Full title of the study

Diabetic Retinopathy Progression in patients under monitoring for treatment or vision loss: External Validation, update, and net clinical benefit of a Multivariable Prediction Model

Short study title / acronym

Diabetic Retinopathy Progression to treatment or vision loss (DRPTVL-UK) Model validation

This protocol has regard for the HRA guidance and order of content

Research reference numbers

1. Funder's reference number (NIHR RfPB) - NIHR203608
2. Sponsor reference number – RG_22-099
3. IRAS reference number - 253774

Protocol version number and date

V 1, 19/08/2022

Sponsor

University of Birmingham

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

Chief Investigator:

Date: 12/09/2022

Signature: 

Name: Nicola Adderley

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

Key study contacts

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Statistician	Kym Snell, k.snell@keele.ac.uk

i. List of contents

ii. List of abbreviations

CI	Chief investigator
DESP	Diabetic eye screening programme
DNA	Did not attend
DR	Diabetic retinopathy
EWDR	() Early worsening of Diabetic retinopathy
GP	General Practitioner
GRIPP 2	Guidance for reporting of patient and public involvement in health and social care research
IMRD	IQVIA Medical Research Data
MFP	Multivariable fractional polynomial
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal investigator
PPIE	Patient and public involvement and engagement
RfPB	Research for patient benefit
STDR	Sight threatening Diabetic retinopathy
UoB	University of Birmingham

iii. Study summary

Study Title	Diabetic Retinopathy Progression in patients under monitoring for treatment or vision loss: External Validation, update, and net clinical benefit of a Multivariable Prediction Model	
Short title	Diabetic Retinopathy Progression to treatment or vision loss (DRPTVL-UK) Model validation.	
Study Design	Mixed methods	
Study Participants	Patients with diabetes aged 12 years and over with referable diabetic retinopathy (patients enter the screening programme from age 12) identified at referral to the NHS hospital trusts from DESP between 2013 and 2016 for close monitoring and treatment.	
Planned Sample Size	A minimum of 200 outcome events are required for external validation. For model updating, a minimum of 1810 patients are required with 293 outcome events. For consensus process there will be around 10-15 participants	
Follow up duration	Participants referred for DESP between 2013 to 2016 and followed up till the outcome of interest or one of the events listed. There is no direct patient contact though as the study is retrospective.	
Planned Study Period	Study will last till the end of 2023	
	Objectives	Study Outcome Measures
Primary	Assess the DRPTVL-UK model's external validity, model update and subgroup analysis.	A validated DRPTVL-UK model with improved performance.
Secondary	Model implementation options choice through consensus development. To assess whether it could be used to inform follow-up intervals.	Implementable model with clinical benefit for patients capable of acting as a decision support mechanism for follow-up intervals.

iv. Funding and support in kind

Funder (Names and contact details of All organizations providing funding and/or support in kind for this study)	**Financial and non-financial support given**
NIHR Grange House 15 Church Street Twickenham Post Code TW1 3NL Telephone 020 8843 8000	Financial

v. Role of study sponsor and funder

The funder (NIHR) provided peer review of the funding application and had an influence on the development of this protocol. This influence was mainly to ensure the focus of the project remains on research for patient benefit. They remain the sole funding source for the project.

The Sponsor will have overall responsibility for the initiation and management of the study.

vi. Roles and responsibilities of study management committees/groups & individuals

Data extractor team in the three NHS trusts will work with DESP and hospital eye service to obtain the list of all the referrals from DESP to surveillance clinics / hospital eye service from beginning 2013 to end 2016. Above mentioned inclusion/exclusion criteria will be applied, recruited individuals' list will be finalised. Clinical nurse specialist from each trust will extract data on the list of variables near baseline, follow ups and outcome status using electronic and /or paper clinical notes. A copy of data extraction sheet will be generated using the master copy, all patient identifiable information will be removed and data completely anonymised. The trust data extraction coordinator will review data on regular basis and feedback to data extraction nurse. Anonymised data will then be sent to the University of Birmingham for analysis on a monthly basis in an encrypted fashion using secure nhs.net email. The university will store the data on a secure local network. Local R&D teams will dispose of master copy of data from each trust accordingly.
The local principal investigators (PIs) will be supported by regstrars / equivalent as data extraction coordinators. There will be a 50% part time clinical nurse specialist role for data extraction in each NHS trust. They will be supported by the PI's, and data extraction coordinators at each trust. The research fellow/data scientist (yet to be recruited) will carry out the data cleaning, data handling and analysis under supervision of SH/NA and KS. The research fellow will receive data on a monthly basis for cleaning and analysis, but will also help writing up and the approval requests etc.

The CI will coordinate all the management activities and with the help of the Co-I interpret the results of the analysis from ophthalmic perspective, in addition to overseeing the project as a whole and writing up.

Krishnajaha Niranthanakumar will advise on data handling, defining variables, public health, and epidemiology aspects. Christopher Sainsbury will provide a diabetologist's clinical and data science perspective.

KS will oversee the statistical analysis, provide expert advice and supervision to the research fellow for the external validation, updating of the prediction model and decision curve analysis.

Mohammad Tallouzi will be responsible for leading PPIE and consensus development among ophthalmic clinician experts on the question of model implementation. He will be in charge of coordinating the qualitative part of the study. He will also oversee the study findings dissemination among patients, their families and carers, and members of the public. During the data extraction months, he will help in the role of data extraction coordinator.

The experts advisory group will comprise consultant eye surgeons, DESP leads from the participating NHS trusts, GPs, patient advocates, and the CI / co-applicants / local PIs. It will meet four times during the study. Meetings will be scheduled to coincide with protocol development, interim analysis, consensus meeting and the culmination of the project (to inform the final reporting and to augment dissemination as part of writing committee). Meetings will be in Birmingham with remote connection to facilitate regular presence of group members based outside Birmingham who may not be able to attend in person.

