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

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Scientific summary

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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.

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.

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.

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