ACE Study

Study of Technologies for the Diagnosis of Angle Closure glaucoma (ACE)

Protocol Number:	B22/08
Protocol Version: *(See Summary of Key Changes Form for Differences From Last Version)*	Version 2.0 Final
Protocol date	19/07/2023
Protocol amendment number	1
ISRCTN Number:	15115867
Sources of monetary or material support	
Funder	National Institute of Health Research (NIHR) Health Technology Assessment (HTA) Programme NIHR134593
Sponsor details	
Sponsor	Queen's University Belfast 63 University Road Belfast, BT7 1NN Phone: 028 9024 5133
Ethics Reference Number:	22/LO/0885
IRAS Reference Number:	IRAS Project ID: 315388
Chief Investigator:	Augusto Azuara-Blanco Professor of Ophthalmology Centre for Public Health Queen's University Belfast Institute of Clinical Sciences (ICS-A), Grosvenor Road Belfast, BT12 6BA

PROTOCOL AUTHORISATION

Protocol Title	Study of technologies for the diagnosis of angle closure glaucoma
Protocol Acronym (if applicable)	ACE
Protocol Number	B22/08
Protocol Version Number/Date	Protocol Version V2.0 Final / Date: 19/07/2023
Protocol Amendments	**V1-V2 Key Changes** Section 6.1 has been updated to remove reference to specialized glaucoma training or expertise to match the skills of community optometrists. Section 8.1 now reads: A minimal dataset will be recorded on these patients which will include age, gender, ethnicity and partial postcode (with the exception of non recruited patients in Scotland), to determine if there are differences with those willing to participate.

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

AUGUSTO AZUARA-BLANCO		____ / ____ / ____
Chief Investigator Name	Signature	Date

CHRIS CARDWELL		____ / ____ / ____
Statistician	Signature	Date

Contents

LIST OF ABBREVIATIONS

Acronym	Full Wording
ACG	Angle Closure Glaucoma
AS-OCT	Anterior Segment Optical Coherence Tomography
BHSCT	Belfast Health and Social Care Trust
CI	Chief Investigator
CARF	Central Angiographic Resource Facility
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
EQ-5D-5L	EuroQol-5 Dimension-5 Level
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Eye Services
HRQOL	Health-Related Quality of Life
HTA	Health Technology Assessment
HSC	Health and Social Care
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LACD	Limbal Anterior Chamber Depth
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health Research
OAG	Open Angle Glaucoma
OCT	Optical Coherence Tomography
PI	Principal Investigator
PIL	Patient Information Leaflet
PPI	Patient and Public Involvement
QALY	Quality Adjusted Life Year
QUB	Queen's University Belfast
REC	Research Ethics Committee
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1 STUDY SUMMARY

Protocol title	Study of Technologies for the Diagnosis of Angle Closure glaucoma (ACE)
Health condition(s) or problem(s) studied	Glaucoma (angle-closure glaucoma)
Study Design	Prospective, multi-centre, cross-sectional diagnostic study.
Study Aim and Objectives	Primary aim: To evaluate the diagnostic performance of two non-contact tests compared to gonioscopy (reference standard) by an expert consultant ophthalmologist. Anterior segment optical coherence tomography (AS-OCT), will be interpreted by optometrists and photographers/imaging technicians and ophthalmologists. Limbal anterior chamber depth (LACD), will be interpreted by optometrists. Secondary aims: a) To explore alternative thresholds for determining test positivity; b) To evaluate the diagnostic performance of combinations of the tests; c) To evaluate the cost-effectiveness of adopting individual tests or a combination of tests in a triage assessment, compared with the current practice of gonioscopy by an ophthalmologist at hospital eye services.
Study Interventions	Health technologies being assessed: - AS-OCT interpreted by optometrists and photographers/imaging technicians and ophthalmologists - LACD interpreted by optometrists Reference standard: gonioscopy by an expert consultant ophthalmologist
Primary Outcome	The primary outcome measure is sensitivity and specificity of the new pathway to detect angle-closure
Secondary Outcomes	Positive/negative likelihood ratios, concordance, cost-effectiveness, proportion of patients requiring subsequent clinical assessment by ophthalmologist, proportion of patients unable to undergo tests and of tests of inadequate quality.
Key Inclusion and Exclusion Criteria	Inclusion Criteria: Adults (≥18 years) referred from community optometry to hospital eye services with suspected angle closure. Exclusion Criteria: Unable to provide informed consent.
Countries of Recruitment	United Kingdom
Study Setting	Specialist Hospital Eye Services (HES) in the UK
Target Sample Size	600 patients
Study Duration	24 months

2 STUDY TEAM

Chief Investigator	**Professor Augusto Azuara-Blanco** Professor of Ophthalmology Centre for Public Health Queens University Belfast ICS-A, Grosvenor Road, Belfast, BT12 6BA
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For full details of co-applicants and co-investigators please request by email from: ACE@nictu.hscni.net

3 BACKGROUND AND RATIONALE

Glaucoma is a chronic optic neuropathy and a leading cause of irreversible blindness [Bourne, Quartilho, Tham]. In the UK, more than 500,000 people have glaucoma, and 4000 new patients are registered each year with sight loss because of glaucoma. Many more people have glaucoma not severe enough to be registered, but severe enough to reduce vision and quality of life (e.g., loss of their driving licence).

