Description of Research

Data sources:

Routinely collected secondary care data from three NHS trusts (Sunderland, Surrey & Sussex, and Greater Glasgow and Clyde) for all patients within the catchment areas of these three service providers were utilised.
Sunderland Eye Infirmary and Sussex Healthcare NHS Trust contributed the data after extracting it from patient clinical notes / electronic hospital records. Glasgow health board extracted the data from their Safe Haven database (Safe Havens | NHS Research Scotland | NHS Research Scotland).

Target Population:

We took a secondary level patients' population approach, specifically focussing on hospital eye service. Patients were eligible for inclusion if they are aged 12 or over at index date (defined below), have a record of Diabetes Mellitus prior to index date and were referred with a diagnosis of referable diabetic retinopathy into hospital eye service between 1st January 2013 and 31st December 2016. The cohort included patients aged 12 years and over with diabetes referred into hospital eye services for close monitoring and treatment of diabetic retinopathy. Records were extracted for patients first entering the services between 1 January 2013 and 31 December 2016, with follow- up information extracted up to 31 December 2021 (Glasgow data was available up to 2022).
The aim of the prediction model is to aid prioritization of higher risk patients among this group of patients (by externally validating the multivariable risk prediction model we previously developed). The index date is the point a patient is referred into hospital eye service. Follow up is from the defined index date to the earliest of date of outcome (treatment or vision failure), date of transfer to another practice, practice stops contributing to the dataset, study end date or death date.

Study Outcome:

We selected the eye with the worse grade of referable diabetic retinopathy. The study outcome was defined as the earliest recorded treatment or visual loss of 3 or more lines on vision chart.
The primary outcome for this study was first treatment for diabetic retinopathy (DR) or vision loss. Patients were included in the study from date of referral to HES (baseline was first appointment) until the date of first treatment or vision loss, death, loss to follow-up or study end.
Vision loss was defined as loss of three Snellen lines of vision (15 letters on EDTRS) or more due to diabetic retinopathy, if it happened before treatment.

Clinical Predictor Variables:

Following are the seven predictors included in the model.

(1) retinopathy stage,

(2) HbA1c (mmol/mol),

(3) eGFR (mL/min/1.73 m2),

(4) total serum cholesterol (mmol/L),

(5) systolic blood pressure (mm Hg), and drug use of

(6) insulin or

(7) statins.

We also looked into feasibility of including any of the following, if possible, for updating the model as they were not available in the development dataset.

1. Early Worsening,
2. High non-attendance rate
3. Pregnancy and
4. Visual acuity

Descriptive Statistics

To summarise the cohorts, for each trust, we generated descriptive statistics for all variables. Categorical and binary variables were summarised using frequencies and percentages and continuous variables were summarised by mean and standard deviation when normally distributed or median and interquartile range when skewed.

Missing data:

The proportion of missing data for each predictor was investigated prior to model validation. For each predictor, descriptive statistics were used to inform the missing data strategy alongside clinical significance of the predictor. Predictors with missing data were imputed for each hospital separately. The imputation model included all predictors as well as the outcome using the event indicator and estimate of the cumulative hazard function. For categorical variables (e.g ethnicity, Townsend score and retinopathy grade), a separate missing category was created.

Sample Size:

Using conservative estimates from our development data, we expected an outcome event rate of 5% per year.
We assumed each trust would receive approximately 200 referrals per year, providing approximately outcomes within two years for validation of DRPTVL-UK.
For model updating, we calculated that we needed a minimum of 1810 patients with 293 outcome events to target a shrinkage factor of 0.9 ensuring minimal overfitting to the data (assuming an event rate of 0.05 per year, mean follow-up of 3.23 years, a default Nagelkerke R2 of 0.15 and up to 19 candidate predictors considered in the model).

External Validation:

The DRPTVL-UK prediction model was externally validated in Sunderland, Surrey & Sussex, and Glasgow datasets. The performance measures from the updated models are presented below.