The PPIE groups, comprising patients, GPs, ophthalmic experts and the PPIE lead, met for a preapplication meeting and for protocol finalisation (details in appendix 4). The groups will meet three more times during the study to ensure the patient perspective is influential throughout the study. These meetings will take place alongside the experts' meetings to maximise communication between all team members. Two patients have agreed to represent patients in the experts' group as patient advocates and help dissemination. Training for PPIE has been carried out in a pre-application meeting.

Regular research team meetings will be held with the senior research team. Additional ad hoc meetings will also be held, with attendance determined by the skill set required for that stage of work., and will include the lead applicant, joint-lead applicant, and other members of the research team. Regular updates will be sought during the data extraction process. During the analysis phase, the CI, co-CI and/or Kym Snell (statistician) will meet with the research fellow regularly to discuss the analysis and results. In addition, the whole team (including PPIE) will be consulted on key clinical/methodological issues as required throughout the project. Research costs have been calculated with support from UoB and R&D Sandwell & West Birmingham NHS Trust (host NHS trust).

vii. Protocol contributors

- Sajjad Haider wrote the protocol / NIHR funding application, with contributions from statistician,

PPIE groups and the co–CI (Nicola Adderley).

viii. Key words

- Clinical prediction model
- External validation
- Model update
- Clinical benefit (decision curve analysis)
- Consensus
- Model implementation

a) Background

Diabetes mellitus is one of the most common chronic conditions affecting nearly 4.9 million people in UK as of 2021 (1). With the prevalence rising each year (2), there is an ongoing global and UK wide increase in the number of people with diabetes mellitus (3-5) and consequently DR. The detection of DR has also improved through wider population screening, further increasing the demand for Hospital Eye Services (6). Diabetes is a major public health concern and `uses a significant proportion of the NHS budget, much of which is spent treating the complications arising as a result of diabetes (7). Complications affect blood vessels in the heart, brain, kidney and eyes (8). Diabetes is the fourth leading cause of preventable vision loss in the UK (9), and therefore patients with diabetes are screened regularly for signs of DR. Screening services are organised by the Diabetic Eye Screening Programme (DESP) for patients without DR or with background DR. However, when a patient develops clinical signs of referable retinopathy, including pre-proliferative diabetic retinopathy (R2), proliferative diabetic retinopathy (R3) and / or diabetic maculopathy (M1), they are referred to hospital eye services or surveillance clinics for closer observation and treatment to prevent vision loss. The patients' flow within the NHS is depicted in the figure below.

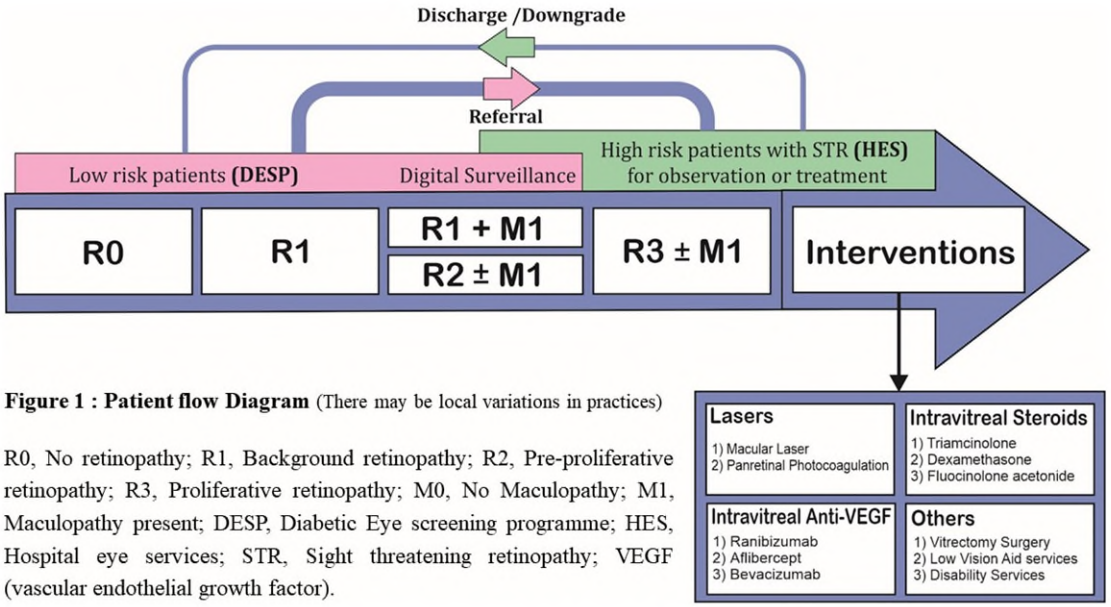

Figure 1 : Patient flow Diagram (There may be local variations in practices)

R0, No retinopathy; R1, Background retinopathy; R2, Pre-proliferative retinopathy; R3, Proliferative retinopathy; M0, No Maculopathy; M1, Maculopathy present; DESP, Diabetic Eye screening programme; HES, Hospital eye services; STR, Sight threatening retinopathy; VEGF (vascular endothelial growth factor).

Figure 1: Patient Flow Diagram

Most referrals made to hospital eye services (50 to 78%) will not yet require treatment (10, 11). Among those that will require treatment, such as patients with diabetic maculopathy, patients may be subthreshold (under 400 microns foveal thickness) for treatment and remain so for a variable period. Patients with pre-proliferative retinopathy are not offered any treatment and are monitored every three to six months until they progress to the proliferative retinopathy stage, at which point they receive treatment. Consequent overburdening of hospital eye services, combined with under-resourced services may be causing delays in patients being seen and causing harm especially the higher risk patients with diabetic retinopathy (12). Therefore, this bottleneck urgently needs addressing. We propose to mitigate this risk by stratifying these patients and prioritise care for higher risk patients.