Hospital eye services (HES) account for 8% of outpatient attendances to the NHS and glaucoma accounts for 25% of outpatient activity of hospital eye services, with more than 1M visits per year in England alone due to glaucoma [NICE glaucoma guideline NG81].
There are two types of glaucoma, according to the appearance of the drainage angle of the eye: open angle glaucoma (OAG), the most common, and angle closure glaucoma (ACG). In ACG, which is the subject of this study, the drainage angle is blocked, leading to acute or chronic elevation of intraocular pressure (IOP) and damage of the optic nerve.
ACG is less common but more severe than OAG and its prevalence increases with age [Bourne, Tham]. Acute angle closure is an uncommon but serious ocular emergency [Chua]. In an early stage of the disease angle closure can be treated with laser to reduce the risk of developing glaucoma and vision loss.

ACG is responsible for approximately 1 in 6 glaucomas in the UK [Azuara-Blanco; Day]. Previous studies have found that angle closure accounts for 10-20% of all referrals to glaucoma units. A recent survey (unpublished, 2020) among glaucoma specialists in Scotland found that 25% of all new glaucoma-related referrals were due to suspected angle closure.

The James Lind Alliance research priorities for glaucoma include two that we address in this study: “what can be done to improve early diagnosis of sight threatening glaucoma” and “how can glaucoma patients with a higher risk to progress rapidly be detected”.
According to ‘The Way Forward Project’, commissioned by the Royal College of Ophthalmologists, the number of people in the UK with glaucoma will rise by 44% from 2015 to 2035, as the population ages [The Way Forward project]. This is against a background that the NHS is already unable to meet the current demand for glaucoma care and some patients are going blind because of lack of capacity [Foot and McEwen].
In 2020, a Healthcare Safety Investigation Branch report (www.hsib.org.uk/investigations-cases/lack-timely-monitoring-patients-glaucoma/) found that:
• “There is inadequate HES capacity to meet the demand for glaucoma services. Current capacity can be maximised… by introducing new ways of working”.
• “The vast majority of suspected glaucoma referrals to HESs are from primary care optometrists. A significant proportion of the patients referred are subsequently found not to have glaucoma.”

A recent Cochrane review [Jindal] found sub-optimal quality evidence regarding the diagnostic performance of non-contact tests, AS-OCT and LACD. Pooled data showed that LACD had high sensitivity and a possibly sufficient specificity for case finding and performed as well as AS-OCT but the authors highlighted “There is still a need for high-quality studies to evaluate the performance of non-contact tests for angle assessment.” Our study will fill this gap and determine their potential in the diagnosis of angle closure.

4 STUDY AIM AND OBJECTIVES

Our hypothesis is that the non-contact tests for diagnosing angle closure will be accurate and will facilitate a safe and efficient pathway for patients with this condition.

Primary aim:
To evaluate the diagnostic performance of two non-contact tests compared to gonioscopy (reference standard) by an expert consultant ophthalmologist.

Anterior segment optical coherence tomography (AS-OCT), will be interpreted by optometrists and photographers/imaging technicians and ophthalmologists. Limbal anterior chamber depth (LACD), will be interpreted by optometrists.

Secondary aims:
a) To explore alternative thresholds for determining test positivity;
b) To evaluate the diagnostic performance of combinations of the tests;
c) To evaluate the cost-effectiveness of adopting individual tests or a combination of tests in a triage assessment, compared with the current practice of gonioscopy by an ophthalmologist at hospital eye services.

5 OUTCOME MEASURES

Primary outcome:
Sensitivity and specificity of the new pathway to detect angle-closure.

Secondary outcomes:
Positive/negative likelihood ratios, concordance, cost-effectiveness, proportion of patients requiring subsequent clinical assessment by ophthalmologist, proportion of patients unable to undergo tests and of tests of inadequate quality.

6 STUDY DESIGN

6.1 Study Design

This study will be a prospective, cross-sectional, multi-centre, diagnostic study of people referred to hospital eye services with suspected angle closure.

Sampling and data collection will be carried out prospectively. Consecutive eligible patients will be approached to take part in the study. Patients will receive the same reference standard (gonioscopy), provided by an expert masked to the tests being evaluated. Investigators interpreting the tests will be masked to the reference standard. Patients referred to hospital eye services with suspected angle closure will be approached and those who consent will undergo testing with the two non-contact technologies (index tests) on the same day. Each test will produce a diagnosis of ‘open angle’ or ‘closed angle’ or ‘indeterminate’. Patients will undergo AS-OCT and the image will be sent to a reading centre. The LACD will be performed by a hospital optometrist (masked to the AS-OCT and to the reference standard.) Each participant will subsequently be examined by a consultant ophthalmologist with glaucoma expertise (masked to the index test results) who will perform a gonioscopy examination to provide the reference standard. Masked optometrists, ophthalmologists and trained

photographers/imaging technicians will interpret AS-OCTs images provided by the reading centre at a different time.

