (approximately 10% : 10% : 80%). The number of patients who had a screen-positive event before the allocated screening date reduced by > 50% and the overall number of screening episodes by 30%.

Our RCE development process is suitable for a wide range of geographical locations and populations, with a minimum prerequisite of a disease register with adequate historical data. Revision/addition of covariates can be accommodated based on the strength that they add to a locally developed model. We give the key steps to developing and building such a system in *Box 2*.

BOX 2 Key steps to developing a locally relevant RCE

RCE development: engage local stakeholders:
Data set

- Approvals and systems for regular data transfers.
- Patient and professional groups for covariate selection.
- First iteration data set.
- Explore data and verify.
- Set data range criteria for local relevance.
- Lock risk engine development data set.
- Handle missingness with multiple imputation.

Covariate

- Select preliminary Markov model using all available covariates selection (model fitting).
- Assign informedness to covariates.
- Review with local patient and professional groups.
- Finalise covariates and fix model structure.

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RCE model

- Build test model.
- Agree choice of screen intervals.
- Run diagnostics and validation.
- Final model version (revise if required).

Implementation

- Secure domain for implementation model.
- Determine frequency to update data (recommend 2 monthly).
- Re-tune model (recommend 3 yearly).

The use of near real-time data and a model developed from local data in our approach is novel. Aspelund *et al.*[13] reported on a risk-estimating model using retinopathy data collected in Iceland between 1994 and 1997, and risks for covariates estimated from data published in the 1980s. This was tested in a prospective cohort of people with type 2 diabetes.[32] Discriminatory ability was good (C-statistic 0.83) but 67 out of 76 people (88.2%) who developed STDR developed it after the time predicted by the model. This overestimation of risk highlights the weakness of using historical data. In 2020, van der Heijden *et al.*[33] reported a systematic review of risk-prediction models in DR screening. Discrimination was reported in seven studies with C-statistics ranging from 0.55 to 0.84. Our study[21] was published subsequently and, therefore, was not included. The corrected C-index in the Liverpool RCE was 0.687.

Access to clinical information is not routinely available. We had to overcome significant challenges in developing a near real-time data flow; this may be too difficult in some populations. However, we determined that including clinical data would aid acceptance among the professional community, offer better prospects for generalisability and allow inclusion of more frequent screening for high-risk individuals. Our view is supported by our own data,[6] those of others[34] and our PPI group. We recognise that estimates of resource requirements for introduction of our type of RCE are not available.

External validation of models is required before general implementation.[32,35] An implementation phase will include model updating (temporal validation and model tuning) and the opportunity for comparative cross-population (external) validation to correct for potential over-performance.[36]

Conclusions

This research programme indicates that the Liverpool RCE is feasible, reliable, safe and acceptable to patients. Our evidence suggests that a RCE could offer potential significant transfer of resources into targeting high-risk and hard-to-reach groups, as well as improved cost-effectiveness. Based on the internal validations we performed, it showed sufficient performance for a local introduction and testing of safety and acceptability within a RCT. However, we did not provide evidence of external validation.

Interrelation with other parts of the programme and overall aims of the programme

The RCE was developed using data from primary and secondary care linked through the ISDR DW developed specifically for this programme. It was required for the development of the RCT and is part of the developed IP. It will form part of any potential future benefit from the programme if deployed within the NHS and other countries. The health economics team worked with the RCE team ensuring that the economic model followed the structure and content of the RCE and could be fully integrated alongside it.

Randomised controlled trial to evaluate the safety and cost-effectiveness of individualised variable-interval risk-based screening

Peer-reviewed publications are available on the ISDR RCT and its protocol.[22,23] Additional information is available in these publications on trial methods, sample size revisions, withdrawals, and additional secondary safety and efficacy data. Our economic analysis is described in *Cost-effectiveness of individualised variable-interval risk-based screening for diabetic retinopathy*.

We followed the CONSORT 2016 reporting guidelines for non-inferiority and equivalence trials.

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Research aims

We designed a RCT to investigate the safety, feasibility, efficacy and cost-effectiveness of extending screening intervals in low-risk PWD and reducing screening intervals in high-risk PWD (WP E). We utilised the emerging methodology and technologies of personalised risk prediction[37,38] and an innovative data linkage system to develop an individualised variable-interval risk-based screening approach. Individualised clinical care offers opportunities for improved patient engagement.

We tested the hypothesis of equivalence between the attendance rates as a primary measure of safety, for individualised and annual screening. An equivalence design was selected, instead of a superiority trial, because the aim was to demonstrate equivalence between attendance rates rather than difference. Our PPI group was involved in all aspects of design, delivery and interpretation (see *Patient and public involvement in the ISDR programme*).

Methods

This was a single site, two-arm, parallel assignment, equivalence RCT conducted in all screening clinics in the LDESP, part of the NDESP. The trial was conducted with the Liverpool Clinical Trials Centre.

The main inclusion and exclusion criteria were: registered with a GP whose postcode was within the city boundaries of Liverpool, aged ≥ 12 years, attending screening for DR and had not opted out of data-sharing. Age-appropriate patient information leaflets were sent to eligible patients with their screening appointment. Participants provided written informed consent. For children aged 12–15 years, proxy consent by the parent/guardian was provided and, where appropriate, assent from the child. Preston Research Ethics Committee approved the trial (14/NW/0034). The trial registry number is ISRCTN87561257.

Allocation was randomly 1 : 1 to individualised variable-interval risk-based screening recall at 6, 12 or 24 months (intervention arm, high-, medium-, low-risk respectively), or annual screening (control arm, current routine care).

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The ISDR DW automatically populated the majority of the fields in the baseline and follow-up electronic CRFs, including data for randomisation. Screening staff and clinical assessors were masked to intervention arm, risk-calculation and interval.

Procedures

Allocation of participants by the RCE (see *The Liverpool Risk-Calculation Engine*) at baseline and each follow-up was against the risk of becoming screen-positive at 6-, 12- and 24-month intervals. The interval was allocated against the criterion deemed appropriate by the PPI group of less than 2.5% risk of becoming screen-positive before the next appointment. Independent risk factor covariates were retinopathy levels in both eyes, age, duration of diabetes, HbA_{1c}, systolic BP and total cholesterol. Participants in the fixed-interval control arm continued with annual screening. For those in the individualised arm, the interval could change at each visit.

Outcomes

The primary outcome of attendance rate at the first follow-up visit assessed the safety of individualised variable-interval risk-based screening. Non-attendance was defined as failure to attend any appointment within 90 days of the follow-up invitation date. Secondary outcomes measuring efficacy and safety were screen-positive disease, number of cases of STDR detected, median VA [logarithm of the minimum angle of resolution (logMAR)] and rates of VI (VA ≥ 0.30 logMAR). All cases of STDR that occurred between baseline and 24 months (+ 90 days) were included in the analysis. A medical retina specialist determined if referred STDR was true- or false-positive using slit-lamp biomicroscopy at a dedicated HES clinic.

Statistical analyses and sample size calculations

The primary analysis was to test for equivalence in attendance rates between individualised and annual screening. The estimated minimum number of patients required was 4460 (90% power, 2.5% one-sided significance level, 5% equivalence margin, 6% loss to follow-up). Primary analysis was per protocol (PP). Intention-to-treat (ITT) and multiple imputation analyses were also conducted.

A secondary aim was to investigate whether or not personalised screening could be considered as non-inferior for the detection of STDR when compared with annual screening; this used a 1.5% non-inferiority margin.

Within the three risk groups, equivalence in attendance rates between the two arms and non-inferiority in the detection of STDR in the individualised arm were explored. For this analysis, participants in the control arm were allocated to risk groups based on the RCE risks at baseline. Generalised linear models were fitted with arm, level of risk and their interaction added as factors.

Results

The trial opened on 1 May 2014, randomisation took place from 12 November 2014 to 14 June 2016 and last follow-up was 16 August 2018. In total, 4069 out of 8607 eligible people were excluded, which meant that there were 4538 individuals who were randomised and allocated to a trial arm (2269 fixed interval, 2265 individualised, 4 withdrawals). In the individualised arm, at baseline 198 participants were allocated their first screening recall at 6 months, 211 at 12 months and 1856 at 24 months, which reflects the allocation to high, medium and low risk by the RCE. The trial profile is shown in *Figure 4*.

Baseline characteristics in the PP data set are shown in *Table 4*; the ITT data set had similar characteristics. Participants had a median age of 63 years (range 14–100 years), 60.4% were male, 94.6% were white and 88.5% had type 2 diabetes. Those in the high-risk group were more likely to have type 1 diabetes, a longer diabetes diagnosis and higher HbA_{1c}, and less likely to have ever smoked, when compared to those in the medium- and low-risk groups.

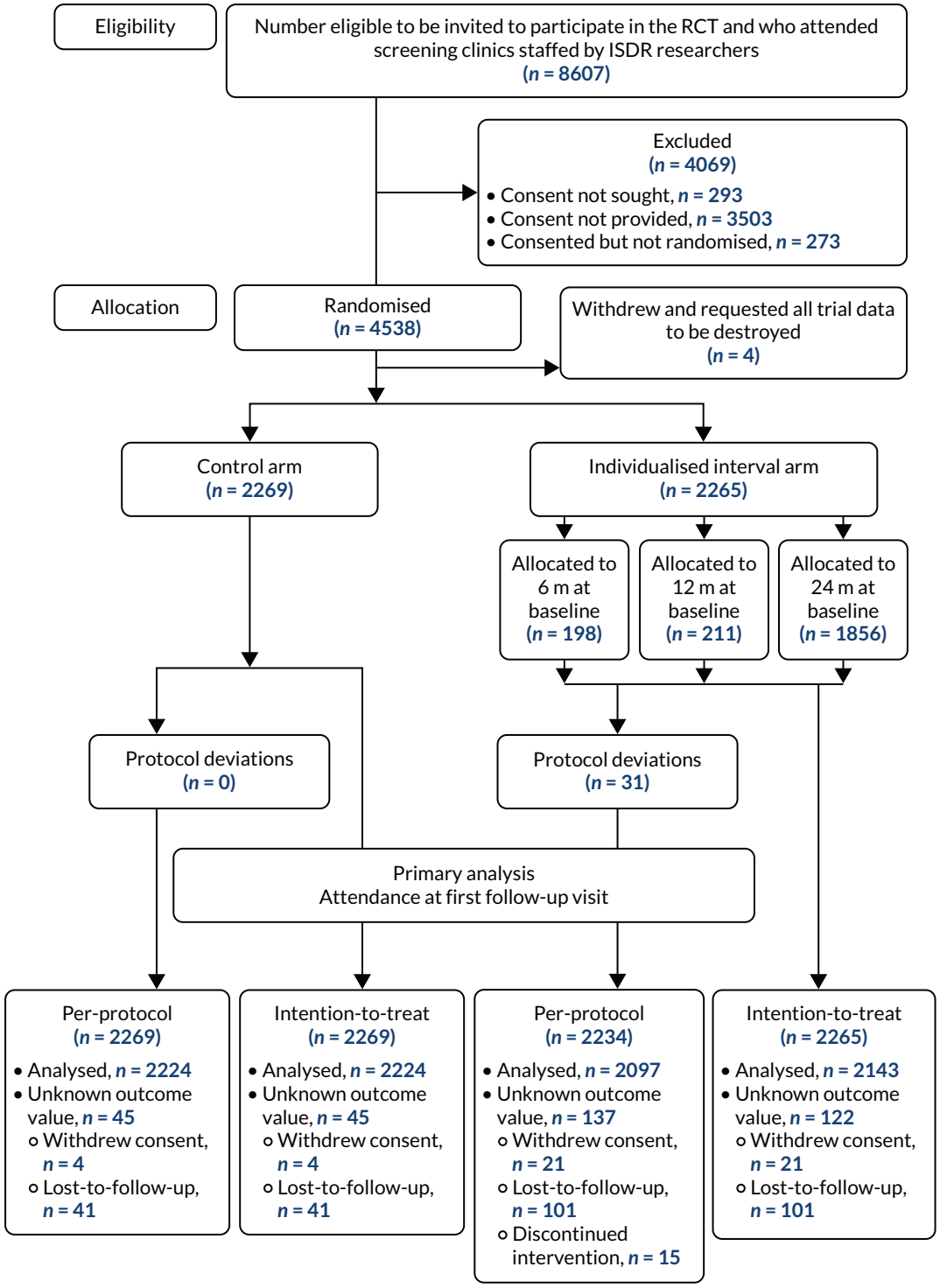


FIGURE 4 CONSORT 2010 flow diagram showing the numbers for eligibility, allocation, withdrawals in the PP and ITT data sets for the primary analysis.

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TABLE 4 Participant baseline characteristics by arm and screening interval allocation in 4503 participants in the PP data set

	Arm		Baseline risk group			
Baseline characteristic	**Fixed (12 m) (*N* = 2269)**	**Individualised (*N* = 2234)**	**High (*N* = 197)**	**Medium (*N* = 211)**	**Low (*N* = 1826)**	**Overall total (*N* = 4503)**
Gender, *n* (%)						
Male	1358 (59.9)	1360 (60.9)	124 (62.9)	135 (64.0)	1101 (60.3)	2718 (60.4)
Female	911 (40.1)	874 (39.1)	73 (37.1)	76 (36.0)	725 (39.7)	1785 (39.6)
Ethnicity, *n* (%)						
White	2140 (94.3)	2120 (94.9)	180 (91.4)	204 (96.7)	1736 (95.1)	4260 (94.6)
Asian	48 (2.1)	30 (1.3)	2 (1.0)	3 (1.4)	25 (1.4)	78 (1.7)
Black	40 (1.8)	43 (1.9)	6 (3.0)	3 (1.4)	34 (1.9)	83 (1.8)
Chinese	7 (0.3)	6 (0.3)	1 (0.5)	1 (0.5)	4 (0.2)	13 (0.3)
Other	25 (1.1)	29 (1.3)	8 (4.1)	0 (0.0)	21 (1.2)	54 (1.2)
Unknown	9 (0.4)	6 (0.3)	0 (0.0)	0 (0.0)	6 (0.3)	15 (0.3)
Smoking status, *n* (%)						
Smoker	419 (18.5)	364 (16.3)	26 (13.2)	39 (18.5)	299 (16.4)	783 (17.4)
Ex-smoker	877 (38.7)	899 (40.2)	69 (35.0)	76 (36.0)	754 (41.3)	1776 (39.4)
Non-smoker	965 (42.5)	967 (43.3)	102 (51.8)	96 (45.5)	769 (42.1)	1932 (42.9)
Unknown	8 (0.4)	4 (0.2)	0 (0.0)	0 (0.0)	4 (0.2)	12 (0.3)
Diabetes type, *n* (%)						
Type 1	80 (3.5)	99 (4.4)	38 (19.3)	14 (6.6)	47 (2.6)	179 (4.0)
Type 2	2024 (89.2)	1962 (87.8)	140 (71.1)	180 (85.3)	1642 (89.9)	3986 (88.5)
Unknown	165 (7.3)	173 (7.7)	19 (9.6)	17 (8.1)	137 (7.5)	338 (7.5)
Age (years)						
Observed, *n*	2269	2234	197	211	1826	4503
Median (IQR)	63.3 (55.0–71.0)	62.8 (54.8–70.3)	58.3 (49.9–66.2)	60.9 (53.4–69.8)	63.7 (55.9–70.8)	63.1 (54.9–70.7)
Range	14.1–100.7	15.4–91.3	17.5–86.8	15.4–86.8	16.8–91.3	14.1–100.7
Disease duration (years)						
Observed, *n*	2267	2231	197	209	1825	4498
Unknown, *n*	2	3	0	2	1	5
Median (IQR)	6.9 (4.2–10.9)	7.0 (4.2–11.2)	11.1 (7.3–16.1)	9.8 (6.3–13.7)	6.4 (4.0–10.1)	7.0 (4.2–11.0)
Range	0.6–66.4	1.0–44.7	1.2–44.7	1.1–37.2	1.0–39.1	0.6–66.4
HbA_{1c}						
Observed, *n*	2269	2232	197	211	1824	4501
Unknown, *n*	0	2	0	0	2	2
Median (IQR) (mmol/mol)	51 (44–61)	52 (44–63)	67 (53–84)	58 (51–67)	50 (44–60)	51 (44–62)
Range | (mmol/mol)	26–146	28–155	33–134	34–155	28–104	26–155
Median (IQR) (%)	6.8 (6.2–7.7)	6.9 (6.2–7.9)	8.3 (7.0–9.8)	7.5 (6.8–8.3)	6.7 (6.2–7.6)	6.8 (6.2–8.8)
Range (%)	4.5–15.5	4.7–16.3	5.2–14.4	5.3–16.3	4.7–11.7	4.5–16.3