Clinical prediction models are statistical models that use multiple predictor variables to predict the risk of a clinical outcome (13). They can be used by clinicians to aid counselling patients, to help make decisions on appropriate treatment strategies, or to stratify care based on risk groups. The DESP uses risk stratification studies (14) to inform suitable screening intervals. There are also prediction models to identify patients at the highest risk of developing referable DR (10, 15, 16), validated in a UK population (17). However, there are currently no such prediction models that can be used to stratify care according to risk in patients under the care of hospital eye services. Such a model could help hospital eye services prioritise patients at high risk of vision loss if left untreated, and to determine suitable follow up intervals based on an individual's risk, thereby increasing

patient safety and thus leading to patient benefit. Such a model could also enable clinicians to better communicate prognosis to patients, and potentially make different and more effective therapeutic choices.

The current length of follow up intervals used within hospital eye services is based on the probability of disease progression from a study conducted in the late eighties (18) and not based on the patient's individual risk. We therefore aim to predict the progression of DR to treatment stage or vision failure, to direct resources toward higher-risk patients so that they are followed-up and treated before vision failure occurs. We propose that use of a validated risk prediction model will facilitate evidence-based decisions and thus reduce the chance of harm to higher risk patients.

There are two recent systematic reviews (15, 19) of existing models for predicting the progression of diabetic retinopathy among the DESP population. A review by the this group of researchers found a total of 14 predictive model development studies, of which 11 had been internally validated and 8 had been externally validated. In the more recent review by Heijden et al., there were 16 model development studies for an outcome of referable DR. Based on these two reviews, it was concluded that a model fully covering our target population (patients under care of hospital eye services / surveillance clinics) and clinically important outcomes of interest (including contemporary treatment modalities and vision loss) did not exist, and therefore a prediction model that could be used to identify patients with a higher probability of requiring treatment or at risk of loss of vision was needed.

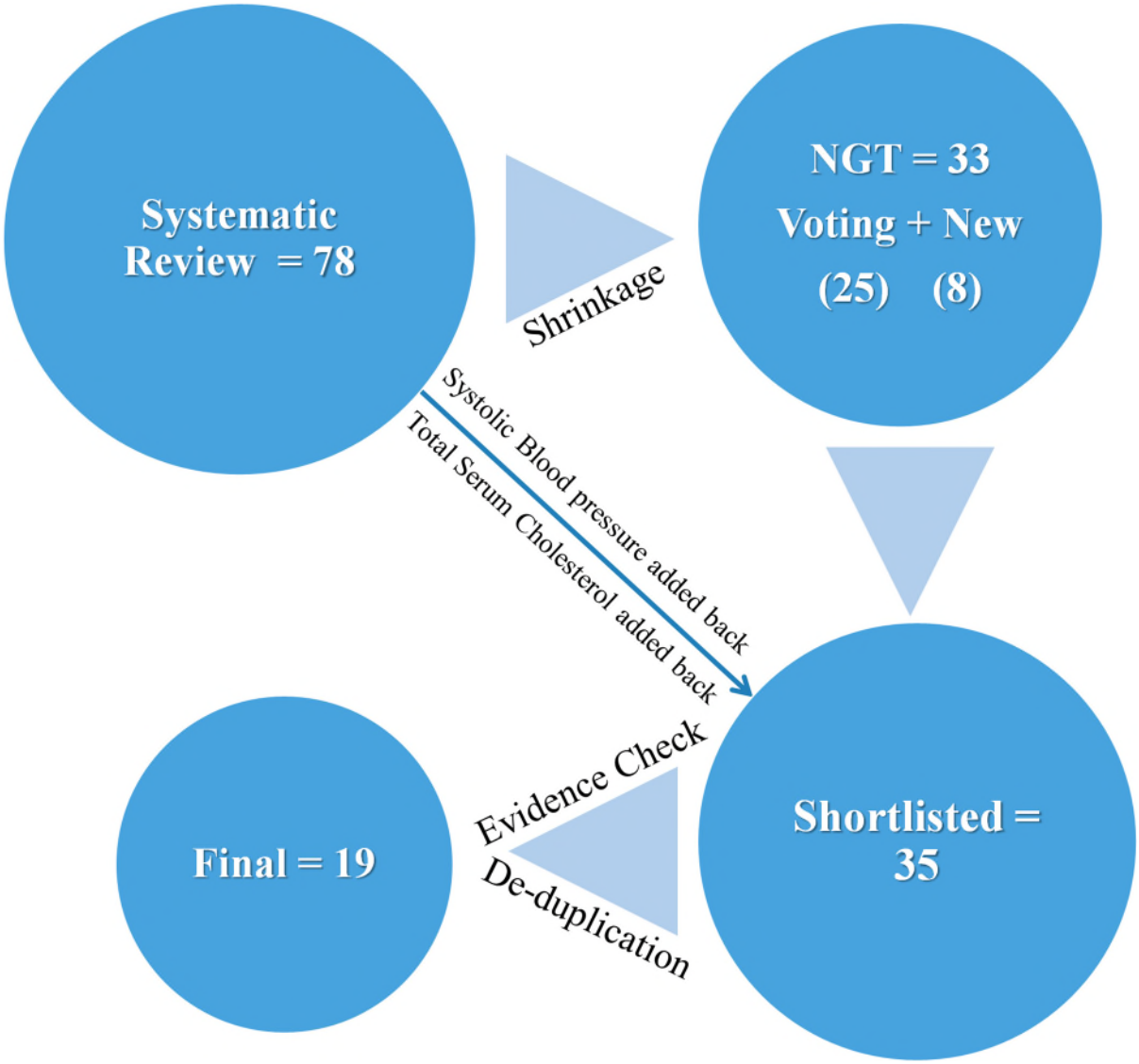

Figure 2: Summary of the sequence involved in reaching the final list of candidate predictors. NGT, Nominal Group Technique

