Individualised variable-interval risk-based screening in diabetic retinopathy: the ISDR research programme and RCT of safety, cost effectiveness and patient experience.

Supplementary material 4 ISDR end of programme symposium

Background

ISDR is a 7-year Programme Grant for Applied Research entitled, "Individualised risk-based variable-interval screening for diabetic retinopathy, ISDR" funded by the UK National Institute for Health Research which completed in 2019. ISDR aimed to develop and implement a major enhancement to screening for sight threatening diabetic retinopathy (STDR) by introducing an individualised approach based on measured patient-centred risk, acceptability to patients and staff, safety and cost effectiveness. A multi-disciplinary team from ophthalmology, social science, health economics, statistics, mathematics, heath services research, diabetes care, primary care and computer science have been working with patient experts and health service managers. Research has been on the whole population of people with diabetes in Liverpool.

Conference Title

Personalised Screening for Sight Threatening Diabetic Retinopathy - Results and Implementation of the ISDR Research Programme

Conference Aims

To receive and review the main results of the ISDR Programme Grant for Applied Research. To consider policy and practice implications, expert patient opinion and plan for future implementation.

Delegates

Around 100 delegates and opinion leaders with relevant experience in screening, clinical trials, statistics, ophthalmology, social science, health economics, mathematics, heath services research, primary care and computer science joined the ISDR investigators. There was a range of national representation including outside the UK and also key policy makers in screening.

Outline of programme

Presentations covered:

- primary and secondary analyses from the ISDR randomised controlled trial (RCT) comparing risk-based variable-interval versus standard fixed interval screening including safety, efficacy and cost effectiveness
- qualitative investigations of patient perceptions of screening and diabetes care
- health economics analyses of the costs of screening, quality of life, models of delivery
- patient involvement programme - the patient expert in research and implementation
- epidemiological observational cohort study - prevalence and incidence in a population with established screening programme
- risk calculation models and data warehouse

Conclusions of the symposium

There was general support for the main quantitative and qualitative findings

- safe to switch to extended intervals in stratified and/or personalised/individualised screening

Scale up through a whole population "pilot" was considered reasonable to include testing feasibility of using clinical data.

Two aspects of failsafe need to be developed

- alternative pathway for changing risk between intervals
- error checking in programme administration

Communication needs revising

Some issues with the ISDR data were raised

- 3503 people did not consent for the RCT
- external validation is needed in another UK programme

Further analysis was recommended

- for the non-consented group, diabetes type, model scale-up by running the cohort dataset through the RCE, a comparison with stratified screening, further cost effectiveness analysis

Results of additional analyses of the ISDR datasets

The non-consented group in the RCT recruitment

The screen positive rate was slightly higher at 5.90% vs 5.09% in recruited participants. The difference of 0.81% was not statistically significant (Chi-square p=0.11).

Allocations by the Liverpool RCE to groups other than the participants in the RCT

We ran data on two wider groups of screen negative individuals through the RCE:

A. People who did not consent to participate in the RCT were allocated to 6m, 12m, 24m (high-, medium- and low-risk) as follows: 294 (9.2), 272 (8.6), 2614 (82.2) total 3180. There was no significant difference compared to those who were consented and randomised: 406 (9.0), 384 (8.5), 3744 (82.6), total 4534; p=0.65

B. People in the cohort study dataset underwent 50360 screen negative episodes between 2010/11 and 2013/14. RCE allocations were 6m (high-risk) 6575 (13.1%), 12m (medium) 454 (9.0%), 24m (low) 39241 (77.9%). Compared to for the RCT (see above) 4.5% more of the cohort study population study were allocated to the high-risk group compared to RCT participants.

Baseline demographic and clinical data on nonparticipants in the RCT

We reviewed the baseline data in the people who did not provide consent in the RCT. Compared to those who did consent there were more females (1418 (44.2%) vs. 1801 (39.7)), more smokers (752(23.5%) vs 790 (17.4%)), older (67.0yrs (57.1-75.9) vs 63.1 (54.9-70.7)) and longer disease duration (7.8 years (4.8-10.6) vs 7.0 (4.2-11.0)); all $p<0.001$. Retinopathy levels, glycated haemoglobin (HbA_{1c}), blood pressure and total cholesterol were similar. Data on ethnicity require further investigation due to a variation in unrecorded ethnicity.

Diabetes type

People with type 1 diabetes had lower attendance compared to type 2: type 1 126 (73.7%), type 2 3250 (84.9). There were no differences for fixed and individualised arms of the RCT.

Failsafe

Based on comments from our Patient and Public Involvement (PPI) sessions we investigated the feasibility of developing a referral pathway for when clinical risk factors change between extended screen intervals. We explored a virtual risk engine annual review as a failsafe.

We re-ran the RCE in the 24 month group (n=1776) at 12 months using updated clinical data and the baseline retinopathy grading.

- 97.1% (1725/1776) remained in the low-risk group.

- reallocation was to 6 months for 2 people (0.1%) and to 12 months for 49 (2.8%).

Comparing IDSR risk-based variable-interval screening with planned NDESP stratified screening

We ran the RCT participants' data through a rule set to replicate the proposed stratification in the extended intervals model planned by the English National Diabetic Eye Screening Programme (NDESP). We applied the stratification rule that people with no DR (i.e. R0) in both eyes on two occasions would be allocated to a 24 months interval with all others continuing at 12 months.

Allocations by the stratification rule were:

- 12-month group 33.1%: allocations in ISDR, 6m (high-risk) 198 (8.7%), 12m 179 (7.9%), 24m (low-risk) 372 (16.4%)
- 24-month group (66.9%): allocations in ISDR, 12m 32 (1.4%), 24m 1484 (65.5%)
- of the 372 people (16.4%) stratified to 12 months who would have been allocated to 24 months in the ISDR, 71 (3.1%) had R1 (background retinopathy) in one eye at RCT baseline, 195 (8.6%) developed R1 or were screen positive at prior visit within18 months before RCT baseline.
- risk based allocation (to three intervals) increases the number of people who can move to extended intervals by 22% (15.0/66.9)
- 26% (8.7/33.1) of people stratified to 12 months are at high-risk according to the ISDR RCE.

Discussion

The additional analysis suggested at the ISDR symposium has provided further evidence on which to design a scale up of the Liverpool approach to screening in ISDR and to plan for future wider implementation. It provides reassurance on a number of key issues. The allocations by the RCE to variable intervals at baseline were similar for the consented and non-consented groups. Extending to the whole cohort there was a slight change in the allocations between 6 and 24 months with 4.5% more of the 24-month group requiring a 6 month visit. This indicates that there are people at higher risk who may not have been eligible for the RCT and who could benefit from targeting more frequent screening.

Further examination of the baseline data showed that people who did not wish to participate in the RCT were older, had longer disease duration and were more likely to be female. These factors are probably linked and are not unexpected findings in RCT recruitment. In addition

these people had a slightly higher screen positive rate; it is not unsurprising that people who decline to participate in a RCT have worse disease.

Our virtual risk engine failsafe review detected a small number of people who had sufficient change in their clinical risk factors to be called in early from the 24 month screen interval. This should provide reassurance to patients and professionals.

If the proposed English NDESP stratification model were implemented in the RCT population 66.9% would receive 24-month interval compared to 82.3% in ISDR. 26% (8.7/33.1) of people stratified to 12 months are at high risk according to the ISDR RCE.