GRIP study protocol

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Chief Investigator:	**Augusto Azuara-Blanco** **Centre for Public Health, ICS-A** **Queen's University Belfast** **Grosvenor Road, Belfast BT12 6BA**

PROTOCOL AUTHORISATION

A review of the protocol has been completed and is understood and approved by the following:

Augusto Azuara-Blanco	A. Azuara-Blanco	**25 / 03 / 2021**
Chief Investigator	**Signature**	**Date**
Yemisi Takwoingi	Y Takwoingi	**26 / 03 / 2021**
Co-Chief Investigator	**Signature**	**Date**

1. FULL TITLE OF PROJECT:

Glaucoma Risk Prediction in ocular hypertension (GRIP): a cohort study using electronic medical records to validate a risk predictor and determine the cost-effectiveness of different monitoring schemes according to risk of conversion to glaucoma

2. SUMMARY OF RESEARCH (ABSTRACT)

Background: Primary open angle glaucoma (POAG) is a chronic eye disease and a leading cause of blindness; ocular hypertension (OHT), defined as an intraocular pressure (IOP) > 21 mmHg, is a risk factor for POAG. A POAG risk predictor, the OHTS-EGPS model, is available but its generalisability to a UK population is uncertain.

Aim: To validate and update a risk predictor of POAG and to model the cost-effectiveness of alternative monitoring frequencies and pathways according to glaucoma risk.

Specific objectives: 1) to validate and update the OHTS-EGPS risk prediction model in a UK population with OHT; 2) to assess the relative efficiency of alternative monitoring pathways for people with OHT according to glaucoma risk compared with standard practice; 3) to determine the clinical and cost effectiveness of treating people with OHT with IOP of 22 or 23 mmHg.

Methods: Retrospective data analysis of electronic medical records of OHT patients from 11 Hospital Eye Services (HES). Conversion to POAG will be defined as two consecutive and reliable visual fields (VFs) with Glaucoma Hemifield Test 'outside normal limits'.

Risk factors: age, ethnicity, sex, IOP, vertical cup-to-disc ratio, central corneal thickness, VF pattern standard deviation, family history of glaucoma, systemic hypertension, diabetes mellitus, and treatment. We will explore the role of Optical Coherence Tomography.
We will have access to over 42,000 patients with OHT who have at least 5 years of follow-up. From this cohort we will have complete data from about 20,000 patients.

Primary outcome: conversion to glaucoma in at least one eye within 5 years.

Model updating and validation: The OHTS-EGPS risk prediction model will be applied to calculate the predicted risk of developing glaucoma in 5 years for each patient. For ocular predictors we will use the mean value of both eyes. Model performance will be assessed in terms of discrimination and calibration. Based on the outcome of the validation, we will update the model by adjusting the baseline risk, re-estimating regression coefficients, and exploring the addition of new candidate predictors.

Sample size: We anticipate a conversion rate to POAG of 0.5% per year among low risk patients untreated for OHT and 1% per year among high risk patients treated for OHT. Based upon person years of follow-up within centres and a conservative 0.5% per year conversion rate, we anticipate 500 events will be adequate to analyse the 12 candidate predictors.

Economic evaluation: we will (1) characterise the current cost of monitoring people with OHT; (2) conduct a model-based cost-utility evaluation comparing alternative treatment and monitoring strategies, with deterministic and probabilistic sensitivity analyses. We will perform subgroup analysis for people with IOP of 22 and/or 23 mmHg. We will estimate the increased severity of glaucoma associated with delayed diagnosis in less frequent

monitoring intervals. We will evaluate the acceptability of and preferences for new models of eye care based on the risk prediction.

Timeline: Duration: 24 months. Prefunding: protocol development and ethics approval. Months 1-6: data collection; Months 7-21: data cleaning and analysis, online calculator development, economic evaluation; Months 22-24: report writing and dissemination.

Anticipated impact: An updated risk prediction tool will inform effective and efficient OHT management in the NHS. Dissemination will include scholarly outputs, and a knowledge transfer day with relevant stakeholders.