Results:

Table 1: Baseline characteristics Table comparing baseline characteristics in validation cohorts and development cohort

Variable	Sunderland	Surrey & Sussex	Greater Glasgow and Clyde	Development data
N	967	936	6115	13691
Mean (SD) age at referral, years	57.95 (15.9)	59.76 (15.5)	60.03 (15.5)	61.69 (15.2)
Male	598 (61.8)	597 (63.9)	3564 (58.3)	8034 (58.7)
Ethnicity				
African Caribbean	4 (0.4)	12 (1.3)	69 (1.1)	232 (1.7)
Asian	43 (4.4)	111 (11.9)	661 (10.8)	602 (4.4)
Caucasian	912 (94.3)	600 (64.2)	5293 (86.6)	6148 (44.9)
Mixed ethnicity	2 (0.2)	7 (0.7)	32 (0.5)	84 (0.6)
Other ethnicity		133 (14.2)	50 (0.8)	47 (0.3)
Missing ethnicity	6 (0.6)	72 (7.7)	10 (0.2)	6578 (48.0)
Deprivation quintile*				
1 (Least Deprived)	90 (9.3)	221 (23.6)	850 (13.9)	2261 (16.5)
2	96 (9.9)	206 (22.0)	737 (12.1)	2415 (17.6)
3	140 (14.5)	223 (23.9)	825 (13.5)	2566 (18.7)
4	291 (30.1)	235 (25.1)	1117 (18.3)	2513 (18.4)
5 (Most Deprived)	295 (30.5)	50 (5.3)	2494 (40.8)	1866 (13.6)
Missing	55 (5.7)		92 (1.5)	2070 (15.1)
Diabetes information				
Type of DM				
Type 1	260 (26.9)	185 (19.8)		
Type 2	703 (72.7)	747 (79.9)		11343 (82.9)
Missing Type of DM	4 (0.4)	3 (0.3)		
Mean (SD) Duration DM	24.01 (10.4)	21.76 (9.9)		9.63 (7.8)
Missing Duration of DM	17 (1.8)	23 (2.5)		
Mean (SD) Age at diagnosis of DM	35.58 (17.8)	38.51 (17.9)		52.07 (17.3)
Missing age at diagnosis	7 (0.7)	9 (1.0)		
Mean (SD) Age at diagnosis of Type 1 DM	16.8 (12.8)	17.29 (13.2)		
Mean (SD) Age at diagnosis of Type 2 DM	42.3 (14.1)	43.7 (14.8)		
Insulin				
Insulin use	482 (49.8)	567 (60.6)	2546 (41.6)	8027 (58.6)
Insulin Missing	128 (13.2)	14 (1.5)		
Statins				
Statin use	427 (44.2)	636 (68.0)	4378 (71.6)	10940 (79.9)
Statins Missing	187 (19.3)	24 (2.6)		
HbA1c				
Mean (SD) HbA1c	71.64 (30.0)	71.50 (21.5)	70.55 (20.9)	67.75 (20.5)
Missing HbA1c	323 (33.4)	295 (31.6)	1097 (17.9)	1936 (14.1)
Cholesterol				
Mean (SD) Total cholesterol	4.77 (8.5)	3.52 (1.5)	4.44 (1.2)	4.38 (1.1)
Missing Total cholesterol	384 (39.7)	173 (18.5)		316 (2.3)
Systolic Blood Pressure				
Mean (SD) SBP	139.7 (21.6)	138.3 (18.5)	134.6 (17.3)	135.1 (16.9)
Missing SBP	668 (69.1)	123 (13.2)	1103 (18.0)	16 (0.1)
eGFR				
<30	30 (3.1)	23 (2.5)	203 (3.3)	487 (3.6)

30-59	128 (13.2)	163 (17.4)	1072 (17.5)	2958 (21.6)
>60	464 (48.0)	635 (67.9)	4112 (67.2)	10058 (73.5)
Missing eGFR	345 (35.7)	114 (12.2)	728 (11.9)	188 (1.4)
Retinopathy stage				
M1	458 (47.4)	629 (67.3)	4578 (74.9)	8402 (61.4)
R2	193 (20.0)	112 (12.0)	518 (8.5)	787 (5.7)
R2M1	172 (17.8)	117 (12.5)	737 (12.1)	580 (4.2)
R3	71 (7.3)	30 (3.2)	90 (1.5)	2267 (16.6)
R3M1	73 (7.5)	47 (5.0)	192 (3.1)	1335 (9.8)
Unclassified retinopathy				146 (2.6)
Events and follow-up				
Treatment or vision loss overall	503 (52.0)	286 (30.6)	1737 (28.4)	2079 (15.2)
Treatment or vision loss overall within 2 years	359 (37.1)	206 (22.0)	566 (9.3)	1272 (9.3)
Median follow-up (95% CI) based on reverse Kaplan-Meier method	3.2 [2.7,3.8]	1.8 [1.5,2.1]	7.1 (7.0, 7.1)	3.9 [3.8,4.0]

Abbreviations: SD- Standard deviation, **DM** – Diabetes mellitus, **SBP** – Systolic Blood Pressure, **eGFR** – Estimated Glomerular Filtration Rate, **IQR** – Interquartile range.