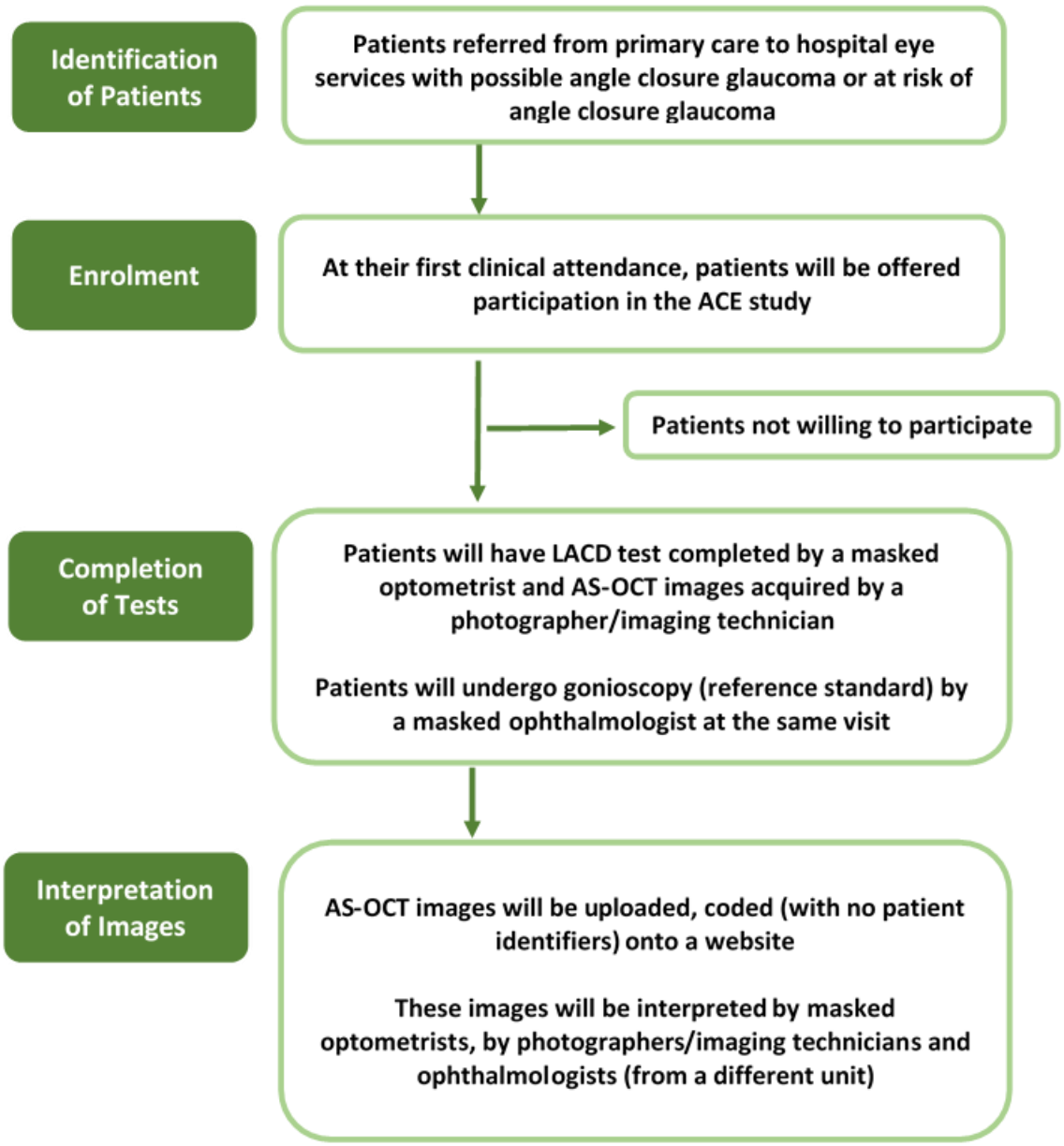
At the beginning of the study we will meet local clinicians and investigators to review and agree on the reference standard and interpretation of tests.

6.2 Study Setting

Hospital Eye Services (HES) in the UK.

6.3 Study Schematic Diagram

Figure 1: ACE Study Flowchart



6.4 End of Study

For the purposes of submitting the end of trial notification to the Sponsor and the Research Ethics Committee (REC), the end of trial will be considered to be when the database lock occurs for the final analysis. The trial will be stopped prematurely if:

- Mandated by the REC
- Mandated by the Sponsor (e.g. following recommendations from the Trial Steering Committee (TSC)
- Funding for the trial ceases

The REC that originally gave a favourable opinion of the trial will be notified in writing when the trial has been concluded or if it is terminated early.