TABLE 4 Participant baseline characteristics by arm and screening interval allocation in 4503 participants in the PP data set (*continued*)

Baseline characteristic	Arm		Baseline risk group			Overall total (*N* = 4503)
	Fixed (12 m) (*N* = 2269)	Individualised (*N* = 2234)	High (*N* = 197)	Medium (*N* = 211)	Low (*N* = 1826)	
Systolic BP						
Observed, *n*	2268	2234	197	211	1826	4502
Unknown, *n*	1	0	0	0	0	1
Median (IQR) (mmHg)	130.0 (121.0–138.0)	130.0 (122.0–138.0)	130.0 (124.0–138.0)	132.0 (124.0–140.0)	130.0 (122.0–138.0)	130.0 (122.0–138.0)
Range (mmHg)	84.0–213.0	90.0–204.0	93.0–175.0	95.0–204.0	90.0–200.0	84.0–213.0
Diastolic BP						
Observed, *n*	2208	2180	193	201	1786	4388
Unknown, *n*	61	54	4	10	40	115
Median (IQR) (mmHg)	76.0 (70.0–80.0)	76.0 (70.0–80.0)	77.0 (70.0–80.0)	77.0 (70.0–80.0)	76.0 (70.0–80.0)	76.0 (70.0–80.0)
Range (mmHg)	46.0–140.0	46.0–130.0	54.0–105.0	57.0–130.0	46.0–110.0	46.0–140.0
Total cholesterol						
Observed, *n*	2258	2224	196	209	1819	4482
Unknown, *n*	11	10	1	2	7	21
Median (IQR) (mmol/l)	4.0 (3.4–4.7)	4.0 (3.4–4.7)	4.0 (3.4–4.9)	4.0 (3.4–4.6)	4.0 (3.5–4.7)	4.0 (3.4–4.7)
Range (mmol/l)	1.4–8.1	1.8–9.7	2.0–9.0	2.2–7.6	1.8–9.7	1.4–9.7
Retinopathy level, *n* (%)						
R0 R0	1857 (81.8)	1800 (80.6)	1 (0.5)	44 (20.9)	1755 (96.1)	3657 (81.2)
R1 R0	262 (11.5)	296 (13.2)	58 (29.4)	167 (79.1)	71 (3.9)	558 (12.4)
R1 R1	146 (6.4)	137 (6.1)	137 (69.5)	0 (0.0)	0 (0.0)	283 (6.3)

Primary safety findings

Attendance rates at the first follow-up visit for the control and individualised arms (primary outcome) were 84.7% (1883/2224) and 83.6% (1754/2097), respectively (difference −1.0%, 95% CI −3.2% to 1.2%, PP analysis). Against an acceptability range of 0.05, these attendance rates were equivalent (*Figure 5* upper panel, *Table 5*). PP and ITT analyses with multiple and simple imputation confirmed equivalence in attendance rates between the two arms.

Equivalence in the analysis of the three risk groups in the individualised arm (see *Figure 5*, lower panel, and *Table 5*) was found for the low-risk group (control 85.7%, individualised 85.1%, difference −0.6%, 95% CI −2.9% to 1.7%). For the medium-risk group, equivalence was not confirmed (control 81.7%, individualised 82.2%, difference 0.6%, 95% CI −7.3% to 8.4%); differences were very small but equivalence was not confirmed because of the relatively wide CIs. Attendance rates were lower in the high-risk group (control 77.3%, individualised 72.3%, difference 5.0%, 95% CI −13.6% to 3.5%) than in the medium- and low-risk groups. Although the hypothesis of equivalence was not supported in this group, the attendance rates observed over 12 months (percentage with at least one attended appointment) were higher in the individualised arm (89.1%) than in the control arm (77.3%).

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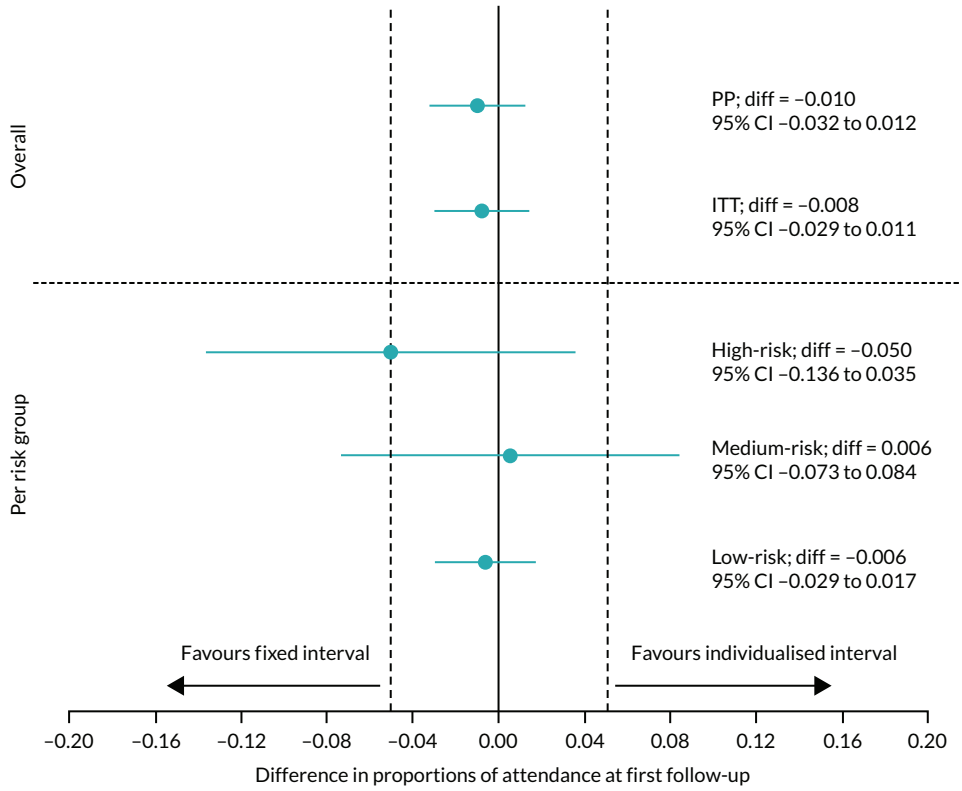


FIGURE 5 Plot showing point estimates and 90% CIs for participants attending the first follow-up visit in the two arms. Upper panel: primary analysis. Lower panel: high-, medium- and low-risk groups in the individualised arm.

Secondary safety findings

There was no evidence of a loss of ability to detect STDR in the individualised arm (1.4% vs. 1.7%, difference −0.3%, 95% CI −1.1% to 0.5%, prespecified non-inferiority margin 1.5%) (see *Table 5*). Similar results were obtained in the ITT and imputation analyses. Non-inferiority was found for the low-risk group (control 0.6%, individualised 0.2%, difference −0.3%, 95% CI −0.9% to 0.1%), but not the high- and medium-risk groups; this was probably explained by the small numbers.

We did not detect any clinically significant worsening of diabetes control. There was no difference in the proportions of participants in each group who had a significant (≥ 11 mmol/mol) increase in HbA_{1c} during the trial: control 15.2%, individualised 14.6%, high 13.4%, medium 15.0% and low 14.7%. We did not detect any differences in logMAR VA (p = 0.64) or in rates of VI in the better eye at the last attended visit between the two arms. Findings for worse eye VA and VI were similar.

Efficacy

In total, 43.2% fewer screening attendances were required in the individualised arm than in the control arm (2008 vs. 3536). Higher rates of screen-positive by screen episode attended were seen in the individualised arm than in the control arm [control 4.52% (160/3536), individualised 5.08% (102/2008)]. Within the individualised arm, the high-risk group had the highest screen-positive rate [high 10.72% (34/317), medium 6.02% (15/249), low 3.7% (53/1442)]. In the low-risk group, most of the screen-positive cases were a result of other eye disease; the rates of screen-positive for DR were low at 0.5% (7/1442). Screening episodes that detected STDR were earlier in the individualised arm than in the control arm: 6–12 months 17.9% (5/28) versus 2.9% (1/35), 12–18 months 32.1% (9/28) versus 60.0% (21/35), respectively.

The number of appointments over the 2 years per participant in the individualised arm varied by allocated group at baseline: 1.83, 1.06 and 0.85 in the high-, medium- and low-risk groups, respectively. The RCE was stable throughout the RCT. A total of 132 participants were switched by the RCE to a longer screening interval and 176 to a shorter screening interval.

TABLE 5 Results of the test for equivalence in attendance rate at first follow-up visit and of the non-inferiority in STDR detection within 24 months, based on the PP, ITT and multiple imputation data sets

	Control arm			Individualised arm			
Approach	*N*	Attended/ STDR detected (*n*)	Proportion	*N*	Attended/ STDR detected (*n*)	Proportion	Difference in proportions (95% CI)
Primary outcome: attendance at first follow-up							
PP							
Overall	2224	1883	0.847	2097	1754	0.836	−0.010 (−0.032 to 0.012)
High risk	203	157	0.773	195	141	0.723	−0.050 (−0.136 to 0.035)
Medium risk	169	138	0.817	208	171	0.822	0.006 (−0.073 to 0.084)
Low risk	1852	1588	0.857	1694	1442	0.851	−0.006 (−0.029 to 0.017)
Multiple imputation	2269	1910	0.842	2234	1870	0.837	−0.005 (−0.026 to 0.017)
ITT							
Overall	2224	1883	0.847	2143	1798	0.839	−0.008 (−0.029 to 0.014)
Multiple imputation	2269	1913	0.843	2265	1903	0.840	−0.004 (−0.025 to 0.018)
Secondary outcome: STDR within 24 months							
PP							
Overall	2042	35	0.017	1956	28	0.014	−0.003 (−0.011 to 0.005)
High risk	176	20	0.114	127	17	0.134	0.020 (−0.053 to 0.100)
Medium risk	157	5	0.032	179	7	0.039	0.007 (−0.038 to 0.051)
Low risk	1709	10	0.006	1650	4	0.002	−0.003 (−0.009 to 0.001)
Multiple imputation	2269	39	0.017	2234	36	0.016	−0.001 (−0.009 to 0.007)
ITT							
Overall	2042	35	0.017	2056	32	0.016	−0.002 (−0.010 to 0.006)
Multiple imputation	2269	39	0.017	2265	39	0.017	−0.001 (−0.008 to 0.008)

Discussion

Our study, which, to the best of our knowledge, is the largest ophthalmic RCT performed in individualised DR screening to date, shows that all parties involved in diabetes care can be reassured that extended and individualised (personalised) interval screening can safely be introduced in an established screening programme. We have shown that variable-interval risk-based screening, as developed by us in Liverpool,

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is equivalent to the current standard of annual screening, in our setting. Our secondary safety findings support this primary result. In the individualised arm, we did not detect any drop in rates of detection of STDR, worse VA or higher rates of VI, or worsening glycaemic control. Attendance levels were maintained throughout the study.

We have also shown improved efficacy for our personalised approach, reducing the number of appointments by 43.2%. In the individualised arm, there were higher proportions of screening episodes that were screen-positive and screening episodes that detected STDR were earlier than in the control arm. In the setting of a RCT, the RCE showed feasibility and reliability with good discrimination.

A move to longer screening intervals for people at low risk of DR has been suggested in the literature prior to[39] and during[40–42] our programme, but without convincing evidence on safety.[8] Overall, 19.0% of people invited to take part in our study explicitly stated that they wished to remain on annual screening or did not want a change of interval. We did not detect a worsening in glycaemic control. Our findings give substantial reassurance that a 24-month interval for low-risk individuals with diabetes is safe in a setting such as ours. However, for resource-poor or rural settings in low- and middle-income countries, further research is required before longer intervals can be contemplated.

Our findings have some limitations when considering wider application. We developed and applied our approach to screening in a single centre with relatively low rates of baseline DR and low rates of progression to sight-threatening disease. Our programme has been running for over 30 years. Participants' glycaemia and BP control were relatively good. Our results should be generalised with caution to other settings with higher prevalence, poorer control of diabetes, wider ethnic group representation, or in programmes in set-up. Our study has important strengths including the RCT design, its size, independent oversight, and involvement of an expert patient group.

Our approach allowed us to target high-risk people using a 6-month screening interval. Attendance rates at first visit in this group were lower in the individualised arm (72.3% vs. 77.3% in the control group) but disease was detected earlier through more frequent screening (1.7 visits, 89.1% attendance over the first 12 months vs. 77.3% estimated in controls) than in the control arm. The rates of detection of STDR were higher in the high- and medium-risk individualised groups (13.4% and 3.9% vs. 1.7% in controls). The proportion of screening episodes that were positive was higher in the individualised arm at 5.1% than in the control arm at 4.5%. By contrast, there very low rates of screen-positive episodes in the low-risk group (0.2%). These rates are similar if slightly lower than the 0.3–1.0% reported over 2 years in people with no retinopathy in either eye in a study of seven screening programmes in England.[41]

The value of adding in clinical data is a matter of debate. Our PPI group advised strongly during the design phase of the study that including clinical data was important to them. It allows the introduction of a high-risk group and better targeting than stratification (see *Further analysis* for post-RCT analysis).[30] We would suggest that the advantages for patient and clinician engagement outweigh the added cost and complexity. Around 15% of people had at least one change in risk-based interval: 59% people allocated to the medium (annual) group experienced a change of interval, adding further evidence to move away from a fixed interval for all.

Interrelation to other work packages and overall aims of the programme

Data collated in the ISDR DW (WP B1) informed the RCE (WP C), which in turn supported the RCT. The PPI group developed the risk criteria, actively supported with the production of patient-related materials and observed clinics to improve recruitment.

Cost-effectiveness of individualised variable-interval risk-based screening for diabetic retinopathy

A peer-reviewed publication[24] describes the cost-effectiveness study[24] and additional information is available in this publication on methods and results. We followed the CHEERS reporting guidance.

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Research aims

We conducted an economic analysis within our RCT to investigate the cost-effectiveness of individualised variable-interval risk-based screening from an NHS and a societal perspective (WP D).

Our review of the literature showed limited evidence on cost-effectiveness of screening. Study designs have been heterogeneous and relied on modelling rather than direct observation. One systematic review of screening called specifically for cost-effectiveness studies.[8]

Methods

Within-trial analysis

The costs of routine screening were directly measured using a mixed micro-costing and observational health economics analysis. Societal costs, including participant and companion costs, which were collected using a bespoke questionnaire, comprised time lost from work (productivity losses) and travel and parking costs. A detailed workplace analysis, measuring resources and staff time to deliver the screening programme, was observed at each screening centre. This ingredient-based bottom-up approach enabled a current resource-based cost to be attributed to the individual patient cost of screening, taking into account both attendees and the related cost of non-attendance. We estimated the additional costs of running the RCE using a screen population of size of 22,000 (Liverpool). Treatment costs were excluded because the design was a within-trial analysis. The study was not designed to make economic inference of eye screening in general.