* Deprivation was assessed using Townsend quintiles for all datasets except for Glasgow where Scotland Index of Multiple Deprivation (SIMD) quintiles were available.

Table 1 shows the baseline characteristics between validation and development cohorts. Key differences observed were:

- Significantly higher proportion of the outcome in validation cohorts compared to development cohort which could be explained by the calendar effect (development data was extracted from 2004 to 2018 while validation data in the two trusts was extracted from 2013 onwards during which diagnosis and treatment of the outcome changed (i.e., anti vascular endothelial growth factor (VEGF) treatments taking over).
- There was a higher proportion of patients with R3 in development data in comparison to validation cohorts and higher R2M1 in validation compared to development data
- Duration of diabetes was more than twice as long in validation cohort compared to development data in both trusts
- Age at diagnosis of diabetes was higher in development
- More patients were on statins in development data (primary care data vs hospital/ ophthalmic data)
- Less missing ethnicity in validation cohorts
- eGFR was less missing in development data (primary care data vs hospital/ ophthalmic data)
- Higher missing eGFR, systolic blood pressure and total cholesterol for Sunderland data

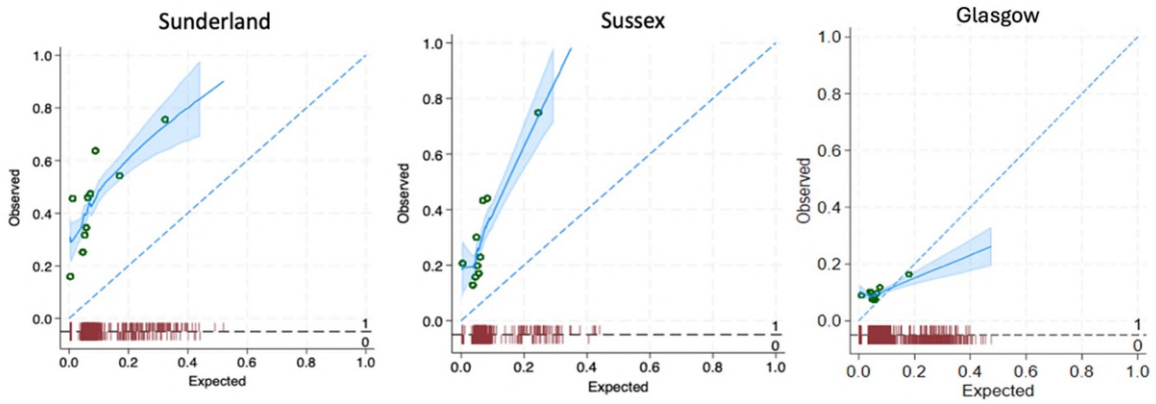
Missing data

For continuous variables the following were the proportions of missing data: SBP was missing in 69.1% of records in Sunderland, while in Sussex it was 13.2% and in Glasgow it was 18%, eGFR was missing in 35.7% of patients in Sunderland while in Sussex it was 12.2% and in Glasgow it was 11.9%, Total cholesterol was missing in 39.7% of patients in Sunderland and 18.5% in Sussex while in Glasgow it was 20.7%, HbA1c was missing in 33.4% of patients in Sunderland and 31.6% in Sussex while in Glasgow it was 17.9%.

Performance Measures for the Validated Model:

External Validation: The DRPTVL-UK prediction model was applied to the Sunderland, Sussex and Glasgow datasets for predicting treatment or vision loss by 2 years, resulting in a Harrell's C-index of 0.69 (95% CI 0.66 to 0.72) for Sunderland, 0.70 (0.66 to 0.75) for Sussex and 0.55 (0.52 to 0.57) in Glasgow. The calibration slope for Sunderland was 0.32 (95% CI 0.26 to 0.38), for Sussex it was 0.87 (95% CI 0.68 to 1.05) while for Glasgow it was 0.18 (0.07 to 0.30). The calibration plots are presented in Figure 1. The model had lower net benefit compared to treat all or treat none models.

Figure 1: Calibration plots of the 2-year DRPTVL-UK in Sunderland, Sussex and Glasgow



Differences in the validation cohorts at baseline in comparison to the development cohort could explain the lower performance of the model in the validation cohorts (Table 1).

Updated models

After evaluation of completeness and quality of additional candidate predictors, only visual acuity was taken forward for analysis. The updated models (which involved re-estimating the coefficients of the predictors from DRPTVL-UK separately for each trust) included visual acuity as an additional variable. This resulted in a Harrell's C index of 0.71 (0.69 to 0.74) for Sunderland, 0.77 (0.73 to 0.80) for Sussex and 0.67 (0.65 to 0.70) for Glasgow. The calibration slope for Sunderland was 0.91 (0.78 to 1.03), for Sussex it was 0.90 (0.78 to 1.01) and for Glasgow it was 1.00 (0.84 to 1.16). The calibration plots are provided in Figure 3. The updated model had higher net benefit compared to the original DRPTVL-UK model, treat all or treat none models across all risk thresholds.

