

NIHR HTA Programme

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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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Comparative study of new imaging technologies for the diagnosis of glaucoma: Protocol Approved by the Ethics Committee

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Other participants: Professor Colm O'Brien (Dublin, Study Steering Committee Chair), and David Wright (patient representative), Anja Tuulonen (independent steering committee member), Anthony King (independent steering committee member)

ACRONYMN: GATE (Glaucoma Automated Tests Evaluation)

INTRODUCTION

Approximately 4000 people are registered either blind or partially sighted each year because of glaucoma in the UK. Many more people have glaucoma not severe enough to be registered, but severe enough to reduce vision and quality of life.

Diagnosis of glaucoma is challenging for health professionals and many people are incorrectly diagnosed as having glaucoma by community optometrists. In fact, only 20-30% of those referred from optometric services have glaucoma and 45% of patients are discharged after their first visit. Secondary care services are very busy (accounting for nearly 10% of all outpatient attendances to the NHS) and glaucoma is a major part of the workload of any eye unit. The referral of so many healthy subjects (less than 1/3 of referrals) is a waste of resources and causes unnecessary worry and distress to the patient. New diagnostic tests are available and are easy to perform. They are based on imaging the posterior part (fundus) of the eye where glaucoma damage can be observed. However, how well such tests perform and which is the best test to use is uncertain. This project will evaluate the performance of three new such tests to prioritise patients referred for possible glaucoma.

If one or more of the tests prove to be sufficiently accurate and easy to perform, the ophthalmologists would have more time and resources to treat patients with eye diseases.

AIM To compare directly the diagnostic performance of three automated imaging technologies within patients referred to secondary care with possible glaucoma and to explore patient test preferences.

METHODS

Study design – A within patient multi-centre comparative study of the diagnostic performance of three automated imaging technologies for glaucoma diagnosis.

The tests – 1) HRT-III: Confocal laser scanning imaging technology, employed by the Heidelberg Retina Tomograph exploits the principle of confocal laser scanning to allow quantitative structural information of the optic disc anatomy. 2) GDx-ECC: Scanning laser Polarimetry measures the retinal nerve fibre layer (RNFL) thickness. It is based on the birefringent properties of RNFL. 3) SD-OCT: Spectral Domain Optical Coherence Tomography is an optical imaging technique capable of providing high resolution, cross-sectional, imaging retina and quantifies the thickness of the RNFL. The Heidelberg Spectralis will be used in this study.

Inclusion and exclusion criteria

Inclusion criteria: Adult patients age 18 and over referred from community optometrists or General Practitioner to hospital eye services with glaucoma, or suspected glaucoma, including those with ocular hypertension, with or without associated ocular co-morbidity

Exclusion criteria: Patients referred to hospital eye services because of other ocular disease; children; patients who cannot give informed consent, patients already diagnosed with glaucoma in secondary care.

Sample and recruitment

Information about this study will be sent by post to eligible patients. The research nurse will discuss the study with the patient when they come to the clinic and will then take them through the consent process. Patients who agree to participate and sign the consent form will be enrolled. Of those patients who do not wish to participate, age and gender information will be collected.

Procedure

1. Each consented participant will undergo testing with the three technologies in both eyes. Each test produces a diagnosis of glaucoma (yes/no) without observer input. The order of testing will be randomly selected for each participant using a sheet with the randomisation order.
2. The research nurse will a) download the results to disks to be stored locally and sent to Aberdeen at the end of the project, ensuring all identifiers are removed, and b) print out the results of each test from the machines, remove the patient identifiers from the print out and write on the designated study number.
3. The participant will be asked to grade the tests in order of preference, using a standard form (see attached)
4. The participants will be examined by an experienced glaucoma clinician who will perform a comprehensive examination including intraocular pressure (IOP) measurement and biomicroscopic slit lamp examination of the optic nerve (with pupil dilated) and visual field testing (with Humphrey SITA 24-2 strategy) and provide the reference standard masked to the results of the imaging technologies. The clinician will complete a clinical data collection form.
5. The research nurse will collate the results for each participant including a copy of the VF test, complete forms for each participant, upload the information into the webpage, and post to the coordinating centre in Aberdeen. Information to be included in the webpage includes demographics (including non-participants), refraction (any method), patient preference, need for pupil dilation, and visual field indices MD and VFI.

Data handling - Confidentiality will be maintained for all participants. All data collection sheets will have a unique study number and access to the data will be restricted to the study team.

The study data will be stored securely for a minimum of 10 years after study completion by the co-ordinating office at the University of Aberdeen (in line with current MRC guidelines).