From predictors identified in our systematic review (15), we selected a set of 19 clinically meaningful candidate predictors of diabetic retinopathy progression using the Nominal Group Technique (20). A prediction model based on 15 out of the 19 candidate predictors (7 finally selected during automated selection) was developed in anonymised, retrospective primary care data from IQVIA Medical Research Data (IMRD). The diabetic retinopathy progression to treatment or vision loss in UK model (DRPTVL-UK) demonstrated moderately good discriminative performance (C-statistic = 0.74).

The model for treatment or vision loss

The previously developed DRPTVL-UK model included 7 predictors measured at the time of or close to referral, namely 1) retinopathy stage, 2) HbA1c, 3) eGFR, 4) total serum cholesterol, 5) systolic

blood pressure, and drug use of 6) insulin or 7) statins. We are interested in higher risk eye (R3M1>R3>R2M1>M1>R2) of the patients to help us develop a decision support system to identify higher risk patients to enable us to prioritise their care as a person. The list of variables required is given in table 1 below. Further discussion on this topic is in appendices 1 and definitions in appendix 2.

Population characteristics like age at baseline, date of birth for age range, date of death for competing risk analysis will be extracted, but after calculation of age, gender distribution and lengths of follow up durations, all the personal identifiable information will be removed to protect the patient privacy/confidentiality.

A composite outcome of treatment (laser, intravitreal injections) and any significant vision loss e.g. registration as visually impaired or persistent loss of 3 lines due to DR (21) will be used. Patients will be followed up from the date of referral to hospital eye services / surveillance clinics until the date of treatment or vision loss. Patients for whom the outcome is not observed will be censored at the date of death, last known follow-up, or the study end date (end 2021), whichever comes first. The main outcome of interest is the time to treatment, but vision loss is included as a safety measure to capture outcome when no treatment was received.

b) Rationale

We now need to assess the model's performance in a secondary care population to ensure it performs adequately to identify patients at high risk of treatment or vision loss. If this model performs well for predicting risk at different time points in hospital eye services / surveillance clinics data during external validation, we propose that it could be used to prioritise individuals at higher risk of vision loss and potentially inform the length of the follow up intervals after referral to hospital eye services / surveillance clinics.

c) Objectives and outcome measures/endpoints

The aim is to externally validate the multivariable risk prediction model we previously developed, recalibration/updating of predictor variables if necessary and clinical benefit analysis. The primary objectives are to:

- `Assess the DRPTVL-UK model's external validity for predicting the risk of need for treatment or vision loss up to 2 years after referral in a hospital-based DR population.
- Evaluate whether recalibration of the baseline hazard or linear predictor (predictor effects) is required and whether including additional predictors improves the model's predictive performance in a hospital eye services / surveillance clinic population.
- Assess the DRPTVL-UK model's external validity in the subgroup of patients with pre-proliferative DR (R2) or M1.

The study primary outcome is a validated DRPTVL-UK model with improved performance.

Secondary objectives are to:

- Determine how the model can be implemented in practice through consensus meetings of expert clinicians
- Validate the model across several time points up to 2 years to assess whether it could be used to inform follow-up intervals.

The study secondary outcome is an implementable model with clinical benefit for patients (by increasing safety) and capable of acting as a decision support mechanism for clinicians for follow-up intervals decisions.

d) Study Design

Mixed methods will be used. A retrospective cohort of patients with referable diabetic retinopathy will be used to assess the model performance for external validation. Additional predictor variables / recalibration will be used to update the model. Decision curve analysis and consensus will be used to arrive at the final implementable model.

e) Study setting and Data Source

The data (variables in table 1) on patients will be collected from hospital eye services/Surveillance clinic and other related databases/patient notes from three NHS trusts. Data missing from the hospitals' notes will be obtained from surveillance clinics (and vice versa) by the participating NHS trusts. The cohort will include all patients with type 1 and 2 diabetes in the catchment area of the Sandwell and Birmingham, Sunderland, and Sussex NHS trusts, referred into hospital eye service or surveillance clinics between 2013 and 2016. The Birmingham trust cares for an ethnically and socio-economically diverse range of communities and was chosen to ensure equality, diversity, and inclusion. The Sussex provides secondary care to a less diverse population and Sunderland is a primarily Caucasian population.

f) Participants eligibility criteria

Patients with diabetes aged 12 years and over with referable diabetic retinopathy (patients enter the screening programme from age 12) will be identified at referral to the NHS hospital trusts from DESP between 2013 and 2016 for close monitoring and treatment. Patients with the specific outcome of retinopathy treatment or vision loss at referral or those referred for reasons other than retinopathy will be excluded. Patients objecting to their information being used (through a local or national opt out scheme) will also be excluded.

g) Statistics and data analysis

The DRPTVL-UK model was developed using Cox regression and later refitted using a flexible parametric approach to obtain the baseline hazard function over time. The model can be used to predict the absolute risk of progression from referable DR to the time at which a patient requires treatment or when vision loss occurs within a 2-year period, based on an individual's risk factor values. Thorough evaluation of the model's external validity and net benefit is now required to establish whether the model is suitable for use in clinical practice in hospital eye services/surveillance clinics. The DRPTVL-UK model can also be used to predict the time at which an

individual reaches a particular risk threshold (to be agreed in a consensus meeting of clinical experts and patients planned after final analysis) which may be useful for determining appropriate follow-up intervals after referral to hospital eye services/surveillance clinics. This will be evaluated as a secondary objective.