The application of the updated model for Sunderland in Sussex and Glasgow resulted in lower performance (Harrell's C index of 0.68 (0.64 to 0.73) for Sussex and 0.55 (0.52 to 0.57) for Glasgow) and similar results were found when we applied the updated Sussex model in Sunderland and Glasgow (Harrell's C index 0.66 (0.63 to 0.69) for Sunderland and 0.66 (0.63 to 0.68) for Glasgow). The discrimination statistics of updated model for Glasgow in Sunderland was 0.63 (0.60 to 0.66) and in Sussex it was (0.73 (0.69 to 0.76). The calibration slope of the updated Sunderland model in Sussex cohort was 1.00 (0.84 to 1.17) and in Glasgow it was 0.53 (0.39 to 0.67), the calibration slope of the updated Sussex model in Sunderland was 0.43 (0.35 to 0.51) and in Glasgow it was 0.54 (0.45

to 0.62) and the calibration slope of updated Glasgow model in Sunderland was 0.48 (0.35 to 0.62) and in Sussex it was 1.18 (0.97 to 1.39). The calibration plots are provided in Figure 4.

Figure 2: Calibration plots based on recalibrating the baseline risk of the DRPTVL-UK 2-year model in Sunderland, Sussex and Glasgow

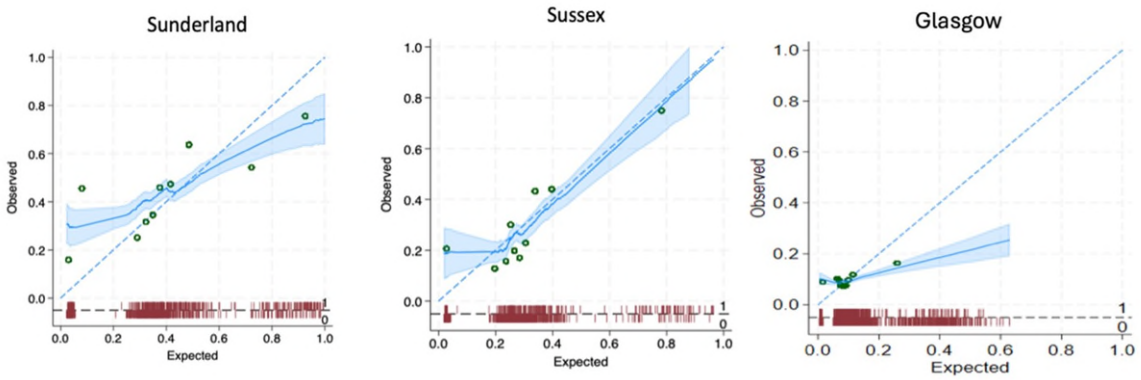


Figure 3: Calibration plots of updated 2-year models in Sunderland, Sussex and Glasgow