3. BACKGROUND AND RATIONALE

3.1. Problem being addressed

Glaucoma is a chronic progressive optic neuropathy and a leading cause of irreversible blindness [Bourne 2018]. Ocular hypertension (OHT) is a risk factor for glaucoma and defined as an IOP of >21mmHg with normal optic disc and visual field (VF). According to the NICE 2017 updated glaucoma guideline, around 1.3 million people aged over 40 in the UK have OHT. 'The Way Forward Project', commissioned by the Royal College of Ophthalmologists, predicts that from 2015 to 2035 the number of people in the UK with glaucoma will rise by 44% and with OHT by 16%, caused by a 'perfect storm of increased demand due to more eye disease in an ageing population' [The Way Forward project]. Current standard practice is to monitor OHT in hospital eye services, although there is potential for community optometrists to manage this condition, which could reduce pressures on hospital eye services, and waiting times for patients. NICE guidelines recommend treating individuals with IOP of 24 mmHg or greater, but at present there is variability in the management of OHT in the UK. Robust data on the risk of developing glaucoma will be useful to develop monitoring strategies, e.g. from no or minimal follow-up to treatment and frequent follow-up.

A glaucoma risk prediction model, based on the results of the Ocular Hypertension Study (OHTS) [Kass 2002] and the European Glaucoma Prevention Study (EGPS) [Miglior 2005], is available online: http://ohts.wustl.edu/risk/calculator.html. This OHTS-EGPS risk calculator included age, IOP, central corneal thickness (CCT), a measure of the visual field test (pattern standard deviation; PSD) and the optic nerve (the vertical cup to disc ratio; VCDR) [Ocular Hypertension Treatment Study Group and the European Glaucoma Prevention Study Group]. However, the NICE guidelines did not recommend the use of the OHTS-EGPS risk calculator because of its high risk of bias and uncertain generalisability to UK patients.

A NIHR-funded study completed by our group [Burr 2012, HTA 07/46/02] recommended the validation of the OHTS-EGPS risk calculator as a research priority [Burr 2012]. In 2013 the NIHR-HTA commissioned a topic: "Validation of a risk prediction model for Ocular Hypertension". The prospective cohort study we proposed was not funded, mainly due to the prohibitive costs of a prospective cohort of untreated OHT with five year follow up. This question was also a top research priority in the 2017 NICE glaucoma guideline. Another top research priority by NICE is the question: "What is the clinical and cost effectiveness of treating an IOP of 22 or 23 mmHg in people with normal optic discs and visual fields?" A third NICE research recommendation is about the effectiveness and cost-effectiveness of optical coherence tomography (OCT) for glaucoma. Further, the Public Health Outcomes Framework for England made reducing numbers of people living with preventable sight loss a priority (39-DH/HIPD/PHDU. Health Lives, Health People: Improving Outcomes and Supporting Transparency. London: DoD; 2012).

3.2. Importance of research in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services

As well as directly addressing NICE research recommendations, our study will address a top research recommendation by the James Lind Alliance, i.e., "What can be done to improve early diagnosis of sight-threatening glaucoma?" Validated risk prediction tools are used in other conditions to guide treatment decisions such as the need for lipid lowering therapy to prevent cardiovascular disease [Collins 2012; Collins 2016].

3.3. Review of existing evidence

Our group has used very large archives of clinical data (e.g. >600,000 records) in order to assess eye care in hospital eye services [Kelly 2019].

The last systematic literature search by NICE relevant to our study was done in January 2017. Since then, our literature search (March 2020) identified only one relevant study performed by our group [Kelly 2020] using electronic medical records (EMR) from five NHS units to determine conversion rates of OHT. In this study about 1/5 of patients with OHT converted to glaucoma after 5 years. Specifically, the cumulative risk of conversion to POAG was 17.5% (95% CI 15.4% to 19.6%) at 5 years. This study critically confirmed the feasibility of our proposal of using EMR from people with OHT and supports our (conservative) estimation of proportion of conversion in our study. We have adopted a conservative conversion rate of 0.5% per year giving a 5-year cumulative incidence of 2.47% for glaucoma.

3.4. Research questions:

1. Can we predict the 5-year risk of onset of glaucoma in a U K population with OHT?
2. Is it clinically effective and cost-effective to use a UK-based risk prediction tool for glaucoma in the NHS?
3. What is the effectiveness and cost-effectiveness of treating people with OHT with an IOP of 22 or 23 mmHg?

4. AIMS AND OBJECTIVES

The overall aim of this study is to validate and update a model to optimise the management of people in the UK with OHT using data on the risk of conversion to glaucoma, and to compare the clinical and cost-effectiveness of different monitoring schemes proportionate to 5-year glaucoma risk.