The first 868 participants enrolled into the RCT completed the EuroQol-5 Dimensions, five-level version (EQ-5D-5L),[43] and Health Utilities Index Mark 3 (HUI3)[44] instruments at baseline and follow-up visits. Health state utilities were mapped[45] from the EQ-5D-5L to the EQ-5D three-level version and used a UK population tariff.[46] We applied a relevant Canadian tariff [47] to health state classifications of the HUI3 in the absence of an English or UK valuation set. Discounting was not applied as both costs and quality-adjusted life-years (QALYs) were assumed to be assigned and incurred on an annual basis.

A 90-day attendance window was utilised with a further 90 days added at 24 months to allow for the compounding lag in scheduling.

QALYs were constructed using AUC, and incremental QALYs estimated through ordinary least squares regression (for the univariate distributions of complete cases) and seemingly unrelated regressions (for

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the joint distributions of multiply imputed sets) on baseline utilities. Unadjusted estimates were used as sensitivity analyses. We bootstrapped these regressions to characterise sampling distributions and derive 95% bias-corrected CIs around trial arm means and mean differences.[48] ITT analyses were conducted in Stata/SE (Release 16; StataCorp LP, College Station, TX, USA) from an NHS/societal perspective, and post-multiple imputation analyses followed Rubin's combination rules for estimation within multiply imputed sets.[49] Incremental cost-effectiveness ratios (ICERs) were generated from mean differences in QALYs and NHS screening costs, as well as incremental net monetary benefit (INMB) derived from a £20,000 threshold.[50] Multiple imputation of chained equations was run using available case data. Bootstrapping was used to characterise sampling distributions and derive 95% CIs around mean differences.

Results

The costs of screening are shown in *Table 6*. Costs per attendance (n = 16,736) were £11.73 for programme costs, £10.00 for photography and £7.00 for grading, with a total NHS cost of £28.73. The cost for non-attendance at £12.73 was principally the programme cost, with a small contribution for lost photographer time. Additional productivity losses and out-of-pocket payments by the patient accounted for £9.00.

The estimated cost of running the RCE was £40,000 per annum for a total screen population of 22,099 in Liverpool allocated to the intervention arm as £1.81 per person.

Table 7 shows summary health economic and cost-effectiveness data. There was no statistically significant difference in QALY scores between the trial arms (EQ-5D 0.006, 95% CI −0.039 to 0.06; EuroQol Visual Analogue Score 0.004, 95% CI −0.049 to 0.052; and HUI3 −0.017, 95% CI −0.083 to 0.04). We observed incremental cost savings per participant of £17.34 (£17.02 to £17.67) from an NHS perspective (not including treatment costs), corresponding to a potential reduction in total programme costs of 20% (95% CI from £193,983 to £154,386), and £23.11 (95% CI £22.73 to £23.53) from a societal perspective, and an INMB for the EQ-5D-5L of £736 (95% CI −£239 to £1718) and £178 (95% CI −£919 to £1338) for the HUI3 £26.19 (95% CI £24.41 to £27.87).

Results following multiple imputation indicated the dominance of the individualised arm in both QALY gain (EQ-5D-5L and HUI3) and cost savings (screening and societal) (*Figure 6*). All ICER point estimates fell in the south-east and south-west quadrants of the cost-effectiveness plane, signifying the dominance in cost savings, with mean differences in QALYs clustered around the zero threshold, EQ-5D-5L reporting a marginal benefit, and the HUI3 reporting an incremental distribution of near equivalence between the arms.

Economic model

Risk-based cohort model

We worked with the RCE team (WS C) to develop a risk-based economic model that closely followed the structure and content of the RCE. The economic model was designed to be fully integrated and usable with the risk engine. We evaluated three alternative screening programmes: (1) current practice, (2) biennial stratification (as proposed by the English NDESP) and (3) ISDR individualisation using the ISDR RCE.

A microsimulation state transition (semi-Markov) model was developed based on DR disease states, as identified through photographic screening, with time- and event-dependent transition probabilities. The patient-level simulation (an individual sampling model) tracked individual characteristics through time, so that their changing risk of disease onset could be used to determine their pathways through the model. The simulation incorporates both disease states and events that determine individuals' pathways through the model, which are observed in discrete units of time. Parameters used in this analysis were drawn from both published literature and local data.

TABLE 6 Within-trial microcosting of the LDESP and estimated costs of the Liverpool RCE

Variable	Top-down annual total (£)	Per attendance (*n* = 16,736) (£)	Per non-attendance (*n* = 6179) (£)
Programme costs			
Staff (including oncosts)	242,715	10.59	10.59
Stationery	3056	0.13	0.13
IT	22,988	1.00	1.00
Total	268,759	11.73	11.73
Photography			
Staff	157,528	9.08	0.91
Cameras and equipment	11,777	0.68	0.07
Medical consumables	4229	0.25	0.00
Total	173,534	10.00	1.00
Grading (P3–P6)			
Staff	117,234	7.00	0.00
Total NHS cost	559,528	28.73	12.73
Societal costs associated with screening attendance			
Patient-borne costs	–	2.64	–
Productivity loss	–	6.36	–
Total societal cost	–	9.00	–
Estimated Liverpool RCE costs	Annual total	Per patient	
Database administrator	34,000	1.54	
CCG administrator (20% FTE)	6000	0.27	
RCE total	40,000	1.81	

Not all values sum perfectly because of rounding. Estimated costs to run and maintain a DW and RCE based on the eligible population of Liverpool of 22,099. Excludes start-up costs.

Model structure

The disease states used in the model were defined in the terms used by the NDESP, namely 'R0M0' gradings. Retinopathy is graded as R0 (no retinopathy), R1 (background), R2 (pre proliferative) or R3 (proliferative). Maculopathy is graded as either M0 (absent) or M1 (present).

All individuals were in the screening programme, except for those who had experienced a screen-positive event and were, therefore, in follow-up and may have been receiving treatment. However, those who receive treatment that was successful may have been referred back to the screening programme. Therefore, the model allows for individuals to be in either screening or follow-up, whether or not they received treatment.

Individuals who went on to receive treatment were subject to different progression rates. Therefore, it was necessary to divide the model further based on the stages of the treatment pathway. The model allowed for four separate groups of individuals: (1) those in screening who had not received treatment, (2) those in screening who had previously received treatment, (3) those in follow-up who had not yet

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TABLE 7 Within-trial ITT QALYs and costs: individualised vs. annual screening

Variable (*n*/N)	Mean difference (95% CI)	
	Complete case	Multiple imputed
EQ-5D (539/868)		
Unadjusted	0.012 (−0.097 to 0.119)	0.043 (0.032 to 0.055)
Baseline adjusted	0.006 (−0.039 to 0.06)	0.044 (0.038 to 0.05)
EQ-VAS (548/868)		
Unadjusted	−0.033 (−0.109 to 0.044)	0.013 (0.005 to 0.022)
Baseline adjusted	0.004 (−0.049 to 0.052)	0.022 (0.017 to 0.028)
HUI3 (408/868)		
Unadjusted	−0.016 (−0.135 to 0.116)	0.068 (0.056 to 0.081)
Baseline adjusted	−0.017 (−0.083 to 0.04)	0.051 (0.045 to 0.058)
Costs (4389/4534)		
NHS screening	−17.44 (−18.57 to −16.31)	−17.34 (−17.67 to −17.02)
Societal	−23.26 (−24.65 to −21.92)	−23.11 (−23.53 to −22.73)

EQ-5D, EuroQoL-5D; EQ-VAS, EuroQol Visual Analogue Score.
Societal costs report the combination of NHS costs, participant or carer productivity losses, and out-of-pocket expenses. *n* corresponds to the number of univariate complete cases out of the sampled set size of *N*. We estimated 95% CIs through 1000 iteration bootstrap regressions for univariate distributions of complete cases, and seemingly unrelated regressions for multivariate distributions of multiple imputed sets.

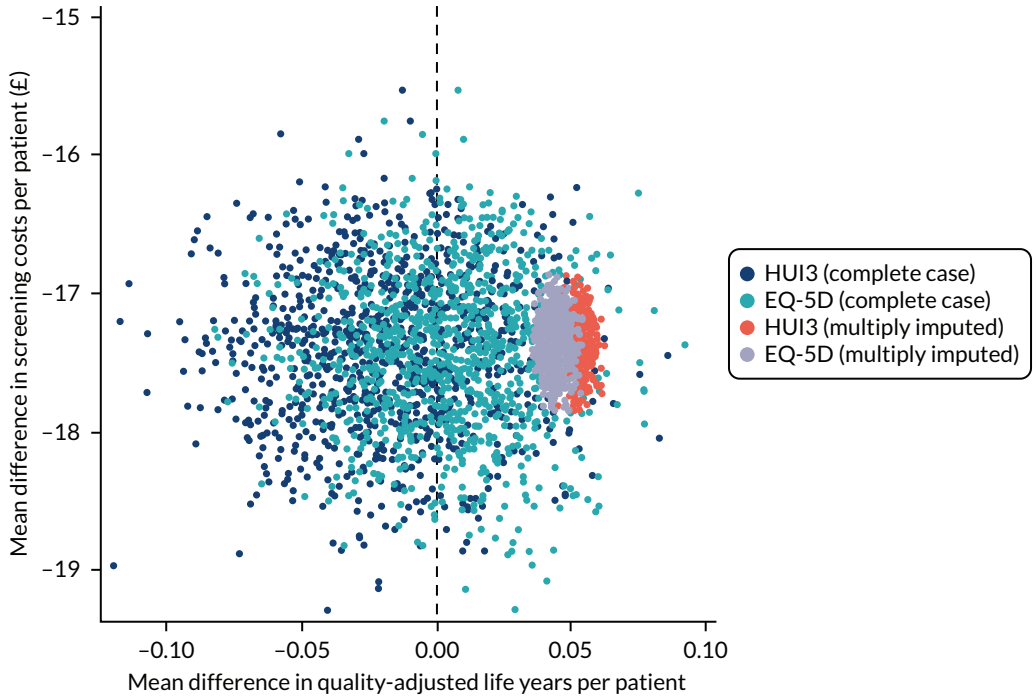


FIGURE 6 Baseline adjusted EQ-5D, HUI3, and NHS perspective incremental cost-effectiveness of individualised vs. annual screening from 1000 iteration bootstraps.

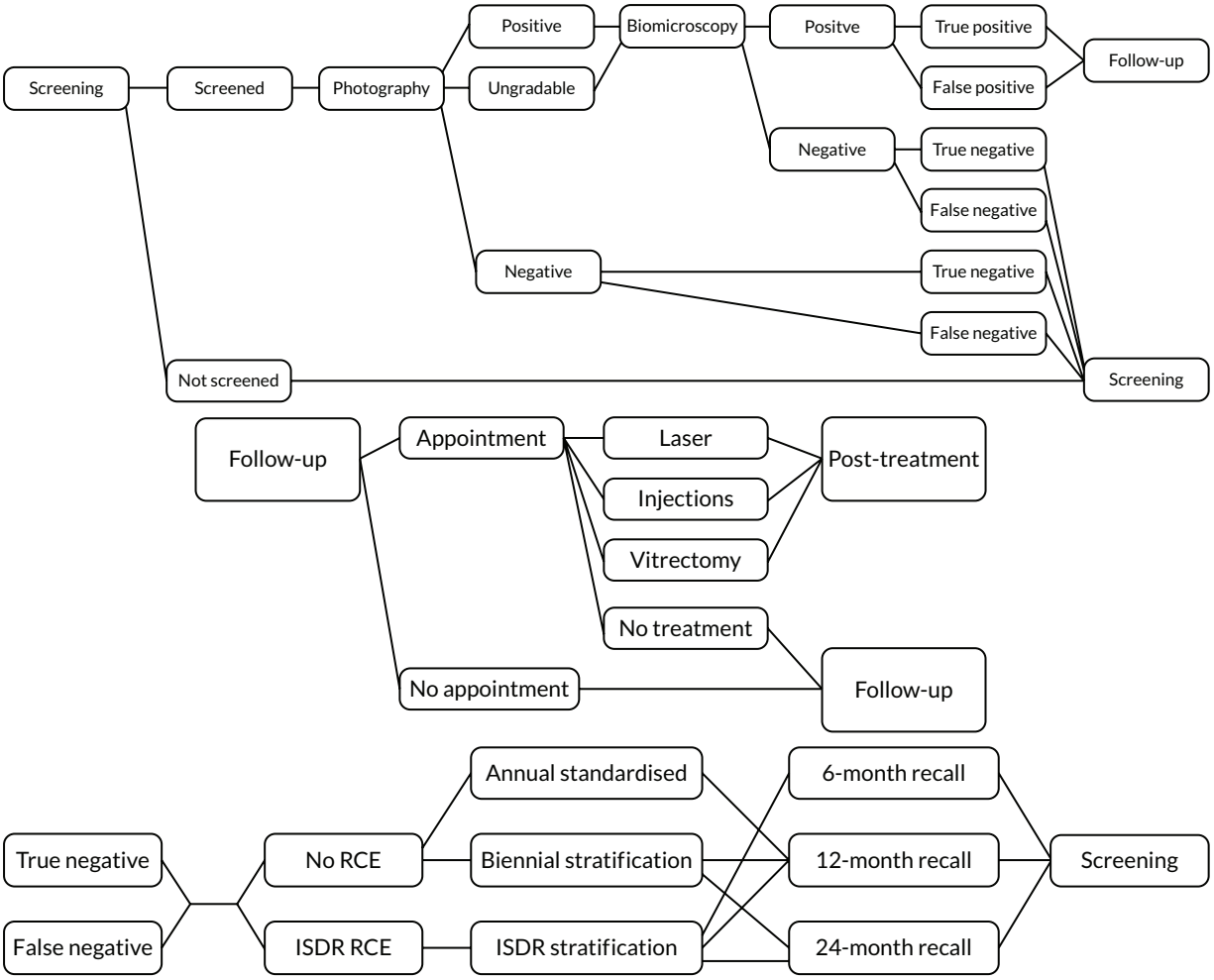


FIGURE 7 Event pathways in the economic model developed within the ISDR programme of applied research. Upper panel: pathway within screening programme; middle panel: pathway within HES for screen-positive individuals; lower panel: pathway showing comparison between three screening models.

received treatment and (4) those in follow-up who had previously received treatment. This increases the number of disease-specific states fourfold, giving 38 states.

The comparators for analysis (described above) are similarly included as an additional event process, applied to all people whose screening outcome is negative and who are referred back to screening. These event pathways are outlined in *Figure 7*.

The model was developed using Microsoft Excel 2013. The intent was to run the model from NHS and Personal Social Services perspectives over a life-time horizon with cycles occurring monthly, and transitions and events occurring at the end of each cycle. The computational and mathematical requirements of such a large-scale model proved non-operational by the end of the programme, requiring around 4 days of processing. Work continued to produce a final version of the model based on 10,000 people.

Discussion

Our data provide evidence that an individualised screening approach may provide cost savings within the programme. We feel that the assumptions and costs applied throughout were conservative and took care not to overstate the benefits of this approach or underplay any of the costs, for example providing a realistic estimate of replicating the cost of a risk engine elsewhere.

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By moving to variable-interval risk-based screening, patients were not compromised on safety or quality of life. We calculated potential incremental cost savings over the 2-year time horizon within the trial of £17.34 NHS costs, rising to £23.11 per patient from a societal perspective. In a population such as in Liverpool, this may amount to potential annual savings in the region of £199,000 in NHS screening programme costs. For England [screening population 2.76M (2018–19)[51]], this could amount to around £23.9M in the NHS, not including treatment costs, rising to £31.9M from a societal perspective. Such resources could be used to target groups that are hard to reach and those at high risk of VI, and more cost-efficiently screen the expanding population of PWD. Individualised screening (on average) reduces the number of attendances required, given that patients in low-risk groups would be spared the inconvenience and additional personal cost of attending non-essential appointments. In brief, fewer visits reduce both patient and hospital costs and the trial shows that this can happen without negative clinical consequences.