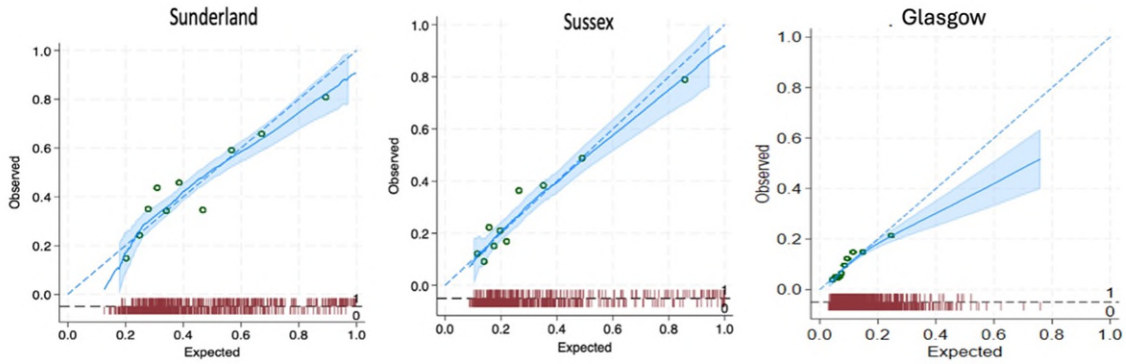
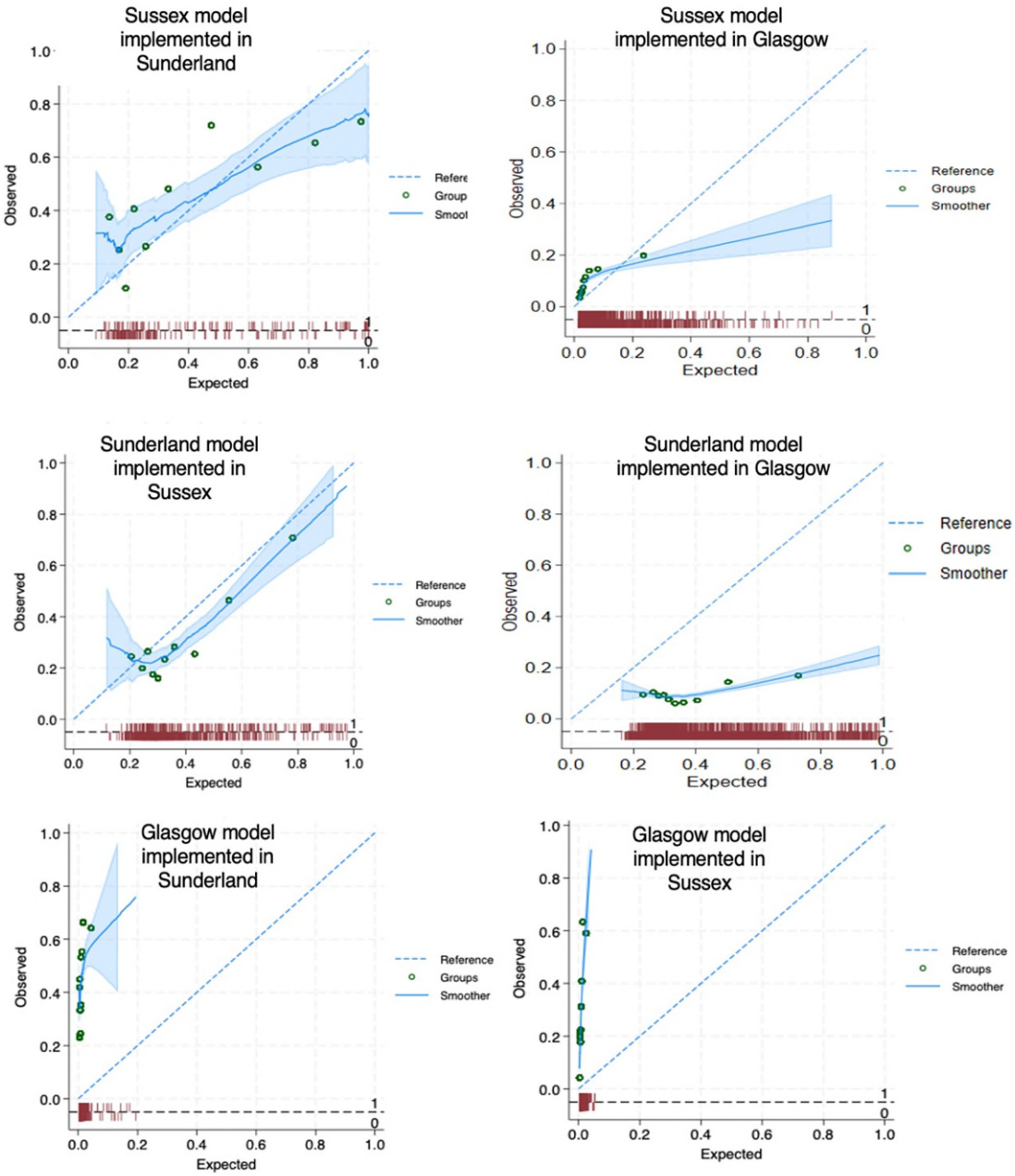


Figure 4: Calibration plots of updated 2-year models in one trust and implemented in the other trusts



Subgroup Analyses

Subgroup analysis by retinopathy grade was planned but was not possible because of only a small number of outcome events occurring within most subgroups.

Conclusion: More work is needed to understand the differences between the patient populations at different trusts to identify useful prognostic factors that can be used to develop a model that could be generalisable. Although the DRPTVL-UK prediction model improved after updating it in each trust, the updated model in one trust did not perform well in the other trust and hence more work is needed to understand the differences between the trusts, to identify useful prognostic factors that can be used to develop a model that could be generalisable.

Stakeholder Involvement and Feedback: An important element of the project was the multi-professional stakeholder on-line meeting by the University of Birmingham. Besides study

researchers the experts from ophthalmology and diabetic eye screening programme were consulted.