7.1 Sample size Calculation

A minimum of 200 outcome events are required for external validation using current guidance for survival outcomes (22). Every trust receives approximately 200 referrals per year and we expect to have 4 years of data available for each trust. Therefore, we expect to have 2,400 patients from across the three trusts. Using conservative estimates from our development data, we expect 15% of those referred to develop the outcome of interest, providing at least 360 outcomes in the data that we will collect. For model updating, we will use the method of Riley et al (23) to calculate the minimum sample size required, assuming an event rate of 0.05 per year, mean follow up of 3.23 years, a default Nagelkerke R^2 of 0.15 and 19 candidate predictors considered in the model. A minimum of 1810 patients are required with 293 outcome events to target a shrinkage factor of 0.9 ensuring minimal overfitting to the data.

7.2 External validation

The DRPTVL-UK model will be used to obtain the predicted probability of the outcome over time for every participant within each of the three trusts. Predictive performance of the model will be assessed using measures of discrimination (Harrell's C-statistic and time-dependent C-statistic), calibration (calibration slope, ratio of Observed to Expected probabilities, and calibration plots at multiple time points up to 2 years). Performance measures will be calculated within each hospital and then pooled on an appropriate scale using random effects meta-analysis to account for clustering by hospital. In addition to external validation of the model in the whole sample, we will also validate the model within the subgroup of R2 / M1 patients to see how well it performs in each.

Missing data

Missing data is a common problem in clinical data and needs to be appropriately accounted for in analyses. An audit using hospital notes from Sunderland Eye Infirmary showed physical examination variables of systolic and diastolic blood pressure nearest to referral were recorded in the clinical notes of 72% of patients; biochemical variables of HbA1c were recorded for 83% of patients, eGFR and cholesterol in 95.5% of patients, measured near to referral. In case of missingness of <40%, variables with missing data will be handled by multiple imputation using chained equations assuming data are missing at random. The missing at random assumption is an untestable one but data checks

comparing characteristics of patients with missing values to those without will be performed to assess if there are any obvious problems with the assumption. To preserve any clustering that may be present, data will be imputed for each hospital separately. Variables with systematically missing data (that are missing for all patients within a hospital) will not be imputed or included in the analysis (24). The imputation model will include all predictors as well as the outcome using the event indicator and estimate of the cumulative hazard function. Auxiliary variables will be considered to improve the missing at random assumption. The number of imputed datasets will be set at least equal to the percentage of observations of missing data for any of the variables of interest (25).

7.3 Statistical analysis plan

7.3.1 Summary of baseline data

Table 1: List of variables for data collection - predictors modified from (20), Outcomes and competing risk variables.

	Group	Required variables	Source
1	*Ocular features	Diabetic retinopathy grade	DESP / Hospital Notes / letter
2		Visual acuity score	Both eyes, Log MAR, every visit with date till the outcome
3	*Biochemical parameters	HbA1c	From Biochemistry database (mmol/mol)
4		eGFR	//, ml min^{-1} 1.73 m^{-2}
5		Total Serum Cholesterol	//, mmol/l
6	*Physical examination	Systolic Blood pressure	From nursing notes, mm Hg
7	*Diabetes treatment	Statin	From GP letter / Diabetology notes
8		Insulin	//
9	*NGT	Pregnancy	During the preceding 2 year before referral
10		Early worsening	From hospital notes
11		Frequent DNA / cancellations (total, two consecutive sets)	With dates (? Patient Administration System)
12	Competing risk variable	Date of death if occurring before the treatment / vision failure / date of discharge	? Available through Patient Administration System. Needed to calculate follow, de-identify after
13	Outcome date / follow up	Treatment (first ever) / vision failure / date of discharge / transfer / end of the study (whichever happens first)	Patient notes
14	Natural history / clinical benefit	Dates of referral / outcome / Total no of visits (before the outcome)	Patient notes
15	// progression from R2 to R3	Dates of referral / progression	Patient notes
16	Demographics	Age, gender, ethnicity distribution (%) and deprivation score quintiles	Patient notes

*Among the predictors ocular features (DR stage in each eye) and Visual acuity on every visit in both eyes will be recorded along with the date of measurement. For analysis, higher risk eye will be used. Rest of the predictor values will be recorded nearest to baseline. Please also see appendices 1 & 2 for details.

7.3.2 Model recalibration and updating

If necessary, we will recalibrate the model for a hospital eye services population (for example, by updating the baseline survival function or recalibrating the linear predictor). Additionally, we will investigate whether updating the model to include additional predictors that were not available in the development dataset improves the predictive performance. Visual acuity, early worsening, pregnancy, and frequent "did not attend" (DNA), were identified as candidate predictors based on expert opinion and evidence evaluation (20). To update the model, flexible parametric models (Royston-Parmar models) will be fitted using a multivariable fractional polynomial (MFP) approach to consider non-linear functions for continuous variables and backward elimination will be applied using a p-value > 0.157 (proxy for selection based on Akaike Information Criterion (26) for elimination for the additional predictors considered (27). All predictors from the original model will be forced to remain in the model regardless of statistical significance, therefore only the four additional variables will be tested. The predictive performance of the updated model will be evaluated using internal-external cross-validation (28) in which the model is developed using the data from two hospitals and externally validated in the third. This is then repeated a total of three times, each time reserving a different hospital for external validation. Predictive performance will be evaluated using the same measures as previously described and will be summarised across the hospitals using random-effects meta-analysis. Predictive performance of the updated model will be compared to the original model.