Strengths of this within-trial cost-effectiveness study are the detailed characterisation of the costs to the health service and society of a person attending screening and the large number of observations. Our work is limited by the 2-year time horizon, which is short for a long-term disease, such as diabetes. Our work could have been further strengthened by taking a long-term time horizon to capture lifetime costing differentials and years of sight loss averted. Treatment costs were excluded as per the within-trial analysis and the study objectives of comparing screening options rather than of a lifetime analysis of screening. We did explore adding a post-screening analysis to include treatment costs but considered it very unlikely to be informative because the numbers progressing to treatment were very small (two in each group).

It may have been useful to collect utility data for the entire cohort. We elected not to undertake this to minimise disruption at screening clinics. Multiple imputation indicated that quality-of-life (QoL) data were robust. At a 2-year time horizon, the effects of screening intervals on QoL appear to be close to negligible, where our between-arm utilities and incremental QALYs demonstrated near-equivalence.

Although the intention had been to report cost-effectiveness acceptability curves, the dominance in cost reduction of variable-interval risk-based screening and little fluctuation in QALYs across all instruments rendered this metric uninformative, as the proportion cost-effective was inelastic to varying thresholds. See *Strengths and limitations* for a further discussion of strengths and limitations.

In 2015, Scanlon *et al*.[42] reported a cost-effectiveness model developed in a historical data set of 10,942 people in Gloucestershire with screening and clinical data over at least 3 years and validated it in three other English programmes. They reported a 3-yearly screening interval to be the most cost-effective in the absence of personalised risk-based intervals. Using their risk-based strategy, the most cost-effective options were to screen those at low risk every 5 years and those at medium and high risk every 3 and every 2 years, respectively. We now add robust RCT evidence to support the introduction of variable-interval risk-based screening.

Interrelation to other work packages and overall aims of the programme

The health economics and RCE teams (WS C, WS D) worked closely together. The economic model was designed to be fully integrated and usable with the RCE. This is an important element should the Liverpool approach be rolled out into wider practice. Co-ordination occurred with WP F to enable a more inclusive and comprehensive understanding of valuation in QoL in DR screening. This was important as this group was under-represented in the trial itself.

Qualitative study with patients and healthcare professionals on changing screening intervals

A peer-reviewed publication is available[24] and includes example narratives of the key findings. COREQ reporting guidelines were followed.

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Research aims

We aimed to explore perceptions of changing from annual to individualised variable-interval risk-based screening and to gain wider insights into users' perceptions to enable successful implementation (WP F). We also wanted to explore the wider aspects of DR screening in general.

Methods

Setting

We conducted our qualitative studies within the setting of our RCT. This allowed for the first time a real rather than theoretical investigation of the perceptions around the acceptability of implementation of varying intervals and the use of a risk calculator in a population from an established screening programme and in a geographical location where annual fixed-interval screening was already established.

Design

Semi-structured interviews were conducted after informed consent was obtained to gather views on variable-interval risk-based screening. Interviews with PWD were conducted before the start of the RCT (phase 1, baseline) and subsequently with a second group (phase 2) during the RCT. All interviews with HCPs took place prior to commencement of the RCT. The research team and PPI group created interview topic guides (see *Supplementary Material 3*) covering participants' background, beliefs and attitudes towards diabetes, management of diabetes, medical management and contact, and future management of screening. For HCP interviews, discussions included participants' background in diabetes, types of patients they see and potential issues with changing screening intervals. Interviews lasted 30–90 minutes, with most lasting around 45 minutes.

Participants

Participants aged over 16 years who were PWD attending the eye screening programme were identified in two GPs in Liverpool. The practices were approached by a research nurse. The practices reflected the range of socioeconomic status, with one located in a disadvantaged location and the other in an affluent location.

We used purposive sampling to identify potential participants aiming to reflect the characteristics of the local diabetic population and of HCPs involved in eye screening. Suitability of potential PWD participants was reviewed by a GP in the practice prior to contact by the research team.

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All participants received a brief overview of individualised variable-interval risk-based screening. Most patient interviews were conducted in participants' homes, although some chose to complete them in a university office and one completed their interview in their own office.

In total, 60 PWD were recruited: 30 to phase 1 (baseline) and 30 to phase 2 (post implementation of variable-interval risk-based screening). Further details are given in *Table 8*. Interviews took place between October 2014 and April 2015 in private NHS offices (with the exception of one joint interview completed at a participant's home). Allocations within phase 2 were balanced to the overall allocations within the RCT.

The PWD participants had a range of social situations; the occupations described by the sample were very mixed, including a range of professionals as well as students and manual workers, retired and unemployed, and one person who was unable to work owing to long-term ill health. A majority described their ethnicity as white British, two as white European and one each of mixed race and Asian.

A total of 21 HCPs involved in eye screening were recruited through existing knowledge networks, building on our 2011–12 programme development work. A small number of these were recruited through 'snowballing' (identified as potential participants by other participating HCPs). In total, 16 out of

TABLE 8 Participant characteristics in the qualitative ISDR study

Variable	*n*
PWD (*n* = 60)	
Male	34
Age	19–83 years
Type 1	8
Time since diagnosis	1–40 years
1–5 years	10
6–10 years	7
11–15 years	4
> 15 years	9
Risk-based screening interval baseline allocation (phase 2)	
6 months	4
12 months	5
24 months	21
HCPs (*n* = 21)	
Professional role	
Screener/grader	7
Consultant ophthalmologist (retina)	5
Eye screening service manager	4
Optometrist providing DR screening	2
Public health specialist	2
GP	1

21 participated in interviews (six in groups of three), while five completed interview questions via e-mail (see *Table 8* for further details).

We attempted in parallel to access and interview a purposive sample of PWD who had been offered and did not attend two consecutive appointments. Despite many efforts to recruit, we were unable to interview non-attenders.

Analysis

Interviews were audio-recorded and transcribed verbatim for detailed analysis. Semi-structured case summaries were produced by a researcher on completion of each interview to provide a summary of key themes and enable identification of emerging themes to inform further data collection and analysis. Thematic analysis was used. Members of the research team (CT, PB and MG) read and coded separately the first three interviews to ensure that emerging themes were captured and had agreement. Further coding was then undertaken at several time points and regular meetings were conducted between the researchers for consistency.

After reading and re-reading the transcripts, data were analysed to identify sections of text that informed understandings of the issues.[52–54] Each concept was assigned a descriptive or analytical code, which was then combined into conceptual categories and broader themes using NViVO software, which enabled searching and retrieval of specific data.

Results

Here we summarise key findings from interviews with PWD and HCPs. Further details included patient narratives, in line with standards for reporting qualitative research,[55] and are reported elsewhere.[24] The narratives give a compelling insight into the perceptions and views of users of screening services.

Acceptability of changing screening intervals

The majority of PWD expressed the view before and during the ISDR RCT that risk-based variable-interval screening was potentially acceptable. They focused on concepts of pragmatism and diverting any cost savings towards other PWD who may need to be seen more often. For HCPs, the majority were also in favour of introducing the proposed new approach to screening. However, implementing such changes to eye screening was accompanied by a range of caveats, which are discussed in the next subsections below.

Safety of the risk calculation engine

Many of the PWD and HCPs indicated that they would be supportive of the introduction of risk-based allocation to variable screening intervals, provided that particular safeguards or service enhancements were introduced. Safeguards around missed STDR needed to be visible and obvious to both groups. Specifically, for a PWD on a 24-month screening interval, if they had any disruptions to their diabetes self-care, then they wanted to be able to self-refer back into the screening programme. Similarly, for HCPs, they also wanted to refer a PWD back into the screening programme if there were changes that they felt were clinically relevant.

Acceptability of 6-month interval

Within the variable screening model, allocation to a 6-month interval meant that a person with diabetes was considered to be at high risk of developing STDR. There were some tensions within PWD's understandings about the 6-month interval, with it being seen as clinical surveillance and reassurance against the clinical reality that being allocated to this interval means that there is a high risk of developing STDR. In addition, there was conflation about the purpose of eye screening, where it was perceived as a preventative measure against DR. For HCPs, the shorter interval was not only welcomed, but also represented an operational issue of managing resources.

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Acceptability of 12-month interval with conditions

As the current annual screening interval is established and embedded into practice, it was foreseeable that PWD felt that this was an appropriate length of time for their eye screening. However, discussions also highlighted misunderstandings about the purpose of eye screening as a preventative measure against the development of DR and related to diabetes control.

Acceptability of 24-month interval with conditions

For PWD and HCPs, there were a range of responses to extending screening intervals to 2 years. For some PWD, an extension was welcome because it reflected good diabetes self-care, contrasting with outright rejection from others over concerns about developing eye disease in the extended time period. For HCPs, the 2-year interval was acceptable in the context of many patients having minimal or no disease. There was some apprehension about the perceptual impact on patients of changing screening intervals, with PWD feeling that screening was not as important if it was changed to a 2-year interval.

Macro impact of changing screening intervals

Although our participants discussed the impact on themselves of changing screening intervals, they also reflected on the consequences in a much broader societal viewpoint, for which we have used the term 'macro'. There was a recognition that against a backdrop of increasing numbers of PWD, current screening intervals are unsustainable. In addition, it was also seen as an inefficient use of finite resources, which would be better deployed in targeting PWD who do not attend eye screening appointments. It was recognised that the variable screening may well save money, but this was also seen as a restrictive practice in accessing healthcare services. There was considerable conflation and misunderstanding about different eye-related appointments within secondary care and at opticians.

Discussion

To the best of our knowledge, our qualitative study was the first to explore perceptions of changing screening intervals, with our findings showing general support from PWD and HCPs for the introduction of variable-interval risk-based screening. This is reassuring for policy-makers and service providers who are considering introducing variable-interval screening, stratified based on either retinal grading or variable intervals based on risk estimation. Support was more clearly expressed by HCPs who had a better understanding of the aims and current pressures in screening. Our findings also have relevance to other screening programmes with fixed intervals and help to mitigate in part the concerns raised recently in cancer screening.[15,56]

For HCPs, and to a lesser extent PWD, the safety of the RCE was crucial to it being accepted into clinical practice. Safeguards for the RCE had to be made visible and obvious to HCPs and PWD, including the opportunity for HCPs or PWD to refer or self-refer back into the eye screening programme.

In terms of variable screening intervals, there were some misunderstandings among PWD participants about the 6-month interval, whereas HCPs welcomed the opportunity for increased surveillance for high-risk groups. PWD and HCPs were supportive of the current 12-month interval, while recognising that NHS resources are finite.

There were widely differing views on extending screening intervals to 24 months, with both groups of participants having significant concerns about safety. There were worries that any changes in a person's diabetes eye health would be missed, which could lead to developing STDR in this time, leading to poor quality of life for a patient and increased costs to the NHS.

There was a recognition by both groups of participants that against a backdrop of increasing numbers of PWD, current screening intervals are unsustainable and resources could be better used to target high-risk groups. The considerable conflation and misunderstanding about different eye-related appointments

has been reported elsewhere in the literature.[57,58] Changing the message to PWD from regular annual check-ups to extended eye screening will be a challenging message to convey positively.

We attempted to recruit PWD who had a history of multiple non-attendance for screening. Our research team tried contacting over 30 people in this group without success. Poor attendance, known to be a risk factor for STDR,[59,60] is a major issue for all stakeholders involved in screening. Novel ways need to be developed to approach these individuals so that the reasons for non-attendance can be investigated and addressed.

We had intended to investigate changes in attitudes through sampling prior to and during the RCT but follow-up interviews proved to be difficult to obtain. However, we did not identify any themes suggesting differences in perceptions in those who had already been enrolled in the RCT compared with the pre-trial group.

Among the multiple healthcare-related appointments for diabetes, there are misunderstandings by PWD of NHS systems and other appointments with HCPs. Understanding the frequency of screening required to prevent the development of DR[61] was another barrier for PWD and was echoed by HCPs. Allied to appointments related to eye care, there can often be misinterpretations by PWD about the relationship between diabetes and DR, and differences between DR screening and routine eye tests, which in turn led to beliefs that screening appointments had been fulfilled when they had not,[62] as well as related anxiety about screening.[63] A study by Strutton *et al*.[64] concluded that screening attendance could be improved by the sharing of pertinent information between healthcare providers and a greater understanding of patients' circumstances and barriers.

Conclusions

It is reassuring that PWD and HCPs appear to be supportive of variable intervals in DR screening. However, for successful implementation, important caveats and misconceptions must be addressed. Interpretable and clear safeguards for individual PWD are required against increasing non-attendance, loss of diabetes control and system failures. Alternative referral pathways are required for those lost to follow-up or whose risk factors change substantially over longer intervals. For risk-calculation systems, reliable monitoring and clear communication are necessary.

Interrelation with other parts of the programme and overall aims of the programme

The implication of our evidence is that a clear and sustained communication strategy around eye screening and intervals is needed both in the current screening programme and in any future revision. These were considered in WP G.

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Observational cohort study in people attending screening for diabetic retinopathy

A peer-reviewed publication[25] provides additional detail on methods and a discussion on the censoring effect. STROBE reporting guidelines were followed.

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Research aims

We conducted an observational cohort study to estimate the prevalence and incidence of DR and STDR in the established screening programme in Liverpool (WP B). We wanted to provide up-to-date data to inform clinical services and screening programmes, and for clinical research programmes, especially in early disease.

Up-to-date epidemiological data on DR are limited. Much of the population data comes from landmark epidemiological studies in the 1970s and 1980s[16,17] before systematic screening was introduced. Data from screening programmes are limited and reported inconsistently. When programmes are introduced, those in the community with long-standing disease are detected for the first time and referred into the HES; as this 'first pass effect' wanes, the prevalence of referable DR and STDR in the screening population falls. Populations attending for systematic screening are dynamic and subject to several long-term influences. In recent years, there have been changes in the diagnosis of diabetes,[18] and improvements in some populations in glycaemic and BP control. On the other hand, there has been a long-term increase in prevalence of diabetes.

Methods

The cohort study was approved separately by the Preston North West NHS Ethics Committee (13/NW/0196), the local governance committees and Caldicott Guardian. The Liverpool Local Medical Committee (LMC) and Primary Care Research Group and LCCG supported Liverpool general practices who were invited to participate in the study. Data-sharing agreements were prepared with each practice, the RLBUHT and LCCG to include all retrospective and prospective demographic and clinical records collected by practice electronic records systems (EMIS web, EMIS Health, www.emishealth.com).

Data for the cohort study were held in the DW described in *The ISDR study data warehouse*. Individuals were identified from the patient register of all PWD in Liverpool held by the LDESP. Consent for data collection and analysis was through an 'opt-out' process (see *page 13*). Eligible participants comprised all PWD aged ≥ 12 years diagnosed with diabetes who were registered with a practice in Liverpool. PWD aged 12–15 years received a letter and booklet written specifically for young people. Recruitment of general practices commenced in 2013; by 2016, all had agreed to participate. Once a practice had been recruited, newly diagnosed PWD and those moving into the area continued to be invited to the programme.

The following data sets were available: Diabolos (from 1995), a bespoke screening-management software developed in Liverpool; Orion (2005–13), the first iteration of the English NDESP standardised screening-management software; and OptoMize (from 2013), the current NDESP system.

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Data underwent credibility checks using MATLAB (version 8.3, Mathworks, Inc., Natick, Massachusetts, USA) before being merged for analysis. The values of the time-dependent clinical variables closest to the time of the screen episodes were used.