Objectives:

1) To validate and update the OHTS-EGPS risk prediction model in a large population of UK adults with OHT.
2) To assess the effectiveness of alternative monitoring pathways for people with OHT according to the 5-year predicted risk of glaucoma compared with standard UK practice.
3) To determine the clinical and cost effectiveness of treating people with OHT who have IOP of 22 or 23 mmHg.

5. RESEARCH PLAN/METHODS

5.1. Study design: Retrospective data analysis of electronic medical records obtained from Medisoft and OpenEyes.

5.2. Setting and recruitment: 11 Hospital Eye Services.

5.3. Health Technology: Tool for predicting risk of conversion from OHT to glaucoma.

5.4. Target population: People with OHT. We will include adults with newly diagnosed OHT in one or both eyes, as recorded in the EMR. Confirmation of new diagnosis will be possible at the time of the first visit and first visual field testing. OHT is defined as a IOP>21 mmHg measured using Goldmann applanation tonometry, no clinical signs of POAG (i.e., normal optic nerve examination and normal visual field test), and no associated abnormalities on clinical exam (e.g. pigment dispersion or pseudoexfoliation, normal anterior chamber angle). 'Normal' visual fields are defined as two consecutive reliable Humphrey visual fields (HVF) with a Glaucoma Hemifield Test (GHT) 'within normal limits'.

5.5. Inclusion/Exclusion criteria:
We will include adults with newly diagnosed OHT in one or both eyes with IOP between 22 mmHg and 32 mmHg and normal VF, defined as Glaucoma Hemifield Test (GHT) within normal limits on two consecutive examinations.

We will exclude eyes with clinically significant ocular comorbidity, such as maculopathies, as the change in visual field may be due to retinal disease and monitoring pathway would be determined by the comorbid condition. We will also exclude patients with glaucoma (any type) in one eye, and people diagnosed as 'glaucoma suspects' at baseline. We will exclude those who do not have any VF testing and those without reliable VF testing. An unreliable VF is defined as a high frequency of false positives, more than 15%.

5.6. Sampling and sample size: We will use EMR data from Medisoft (n=10) and OpenEyes (n=1) hospital eye services. We will include patients from different ethnicities and socio-economic backgrounds.

The 11 hospital eye services will include over 42,000 patients with OHT with at least 5 years of reliable data. Of this cohort we will have complete data with series visual field tests in 20,000 patients. We anticipate a conversion rate to glaucoma of 0.5% per year among low risk patients untreated for OHT and 1% per year among high risk patients treated for OHT [Kass 2002; Artes 2010; Kelly 2020]. As our cohort will include a spectrum of low to high risk individuals and the preliminary review of data indicated that about 10% of people with OHT were treated [Pajouheshnia 2017], we have adopted a conservative conversion rate of 0.5% per year giving a 5-year cumulative incidence of 2.47% for glaucoma. Thus, we expect to have approximately 500 patients converting to glaucoma (i.e. events). This is a conservative estimate as our recent work [Kelly 2020] using Medisoft electronic data reported a conversion rate of over 15% at 5 years. A minimum of 100 events and ideally 200 (or more) events has been suggested for external validation of a prognostic model [Collins 2016]. For model development, the commonly used rule of thumb of 10 events per variable (EPV) for fitting multivariable models can lead to small samples which may result in overfitting and optimism. EPV values are not definitive and higher EPV values (≥ 20) can eliminate bias in regression coefficients if there are low prevalence predictors in a Cox model [Ogundimu 2016]. Therefore, based on 12 candidate predictors (seven new predictors plus five from the existing OHTS-EGPS model), our cohort size will be adequate for validating and updating the risk prediction models.

5.7. Feasibility of data acquisition from EMRs: Our group has experience with analysing UK-wide EMR data in glaucoma and retinal diseases [Saunders 2014, Boodhna 2015]. We have confirmed that demographics, ocular data, self-reported family history of glaucoma, diabetes, and systemic hypertension are routinely collected and available in Medisoft [Kelly 2020] and OpenEyes.

Ethnicity data will be available via the Patient Administration System (PAS), which is linked with EMR. It is well known in the literature that the prevalence and severity of POAG is highest in people of black ethnicity, although it is unclear whether ethnicity may influence the risk of conversion from OHT to POAG. Ethnicity will be categorised as categorised as caucasian versus non-caucasian. We are uncertain if ethnicity data will be complete.