7 PATIENT ELIGIBILITY

7.1 Eligibility Criteria

Patients will be screened for eligibility based on the inclusion and exclusion criteria outlined below. Eligibility will be confirmed by an ophthalmologist and documented on the case report form (CRF).

7.2 Inclusion criteria

Adults (≥18 years) referred from community optometry to hospital eye services with suspected angle closure.

7.3 Exclusion criteria

Unable to provide informed consent.

7.4 Co-enrolment guidelines

Patients enrolled in observational studies are potential candidates for ACE. Whether or not patients enrolled in ACE are also involved in other observational studies is at the Principal Investigator's (PI) discretion and should be considered when the burden on patients is not expected to be onerous.

8 PATIENT SCREENING, CONSENT AND RECRUITMENT

8.1 Screening Procedure

The NICTU will provide screening logs. The screening log will collect data on the patients meeting the eligibility criteria for the trial and recruited.

The screening log will also include data on patients meeting the eligibility criteria for the trial but not entered into the trial, including the reason for non-enrolment. A minimal dataset will be recorded on these patients which will include age, gender, ethnicity and partial postcode (with the exception of non recruited patients in Scotland), to determine if there are differences with those willing to participate. The PI or designee will be required to submit screening logs to the NICTU.

8.2 Informed Consent

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Eligible patients will only be included in the trial after written informed consent is obtained. Informed consent must be obtained prior to conducting any trial specific procedures and the process for obtaining informed consent must be documented in the patient's medical records (source documents will be reviewed at the time of on-site monitoring visits).

Informed Consent Forms (ICF) approved by the REC will be provided by the NICTU. The PI or designee is responsible for ensuring that informed consent for trial participation is given by each patient prior to any trial procedure being performed. This requires that the ICF be signed and personally dated by the patient prior to any trial procedures are undertaken. If no consent is given, a patient cannot be recruited into the trial. Two copies of the ICF must be signed and personally dated by the patient and the individual taking consent. A copy of the signed ICF will be filed in the patient's medical records, whilst the originals will be retained by the patient and by the PI in the Investigator Site File (ISF).

8.3 Withdrawal of Consent

As the study involves one research visit, it is not envisaged that patients will withdraw consent. If they were to withdraw consent once the images had been obtained and/or questionnaires being completed, then the images/questionnaires will not be used for the study. Withdrawal of consent will be recorded on the Case Report Form (CRF).

8.4 Selection of Ophthalmic Photographers / Imaging Technicians, Optometrists and Ophthalmologists

Currently in ophthalmic clinical practice ophthalmic photographers/imaging technicians obtain images and interpret them routinely, but make no decisions with regards to the care of patients.

For ACE the ophthalmic photographers/imaging technicians at each participating site will be selected as follows. First, local PIs will provide names of individuals they believe have experience obtaining and/or grading images of patients with glaucoma; these individuals will be asked to confirm their interest and willingness to participate in ACE.

Ophthalmic photographers/imaging technicians identified by the PIs, as explained above, will be asked to fill out questionnaires detailing their imaging experience as well as there experience of recognising features of glaucoma. Ophthalmic photographers/imaging technicians stating that they do not have experience will not be invited to take part in ACE.

In addition to the above, formal training will be provided to all ACE Ophthalmic photographers/imaging technicians prior to the initiation of the study.

Hospital optometrists and ophthalmologists are clinicians who make decisions on clinical diagnosis and treatment. A similar process as above will be used to select and train hospital optometrists and ophthalmologists to participate in ACE.

8.5 Recruitment

We are aiming to recruit 600 participants over 12 months from at least 12 sites. Site opening will be staggered but it is envisaged that each of the sites will recruit 50 to 60 patients i.e., approximately 5 patients per month per site. At the time of recruitment the patient will be allocated a unique trial identifier.

8.5.1 Patient Recruitment

Potential patients will be identified through referral letters from optometrists to hospital eye services. Potential patients with possible angle closure will be approached either before they come for their routine clinical appointment, by phone or via an invitation letter, or at the time they are in clinic for a routine review appointment (see study flow chart above).

When approached by phone, the potential patients will be informed about the study before they come to their hospital appointment; if willingness to participate is demonstrated, a patient information leaflet will be sent to them prior to the clinical appointment. Then, at their clinical appointment and if agreeable to participate, informed consent will be obtained and the patient will be recruited in the study while in clinic. If they are approached by letter, a letter of invitation to participate in the study and a patient information leaflet will be provided to the potential patient prior to their clinical appointment. Then, as above, when the patient comes to their clinical appointment, if willing to participate, they will be consented and enrolled in the study. Under the above circumstances, potential patients will have a minimum of 24 hours to decide whether or not they wish to participate in the study.