Data from the HES were used to investigate the outcomes of a positive screen event. Data from the first biomicroscopy recorded within 1 year of the positive screen event were used to provide the final outcome for that event. The first recorded attended screening appointment was defined as the first recorded attended appointment at which there were no earlier recorded attended screening appointments or biomicroscopies for that individual.

Confounders

Demographic and clinical data from primary care exhibited a censoring effect prior to 2013; data governance rules removed data from PWD who had died prior to a practice joining the study. This effect phased out during the 3-year period of recruitment of practices.

Data on annual incidence were adjusted for the 2265 participants who were allocated to individualised screening in the ISDR RCT (see *Randomised controlled trial to evaluate the safety and cost-effectiveness of individualised variable-interval risk-based screening*). Those who were assigned to 24 months would under normal circumstances have been screened annually in these years. All were assumed to be screen-negative. The attendance rate was assumed to be 0.85.

Results

Data set

Data collection commenced on 31 October 2013. Data presented here come from an analysis data set including all relevant data extracted up to at least 31 March 2017. Data were extracted on 25 September 2017.

For the primary analysis, we censored the data until 1 April 2006. EMIS web systems started to be introduced into GPs only in 2009, and the data quality was very variable in the first 12 months.

The size of the data set varied throughout the 11 years studied, with year-end effects and variation owing to sampling time. On 25 September 2017, 42,334 people were registered as having diabetes with a Liverpool general practice. After exclusions/ineligibility, the number of people eligible to be invited to join the ISDR cohort study was 30,771. Data distribution is shown in *Figure 8*; data from 28,384 PWD were available for analysis.

Demographics

Overall demographics are shown in *Table 9*. The number of individuals with at least one screening appointment recorded each year increased steadily between 2006/07 and 2014/15 to 15,518, and with adjustment for the effect of the ISDR RCT to 16,001 by 2016/17. Over the 11 years, the median age increased steadily from 60.3 to 64.5 years, and the median disease duration increased from 2.3 to 7.0 years, which was most likely because of the censoring effect prior to 2013/14. Gender proportions were relatively stable across all screening years (55–58% male, 40–43% female, 1–3% unknown). The proportion with type 2 diabetes rose steadily from 76.1% to 81.4%, whereas the median HbA_{1c} was stable (50–52 mmol/mol). Data on ethnicity appeared to be subject to some inconsistencies, mainly around data quality.

Incidence

Data on incidences are shown in *Table 10*. There was some variation of rates of screen-positive across the 11 years, with an overall reduction from 7.9–10.6% in the early years to 4.4–6.7% in the later years.

The annual incidence of screen-positive owing to DR appeared to decrease from 4–5% (2006/07 to 2009/10) to 2–3% (2010/11 to 2016/17). The rates of screen-positive for unassessable images

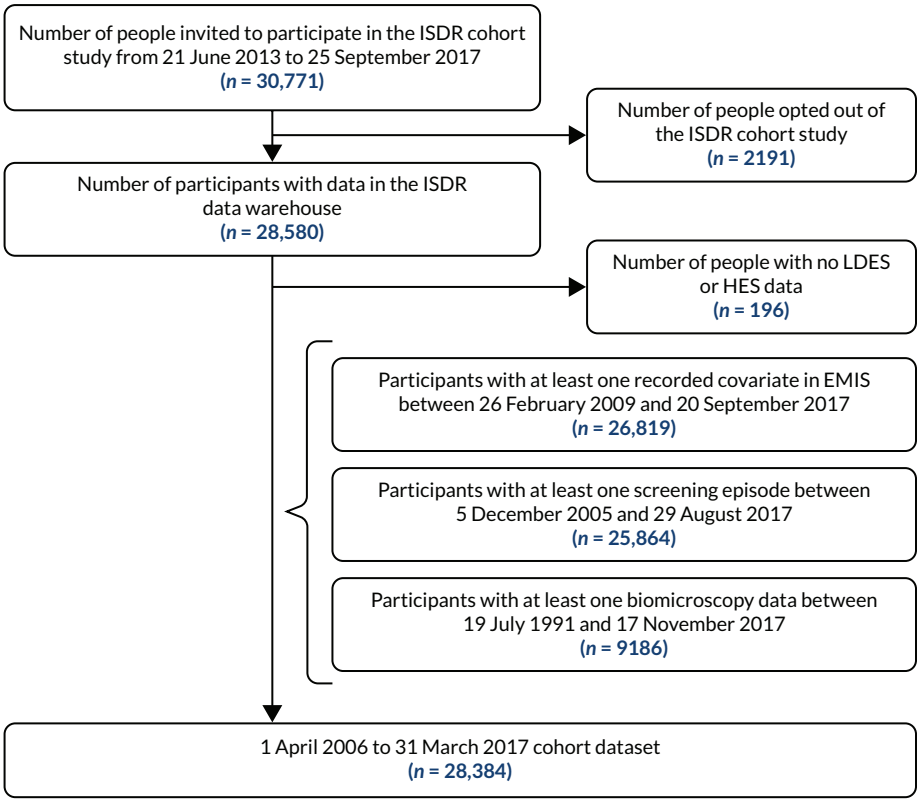


FIGURE 8 Data flows in the ISDR cohort study with figures from an illustrative timepoint close to the mid-point of the last full year (25 September 2017).

appeared to fluctuate by around 2–3% (highest proportion 4.1% in 2008/09, lowest proportion 1.2% in 2013/14) and for other eye disease was stable (around 1%) apart from a peak in 2008/9 (1.9%). Rates of STDR (true-positive, examined by a medical retina specialist using biomicroscopy) were relatively stable at around 1.5–2% [sight-threatening retinopathy (STR) around 0.6%, sight-threatening maculopathy (STM) 1.0–1.5%]. *Figure 9* illustrates these trends.

Of the 133,554 screening episodes across the 11 years studied, 6.7% (8906) were screen-positive, 3.0% (4073) were screen-positive for DR, 2.6% (3444) due to ungradeable images and 1.0% (1389) due to other significant eye disease.

Of the 7802 screen-positive individuals who attended the HES and were examined by a medical retina specialist, only 28.1% (2192) were confirmed as having STDR [overall incidence 1.6% (2192/133,554)], with 71.6% (5584/7802) having unassessable images, other disease or a false positive. A total of 53.8% (2192/4073) of the people referred with screen-positive disease due to DR were true-positive. In total, 82.2% (1801/2192) of individuals had STM and 35.6% (781/2192) had STR.

People attending for their first visit

Annual incidences of screen-positive/negative and STDR for individuals attending their first ever recorded attended screening appointment were 2–4% higher (absolute difference) than the rates for the overall group (*Tables 11* and *12*). Screen-positive rates were 62.3% higher (9.9% vs. 6.1%) and STDR was 37.5% higher (2.2% vs. 1.6%) than the rates seen in those who had had at least one previous screening year. However, much of the screen-positive effect appears to have been due to unassessable images (78.3%, 4.1% vs. 2.3%) and other eye disease (200%, 2.4% vs. 0.8%).

Type 1 and type 2 diabetes

Rates of screen-positive (11.9% vs. 6.0%) and screen-positive because of DR (10.7% vs. 2.3%) were higher in people with type 1 diabetes. Rates of STDR were much higher (6.4% vs. 1.2%) in people with type 1 diabetes and a higher proportion of STDR was because of STR (47% vs. 33%).

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TABLE 9 Overall demographics of the ISDR observational cohort study: 2006/07 to 2016/17

Variable	Screening year[a]										
	2006/07 (*N* = 6637)	2007/08 (*N* = 8088)	2008/09 (*N* = 8664)	2009/10 (*N* = 10,266)	2010/11 (*N* = 11,214)	2011/12 (*N* = 13,124)	2012/13 (*N* = 13,518)	2013/14 (*N* = 15,115)	2014/15 (*N* = 15,552)	2015/16 (*N* = 15,054)	2016/17 (*N* = 14,864)
Gender, *n* (%)[b]											
Male	3647 (54.9)	4508 (55.7)	4804 (55.4)	5740 (55.9)	6367 (56.8)	7444 (56.7)	7713 (57.1)	8660 (57.3)	8956 (57.6)	8569 (56.9)	8243 (55.5)
Female	2823 (42.5)	3367 (41.6)	3670 (42.4)	4287 (41.8)	4603 (41.0)	5406 (41.2)	5533 (40.9)	6265 (41.4)	6478 (41.7)	6171 (41.0)	5997 (40.3)
Unknown	167 (2.5)	213 (2.6)	190 (2.2)	239 (2.3)	244 (2.2)	274 (2.1)	272 (2.0)	190 (1.3)	118 (0.8)	314 (2.1)	624 (4.2)
Diabetes type, *n* (%)[b]											
Type 1	441 (6.7)	537 (6.6)	536 (6.2)	576 (5.6)	579 (5.2)	687 (5.1)	684 (5.1)	754 (5.0)	795 (5.1)	750 (5.0)	731 (4.9)
Type 2	5053 (76.1)	6241 (77.2)	6784 (78.3)	8194 (79.8)	9081 (81.0)	10,645 (81.1)	11,078 (81.9)	12,486 (82.6)	12,962 (83.3)	12,417 (82.5)	12,104 (81.4)
Unknown	1143 (17.2)	1310 (16.2)	1344 (15.5)	1496 (14.6)	1554 (13.9)	1792 (13.7)	1756 (13.0)	1875 (12.4)	1795 (11.5)	1887 (12.5)	2029 (13.7)
Ethnicity, *n* (%)[b]											
White	5327 (80.3)	6456 (79.8)	6920 (79.9)	8094 (78.8)	8729 (77.8)	9940 (75.7)	10,156 (75.1)	11,258 (74.5)	11,478 (73.8)	10,811 (71.8)	10,252 (69.0)
Asian	158 (2.4)	183 (2.3)	224 (2.6)	256 (2.5)	271 (2.4)	353 (2.7)	369 (2.7)	428 (2.8)	460 (3.0)	438 (2.9)	456 (3.1)
Black	105 (1.6)	116 (1.4)	139 (1.6)	175 (1.7)	197 (1.8)	243 (1.9)	253 (1.9)	293 (1.9)	286 (1.8)	305 (2.0)	309 (2.1)
Chinese	57 (0.9)	75 (0.9)	85 (1.0)	79 (0.8)	85 (0.8)	108 (0.8)	121 (0.9)	125 (0.8)	144 (0.9)	150 (1.0)	160 (1.1)
Other	88 (1.3)	103 (1.3)	108 (1.2)	127 (1.2)	135 (1.2)	169 (1.3)	166 (1.2)	201 (1.3)	210 (1.4)	202 (1.3)	199 (1.3)
Unknown	902 (13.6)	1155 (14.3)	1188 (13.7)	1535 (15.0)	1797 (16.0)	2311 (17.6)	2453 (18.1)	2810 (18.6)	2974 (19.1)	3148 (20.9)	3488 (23.5)
Age (years)											
Observed (*n*)	6470	7875	8474	10,027	10,970	12,850	13,246	14,925	15,434	14,740	14,240
Unknown (*n*)	167	213	190	239	244	274	272	190	118	314	624
Median	60.3	61.0	61.5	62.3	62.6	62.9	63.3	63.9	64.2	64.5	64.5
IQR	51.2–68.7	51.9–69.4	52.4–70.1	53.1–70.6	53.4–71.1	53.6–71.5	54.0–72.1	54.4–72.6	54.6–73.0	55.0–73.1	55.1–73.3
Range	12.0–92.1	12.0–93.4	12.0–94.4	12.1–94.5	9.9–96.5	11.9–98.1	12.0–97.7	12.1–98.7	12.2–112.9	13.3–113.6	13.7–114.6

TABLE 9 Overall demographics of the ISDR observational cohort study: 2006/07 to 2016/17 (*continued*)

Variable	Screening year[a] 2006/07 (*N* = 6637)	2007/08 (*N* = 8088)	2008/09 (*N* = 8664)	2009/10 (*N* = 10,266)	2010/11 (*N* = 11,214)	2011/12 (*N* = 13,124)	2012/13 (*N* = 13,518)	2013/14 (*N* = 15,115)	2014/15 (*N* = 15,552)	2015/16 (*N* = 15,054)	2016/17 (*N* = 14,864)
Disease duration (years)											
Observed (*n*)	6637	8088	8664	10,266	11,214	13,124	13,518	15,115	15,552	15,054	14,864
Unknown (*n*)	0	0	0	0	0	0	0	0	0	0	0
Median	2.3	2.6	2.9	3.5	4.2	4.9	5.5	6.1	6.4	6.7	7.0
IQR	0.2–5.6	1.1–6.1	1.7–6.5	2.1–6.9	2.1–7.2	2.2–7.7	2.6–8.2	3.1–8.9	3.3–9.4	3.5–9.9	3.1–10.5
Range	0.0–53.7	0.0–54.7	0.0–55.4	0.0–56.6	0.0–57.7	0.0–55.2	0.0–59.3	0.0–60.4	0.0–61.6	0.0–62.6	0.0–63.7
HbA_{1c} (mmol/mol)											
Observed (*n*)	0	0	123	6216	8495	11,188	11,972	13,869	14,638	14,006	13,540
Unknown (*n*)	6637	8088	8541	4050	2719	1936	1546	1246	914	1048	1324
Median	–	–	50	50	51	51	52	51	51	51	52
IQR	–	–	43–60	44–60	45–61	45–61	45–62	44–61	44–61	45–62	46–62
Range	–	–	33–117	23–157	21–160	24–172	22–168	22–166	22–174	20–156	22–140

a Screening year is from 1 April to 31 March.
b Note that all percentages are calculated out of the number of individuals with at least one attended screening appointment.