5.8. Data collection and analysis

5.8.1. Data acquisition: Following receipt of the relevant permissions from a participating site, the data extraction process will operate as follows:
i. Medisoft or OpenEyes will connect to the site's database over the secure NHS network (N3/HSCN);
ii. Using the bespoke data extraction tool, each data field required to support the analysis will be extracted into a new database;
iii. All patient identifiers will be stripped from the data and replaced with a site-unique identifier for each patient;
iv. Medisoft or OpenEyes will securely transfer the data to its NHS analysis server and conduct initial data validation and cleansing, linking with visual field test and OCT.
v. Following validation, data will be collated for all sites and securely sent to the Queen's University Belfast.

5.8.2. Evaluation of risk predictors:
The original five risk factors used in the OHTS-EGPS risk predictor are:

1. Age: patient's age and date of birth is obtained from the hospitals PAS. To protect anonymity we will only record age in years and not date of birth.
2. Intraocular pressure.
3. Central corneal thickness.
4. Visual field pattern standard deviation (PSD).
5. Vertical cup-to-disc ratio (VCDR) obtained during clinical exam and thus it is subjective but frequently recorded.

All five factors will be analysed as continuous variables.

The additional risk factors that we will evaluate in the model updating are:

1. Ethnicity: There is an increased prevalence of glaucoma among African-Americans compared with whites [Tielsch 1991; Burr 2007]. Ethnicity will be categorised as caucasian versus non-caucasian.
2. Family history of glaucoma: a systematic review and meta-analysis of four studies evaluating the relationship between family history of glaucoma and POAG showed that a family history of glaucoma (self-reported) is associated with a three-fold excess risk of POAG [Burr 2007]. Family history (self-reported) will be categorised as yes/no.
3. Diabetes mellitus: a systematic review and meta-analysis of four studies evaluating the relationship between diabetes mellitus and POAG demonstrated almost twice the risk of POAG onset when compared with people without diabetes mellitus [Burr 2007]. Diabetes mellitus (self-reported) will be categorised as yes/no.
4. Systemic hypertension: a systematic review and meta-analysis of the association between blood pressure levels and systemic hypertension with POAG included 60 studies. The pooled relative risk for POAG comparing patients with hypertension to those without hypertension was 1.16 (95% CI = 1.05-1.28), with modest heterogeneity across studies (I^2 = 34.5%). Systemic hypertension (self-reported) will be categorised as yes/no.

5. Treatment for glaucoma: patients with OHT and high risk of conversion to glaucoma (e.g. high IOP) received IOP lowering medical treatment following the 2009 NICE glaucoma guidelines. Treatment will categorised as yes/no.
6. Optical coherence tomography retinal nerve fiber layer global thickness: due to the differences in commercially available OCTs in their analysis of the RNFL thickness we will not be able to explore the OCT RNFL thickness as a continuous variable. However, we will use the common classification of "within normal limits", "borderline" and "outside normal limits". We will only use OCT images that have good quality according to the manufacturer recommendation. We expect 95% of OCT images will have good quality [Azuara-Blanco 2016].
7. Sex: male/female

5.8.3. Updating and validation of the OHTS/EGPS risk prediction tool:
The primary outcome is conversion to glaucoma within 5 years. We will use VF tests to detect conversion to glaucoma, defined as two consecutive abnormal VF examination results, i.e., GHT outside normal limits [Duggan 1985; Katz 1995, Asman 1992, Kelly 2020]. The date of conversion will be the date of the first abnormal test result.

Unit of analysis: If values are available for both eyes, similar to the OHTS-EGPS model, average baseline values of eye-specific predictors will be used.

The original OHTS-EGPS risk prediction model will be applied to all 11 hospital eye services data to calculate the predicted risk of developing glaucoma in 5 years for each participant as previously described [Takwoingi 2014]. Model performance will be assessed in terms of discrimination and calibration (i.e. agreement between predicted and observed risk). Discriminative ability will be assessed using Harrell's c-index [Harrell 1996]. Calibration plots of average observed risk against predicted 5-year risk will be used to assess calibration [Steyerberg 2016]. Participants will be divided by tenth of predicted risk, and the average predicted risk for each decile will be compared with the corresponding Kaplan–Meier estimate of the observed risk. Additionally, we will quantify calibration by estimating the slope of the prognostic index (linear predictor), using Cox regression as it was used to fit the original model.