Potential patients may also be identified and approached at the time they attend the clinic for their routine appointment. In this case, information about the study will be given there and then, including a patient information leaflet. Under these circumstances, patients will be asked whether they wish to have time to think about their participation in the study once information has been provided to them and once they have had time to ask questions about it.
As from the patients perspective, ACE involves undertaking tests routinely used in clinical practice, and it is envisaged that patients will be able to determine, while in clinic, whether or not they wish to participate in the study and, if willing to be recruited on the same day, following informed consent, they will be recruited into the study.

The recruitment progress will be monitored by the Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC).

8.5.2 Pilot Study

Table 1 (below) presents a detailed breakdown of the progression criteria (red, amber, green) according to internal pilot recruitment outcomes. The total number of patients recruited is based on the recruitment rate and the number of sites open during the pilot period. The intention is to commence recruitment at 3 sites. An additional 3 sites will be opened every month, with at least 12 sites open and recruiting during months 4 to 6 of the internal pilot.

Table 1. Detail of internal pilot phase during the first 6 months of recruitment

	Red	Amber	Green
% Threshold	<50%	51-99%	100%
Recruitment rate/site/month	<2	2-3	4-5
Number of sites opened	<6	6-9	12
Total number of participants recruited	<122	122-238	240

9 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

9.1 Training

Prior to the initiation of the study, training will be provided to the investigators on the interpretation and grading of the tests (AS-OCT, LACD, gonioscopy). A web-based teaching module on AS-OCT images will be prepared for investigators and although hospital optometrists will be familiar with LACD, training will also be provided for this test to ensure consistency.

9.2 Schedule of Assessments

Patients will be required to attend one study visit (Baseline/Visit 1). At this visit, eligibility will be confirmed, consent obtained and all study procedures will be completed.

Baseline/Visit 1

Step 1
Confirmation of eligibility by an ophthalmologist.
Written patient informed consent obtained to participate in the ACE study.

Step 2
Patients will undergo the following tests:

- AS-OCT, by an ophthalmic photographer/imaging technician
- Limbal anterior chamber depth (LACD), by a hospital optometrist
- Gonioscopy, by an ophthalmologist glaucoma expert

Step 3
Patients will complete the EQ-5D-5L questionnaire.

Step 4
The patients' information obtained during the standard care pathway will be recorded in the CRF including details on:

- Demographics and postal code
- Relevant medical and ophthalmic history
- Best corrected visual Acuity
- Refractive error
- Intraocular pressure
- Details on the presence/absence of glaucomatous damage
- If there is glaucomatous damage the MD value of the visual field test and reliability (percentage of false positives) will be recorded, if available.
- Any significant ocular co-morbidity

All ocular data will be obtained for both eyes separately.

Step 5
AS-OCT scans will be anonymised and transferred to QUB reading centre where they will be uploaded to an electronic website developed for the ACE study. The reading centre will then create folders and make these anonymised images accessible to the optometrists, ophthalmic photographers/imaging technicians and ophthalmologists.

Step 6
AS-OCT images will be interpreted by optometrists, ophthalmic photographers/technicians and ophthalmologists, masked to the reference standard (gonioscopy by ophthalmologists).

Optometrists, ophthalmic photographers/imaging technicians and ophthalmologists reading the images will not evaluate images of patients from their own institution to assure masking (see below). Once the images are read, the optometrists, ophthalmic photographers/imaging technicians and ophthalmologists will determine:

- whether there is angle closure or not
- whether they are unsure and reasons (e.g., poor image quality)

The optometrists, ophthalmic photographers/imaging technicians and ophthalmologists will record this information in the appropriate CRF.

9.3 Masking

The optometrists performing the LACD test and the optometrists, ophthalmic photographers/imaging technicians and ophthalmologists interpreting patients' images will be masked to the reference standard.

Ophthalmologists performing the gonioscopic evaluation will also be masked to the optometrist LACD test result and to the AS-OCT test, including the findings/decisions made by the optometrists, ophthalmic photographers/imaging technicians and ophthalmologists (who will be reviewing the images at a later date).

10 DATA COLLECTION AND DATA MANAGEMENT

10.1 Data Quality

Data integrity and study credibility depend on factors such as ensuring adherence to the study protocol and using quality control measures to establish and maintain high standards for data quality.

The Chief Investigator (CI) and NICTU will provide training to site staff on trial processes and procedures, including the completion of the CRF and data collection.

Monitoring during the trial will check the accuracy of entries on CRF's against the source documents, the adherence to the protocol, procedures and GCP, as outlined in the trial monitoring plan.

Quality control is implemented by the NICTU in the form of Standard Operating Procedures (SOPs), which are defined to encompass aspects of the clinical data management process, and to ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database.

10.2 Data Collection

To ensure accurate, complete and reliable data are collected, the NICTU will provide training to site staff either through investigator meetings or site initiation visits.

All data for an individual patient will be collected by the PI or designee and recorded in source documents and/or the CRF for the study. The EQ-5D-5L questionnaires will be completed by the patient. Patient identification on the CRF and questionnaires will be through their unique trial identifier, allocated at the time of recruitment.

Case report forms and questionnaires are to be submitted to the NICTU as per the CRF submission schedule.