Data analysis –

Primary diagnostic performance outcomes: sensitivity, specificity of the three imaging technologies HRT III (GPS and MRA output), GDx-ECC, and OCT will be compared using McNemar's test at the 5% significance level. Corresponding 95% confidence intervals for the paired difference will also be generated. For the primary analysis, the cut-off values for a positive diagnosis will be the respective manufacturer's recommended level. However, possible threshold effects will also be investigated in the study by varying the respective cut-off. The area under the ROC curve will also be formally compared between technologies.

Secondary diagnostic performance outcomes: ROC curves (thresholds varied for test positivity), diagnostic odds ratio, likelihood ratio, proportion of indeterminate tests, patient preference for test.

Primary and secondary diagnostic measures (area under ROC curve, likelihood ratios and diagnostic odds ratio) will be presented for each technology with appropriate 95% confidence intervals. We shall also measure the proportion of tests that are indeterminate. All analyses will follow a patient-based (referral eye) approach. For referrals where bilateral disease is suspected, a study eye will be selected at random at the analysis stage. Additionally, the level of diagnostic performance across the disease spectrum (as defined by the reference standard) will be explored.

The overall diagnostic performance of combinations of these three technologies will also be evaluated, and their relative performance. The diagnostic performance of the tests (and corresponding combinations) will also be assessed according to the spectrum of glaucoma (mild, moderate, severe), as defined by the specialist ophthalmologist. Additionally, the impact of introducing a measure of IOP into the triage test will be explored.

A further analysis will consider the impact on diagnostic performance of using combinations of these technologies under three approaches: both positive, either positive or by generating a prognostic rule using multivariable logistic regression model. Furthermore, the impact of using these technologies in tandem with a measure of IOP to identify suspected cases of glaucoma and/or ocular hypertension for referral, as might occur in a clinic setting, will also be examined. For this analysis,

disease will be defined as the presence of either condition. The analysis would follow the above comparative approach.

Economic outcomes: costs of providing the tests (initially retrieved from the four study sites), costs (of testing and subsequent management), QALYs, and incremental cost per QALY.

Economic evaluation

Modelling will be used to determine which test or combination of tests would be effective and cost-effective compared with current practice. The results of the modelling will be diagnostic performance. We will develop a new economic model which will estimate the costs and outcomes of diagnosing glaucoma in secondary care. We will consider the use of the diagnostic tests used alone or in combination in secondary care. The model will compare the diagnostic performance of the tests and effect of longer term outcomes (e.g. Quality Adjusted Life Years – QALYs). The costs of current management alternative diagnostic pathways will depend upon the findings of the diagnostic performance analyses, the literature and advice from the project team. Costs and outcomes following diagnosis (both for those with true and false diagnoses) will be derived from an updated version of an existing economic model. The perspective of the economic analysis will be that of the NHS. The results of the model will be presented in terms of (i) costs (of testing) and diagnostic outcomes, (ii) costs (of testing and subsequent management), (iii) QALYs and incremental cost per QALY. The results will be presented as point estimates and cost-effectiveness acceptability curves (cost per QALY data). Deterministic sensitivity analysis will be combined with probabilistic sensitivity analysis to explore different types of uncertainty (e.g. impact of the scale of the service on cost-effectiveness).

Sample size considerations

The sample size calculation and analysis are based on standard McNemar diagnostic accuracy study methods. The sensitivity and specificity of each of the automated tests will be compared. A 5% significance level based upon a 2-sided test was used in the sample size calculations. A study of 897 individuals would have 90% power to detect a difference in accuracy of 9% for the primary outcome of diagnosis of glaucoma. This is based upon conservative assumptions of a probability of disagreement of 0.18 (maximum level possible), a glaucoma rate of 25% (as seen

in similar populations) and a sensitivity of 86% as found in a systematic review for HRT II. Given this sample size, there would also be 80% power for detecting a 6% difference in accuracy should the sensitivity be 93% (the current best estimate from meta analyses of high quality diagnostic studies). For specificity, we would have over 90% power to detect a 5% difference. Based upon current available evidence, a rate of 6% indeterminacy of tests results was assumed which increased the sample size to 954 in total. A sample of this size would be of sufficient size for other measures of diagnostic performance (e.g. the sensitivity and specificity of individual technologies would be estimated to 95% confidence interval of width 10% and 5% respectively).

Dissemination

Participants will be offered a summary of the study findings once the study is complete. Papers will be submitted for publication to peer reviewed journals and submitted for oral/poster presentation at both international and national conferences.

We are also required to report these findings to the NIHR HTA who are funding this study.

Timelines

Pre-funding

Ethics

Start date

1 December 2010

October 22

First steering group meeting

Month 1-3

Study set-up, authorisations, protocol finalised

Month 4-32

Patient recruitment (from March 2011)

Month 12

Second steering group meeting

Month 19

Third steering group meeting

Month 28

Data cleaning and preliminary analysis

Month 32

Close down centre study processes

Month 30-33

Final analysis and reporting