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TABLE 10 Overall screen-positive/negative/STDR (STR/STM) annual incidences: 2006/07 to 2016/17 (out of the number of people with at least one attended screening appointment)

	Screening year*, *n* (%^)											
Variable	**2006/07**	**2007/08**	**2008/09**	**2009/10**	**2010/11**	**2011/12**	**2012/13**	**2013/14**	**2014/15**	**2015/16**	**2016/17**	**Overall, *n* (%^; 95% CI^^^)**
Number of individuals with at least one attended screening appointment	6637 (100.0)	8088 (100.0)	8664 (100.0)	10266 (100.0)	11214 (100.0)	13124 (100.0)	13518 (100.0)	15115 (100.0)	15552 (100.0)	15280^^ (100.0)	16096^^ (100.0)	133554 (100.0)
Screen-positive	527 (7.9)	714 (8.8)	922 (10.6)	854 (8.3)	695 (6.2)	921 (7.0)	774 (5.7)	669 (4.4)	805 (5.2)	1031 (6.7)	994 (6.2)	8906 (6.7; 6.5 to 6.8)
Screen-positive for DR	271 (4.1)	355 (4.4)	401 (4.6)	360 (3.5)	327 (2.9)	419 (3.2)	330 (2.4)	345 (2.3)	387 (2.5)	441 (2.9)	437 (2.7)	4073 (3.0; 3.0 to 3.1)
Screen-positive for unassessable images	201 (3.0)	255 (3.2)	358 (4.1)	372 (3.6)	283 (2.5)	425 (3.2)	322 (2.4)	179 (1.2)	258 (1.7)	408 (2.7)	383 (2.4)	3444 (2.6; 2.5 to 2.7)
Screen-positive for other eye disease requiring HES**	55 (0.8)	104 (1.3)	163 (1.9)	122 (1.2)	85 (0.8)	77 (0.6)	122 (0.9)	145 (1.0)	160 (1.0)	182 (1.2)	174 (1.1)	1389 (1.0; 1.0 to 1.1)
Biomicroscopy recorded***	446 (6.7)	618 (7.6)	794 (9.2)	712 (6.9)	612 (5.5)	774 (5.9)	650 (4.8)	621 (4.1)	742 (4.8)	965 (6.3)	868 (5.4)	7802 (5.8; 5.7 to 6.0)
STDR	116 (1.7)	145 (1.8)	192 (2.2)	178 (1.7)	160 (1.4)	223 (1.7)	179 (1.3)	212 (1.4)	246 (1.6)	251 (1.6)	290 (1.8)	2192 (1.6; 1.6 to 1.7)
STR[$]	41 (0.6)	44 (0.5)	81 (0.9)	65 (0.6)	56 (0.5)	75 (0.6)	57 (0.4)	69 (0.5)	98 (0.6)	85 (0.6)	110 (0.7)	781 (0.6; 0.5 to 0.6)
STM[$]	91 (1.4)	119 (1.5)	157 (1.8)	135 (1.3)	130 (1.2)	197 (1.5)	149 (1.1)	179 (1.2)	191 (1.2)	216 (1.4)	237 (1.5)	1801 (1.3; 1.3 to 1.4)
Unknown STR & unknown STM	0 (0.0)	0 (0.0)	2 (< 0.1)	2 (< 0.1)	4 (< 0.1)	0 (0.0)	4 (< 0.1)	1 (< 0.1)	1 (< 0.1)	0 (0.0)	0 (0.0)	14 (< 0.1; 0.0 to 0.0)
Not STDR	330 (5.0)	473 (5.8)	602 (6.9)	534 (5.2)	452 (4.0)	551 (4.2)	471 (3.5)	406 (2.7)	496 (3.2)	714 (4.7)	555 (3.4)	5584 (4.2; 4.1 to 4.3)
Unknown STDR status	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (< 0.1)	0 (0.0)	0 (0.0)	23 (0.1)	26 (< 0.1; 0.0 to 0.0)
No biomicroscopy recorded***	81 (1.2)	96 (1.2)	128 (1.5)	142 (1.7)	83 (0.7)	147 (1.1)	124 (0.9)	48 (0.3)	63 (0.4)	66 (0.4)	126 (0.8)	1104 (0.8; 0.8 to 0.9)
Screen-negative	6110 (92.1)	7374 (91.2)	7742 (89.4)	9412 (91.7)	10,519 (93.8)	12,203 (93.0)	12,744 (94.3)	14,446 (95.6)	14,747 (94.8)	14,249 (93.3)	15,102 (93.8)	12,4648 (93.3; 93.2 to 93.5)

TABLE 10 Overall screen-positive/negative/STDR (STR/STM) annual incidences: 2006/07 to 2016/17 (out of the number of people with at least one attended screening appointment) (*continued*)

	Screening year*, *n* (%^)											
Variable	**2006/07**	**2007/08**	**2008/09**	**2009/10**	**2010/11**	**2011/12**	**2012/13**	**2013/14**	**2014/15**	**2015/16**	**2016/17**	**Overall, *n* (%^; 95% CI^^^)**

*Screening year is from 1 April to 31 March.
**Based on assumption that if category is unknown, then assume category is OED.
***Biomicroscopy must be recorded within 1 year of screening appointment when positive screen result occurred.
^Note that all percentages are calculated out of the number of individuals with at least one attended screening appointment.
^^Adjusted for those in the RCT and assigned to 24 m who under normal circumstances would have had a screening appointment in these years. In 2015/16 this amounts to 226 individuals (266*0.85 which is the approximate assumed attendance percentage) and in 2016/17 it affected 1232 individuals (1449*0.85). All are assumed to be screen-negative.
^^^Wilson score confidence intervals.
$Note that these are not mutually exclusive categories.

Notes
In 2006/07 there were 16 (0.2%) cases with both STR and STM. Additionally, 1 (< 0.1%) STR case had unknown STM and 1 (< 0.1%) STM case had unknown STR.
In 2007/08 there were 18 (0.2%) cases with both STR and STM.
In 2008/09 there were 48 (0.6%) cases with both STR and STM.
In 2009/10 there were 24 (0.2%) cases with both STR and STM. Additionally, 1 (< 0.1%) STR case had unknown STM and 3 (< 0.1%) STM cases had unknown STR.
In 2010/11 there were 30 (0.3%) cases with both STR and STM. Additionally, 1 (< 0.1%) STR case had unknown STM and 1 (< 0.1%) STM case had unknown STR.
In 2011/12 there were 49 (0.4%) cases with both STR and STM. Additionally, 1 (< 0.1%) STR case had unknown STM.
In 2012/13 there were 31 (0.2%) cases with both STR and STM. Additionally, 2 (< 0.1%) STR cases had unknown STM.
In 2013/14 there were 37 (0.2%) cases with both STR and STM. Additionally, 2 (< 0.1%) STR cases had unknown STM and 3 (< 0.1%) STM cases had unknown STR.
In 2014/15 there were 44 (0.3%) cases with both STR and STM. Additionally, 3 (< 0.1%) STR cases had unknown STM and 3 (< 0.1%) STM cases had unknown STR.
In 2015/16 there were 50 (0.3%) cases with both STR and STM. Additionally, 1 (< 0.1%) STR case had unknown STM.
In 2016/17 there were 57 (0.4%) cases with both STR and STM. Additionally, 5 (< 0.1%) STR cases had unknown STM and 9 (0.1%) STM cases had unknown STR
This table does not include any HES pathway appointments (screening or biomicroscopies).

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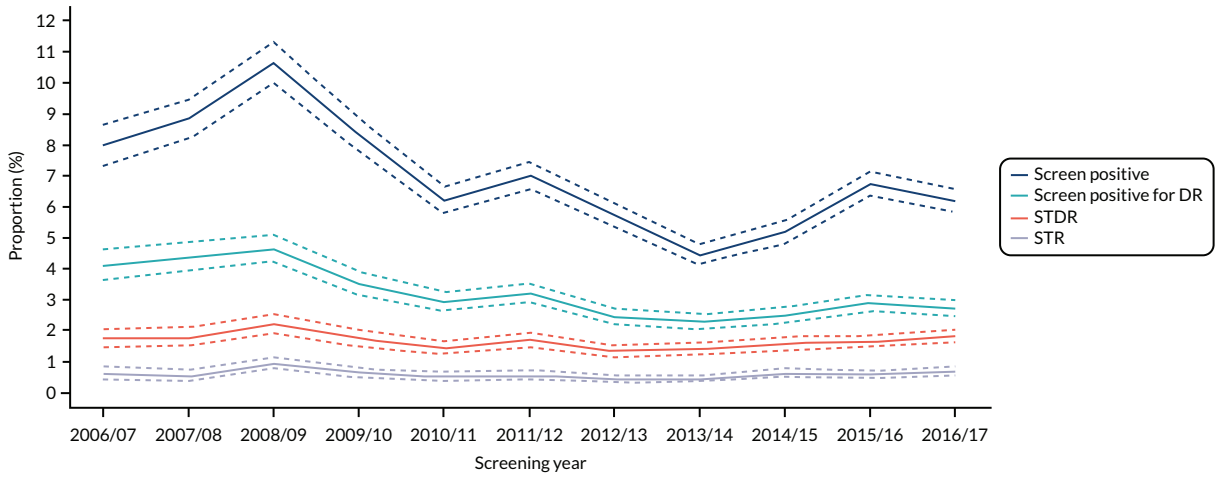


FIGURE 9 Plot of overall screen-positive/STDR/STR annual incidences 2006/07–2016/17 (out of number of people with at least one attended screening appointment) by screening year (with 95% wilson score cis). STM not shown.

Discussion

Our data from an established screening programme give up-to-date estimates of current incidences of key stages in the diabetes care pathway of importance to patients, namely progression to screen-positive, screen-positive because of DR and STDR. The annual incidence of screen-positive cases showed a consistent fall over a decade from 8–10% to around 5–6%. The rates of screen-positive attributed to DR also fell over time to around 3%, slightly lower but consistent with a referable retinopathy rate (equivalent to our screen-positive because of DR) of 4.3% reported in 2013 from Scotland.[9] Both of these trends occurred against a background of stable rates of true-positive STDR. These reductions require further investigation in other screening programmes. They may represent improvements in grading.

The rates of STDR were stable and consistently under 2.0% apart from 1 year early in the study. These low rates have also been reported in 2015 from Gloucestershire, a programme similar to ours in Liverpool.[42]

The strengths of our study include the size of the data set, the duration of data collection and the robust analysis. Previous studies were from several decades ago, when levels of diabetes control were poorer. HbA_{1c} levels were generally well controlled in our population.

The main limitation of this study is the nature of data availability, which meant that the data set was partly retrospective. Around 5% of the population died or moved away each year and without consent we were unable to access their historical data. This censoring could have affected our estimates of DR and STDR between 2006/7 and 2012/13.

The ISDR RCT commenced in 2014, resulting in a proportion of patients moving to 2-yearly screening. We corrected for this effect in the last two years of our analysis.

In Liverpool in 2017/18, 9.4% (2054/21853) people were attending the hospital for management of their diabetes or slit-lamp-based screening. Nonetheless we are able to estimate a rate of STDR in people attending screening of 164/10,000 PWD/annum (2192/133,554*10,000), useful data for people running established screening programmes and in designing future RCTs. Around 82% of these people had STM and 36% STR.

We detected a shift in ethnicity over the 11 years of the study but the data were difficult to interpret due to the increase in unknown data on ethnicity caused by changes in the methods of collection.

TABLE 11 Screen-positive/negative/STDR (STR/STM) annual incidences 2007/08 – 2016/17 for people attending their first screening appointments only (out of number of people with at least one first recorded attended screening appointment)

Variable	Screening year*, *n* (%^)										
	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17	Overall, *n* (%^; 95% CI^^)
Number of Individuals with a first ever recorded attended screening appointment	1883 (100.0)	1542 (100.0)	1566 (100.0)	1665 (100.0)	1941 (100.0)	1503 (100.0)	1588 (100.0)	1634 (100.0)	1629 (100.0)	1877 (100.0)	16828 (100.0)
Screen-positive	230 (12.2)	226 (14.7)	169 (10.8)	148 (8.9)	197 (10.1)	131 (8.7)	112 (7.1)	129 (7.9)	157 (9.6)	160 (8.5)	1659 (9.9; 9.4 to 10.3)
Screen-positive for DR	98 (5.2)	67 (4.3)	48 (3.1)	52 (3.1)	64 (3.3)	42 (2.8)	40 (2.5)	49 (3.0)	55 (3.4)	56 (3.0)	571 (3.4; 3.1 to 3.7)
Screen-positive for unassessable images	83 (4.4)	88 (5.7)	87 (5.6)	72 (4.3)	103 (5.3)	57 (3.8)	33 (2.1)	43 (2.6)	55 (3.4)	62 (3.3)	683 (4.1; 3.8 to 4.4)
Screen-positive for other eye disease requiring HES**	49 (2.6)	71 (4.6)	34 (2.2)	24 (1.4)	30 (1.5)	32 (2.1)	39 (2.5)	37 (2.3)	47 (2.9)	42 (2.2)	405 (2.4; 2.2 to 2.6)
Biomicroscopy recorded***	186 (9.9)	197 (12.8)	135 (8.6)	127 (7.6)	169 (8.7)	114 (7.6)	106 (6.7)	119 (7.3)	145 (8.9)	144 (7.7)	1442 (8.6; 8.2 to 9.0)
STDR	39 (2.1)	37 (2.4)	31 (2.0)	31 (1.9)	42 (2.2)	30 (2.0)	33 (2.1)	36 (2.2)	40 (2.5)	45 (2.4)	364 (2.2; 2.0 to 2.4)
STR$	15 (0.8)	26 (1.7)	18 (1.1)	14 (0.8)	20 (1.0)	13 (0.9)	14 (0.9)	23 (1.4)	14 (0.9)	23 (1.2)	180 (1.1; 0.9 to 1.2)
STM$	35 (1.9)	29 (1.9)	21 (1.3)	25 (1.5)	39 (2.0)	26 (1.7)	28 (1.8)	23 (1.4)	35 (2.1)	38 (2.0)	299 (1.8; 1.6 to 2.0)
Unknown STR & unknown STM	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (< 0.1; 0.0 to 0.0)
Not STDR	147 (7.8)	160 (10.4)	104 (6.6)	96 (5.8)	127 (6.5)	84 (5.6)	73 (4.6)	83 (5.1)	105 (6.4)	96 (5.1)	1075 (6.4; 6.0 to 6.8)
Unknown STDR status	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	3 (< 0.1; 0.0 to 0.1)
No biomicroscopy recorded***	44 (2.3)	29 (1.9)	34 (2.2)	21 (1.3)	28 (1.4)	17 (1.1)	6 (0.4)	10 (0.6)	12 (0.7)	16 (0.9)	217 (1.3; 1.1 to 1.5)
Screen-negative	1653 (87.8)	1316 (85.3)	1397 (89.2)	1517 (91.1)	1744 (89.9)	1372 (91.3)	1476 (92.9)	1505 (92.1)	1472 (90.4)	1717 (91.5)	15,169 (90.1; 89.7 to 90.6)

*Screening year is from 1 April to 31 March.
**Based on assumption that if category is unknown, then assume category is OED.
***Biomicroscopy must be recorded within 1 year of screening appointment when positive screen result occurred.
^Note that all percentages are calculated out of the number of individuals with at least one attended screening appointment.
^^Wilson score confidence intervals.
$Note that these are not mutually exclusive categories.

Notes
In 2006/07 there were 9 (0.2%) cases with both STR and STM. Additionally, 1 (< 0.1%) STR case had unknown STM.
In 2007/08 there were 11 (0.6%) cases with both STR and STM.
In 2008/09 there were 18 (1.2%) cases with both STR and STM.
In 2009/10 there were 9 (0.6%) cases with both STR and STM. Additionally, 1 (0.1%) STM case had unknown STR.
In 2010/11 there were 9 (0.5%) cases with both STR and STM.
In 2011/12 there were 17 (0.9%) cases with both STR and STM. Additionally, 1 (0.1%) STR case had unknown STM.
In 2012/13 there were 9 (0.6%) cases with both STR and STM.
In 2013/14 there were 9 (0.6%) cases with both STR and STM. Additionally, 1 (0.1%) STR case had unknown STM.
In 2014/15 there were 10 (0.6%) cases with both STR and STM.
In 2015/16 there were 9 (0.6%) cases with both STR and STM.
In 2016/17 there were 16 (0.9%) cases with both STR and STM. Additionally, 1 (0.1%) STR case had unknown STM and 2 (0.1%) STM cases had unknown STR.
This table does not include any HES pathway appointments (screening or biomicroscopies).

