Health Technology Assessment Programme

National Institute for Health Research

NIHR HTA Programme

22 November 2013

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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Full Protocol Title

Assessing the Effectiveness of Imaging Technology to Rapidly Detect Disease Progression in Glaucoma: 'stable data' collection

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Funding

Research funded by the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) Programme: *Rapid Trials to Inform Clinical Decision Making in the NHS* (£327,458.80). A summary of the research costs covered by the NIHR is shown below.

PROJECT FINANCIALS SUMMARY

Research Costs Requested from Funder

	Direct costs	Indirect costs	Total costs	% Costs paid by NIHR	Amount requested
Total Higher Education Institution Costs	198,665.00	129,651.00	328,316.00	80%	262,652.80
Total NHS Costs	64,806.00		64,806.00	100%	64,806.00
Total Commercial Costs			.00	100%	.00
Total Other Partnership Organisation Costs			.00	100%	.00

Total Research Costs Requested from Funder	**£327,458.80**

Study site

Clinical Research Facility,
Moorfields Eye Hospital,
162 City Road,
London, EC1V 2PD.

Signature

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Prof. David Garway-Heath

Summary of Research

Glaucoma is the leading cause of irreversible blindness worldwide. (1)(1)(1)Early detection is important for blindness prevention, and regular monitoring for deterioration ('progression') in vision is a fundamental aspect of glaucoma management.

Glaucoma management aims to preserve the patient's vision. Tests of vision, such as the visual field (VF) test, are, therefore, of considerable clinical importance. VF testing (also known as perimetry) aims to locate damaged areas in a patient's field of vision using an automated machine that systematically measures the patient's ability to identify the presence of a small disc of light at different locations in their VF. Perimetry, however, poses a major challenge because VF measurements are very variable, which necessitates frequent monitoring and/or a long period of time to accurately detect true disease deterioration ('progression'). The requirement for frequent VF tests over extended periods of time results in delayed identification of vision loss and is a burden to patients and the NHS. In terms of clinical trials, VF variability results in the requirement for large numbers of patients over long durations. This causes a delay in bringing new treatments to patient benefit and trials become prohibitively expensive with a consequence that potentially beneficial treatments may not be evaluated.

Glaucoma also causes structural damage to the eye. Nerve cells in the retina (retinal ganglion cells) transmit light sensitivity information to the brain through fibres which form a layer on the retinal surface, known as the retinal nerve fibre layer (RNFL). These fibres collect together at the optic nerve head (ONH) forming the neural rim of the ONH (see Figure 1). It is these nerve cells and fibres that are damaged in glaucoma. The optic nerve and neural rim can be examined using automated **imaging technology** to quantify the degree of structural damage. However, currently, glaucoma is identified and monitored in the clinic using either structural *or* VF change, with integration of information gained from either being done subjectively by the clinician.

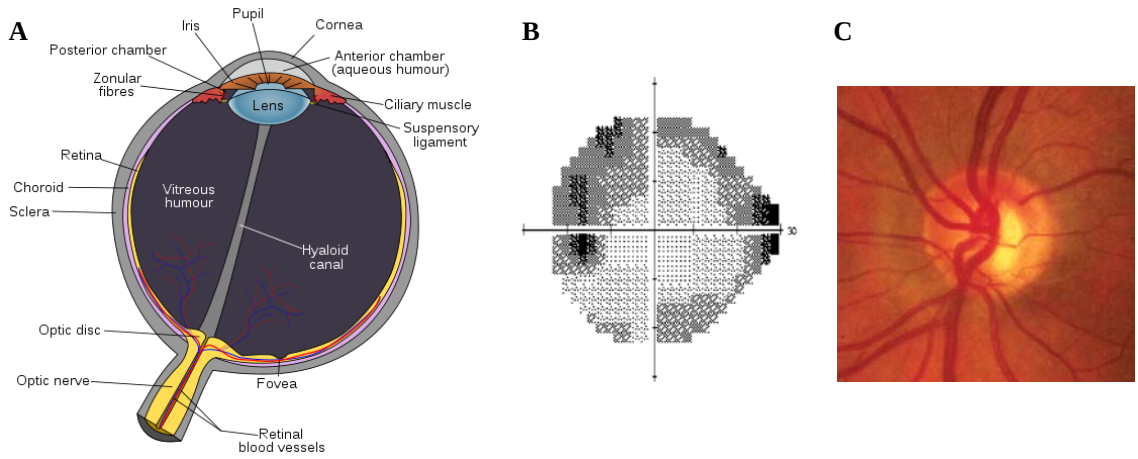

Figure 1. A: Schematic of the eye and optic nerve. B: Visual field greyscale from Standard Automated Perimetry. C: Damaged optic nerve from a glaucoma patient.