In addition to the data specified in the sections above, the following information will be obtained and recorded in the appropriate CRF:

1) The time the patient spent with a photographer/imaging technician to complete the AS-OCT images, the time the patient spent with the optometrist to complete the LACD test, and time the patient spent with the ophthalmologist to complete the gonioscopic. This information will be obtained in a consecutive group of patients until saturation is reached.

2) The time required by the optometrist, the ophthalmic photographer/imaging technician and the ophthalmologist to interpret the images and to determine whether there is angle closure or not.

3) Scores obtained in the health related quality of life questionnaire (EQ-5D-5L) filled in by patients and collected at the study visit, which will provide utility data for different health states.

4) Resource use data will be collected to explore the costs of delivering the standard care pathway and the new proposed triage pathway and to find the key cost drivers.

10.3 Data Management

Study data, including the CRF and questionnaires, will be entered onto the Clinical Trial Database (MACRO) by NICTU personnel and processed as per NICTU SOPs and the study specific Data Management Plan (DMP). Data queries will be generated for site staff as required to clarify data or request missing information. The designated site staff will be required to respond to these queries and any amended information will then be entered in the study database.

Ophthalmic images will be anonymised and uploaded electronically at a specifically designed ACE imaging website. This website will be established at the Queen's University reading centre where images will then be made accessible in specific folders to the optometrists, photographers/imaging technicians and ophthalmologists as stated above, using a username/password.

All essential documentation and trial records will be stored securely and access will be restricted to authorised personnel. All study documentation (including participant medical records) and data will be archived as per regulatory requirements and those responsible for archiving will be included in the agreements that will be put in place between the Sponsor and each organisation.

11 STATISTICAL CONSIDERATIONS

11.1 Sample size

We will recruit 600 individuals who have been referred with suspected angle closure from primary care (community optometry). According to our feasibility work, we estimate that approximately half of these 600 individuals will have angle closure and that half will not have it. Angle closure is typically a bilateral disease, and, thus, the majority of individuals will have similar angle characteristics in both eyes but, in the rare case of an individual having angle closure in only one eye, they will be considered to have angle closure.

Previous studies have shown that using a cut off to capture 90% sensitivity corresponds to a specificity of around 75% with AS-OCT [Baskaran] or with LACD [Dabasia]. Therefore the study will have a 95% probability of detecting the true sensitivity of either test to within ±3.5% (i.e. the confidence interval for the true sensitivity would be approximately 7 percentage points in width), based upon a sensitivity of 90%. The study would also have a 95% probability of detecting the true specificity of either test to within ±5% (i.e., the confidence interval for the true specificity would be 10% in width), assuming a true specificity of 75%. These sample size are conservative because they are based on using only one eye per person, while in practice, as described below, information from both eyes will be used.

11.2 Data analysis

Sensitivity and specificity will be calculated using data from both eyes, confidence intervals will then be calculated using variance inflation factors to account for the lack of independence of each eye in the same person (using the svy function in STATA) [Genders]. A sensitivity analysis will be conducted calculating test performance measures using a multi-level logistic regression model, with eyes nested within person, and person as a random effect. We will extend this model to include site and operator of the various tests to explore the impact these have on the width of the confidence intervals for sensitivity and specificity.

Initially, a cut-off will be selected to obtain a sensitivity of 90% and the resulting specificity will be determined. We will explore the diagnostic accuracy of combining both tests (LACD and AS-OCT), and of using different thresholds for a positive result. We will also compare the diagnostic accuracy of AS-OCT images interpreted by optometrists, photographers/imaging technicians and ophthalmologists.

11.3 Health economics analysis

We will evaluate LACD and AS-OCT as part of a triage test to diagnose angle closure in patients referred to hospital eye services with possible glaucoma. To evaluate their diagnostic performance, individuals will be assessed using LACD by optometrists and AS-OCT by optometrists, photographers/imaging technicians and ophthalmologists as index tests and using gonioscopy by hospital consultants as the reference standard. Disagreements will be due to either missing cases that will delay the diagnosis (suboptimal sensitivity) or false positives that would lead to unnecessary referrals (suboptimal specificity).

We propose to use a Markov model to assess the longer term costs and effects of alternate tests. We propose to run this over an expected life time of lifetime horizon. We propose to adapt a model developed and published by members of the study team (DOI:https://doi.org/10.1016/S2214-109X(19)30201-3). The model comprises 6 states – normal vision, suspected glaucoma, glaucoma without blindness, glaucoma-related unilateral blindness, glaucoma-related bilateral blindness and dead. Accurate testing may delay

progression, through earlier identification and treatment. Transition probabilities, costs (beyond those observed in the trial) and outcomes associated with the various states will be taken from the literature, supplemented where appropriate with expert opinion and uncertainty explored using sensitivity analyses.