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TABLE 12 Screen-positive/negative/STDR (STR/STM) annual incidences 2007/08 – 2016/17 for people attending screening appointments that are not their first (out of number of people with at least one first recorded attended screening appointment)

Variable	Screening year*, *n* (%^)										
	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17	Overall, *n* (%^; 95% CI^^^)
Number of Individuals with an attended screening appointment (not first ever recorded)	6349 (100.0)	7155 (100.0)	8769 (100.0)	9585 (100.0)	11,248 (100.0)	12,037 (100.0)	13,561 (100.0)	13,935 (100.0)	13,656^^ (100.0)	14,230^^ (100.0)	11,2173 (100.0)
Screen-positive	486 (7.7)	698 (9.8)	686 (7.8)	549 (5.7)	724 (6.4)	644 (5.4)	557 (4.1)	676 (4.9)	875 (6.4)	835 (5.9)	6929 (6.2; 6.0 to 6.3)
Screen-positive for DR	258 (4.1)	334 (4.7)	313 (3.6)	276 (2.9)	355 (3.2)	289 (2.4)	305 (2.2)	338 (2.4)	387 (2.8)	382 (2.7)	3351 (3.0; 2.9 to 3.1)
Screen-positive for unassessable images	173 (2.7)	271 (3.8)	285 (3.3)	212 (2.2)	322 (2.9)	265 (2.2)	146 (1.1)	215 (1.5)	353 (2.6)	321 (2.3)	2632 (2.3; 2.3 to 2.4)
Screen-positive for other eye disease requiring HES**	55 (0.9)	93 (1.3)	88 (1.0)	61 (0.6)	47 (0.4)	90 (0.7)	106 (0.8)	123 (0.9)	135 (1.0)	132 (0.9)	946 (0.8; 0.8 to 0.9)
Biomicroscopy recorded***	432 (6.8)	598 (8.4)	578 (6.6)	485 (5.1)	605 (5.4)	537 (4.5)	515 (3.8)	623 (4.5)	820 (6.0)	724 (5.1)	6082 (5.4; 5.3 to 5.6)
STDR	106 (1.7)	155 (2.2)	148 (1.7)	129 (1.3)	181 (1.6)	149 (1.2)	179 (1.3)	210 (1.5)	211 (1.5)	245 (1.7)	1766 (1.6; 1.5 to 1.6)
STR$	29 (0.5)	55 (0.8)	47 (0.5)	42 (0.4)	55 (0.5)	44 (0.4)	55 (0.4)	75 (0.5)	71 (0.5)	87 (0.6)	579 (0.5; 0.5 to 0.6)
STM$	84 (1.3)	128 (1.8)	115 (1.3)	105 (1.1)	158 (1.4)	123 (1.0)	151 (1.1)	168 (1.2)	181 (1.3)	199 (1.4)	1453 (1.3; 1.2 to 1.4)
Unknown STR & unknown STM	0 (0.0)	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)	0 (0.0)	4 (< 0.1)	1 (< 0.1)	1 (< 0.1)	0 (0.0)	0 (0.0)	12 (< 0.1; 0.0 to 0.0)
Not STDR	326 (5.1)	443 (6.2)	430 (4.9)	356 (3.7)	424 (3.8)	388 (3.2)	333 (2.5)	413 (3.0)	609 (4.5)	459 (3.2)	4293 (3.8; 3.7 to 3.9)
Unknown STDR status	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (< 0.1)	0 (0.0)	0 (0.0)	20 (0.1)	23 (< 0.1; 0.0 to 0.0)
No biomicroscopy recorded***	54 (0.9)	100 (1.4)	108 (1.2)	64 (0.7)	119 (1.1)	107 (0.9)	42 (0.3)	53 (0.4)	55 (0.4)	111 (0.8)	847 (0.8; 0.7 to 0.8)
Screen-negative	5863 (92.3)	6457 (90.2)	8083 (92.2)	9036 (94.3)	10,524 (93.6)	11,393 (94.6)	13,004 (95.9)	13,259 (95.1)	12,781 (93.6)	13,395 (94.1)	105,244 (93.8; 93.7 to 94.0)

TABLE 12 Screen-positive/negative/STDR (STR/STM) annual incidences 2007/08 – 2016/17 for people attending screening appointments that are not their first (out of number of people with at least one first recorded attended screening appointment) (*continued*)

Variable	Screening year*, *n* (%^)										Overall, *n* (%^; 95% CI^^^)
	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17	

*Screening year is from 1 April to 31 March.
**Based on assumption that if category is unknown, then assume category is OED.
***Biomicroscopy must be recorded within 1 year of screening appointment when positive screen result occurred.
^Note that all percentages are calculated out of the number of individuals with at least one attended screening appointment.
^^Adjusted for those in the RCT and assigned to 24 m who under normal circumstances would have had a screening appointment in these years. In 2015/16 this amounts to 226 individuals (266*0.85 which is the approximate assumed attendance percentage) and in 2016/17 it affected 1232 individuals (1449*0.85). All are assumed to be screen-negative.
^^^Wilson score confidence intervals.
$Note that these are not mutually exclusive categories.

Notes
In 2006/07 there were 7 (0.4%) cases with both STR and STM. Additionally, 1 (0.1%) STM case had unknown STR.
In 2007/08 there were 7 (0.1%) cases with both STR and STM.
In 2008/09 there were 30 (0.4%) cases with both STR and STM.
In 2009/10 there were 15 (0.2%) cases with both STR and STM. Additionally, 1 (< 0.1%) STR case had unknown STM and 2 (< 0.1%) STM cases had unknown STR.
In 2010/11 there were 21 (0.2%) cases with both STR and STM. Additionally, 1 (< 0.1%) STR case had unknown STM and 1 (< 0.1%) STM case had unknown STR.
In 2011/12 there were 32 (0.3%) cases with both STR and STM.
In 2012/13 there were 22 (0.2%) cases with both STR and STM. Additionally, 2 (< 0.1%) STR cases had unknown STM.
In 2013/14 there were 28 (0.2%) cases with both STR and STM. Additionally, 1 (< 0.1%) STR case had unknown STM and 3 (< 0.1%) STM cases had unknown STR.
In 2014/15 there were 34 (0.2%) cases with both STR and STM. Additionally, 3 (< 0.1%) STR cases had unknown STM and 3 (< 0.1%) STM cases had unknown STR.
In 2015/16 there were 41 (0.3%) cases with both STR and STM. Additionally, 1 (< 0.1%) STR case had unknown STM.
In 2016/17 there were 41 (0.3%) cases with both STR and STM. Additionally, 4 (< 0.1%) STR cases had unknown STM and 7 (< 0.1%) STM cases had unknown STR.
This table does not include any HES pathway appointments (screening or biomicroscopies).

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Fewer than half of people graded as screen-positive were considered to have DR by the grading teams and around half of these were judged as true-positive in medical retina clinics. A debate needs to take place about these levels of positivity, preferably with patient groups and other stakeholders. This is especially clear in new screenees, where only a 1/5th (21.7%) of people identified as screen-positive had true-positive disease. Much of the screen-positive disease is due to unassessable images, most likely due to cataract, and other significant eye disease, none of which are the objectives of DR screening.

In spite of the high levels of previously undetected cataract and other eye disease (80% of screen-positives due to unassessable images or other significant eye disease), people undergoing their first screening visit did have higher rates (37.5%) of STDR, suggesting that these individuals might be targeted specifically in screening programmes. We detected screen-positive rates in these new screenees of 9.9%. In Hong Kong, which introduced screening in 2015, a similar 10% of screen-positives were detected in their first year of screening a population that had not been screened previously.[65]

Conclusions

In an established screening programme with a stable population, rates of screen-positive overall and due to DR show a consistent fall over time to a low level. The annual incidence of STDR is under 2%, suggesting future work on defining screen-positive and supporting extended intervals for people at low risk. Current screening definitions and pathways were established over 15 years ago at the introduction of screening and were consensus-based and large numbers of people appear to be being referred unnecessarily to the HES. Higher rates of disease are seen in new screenees, especially those with a history of non-attendance, suggesting specific targeting of this group. Our data are useful for the design of future epidemiological and intervention studies. For epidemiological data from screening programmes to be interpretable, future reporting should clearly differentiate between screen-positive, screen-positive due to DR, ungradeable and other eye disease, as well as STDR.

Interrelation to other work packages and overall aims of the programme

This work package was supported by work from the PPI group around patient-centred outcomes as well as data collected in the ISDR DW (WP B1).

Knowledge transfer

Research outputs

Programme outputs (work package G) as of 30 September 2021 are listed in *Peer reviewed, full publications* and *Other publications*.

Dissemination activities

Simon Harding, programme CI, is a member of the Research Advisory Committee, English NDESP and reports on findings and policy implications of ISDR. He has attended UK and international conferences 2017–2020 raising awareness of individualised screening.

We held a dissemination event (25 September 2019) for the screening community and commissioners from the home nations and outside the UK and to involve patient groups.

There was general support on safety of switching to extended intervals in stratified and/or personalised/individualised screening. Scale-up through a whole population 'pilot' was considered reasonable. Failsafe and communication needed revising.

Facilitated discussion identified a number of issues in the ISDR data set to be addressed:

- 3503 people did not consent for the RCT during recruitment
- external validation was needed in another UK programme
- further analysis was recommended: non-consented group, model cohort data set through RCE, compare with the stratification model to be used in the NDESP.

Further analysis

The team conducted further analyses within the programme in response to the symposium (see *Supplementary Material 4*).

People who did not consent to recruitment in the RCT were more likely to be female, older, have longer disease duration, be smokers (all $p < 0.001$) and had slightly higher screen-positive rates ($p = 0.11$). They had similar other clinical risk factors. This is likely to reflect older people being less likely to agree to participate in research.

Allocations by the RCE to 6-, 12- and 24-month intervals in the non-consenting group in the RCT ($n = 3180$) were similar to those who consented. For the ISDR cohort study data set there was a slightly higher (4.5%) allocation to 6 months (high-risk) and a corresponding reduction in the 24-month (low-risk) group. In scaling-up to whole populations there may be a small reduction in resources being freed up and a small increase in the high-risk group.

We compared IDSR variable-interval risk-based screening with the planned English NDESP stratified screening[30] by applying the proposed rules to the RCT data set. We estimated that the NDESP stratification will allocate 33.1% of the RCT group to 12-months rescreening and 66.9% to 24-months (ISDR 82.3%), a 26% reduction in the move to an extended interval.

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We modelled a 'virtual RCE annual review' as a failsafe for people being allocated to extended interval to run at 12 months using updated clinical data and baseline grading. We ran the RCE in the 24-month RCT group (*n* = 1776) at 12 months; 97.1% (1725/1776) remained in the low-risk group. Two people (0.1%) were reallocated to 6 months and 49 (2.8%) to 12 months.

The Liverpool RCE was 're-run' at the end of the study to act as an internal validation and check of robustness of the model, which showed the RCE model is 'stable' in the Liverpool population.

An executable RCE package has been produced. Independent external validation will be completed (at the time of writing, under way in partnership with the Diabetes Research Unit Cymru). We have designed a pilot phase IV whole-population scale-up in Liverpool to start in 2022 (at the time of writing under review by the UK National Screening Committee).

Intellectual property

The team has worked with the RLBUHT Innovation Team's partner, 2Bio Ltd, throughout the programme. Two components have been assessed as having potential for IP, the RCE and the DW.

RCE

- mathematics, covariate selection, import scripts, imputation protocols
- potential to function as a stand-alone clinical tool.

DW

- SQL server integration service protocols, real-time DW, imputation and credibility systems
- potential to be developed as a NHS clinical tool.

In any future commercialisation or deployment of these systems re-writing in a more portable and commercially attractive programming language will be required. The original code base built in MATLAB and MatSoap for the RCE has been ported into Python and validated using risk-calculations from the RCT.

The RLBUHT Innovation team will support the process of commercialisation, including discussions and negotiations with potential partners and licensees.

Conclusions and recommendations

Reflections on the programme

A PGfAR offers long-term funding for a large piece of work. Much can be achieved. We completed a large RCT and produced evidence of global significance which will underpin the next 10–15 years of development of DR screening. We completed a large qualitative study that will underpin the future implementation of screening and diabetes services, with relevance outside ophthalmology. We undertook micro-costing and economic analyses using real-world resource data rather than modelling. We overcame the challenges of data access and variability to develop a data linkage and integration system implemented into NHS clinical care. We built and tested a RCE for ophthalmology, tuneable for local populations.

Our findings have given new impetus to the introduction of extended screening in England, due to be introduced in 2022/23. Our RCT has given impetus to the development of variable-interval risk-based screening which is being rolled out in other countries, including Hong Kong, Denmark and Singapore. Our team are engaged in global DR screening research in Malawi, Malaysia and China. Our expertise has been utilised in 2020 by WHO Europe in developing guidance for policy-makers on DR screening.[66]

We were not able to deliver on all aspects of the planned work. The recruitment of such a large sample required screening of over 8000 individuals, each requiring identification, information and consenting. It took time to mobilise recruitment teams and we were about 12 months late in delivering the recruitment milestone. The teams that we had originally planned for proved unavailable at a key stage. Accessing the data proved more challenging than expected. The multiple data platforms and the poor or absent documentation prevented us from accessing all the planned data types. We received substantial additional research capacity and sustainability funds from our sponsor at two key stages, to expand the recruitment teams and for the data engineering, both of which we had underestimated in our funding model. We also needed to reallocate resources from our observational cohort study to support the RCT. This meant that we cut the section in WP B on collection of VA and grading data from the HES, to the significant disappointment of the PPI team. Nonetheless we did complete a longitudinal cohort study on over 28,000 individuals attending the screening programme.

Our development grant phase was essential. It allowed us to develop a comprehensive and effective team of co-investigators including a patient representative and a local manager and develop relationships with key stakeholders especially in primary care. We addressed key areas of uncertainty:

- We were able to identify and extract sample data from the widely varying domains in primary care, the screening programme and the hospital.
- We explored and made progress with the challenging governance and data-protection environments in the NHS.
- We built a demonstration version of the RCE.

Managing a long and complex programme of work must not be underestimated. It requires substantial commitment from the CI and an effective and able programme manager. The role of the WP leads is critical. Regular investigator meetings are essential to maintain enthusiasm and engagement. Inevitably co-investigators' priorities can change or there can be extended periods of leave. Effective support for the CI from senior members of research departments can help maintain momentum or input additional resources and this needs to happen early. An effective Programme Steering Committee is a 'critical friend' at challenging times.

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Strengths and limitations

Our programme provides for the first time RCT evidence on individualised DR screening with a full economic evaluation with the quality assured by a clinical trials centre. Recommendations are supported by qualitative evidence, not previously reported, and an active PPI group was embedded throughout. Our findings do come with a number of limitations, which have been described above. Here we briefly summarise the most important of these.

Participants were enrolled from a long-established programme with low rates of DR and progression to STDR. Good glycaemic and BP control and a relatively low proportion of type 1 diabetes (4.0%) might have biased the sample. Findings may not be generaliseable across other programme in the UK with differing ethnicity. Low rates of DR have been reported in other similar settings, but our results should be treated with caution in areas with a higher prevalence, poorer control of diabetes or wider ethnic mix, or in programmes during the set-up process.

Our trial had only a 2-year time horizon, which is short in the context of a life-long condition. With a move to extended-interval screening in several countries, we wanted to provide high-quality RCT evidence on how people act when given variable-interval risk-based screening. The study was designed to compare safety and effectiveness of two screening regimens, not the cost-effectiveness of screening versus no screening. To allow for two cycles for the low-risk group would have extended the study duration from 4 to 6 years. The low rates of retinopathy and STDR in the low-risk group suggest that our findings on effectiveness would be unlikely to change; most disease was detected in the high- and medium-risk groups. Our relatively short time horizon could have been mitigated by an extensive risk-based economic model based on the RCE (described in *Economic model*) but the model ran into computational difficulties. It will be important in future testing to recognise this limitation and ensure robust monitoring of attendance rates. It may also be informative to extend the cost-effectiveness analysis to include the whole care pathway, including downstream costs and outcomes.

Some of our secondary analyses within the individualised group relied on small numbers, especially in the high- and medium-risk groups. Conclusions based on these analyses need to be treated with some caution.

We were unable to recruit a cohort of regular non-attenders so cannot address this important issue. We were unable to complete the component of the cohort study in the HES, so were only able to provide data on incidences in the screening population.

Conclusions

Here we summarise the key findings:

- Evidence from the ISDR RCT shows that extended and personalised interval screening can safely be introduced in established screening programmes.
- Our data provide evidence that an individualised variable-interval risk-based approach has the potential to give improvements in cost-effectiveness without compromising safety or quality of life, but we did not include treatment costs in our economic analyses.
- Our qualitative evidence shows that PWD and HCPs appear to be supportive of variable intervals in screening but with important caveats. For successful implementation interpretable and clear safeguards against increasing non-attendance, loss of diabetes control and system failures are required. Alternative referral pathways are required for those lost to follow-up or whose risk factors change substantially over longer intervals.
- Variable-interval screening supported by clinical data allows 6-monthly targeting of a high-risk group, detecting disease earlier, while substantially reducing the number of appointments for a low-risk group.