We will investigate updating the model to improve performance in a real world setting. We will update the model by adjusting the baseline risk, re-estimating regression coefficients, and exploring the addition of new candidate predictors (sex, treatment, ethnicity, family history of glaucoma, diabetes, systemic hypertension, and OCT RNFL thickness). Although the adoption of OCT has been variable, due to its increasing use in clinical practice, we plan to produce two models – with and without OCT.

The inclusion of any new predictor in the updated models is subject to improvement of the predictive ability of the resulting models [Hilden 2014]. We will internally validate the new models using bootstrap methods so that regression coefficients can be adjusted for optimism [Steyerberg 2016]. Based on current recommendations we will not split the cohort into development and validation sets, but rather conduct internal-external validation using a cross-validation technique in which the updated models will be developed using 10 hospital eye services and model performance will be investigated in the remaining hospital eye services [Steyerberg 1999]. Missing data is inevitable, and so to avoid excluding participants and introducing bias, we will use multiple imputation by chained equations (MICE) to impute missing data [Van Buuren 1999]. Analysis will be reported according to the TRIPOD statement [Moons 2012; Moons 2015].

We will then apply the model of risk of conversion to people with IOP of 22/23 mmHg within the same cohort to inform objective 3.

5.9. Severity of glaucoma at diagnosis associated with different monitoring intervals.
A secondary aim of this study is to examine the optimal frequency of visual fields (VFs) to detect conversion from OHT to POAG and to quantify the severity of VF loss associated with less frequent monitoring intervals.

We will examine the difference between 'standard' (every 12 months) against 'sparse' (every 60 months) VF monitoring for people with OHT. The difference will be quantified (modelled) by a **penalty** of visual function loss due to 'sparse' (infrequent) VF monitoring. **'Standard' monitoring** will be defined as yearly VF testing. **'Sparse' monitoring** will be associated with delayed diagnosis and untreated disease progression that will be modelled from the literature [Crabb 2012 and 2014].

The outcome from '**sparse'** monitoring will be estimated in at least two ways:
[1] Average delay in detection of POAG.
[2] Average VF loss (penalty) resulting from the delayed detection of conversion to POAG.

See Figure 1 below for an illustrative example.

An illustration of post-hoc analysis of data to examine optimum frequency of testing for detecting 'conversion' to glaucoma. Red represents cumulative time after detection. Delay to detection is the difference between time at which detection is picked up with 12 and 36 month testing. These values will allow for a test of the null hypothesis that there is no significant delay. Delay can be converted to a penalty value which will represent the amount of VF loss suffered by the patient due to delay of detection. See [2].							estimates actual conversion	* 12 month testing	** 36 month testing	**Delay to detection**
time (t)	**0**	**12**	**24**	**36**	**48**	**60**				
Person 1		*		**			6.0	12.0	36.0	**24**
Person 2							X	X	X	**X**
Person 3					*		42.0	48.0	72.0	**24**
Person 4				* **			30.0	36.0	36.0	**0**
Person 5			*	**			18.0	24.0	36.0	**12**

*Figure 1 legend. For every patient that converts to POAG we will have a detection time (t) and also a delay to detection time (numbers in column highlighted in yellow). We can examine the average and distribution of the delay in detection time in the entire cohort. To examine the clinical effect of the delay in detection time we will model a **penalty** for delayed detection by calculating the VF loss resulting from the delayed detection of conversion to POAG. A suitable index to measure disease severity will be the Mean Deviation (MD) global index of the VF. For each patient that converts we will have an MD at conversion (MDC – MD recorded on the day of conversion) and an MD at baseline (MDB – MD recorded at*

baseline when they entered the study). Speed of MD loss (per year) at conversion can be defined as:
***S: (MDC-MDB)/t** in dB/year. This speed of loss can then be used to calculate a **penalty** for **standard monitoring** (e.g. VF every 12 months) and **sparse monitoring** (VF every 60 months). This can be more easily explained by a numerical example, using 'Person 1' in Figure 1 above.*

Assuming an MD at the baseline visit, MDB, (t=0) is -1dB and at conversion (tested at 12 months) the MDC was -3 dB:
*The speed of loss (at conversion) is **S = 2.0 dB** year [(-1-(-3))/1.0].*
*The modelled loss with **standard** testing would be = **2dB (1 year × S)***
*The modelled loss with **sparse** testing (detection at 60 months) would be e.g., **6dB (3 years × S).***
*In this one example, the penalty for **sparse** testing (a visit every 60 months) is 6dB compared with 2dB loss for **standard** testing. In other words, this one patient would have lost 4dB of their VF because the monitoring was not frequent enough. This amount of VF loss will be informed by the literature and integrated into the economic modelling.*

5.10. Economic evaluation:

To explore the impact of introducing such a tool within clinical practice we will: (1) characterise the current cost of monitoring individuals with OHT; and (2) conduct a model based economic evaluation to compare alternative monitoring strategies (a. reflecting UK current practice and b. stratifying and managing individuals according to 5-year glaucoma risk).