Three tests will be used in the study: gonioscopy as gold standard; LACD; AS-OCT and concordant LACD/AS-OCT results as triage tests. Three comparison groups will be created based on data collected: (A) comparison of gonioscopy versus LACD only; (B) comparison of gonioscopy versus AS-OCT only; and (C) comparison of gonioscopy versus LACD and AS-OCT concordant responses. The proportion of accurate diagnoses across modalities using gonioscopy as reference standard will provide a measure of effect and the differences in these will provide a measure of the incremental effect.

An NHS healthcare perspective will be used to evaluate cost effectiveness. For the cost-utility analysis, EQ5D5L data will also be gathered at baseline and provide the “starting point” against which subsequent decrements in health-related quality of life (HRQOL) arising from deteriorating vision will be compared. The trajectory of HRQOL after “normal vision” will be based on estimates from a systematic review of the literature for the health states specified in the Markov model. As HRQOL will vary based on age and time spent in a given state, adjustments for these will be made to reflect changes associated with cohort aging over repeated cycles of the model up to termination (death) for all members.

A similar approach will be adopted with respect to costs. In both cases a survey of experts will be used to address gaps in estimates and one-way and probabilistic sensitivity analysis will be used to explore uncertainty in such estimates. It is anticipated that cycle length will be one year.

The alternative test arrangements will have differential costs associated with them – for example, gonioscopy for all referrals likely being more expensive than those triaged based on LACD only or LACD only being less expensive than those triaged on a combination of LACD and AS-OCT. They may also have differential effects in terms of identification for further investigation and treatment. While we anticipate false negatives/positives will be identified quickly without adverse health effects, the model will allow us to examine differential costs over a hypothetical lifetime for the cohort as well as to explore scenarios in which delayed identification does result in adverse effects.

Incremental QALYs and costs will be estimated for cohorts across triage and gonioscopy tests and expressed in terms of cost per QALY gain. Uncertainty around the threshold willingness to pay for a QALY will be explored using cost-effectiveness acceptability curves. Costs and outcomes will be discounted at 3.5% per annum as per current NICE guidance (https://www.nice.org.uk/process/pmg6/chapter/assessing-cost-effectiveness). Sub-group analyses will examine potential difference in ICERs across groups differentiated by age at screening sex and ethnic group. Reporting of results will adhere to revised-CHEERS checklist (Husereau et al. Value Health 2022, 25, 3 – 9) and ISPOR modelling good practice.

12 METHODS: MONITORING

12.1 Data Monitoring and Data Access

Prior to commencement of the study, the PI will give permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Consent from patients for direct access to their data will also be obtained. Patients’ confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.2 Monitoring Arrangements

The NICTU will be responsible for monitoring the study. The frequency and type of monitoring (on site or remote) will be detailed in the monitoring plan and agreed by the trial Sponsor.

Before the trial starts at a participating site, training will take place to ensure that site staff are fully aware of the trial protocol and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place. Monitoring during the trial will check the accuracy of data entered into the CRF against source documents, adherence to the protocol, procedures and GCP, and the progress of patient recruitment.
The PI or designee will ensure that access to all trial related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan.

13 TRIAL COMMITTEES

13.1 Trial Management Arrangements

The CI will have overall responsibility for the conduct of the study. The NICTU will undertake trial management including all clinical trial applications (Ethics and Research Governance), site initiation and training, monitoring, and reports to ethics, Sponsor and Funder. The trial co-ordinator will be responsible on a day to day basis for overseeing and co-ordinating the work of the multi-disciplinary trial team, and will be the main contact between the trial team and other parties involved. Before the trial starts, site training will take place to ensure that all relevant essential documents and trial supplies are in place and that site staff are fully aware of the trial protocol and procedures. The NICTU will assist and facilitate in the setting up and co-ordination of the trial committees including the TMG, TSC and DMEC.

13.2 Trial Management Group (TMG)

A TMG will be established and Chaired by the CI. The TMG will include representation from the NICTU and other investigators or collaborators who are involved in the study and provide trial specific expertise (e.g. trial statistician, health economist). This group will have responsibility for the day to day operational management of the trial. Regular meetings of the TMG will be held to discuss and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the Trial Master File.

A TMG Charter will be drawn up to detail the terms of reference of the TMG, including roles and responsibilities of the members.

13.3 Trial Steering Committee (TSC)

The conduct of the trial will be overseen by an independent TSC. The TSC is a group that act as the oversight body for the trial on behalf of the Sponsor and Funder. Throughout the study, the TSC will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of patients enrolled in the study.

The TSC will include an independent statistician, a health economist, at least two independent clinicians and a patient representative. The CI will attend the TSC meetings. Representatives of the Sponsor, Funder and the NICTU may attend TSC meetings as observers and at the discretion of the Chair. The TSC Charter will outline the terms of reference of the TSC including roles and responsibilities, membership, organisation of meetings (including frequency), reporting, decision making and the relationship with the other trial committees.