7.3.3 Clinical Benefit

We will also evaluate the clinical utility of the model using decision curve analysis in which the net benefit of using the model at different risk thresholds (at a particular time point) is plotted and compared to strategies of following up everyone more frequently or no-one more frequently (29).

As another potential use of the model would be to determine appropriate follow up intervals based on the individual's risk, it will also be crucial to ensure that the model performs well for predictions at all time points to ensure risk predictions are accurate at all time points. Therefore, we will also evaluate calibration performance at multiple time points. In addition to this, we will look at the predictions over time (predicted survival curves) and compare these to the observed survival curves for risk groups.

7.3.4 Clinical consensus

The results of analysis will be presented to the expert clinical panel for discussion on how the model can be implemented. This will include discussion and agreement on a suitable threshold for identifying higher risk patients and potential thresholds for determining the follow-up intervals. The consensus process was first used in the United States of America in the early 1970s to address the National Institutes of Health development programme to seek agreement on the safety and efficacy of medical procedures, drugs and devices (30). Consensus development meetings were introduced to the UK health system to discuss healthcare policies and its implementation in clinical practice (31)

Consensus process will be used in this expert group to reduce the range of potential options presented to facilitate joint decision-making by the group on the most appropriate choice of the model implementation strategies. The consensus process will help us evaluate the list of options and combine them if an overlap is noted between different options. It can also accommodate the inclusion of further options, check for redundancy between included options and reach agreement through sharing information and knowledge of the participants (32). The consensus process described below also enhances the critical thinking of the key stakeholders and facilitates joint decision-making of the diverse groups (33). Communication and cooperation between participants are the keys to reach successful agreement on the options discussed and to increase the chances of wider acceptance for implementation (34). Here we aim to reach an agreement on participants' opinions on the various options under consideration.

In this study participants will be asked to rate the importance of each of the options based on a nine-point Likert scale that has been adopted in the COMET consensus style; (1-3 = less important, 4-6 = important and 7-9 = critical) using a 70% threshold agreement to score the quality of evidence for outcomes in systematic reviews, and has been adopted in other core outcome development research groups using Delphi methods (35). Therefore, participants will be asked to vote on whether an option should be included in the model, excluded, or requires further discussion. For each option presented, the proportion of participants scoring 1-3, 4-6 and 7-9 on the nine-point Likert scale will be calculated for each item. "Consensus in" will be defined as greater than 70% of participants scoring as 7-9. 'Consensus Out' is based on an item being scored 1-3 by more than 70%. No consensus is based on an item where the level of importance was not decided due to uncertainty (36). We anticipate that this group joining the consensus process will be around 10-15 participants strong, ensuring an appropriate balance of representation of the different participants.

8. Data management

8.1 Data collection tools and source document identification

The source documents for our study will be hospital records (paper notes, electronic patient records, nursing notes, laboratory notes, patient administration system). The data will be entered directly onto the case report forms (CRF), created in excel spread sheet. Sufficient information of all participating patients will be kept to link records from source documents as above by the contributing NHS trusts. They will anonymise the data before sending it to research team in the university of Birmingham in an encrypted fashion to protect patient confidentiality.

8.2 Data handling and record keeping

There will be no deletion of entered data. 2) A security system will be maintained to protect against unauthorized access and a list of the authorized individuals will be maintained to carry out data extraction. 3) An adequate backup of the data will be maintained by the contributing trusts. 4) Safeguarding and archiving of any source data (i.e. hard copy and electronic). 5) The contributing trusts data extraction team will use an unambiguous unique participant identification code allowing identification of all the data reported for each participant**.** 6) Contributing trusts will remove all person identifiable data before sending it to the research team at the University by completely anonymising it.

Data flow and management stages are given in figure 3 below.