We will characterise the cost of monitoring individuals with OHT using hospital eye services resource use data retrieved from Medisoft and OpenEyes (i.e. number of visits to hospital eye services, treatment received, number and type of tests conducted). Based on our group's extensive experience [Hernandez 2016, Burr and Azuara-Blanco] we will develop a new decision analytic model (i.e. discrete event simulation). We will define the health care pathways according to published NICE glaucoma guideline and in consultation with project clinical experts. We will use data from the validation exercise to characterise a UK representative cohort entering the model and define the risk of conversion to glaucoma for each simulated individual. Glaucoma progression data will be obtained from the literature [Burr 2012, Musch 1999, Leske 1999]. Resource use data from Medisoft and OpenEyes will be representative of standard clinical practice. Structured literature searches will be used to obtain additional model input data.

We will conduct cost-effectiveness (CEA) and a cost-utility (CUA) analysis. Benefits will be measured as i) number of severe glaucoma cases avoided; and ii) quality adjusted life years (QALYs) using EQ5D-3L and the Glaucoma Utility Index (GUI) [Burr 2007]. We will conduct subgroup analysis for individuals with IOP level of 22 and/or 23 mmHg with normal optic disc and VFs to assess the cost-effectiveness of treating this patient group (Objective 3).

We will report incremental cost per (i) severe glaucoma cases avoided and ii) QALYs. Deterministic and probabilistic sensitivity analyses will be conducted to explore the importance of key areas of uncertainty. The perspective of the CEA and CUA will be that of the NHS and personal social services [Guide to the methods of technology appraisal 2013].

We will define a current practice monitoring strategy in the model according to 2017 NICE glaucoma guidelines [https://www.nice.org.uk/guidance/ng81] for management of individuals with ocular hypertension and glaucoma. In particular, for individuals with ocular hypertension (i.e. ≥24mmHg) we will specify the monitoring frequency as follows:

- If conversion to chronic open angle glaucoma (COAG) is not detected and the level of IOP is not acceptably controlled, clinical management will be reviewed and reassessed between 1 and 4 months
- If uncertain about conversion to POAG and IOP acceptably controlled, individuals would be reassessed in the model every 6 to 12 months
- Finally, if conversion to POAG is not detected and IOP acceptably controlled, individuals will be reassessed between 18 and 24 months"

Also, we will use the delayed detection penalty to estimate health related quality of life loss due to conversion and disease progression. Furthermore, we will use the DCE, the literature and project group discussions and agreement to define alternative monitoring strategies according to the risk of conversion to POAG. Finally, we will explore the cost-effectiveness of alternative monitoring intervals by conducting economic model sensitivity analysis (e.g. subgroup, scenario and threshold analyses).

5.11. Acceptability of and preferences for new models of eye care based on the risk prediction

The risk prediction tool will change patients' care pathway. Those at low risk of conversion could be discharged. Those remaining at hospital services can be streamed into appropriate monitoring services depending on their risk. The monitoring interval can be determined by risk and thus prevent unnecessary monitoring visits. This service redesign needs to be informed by patients' preferences for alternative service deliveries. The risk thresholds that patients are willing to accept for service change may differ from those of clinicians. Furthermore, there may be meaningful differences in preferences across patient groups. If service are redesigned in a way that conflicts with patients' preferences this may lead to lower compliance and consequently poorer health outcomes. If compliance differs across patient groups this may widen health inequalities. Discrete Choice Experiments (DCEs) are widely used to measure such values [Hensher 2005; De Bekker-Grobb 2012; Vass 2017] including in previous glaucoma studies by our group [Burr 2007 and 2012].