13.4 Data Monitoring and Ethics Committee (DMEC)

The main role of the DMEC will be to monitor the trial data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue

The DMEC will include a researcher, a statistician and a clinician. Attendance at DMEC meetings by non-members will be at the discretion of the Chair. The primary DMEC reporting line will be via the Chair to the TSC. The DMEC Charter will outline the terms of reference of the DMEC including roles and responsibilities, membership, organisation of meetings (including frequency), reporting, decision making and the relationship with the other trial committees.

13.5 Patient and Public Involvement (PPI) Group

The PPI co-applicants will be supported to convene a PPI Group that will actively contribute and advise on all patient- and public-facing documentation, including promotional patient information leaflets, informed consent forms and plain language summaries. They will also be involved in dissemination of the study's results to patients and the public. The PPI group will meet during the development phase, at the end of the internal pilot phase (when the progression criteria are being considered) and at the end of the study.

14 REGULATIONS, ETHICS AND GOVERNANCE

The study will comply with the principles of GCP, and the requirements and standards set out in the UK policy framework for health and social care research.

14.1 Sponsorship

Queen's University Belfast (QUB) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the study. Separate agreements will be put in place between the Sponsor and each organisation who will undertake Sponsor delegated duties in relation to the management of the study.

14.2 Funding

Funding was obtained from the National Institute of Health Research (NIHR) Health Technology Assessment Programme (HTA). Project ID: HTA NIHR134593. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

14.3 Indemnity

QUB as Sponsor will provide indemnity for the management and design of the study. QUB will provide indemnity for negligent and non-negligent harms caused to patients by the design of the research protocol. The NHS/HSC indemnity scheme will apply with respect to clinical conduct and clinical negligence.

14.4 Competing Interests

The research costs are funded by NIHR HTA Programme. The CI and members of the TMG have no financial or non-financial competing interests and the members of the TSC and DMEC

will be asked to confirm that they have no conflict of interest. In the event that a TSC or DMEC member reports a conflict of interest, advice will be sought from the Sponsor.

14.5 Ethical Approvals

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee.

14.6 Good Clinical Practice

The study will be carried out in accordance with the principles of the ICH-GCP guidelines (www.ich.org). All members of the trial team will be required to have completed GCP training.

14.7 Protocol Compliance

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the study process. Any deviations from the protocol will be fully documented on the protocol deviation form in the CRF.

A serious breach is defined as a deviation from the study protocol or GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the patients in the trial; or
(b) the scientific value of the trial

The PI or designee is responsible for ensuring that serious breaches are reported directly to the NICTU within one working day of becoming aware of the breach, using the dedicated email address (clinicaltrials@nictu.hscni.net). The NICTU will notify the CI and Sponsor immediately to ensure adherence to the reporting requirements to REC where a serious breach has occurred.

Protocol compliance will be monitored by the NICTU who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRFs, patient consent) is being completed appropriately.

14.8 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval or favourable opinion by the Research Ethics Committee (REC). Changes to the protocol may require ethics committee approval or favourable opinion prior to implementation. The NICTU in collaboration with the sponsor will submit all protocol modifications to the REC for review in accordance with the governing regulations.

14.9 Patient Confidentiality

In order to maintain confidentiality, all CRFs, questionnaires, study reports and communication regarding the study will identify the patients by their assigned unique trial identifier only. Computers where information will be stored will be password protected. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.10 Record Retention

The PI will be provided with an ISF by the NICTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The TMF will be held by the NICTU within

the BHSCT and the essential documents that make up the file will be listed in a SOP. On completion of the trial, the TMF and study data will be archived by the NICTU according to the applicable regulatory requirements and as required by the Sponsor (QUB). Following confirmation from the Sponsor the NICTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the NICTU and Sponsor.

15 DISSEMINATION/PUBLICATIONS

15.1 Study Publications

It is anticipated that the study findings will be published in national and international peer review journals and these articles will be led by the CI. This will secure a searchable compendium of these publications and make the results readily accessible to the public and health care professionals. In addition, study findings may be presented at both national and international meetings and to appropriate patient groups.

A report containing the methodology and results of this diagnostic study will be published as a Health Technology Assessment monograph, freely accessible via the NIHR HTA webpage. The Royal College of Ophthalmologist will be contacted once the study is completed to allow the trial's findings to be incorporated in future glaucoma guidelines.

15.2 Authorship Policy

Authorship will be determined according to the internationally agreed criteria for authorship www.icmje.org.

15.3 Trial Registration

The trial will be registered with ISCTRN.

15.4 Data Sharing Statement

Requests for data sharing will be reviewed on a case by case basis by the CI and TMG. The study will comply with the good practice principles for sharing individual participant data from publicly funded clinical trials and data sharing will be undertaken in accordance with the required regulatory requirements.

15.5 Data Access

Following the publication of the primary and secondary outcomes, there may be scope to conduct additional analyses on the data collected. In such instances, formal requests for data will need to be made in writing to the CI who will discuss this with the TMG and obtain approval from the Sponsor. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission. Authorship will need to take the format of "[name] on behalf of the ACE Clinical Trial Group" or something similar, which will be agreed by the TMG.

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