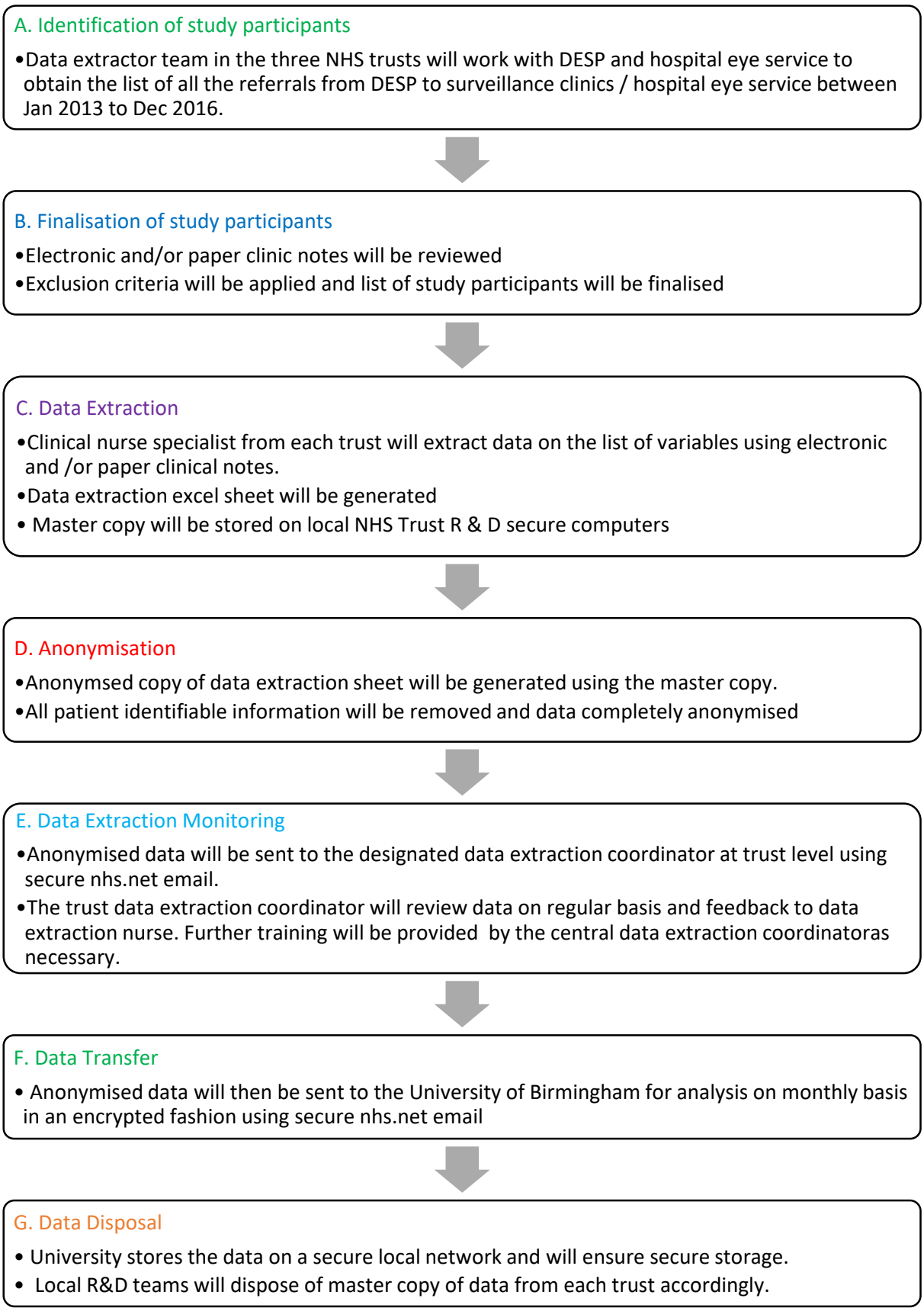

Figure 3: Data flow

8.3 Access to Data

Data extraction team will have access to patient identifiable data and direct access may be provided to representatives of the sponsor and the host institution for monitoring and audit purposes.

8,.4 Archiving

Contributing NHS trusts will arrange to destroy the patient identifiable data within 6 months of completion of the study. Sponsor will retain the anonymised data for 10 years and store it on its secure university network and will then arrange to destroy the data.

9. Monitoring, audit & inspection

- On site monitoring will be carried out by the local NHS trust R & D, supported by the local PI, with procedures and frequency recommended by the central data extraction coordinator
- The processes to be reviewed can be participant enrolment, completeness, accuracy, and timeliness of data collection.
- Monitoring will be done by evaluating the monthly returns of the extracted datasets.

10. Ethical and regulatory considerations

While the data we are planning to use is retrospective routinely collected data and will be anonymised before sending to UoB in encrypted fashion, it will require approvals from HRA/Ethics/CAG.

Personal information namely NHS number is required by data extractors for linkage to hospital / surveillance clinic data and biochemistry lab results. Date of birth / death are also required to calculate age / follow up and competing risk analysis. All personal information will be removed for the sake of de-identification, before sending completely anonymised data to the university for analysis.

- HRA / REC / CAG approval will be applied for on the integrated IRAS form.
- Data extraction will only start after approval.
- All correspondence with the HRA/ REC/CAG / NIHR will be retained in the study Master File.
- Chief investigator will submit annual progress report (APR) to the HRA / REC / CAG / NIHR as required and will notify them at the end of the study.
- if the study ends prematurely, the Chief Investigator will notify the above, including the reasons for the premature termination

- within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the HRA / REC / CAG / NIHR.

11. Dissemination policy

The success of this study (good model performance with demonstrable clinical utility will be to take us a step closer to the model being implemented and help us disseminate the findings across academic, clinical and PPIE societies. Academic publication of the research in a peer-reviewed scientific journal and dissemination to national and international specialty bodies and other stakeholders will be achieved by presenting at The Royal College of Ophthalmologists meeting, The Medical Retina Group Meeting and/or Diabetes Society meeting. PPIE Information will be disseminated through national and international PPIE associations. We will share results via print (newsletter via NHS trusts/University of Birmingham (UoB)) and social media channels (website, Facebook, Twitter). We will share methodological findings through the NIHR Statistics Group and statistical conferences such as the International Society for Biostatistics and Methods for Evaluation of Medical Prediction Models, Tests and Biomarkers.

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13. Appendices

Appendix 1: Feasibility of NGT suggested variables:

Early worsening of DR (EWDR)

EWDR arises within 6 months after abrupt improvement of glucose control (during intensive treatment - insulin pump therapy and after pancreas transplantation or bariatric surgery). Follow up is required over the following 12 months. EWDR is often transient, with regression of retinal signs after 12 months in the Oslo study in all except four patients [8] and in nearly half of the DCCT patients (37).

Audit data from a trust contributing data, impression was that this variable is not well recorded. From prediction point of view, we can look at feasibility of it once data is available. If feasible, then can include it in the model to see if it makes a difference to the model performance. For the patients with the outcomes of treatment and vision loss, we shall look back at the last 12/12 for the presence of early worsening with evidence of intensive treatment, bariatric / pancreatic surgery.

Pregnancy: While pregnancy is associated with progression of diabetic retinopathy (38), and in type 1, it induces a transient increase (2.5-fold) in the risk of retinopathy (39). There is also a low risk of progression of DR in type 2 diabetes (40) as well. Increased ophthalmic surveillance is needed during pregnancy and the first year postpartum. From modelling perspective this variable may not be relevant as most patients are beyond reproductive age (> 60 years mean). But we shall use the variable as history of pregnancy less than two years before the outcome of need for treatment.