We will develop the DCE following best practice recommendations and using qualitative methods to define service characteristics (focus groups) and test the survey (think aloud interviews). [Ritchie 1994]. We will use experimental design methods to select the DCE choice tasks to present to patients. We will survey a sample of 390 patients with OHT to assess their preferences for different monitoring schemes. We will analyse the data using logistic regression and model preference heterogeneity. Assuming a 20% response rate we will need to contact 2,000 patients for a sample of 390 respondents [Watson 2017]. To assess patient acceptability, we will estimate the uptake probability for different redesigned services, and patients' willingness to pay for service characteristics.

The findings of the DCE will be interpreted alongside the cost-effectiveness results. The outcomes of the DCE will inform the monitoring strategies incorporated in the economic model. For example, the results of the DCE could be used alongside clinical data to define the longest possible interval that is clinically safe/acceptable in the model as an alternative to current practice. Similarly, the results of the DCE can be used to gauge acceptability of primary care-based monitoring. The DCE and model will be developed in parallel to ensure that it can be as informative as possible about preferences for the monitoring strategies included in the model.

A separate ethics application will be submitted for the DCE work. Description of the DCE in this protocol is provided for context only.

6. DISSEMINATION, OUTPUTS AND ASSOCIATED IMPACTS

Our dissemination plan will ensure the findings from this study influence health services policy to deliver public benefit. We will use the following approaches.

6.1. Knowledge exchange event: The main outcome from the cohort study will be a validated risk-prediction model for OHT. This will allow risk-stratification of presenting patients and opens up new possibilities for service redesign (e.g. better triage and referral patterns, more cost-effective monitoring). We will host a one-day knowledge exchange event to explore how a risk prediction tool could be implemented in practice. The event will be hosted by Queen's University Belfast, bringing together policy makers, commissioners, clinical guideline groups (SIGN and NICE), practitioners, patients, professional colleges, and academic researchers to disseminate the study findings, pool information and ideas. This strand of the study will explore the service implications of a POAG risk model.

6.2 Scholarly outputs: The protocol will be published on the HTA website as primary research. The protocol will also be submitted to an open access journal for publication. The study results will be disseminated to a wide clinical audience through publication in the HTA journal series and other high impact international peer reviewed scientific journals. The eye care community will be targeted through presentations at International meetings. PPI Representatives involved in the study will also be invited to attend and/or present. Outputs will be published in open access and specialist journals and will include a programme funding statement and disclaimer.

6.3. Online risk calculator: The algorithms underlying the risk calculator will be made available to suppliers to ensure uptake in commercially deployed electronic patient records in the UK (and beyond). We will develop a web-based risk calculator hosted and maintained by the sponsor (QUB) that will be available for clinicians and services where an electronic patient record is not available. The code for the calculator will be made available.

7. PROJECT/RESEARCH TIMETABLE

Task		M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12	M 13	M 14	M 15	M 16	M 17	M 18	M 19	M 20	M 21	M 22	M 23	m 24
Finalise protocol	X	X																							
Ethics approval	X	X	X																						
R&D approval	X	X	X																						
Funding starts 1 June 2021 (M 1)				X	X	X	X																		
EMR connection to site				X	X	X	X																		
EMR data extraction				X	X	X	X																		
EMR data cleansing and validation				X	X	X	X																		
Statistical analysis plan		X	X	X	X																				
Visual field analysis plan		X	X	X	X																				
Health economics analysis plan		X	X	X	X																				
Data analysis						X	X	X	X	X	X	X	X	X	X	X	X								
Data linkage								X	X	X	X	X	X	X	X	X	X								
Model validation and updating																X	X	X	X	X	X				

Development of online calculator																						x			
Review of literature for economic modelling		x	x	x																				
Update of economic modelling				x	x	x	x	x	x	x	x	x	x												
Economic analysis														x	x	x	x	x	x	x					
Write up																						x	x	x	
Knowledge exchange																									x
Final report																									x
Steering Committee meeting		x					x						x						x						x
Project management group meeting	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

8. PROJECT MANAGEMENT

The study will be sponsored by Queen's University Belfast.
We will have a study steering committee with an independent chair and members, including representation from Glaucoma UK and two patients. Chair and membership will be subject to agreement by the HTA programme.

9. ETHICS

Research ethics approval and NHS Trust R&D approvals for the study will be obtained.
General data protection regulation guidelines will be followed. All data will be collected and pseudonymised by Medisoft and OpenEyes, and no patient identifiers will be sent to the academic units that will conduct the analyses.
The research team will only be analysing anonymous data and will have no way to link the information back to an individual.
Separate ethics approval will be obtained for the patient acceptability and preference (DCE) work package (section 5.11).

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