- The rates of STDR in our long-established screening programme have dropped to a very low level, supported by other limited UK data. Higher rates are seen in those attending screening for the first time and with type 1 diabetes. The majority of cases classed as screen-positive do not have sight-threatening disease.
- Robust monitoring of attendance and retinopathy rates should be included in any wider testing. Our trial was over a 2-year time horizon when the disease has a long time-frame, and our findings come from a single centre with a relatively stable mainly white population.
- Findings from this research show that PPI can produce key decisions to underpin critical parts of the design and delivery of applied research. Strong commitment of the senior investigators is essential.
- The evidence from our programme and elsewhere shows that RCEs can be feasible, reliable, safe and acceptable to patients with the caveat that reliable monitoring and clear communication to stakeholders are necessary.
- Evidence from our programme has demonstrated that real-time integration of data from primary and secondary care sectors can be achieved, and indeed is necessary for the RCE, but relies on successful engagement of key stakeholders. This may not be feasible in some settings.

Recommendations for future research

Our recommendations are based on the evidence from the ISDR programme and elsewhere.

1. Individualised variable-interval risk-based screening is ready to be upscaled in a phase IV whole-population pilot. Evidence of repeatable results as seen in ISDR should be collected before considering wider dissemination.
2. Further health economics research is required to support potential adoption of individualised/personalised screening, including modelling beyond the 2-year time horizon and extending to include lifetime costs of treatment and care, and blindness averted.
3. The Liverpool RCE requires external validation with at least one other screening programme before it could be considered for adoption.
4. Further qualitative research is required around the potential adoption of extended and variable-interval screening to develop and implement safeguards and monitoring systems interpretable by end-users.
5. Evidence on efficacy in populations with higher rates of diabetes and different mixes of ethnicity, in newly commencing programmes and in low/middle-income countries is required.
6. New research is needed on methods to address the misunderstandings and conflation in PWD around their diabetes and eye care.
7. Evidence of current rates of VI should be collected in line with this being a key patient-centred outcome.
8. Novel approaches to recruit non-attenders to future qualitative research need to be developed for research into non-attendance.
9. Research is needed to establish more appropriate referral thresholds in DR screening.

The knowledge base in the field of screening for DR is changing in some areas. Technology is developing around automated grading and artificial intelligence. Some work is under way to integrate within screening but progress is not rapid. Digital healthcare is being developed with initiatives on big data and data integration which will support future personalisation. However, these approaches are still yet to be embedded in large health systems such as the NHS. Large epidemiological studies especially on important functional patient-centred outcomes are few, with much of the data being outdated and with limited current and future work planned. Pilot studies on introduction of new technologies are being considered and may move the field forwards in the medium term. The qualitative evidence base is small with little of relevance to screening and is unlikely to move forward rapidly.

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Members of the ISDR Study Group who are not included as primary authors are listed in *Appendix 1*.

Contributions of authors

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Ayesh Alshukri (https://orcid.org/0000-0003-0852-2068) (Research Associate, Computer Science) was part of the observational cohort, RCE and RCT teams.
Deborah Broadbent (https://orcid.org/0000-0002-3195-5024) (Honorary Senior Lecturer, Ophthalmology) was an applicant on the grant and led the RCT.
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Mehrdad Mobayen Rahni (https://orcid.org/0000-0002-1278-8558) (Lead Database Analyst, Business Intelligence) was the data warehouse designer and manager.
John Roberts (https://orcid.org/0000-0003-3392-7243) (Patient representative) was an applicant on the grant and led the involvement of the PPI group.
Christopher Sampson (https://orcid.org/0000-0001-9470-2369) (Health Economist) was part of the team that conducted the cost-effectiveness analysis.

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Daniel Seddon (https://orcid.org/0000-0002-0296-6234) (GP, NHS England) was an applicant on the grant, represented the end-user and contributed to several work packages
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Clare Thetford (https://orcid.org/0000-0003-2188-3052) (Research Fellow) was part of the qualitative team.
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Jiten Vora (https://orcid.org/0000-0002-3488-5287) (Professor/Consultant Endocrinologist) was an applicant on the grant and led the observational cohort study.
Amu Wang (https://orcid.org/0000-0002-1764-6524) (Honorary Research Associate) was responsible for project management (2013–18).
Paula Williamson (https://orcid.org/0000-0001-9802-6636) (Professor of Medical Statistics) was an applicant on the grant and Director of the Liverpool CTRC.

Publications

Cheyne CP, Burgess PI, Broadbent DM, García-Fiñana M, Stratton IM, Criddle T, *et al*. Incidence of sight-threatening diabetic retinopathy in an established urban screening programme: an 11-year cohort study. *Diabet Med* 2021;**38**:e14583.
Eleuteri A, Fisher AC, Broadbent DM, García-Fiñana M, Cheyne CP, Wang A, *et al*. Individualised variable-interval risk-based screening for sight-threatening diabetic retinopathy: the Liverpool Risk Calculation Engine. *Diabetologia* 2017;**60**:2174–82.
Byrne P, Thetford C, Gabbay M, Clarke P, Doncaster E, Harding SP, ISDR Study Group. Personalising screening of sight-threatening diabetic retinopathy – qualitative evidence to inform effective implementation. *BMC Public Health* 2020;**20**:881.
Broadbent DM, Wang A, Cheyne CP, James M, Lathe J, Stratton IM, *et al*. Safety and cost-effectiveness of individualised screening for diabetic retinopathy: the ISDR open-label, equivalence RCT. *Diabetologia* 2021;**64**:56–69.

Peer-reviewed, full publications

Author	Title	Year	Output type	Work package	URL link
Sampson CJ *et al.*	Health state utility values for diabetic retinopathy: protocol for a systematic review and meta-analysis	2015	Peer reviewed publication – Systematic Reviews	D	https://doi.org/10.1186/s13643–015–0006–6
Eleuteri A *et al.*	Individualised variable interval risk-based screening for sight threatening diabetic retinopathy – the Liverpool Risk Calculation Engine	2017	Peer reviewed publication – Diabetologia	C	https://doi.org/10.1007/s00125-017-4386-0
García-Fiñana M *et al.*	Personalised risk-based screening for diabetic retinopathy: a multivariate approach versus the use of stratification rules	2018	Peer reviewed publication – Diabetes, Obesity and Metabolism	E	https://doi.org/10.1111/dom.13552
Broadbent *et al.*	Individualised screening for diabetic retinopathy: the ISDR study – rationale, design and methodology for a randomised controlled trial comparing annual and individualised risk-based variable-interval screening	2019	Peer reviewed publication – BMJ Open	E	http://dx.doi.org/10.1136/bmjopen-2018–025788

Author	Title	Year	Output type	Work package	URL link
Byrne *et al.*	Personalising screening of sight-threatening diabetic retinopathy – qualitative evidence to inform effective implementation	2020	Peer reviewed publication – BMC Public Health	F	https://doi.org/10.1186/s12889-020-08974-1
Broadbent *et al.*	Safety and cost-effectiveness of individualised screening for diabetic retinopathy: the ISDR open-label, equivalence randomised controlled trial	2020	Peer reviewed publication – Diabetologia	D,E	https://doi.org/10.1007/s00125-020-05313-2
Cheyne *et al.*	Incidence of sight-threatening diabetic retinopathy in an established urban screening programme: an 11-year cohort study	2021	Peer reviewed publication – Diabetic Medicine	B	https://doi.org/10.1111/dme.14583

BMJ, British Medical Journal.

Other publications and outputs

Author	Title	Year	Output type	Work package	URL link
Thetford C *et al.*	Patient perspectives of diabetic retinopathy screening and models of diabetes care	2014	Conference presentation – SAPC	F	N/A
Sampson C *et al.*	Individualised cost-effectiveness analysis in risk-based screening: practical and ethical?	2015	Conference presentation – Personalised Medicine and Resource Allocation	D	N/A
Harding S *et al.*	10-year observational study of patient related outcomes during expansion to full population coverage of a systematic diabetes eye care programme – the Liverpool Diabetic Eye Study	2016	Conference presentation – ARVO	B	https://iovs.arvojournals.org/article.aspx?articleid=2559561&resultClick=1
Appelbe D *et al.*	E-trials within the UKCRC CTU network – opportunities and challenges	2017	Conference presentation – NIHR e-trial	E	N/A
García-Fiñana M *et al.*	A novel multivariate discriminant approach to predict sight threatening diabetic retinopathy (STDR) cases – data from the Liverpool Diabetic Eye Study	2017	Conference presentation – ARVO	E	https://iovs.arvojournals.org/article.aspx?articleid=2641391&resultClick=1
Harding SP	The UK as a clinical trials destination – 10 years of the National Institute for Health Research. Personalised medicine in the NHS	2017	Conference presentation – NIHR CRN Ophthalmology symposium, ARVO	E	N/A
Harding SP *et al.*	Detecting sight threatening diabetic retinopathy in the 21st century – lessons from 20 years of screening in Liverpool	2017	Conference presentation – Macula Society	B2,C-F	N/A

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Author	Title	Year	Output type	Work package	URL link
Harding SP	Personalising the interval in screening for sight threatening diabetic retinopathy	2017	Presentation – Royal Society of Medicine	E	N/A
Sampson CJ *et al.*	Systematic review and meta-analysis of health state utility values for diabetic retinopathy: implications for model-based economic evaluation	2017	Conference presentation – HEG	D	N/A
Harding S *et al.*	The costs of screening for sight-threatening diabetic retinopathy	2019	Conference presentation – ARVO	D	https://iovs.arvojournals.org/article.aspx?articleid=2744254&resultClick=1
Broadbent DM	Developments in individualised risk based screening, applicable to large local populations	2019	Conference presentation – EASD	E	N/A
Harding SP	Safety and efficacy of individualised compared with annual screening for diabetic retinopathy in the ISDR randomised controlled trial	2019	Conference presentation – EASD	E	N/A
James M	Cost-effectiveness of personalised screening and scaling up to address a worldwide 'pandemic'	2019	Conference presentation – EASD	D	N/A
Harding *et al.*	Safety, efficacy and cost-effectiveness of individualised screening for diabetic retinopathy: the ISDR open-label, equivalence randomised controlled trial	2020	Conference presentation – Macula Society	D,E	N/A
Broadbent *et al.*	Safety and cost-effectiveness of individualised screening for diabetic retinopathy: the ISDR open-label, equivalence randomised controlled trial	2020	Conference presentation – EASDec	D,E	N/A
Harding SP *et al.*	Individualised risk-based screening for sight threatening diabetic retinopathy – the Liverpool Risk Calculation Engine	2015	Published abstract – ARVO	C	http://iovs.arvojournals.org/article.aspx?articleid=2331769
Appelbe D *et al.*	Introducing personalised risk-based intervals in screening for diabetic retinopathy: development, implementation and assessment of safety, cost-effectiveness and patient experience (ISDR): a case study in the use of automated systems in trials	2015	Published abstract – International Clinical Trials Methodology Conference	E	https://doi.org/10.1186/1745-6215-16-S2-O59
Broadbent DM *et al.*	Introducing personalised risk-based intervals in screening for diabetic retinopathy: the ISDR study	2015	Published abstract – EASDec	E	https://doi.org/10.5301/ejo.5000612
Byrne P *et al.*	Patient perspectives of acceptability of risk-based individualised diabetic retinopathy	2015	Published abstract – EASDec	F	https://doi.org/10.5301/ejo.5000612
Harding SP *et al.*	Individualised risk-based screening for diabetic retinopathy: the Liverpool Risk Calculation Engine	2015	Published abstract – EASDec	C	https://doi.org/10.5301/ejo.5000612

Author	Title	Year	Output type	Work package	URL link
Sampson CJ *et al.*	Cost-effectiveness of a risk-based screening programme for diabetic retinopathy: a modelling approach	2015	Published abstract – EASDec	D	https://doi.org/10.5301/ejo.5000612
Harding SP *et al.*	Individualised risk-based screening for sight threatening diabetic retinopathy – the Liverpool Risk Calculation Engine	2015	Published abstract – ARVO	C	https://iovs.arvojournals.org/article.aspx?articleid=2331769
Harding SP *et al.*	10-year observational study of patient related outcomes during expansion to full population coverage of a systematic diabetes eye care programme – the Liverpool Diabetic Eye Study	2016	Published abstract – EASDec	B	https://doi.org/10.5301/ejo.5000799
James M *et al.*	Micro-costing diabetic eye screening: estimation of personal expense, attendance and health care resource use	2016	Published abstract – EASDec	D	https://doi.org/10.5301/ejo.5000799
Sampson CJ *et al.*	Health-related quality of life of people attending screening for diabetic retinopathy within a trial setting	2016	Published abstract – EASDec	D	https://doi.org/10.5301/ejo.5000799
Thetford C *et al.*	Comparing health professionals' and patient perspectives of individualised screening intervals for diabetic retinopathy screening	2016	Published abstract – EASDec	F	https://doi.org/10.5301/ejo.5000799
Wang A *et al.*	Building a dynamic functional clinical data warehouse (CDW) for personalised health care – lessons from the Individualised Screening for Diabetic Retinopathy (ISDR) study	2016	Published abstract – EASDec	B	https://doi.org/10.5301/ejo.5000799
Harding SP *et al.*	Safety of individualised variable interval screening for referable diabetic retinopathy – baseline data from the ISDR randomised controlled study	2017	Published abstract – EASDec	E	https://doi.org/10.5301/ejo.5000979
Byrne P *et al.*	Putting patients' eyes back into their bodies: implications of a social science study of screening and diabetes eye care	2018	Published abstract – EASDec	F	https://doi.org/10.1177/1120672118773246
Vazquez-Arango P *et al.*	Visual impairment in a population-based evaluation of people with diabetes	2018	Published abstract – EASDec	B	https://doi.org/10.1177/1120672118773246
Wang A *et al.*	ISDR PPI group. Enabling patients to be partners in research – how to ensure publicly funded applied health services research is fit-for-purpose	2018	Published abstract – EASDec	F	https://doi.org/10.1177/1120672118773246
Broadbent DM *et al.*	Individualised screening for diabetic retinopathy: the ISDR study – a randomised controlled trial of safety, efficacy and cost-effectiveness	2019	Published abstract – ADA	E	https://doi.org/10.2337/db19–39-LB

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Author	Title	Year	Output type	Work package	URL link
Harding SP *et al.*	Safety and efficacy of individualised compared to annual screening for diabetic retinopathy in the ISDR randomised controlled trial	2019	Published abstract – EASD	E	https://link.springer.com/content/pdf/10.1007%2Fs00125-019-4946-6.pdf
James M *et al.*	Cost-effectiveness of individualised versus annual screening for diabetic retinopathy in the ISDR randomised controlled trial	2019	Published abstract – EASD	D	https://link.springer.com/content/pdf/10.1007%2Fs00125-019-4946-6.pdf
Stratton IM *et al.*	Individualised screening for diabetic retinopathy. A randomised controlled clinical trial of precision medicine	2019	Poster – ADA Research symposium	E	N/A

ADA, American Diabetes Association; ARVO, Association for Research in Vision and Ophthalmology; CRN, Clinical Research Network; EASD, European Association for the Study of Diabetes; EASDec, European Association for the Study of Diabetes eye complications study group; HEG, Health Economists' Study Group; NIHR, National Institute for Health Research; SAPC, Society for Academic Primary Care North; UKCRC CTU, UK Clinical Research Collaboration Registered Clinical Trials Unit Network.

Data-sharing statement

All requests for data should be sent to the corresponding author. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. *#datasaveslives* You can find out more about the background to this citation here: *https://understandingpatientdata.org.uk/data-citation*.

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Appendix 1 ISDR Study Group

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