Frequent DNA / Cancellations

Patients with history of non-attendance of diabetic eye screening for two consecutive years are at increased risk of developing STDR (41). Evidence of this in patients with referral retinopathy under care of surveillance clinic or hospital services does not exist. However this was voted 8th out of 33 predictors in a nominal group technique exercise (20) attended by ophthalmic clinicians. We shall use this variable during the external validation / update of the model. We shall collect data on total number of non-attendance and cancellations and no of > 1 consecutive non-attendance or cancellations.

Appendix 2: Important definitions

- Early worsening: "DR progression to treatment requiring stage during the first year after rapid improvement in blood glucose will be considered EWDR"if there is history of intensive treatment / bariatric / pancreatic surgery (37).
- Follow up: From the first appointment after referral by DESP to first treatment (laser / injection) or vision failure, whichever comes first, death, discharge, transfer or end of the study.
- Outcome: This is a composite of treatment (photocoagulation, injection, vitrectomy) or vision failure (vision loss or blindness)
- Treatment: photocoagulation, Intraocular injection treatment with any anti VEGF or steroid injections laser or vitreous surgery
- Vision failure: Loss of three lines of vision (10 to 15 letters on EDTRS) or more, only if it happens before treatment. (Conversions-Between-Letter-LogMAR-and-Snellen-Visual-Acuity-Scores.png (605×725) (researchgate.net))

Appendix 3: Gantt Chart

	2022						2023											
	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Protocol development, Contracts Finalisation																		
Project steering group meeting 1: Protocol finalisation																		
Data access approvals/ethics																		
Data extraction																		
Data cleaning and interim analysis																		
Project steering group meeting 2: Interim analysis update																		
Final analysis																		
Consensus process																		
Project steering group meeting 3: Consensus meeting																		
Further analysis if required following consensus meeting																		
Write-up study for publication/dissemination																		
Project steering group meeting 4: End of project meeting																		

Appendix 4: Pre-application patients and public involvement and engagement (PPIE) and consultation with stake holders

The chief investigator (CI) has previously published on the predictors for progression of DR according to the James Lind Alliance priority setting (42) (priority 3 under retinal vascular disease/sight loss and vision) (20). The present study addresses priority 8 on the same top 10 research priorities (barriers that prevent diabetic patients having regular eye checks). For wider clinical expert input, we held consultation meetings with ophthalmologist colleagues with DR as their special interest, their DESP colleagues, diabetologists interested in DR and GP's with specialist interest in diabetes. They all provided detailed written feedback which was incorporated into the research design for funding application. The table below summarises the PPIE activities undertaken.

Table 2: List of PPIE activities (mostly pre-application)

PPIE Activity Report - Modified from GRIPP 2 (43)		
1	**Aims**	The aim of this PPIE exercise was to get patients' perspective about this research and to involve them in the design of the study and in the grant application.
2	**Objectives**	To recruit a diverse group for equitable representation.
		To train patients with diabetic retinopathy under care of the hospital eye services joining the group in PPIE.
		To ensure the use of friendly and plain language in the lay summary.
		To get PPIE input into the research project.
		To form a patient steering group and to recruit a patient advocate as a co- applicant with a deputy.
3	**Methods**	Recruitment through Diabetes UK, Clinical Research Network, three NHS trusts (northeast, midlands and southeast), local research networks, and through GP forums in order to include a diverse group and to ensure equitable access. The patients had been living with diabetic retinopathy and had been under the care of hospital eye services for at least one year.
		A presentation on all aspects of the research followed by questions and answers followed by open ended discussion
		Requested a volunteer to help write the plain English summary.
		In the presentation, we explained important themes of the research design and plans, but also ensured an adequate open-ended discussion to cover unforeseen patient perspectives, experiences, and concerns. We then brainstormed to gain further patient input.
		We invited two volunteers to act as co-applicants as patient advocates.
4	**Study results**	The patient advisory meeting was held remotely on 4th March 2021. 8 participants (including a GP representative) from three different regions of various ages and of different ethnicities attended. Patients without any internet access were invited into a GP practice to provide access to the virtual meeting.

		Participants reviewed the presentation, asked questions, engaged in discussion, and responded to the meeting minutes. They were supportive of the research and felt it will be beneficial for patients.
		One patient revised the summary to make it easier to read through user-friendly language.
		There were two important comments from patients on study design. They wanted to ensure safety for the patients where model does not accurately predict and did not want the ceiling for follow-up intervals to be as high as 2 years as in Diabetic Eye Screening Programme.
		Two volunteers accepted the invitation to act as patient advocates, one as co-applicant and the other as deputy. The group also agreed to be part of patient steering group and play a key role in disseminating the results of the study to the public, patients, their families, and carers.
5	**Discussion and conclusions**	Patients' perspectives regarding the follow up intervals, to be designed up to a maximum of 2 years, was taken on board. The risk arising from uncertainty in the model predictions will be mitigated by raising this issue in the consensus meeting for further discussion before finalising outputs.
6	**Reflections/critical perspective**	A PPIE group comprising a relevant population is now in place. This needs to grow in size for sustainability.

PPIE activity report (Modified from GRIPP 2, Short form https://doi.org/10.1136/bmj.j3453)

After receiving the feedback from NIHR panel on the stage 1 application, we discussed various comments with an ophthalmic expert panel. We have incorporated their advice into this protocol, added a secondary objectives section and added further analysis to external validation in the methods section.

Before starting the data permission applications and regulatory approvals, we tested the acceptability of using patient identifiable data in this study without consent by sending an e mail to the group asking this question. Following were the responses received.

1) “I can’t foresee any issues with using patient data so long as it has been completely anonymised”.
2) “I am happy for mine to be used”.