Optical coherence tomography (OCT) is a modern three-dimensional imaging technology with ultrahigh spatial resolution even in highly scattering media; it is similar to ultrasound, but uses 820nm wavelength light, instead of sound, to image tissue. This beam of light is directed into tissue and reflections coming from different layers of the tissue are received by a detector. OCT provides quantitative measurements of both the ONH and the RNFL, which progressively thins as vision is lost in glaucoma (see Figure 2).

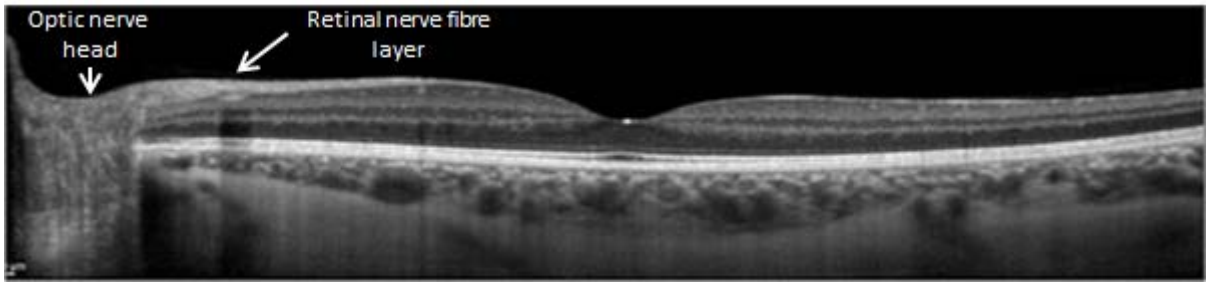

Figure 2. Cross-sectional optical coherence tomography (OCT) image of retinal layers.

Numerous publications support the ability of OCT to identify glaucoma deterioration but its potential to facilitate glaucoma management is unrealised, because the evidence base for the use of OCT images, statistical techniques, and software tools for handling the data in conjunction with VF data are not yet available to the clinician.

Because the sources of measurement variability for VF tests and images are different, the mathematical/statistical 'addition' of VF *and* imaging data would mitigate variability and thereby increase the signal-to-noise ratio of these measurements. Consequently, an improved signal-to-noise ratio would facilitate the identification of true deterioration in vision, enabling more rapid detection of disease worsening.

In this research, we will assess the extent to which OCT imaging technology improves sensitivity, and reduces the time required, to identify glaucoma deterioration in both clinical practice and clinical trials. We will provide the evidence base for combined analysis of images and VFs, statistical tools and software to jointly analyse OCT information with VFs.

To develop the statistical techniques, evaluate their application in clinical data, and their impact on clinical trial design, we will investigate data already acquired from a large cohort of patients with glaucoma from the UK Glaucoma Treatment Study (UKGTS) together with **newly-acquired data from a 'Stable Glaucoma' Cohort** to act as a reference set; see Section "**Research Plan / Methods**" below. The UKGTS data will be used to determine the *sensitivity* of the monitoring approaches (VF-only vs VF +OCT). The 'Stable Glaucoma' Cohort, collected under this protocol, will be used to determine the *specificity* of the monitoring approaches (VF-only vs VF +OCT).

In the UKGTS, 516 patients were recruited to be seen 11 times over 24 months, with VF and imaging tests clustered at the beginning and end of the observation period. The primary trial endpoint was a change-from-baseline of VF measurements alone, which is standard in clinical practice and trials. However, OCT imaging data were also collected. Both OCT and VF data are available in 441 patients.

The benefit of this new approach to patients and the NHS of combining VF and OCT data will be more timely and reliable identification of VF loss, thus reducing the frequency of patient visits and testing, with consequently improved clinical outcomes. This approach will also enable the reduction of study population sizes and study duration in clinical trials, thus allowing a greater number of new treatments to be assessed and brought to patients more rapidly.

Aims and objectives

The 'Stable Glaucoma' Cohort, collected under this protocol, will be used to determine the *specificity* of the monitoring approaches and statistical techniques (VF-only vs VF +OCT).

Research Plan / Methods

Design

The recruitment criteria and number of VF and OCT tests for the 'Stable Glaucoma' Cohort are based on the UKGTS clinical trial. In the UKGTS, patients were monitored with VF testing, quantitative imaging, optic disc photography and tonometry at 11 visits over 24 months.
All tests administered are non-invasive standard clinical tests.
80 patients will be recruited over a period of 18 months and tested weekly for 10 weeks each.

Prospective Data Collection: 'Stable glaucoma' cohort
We will monitor 80 glaucoma patients with VF tests and OCT imaging, approximately once a week for 10 consecutive weeks; this time period is too short for notable deterioration to have occurred. At the baseline visit, patients will receive 2 VF tests and 2 sets of OCT images will be taken (to mimic the UKGTS protocol); at subsequent visits only one VF test and one set of OCT images will be carried out. Thus, in total, 11 observations will be available for each test; this closely mimics the testing strategy in the UKGTS. These data will be used to establish the specificity of the Index and Reference tests, i.e., the percentage of stable (non-deteriorating) patients who are correctly identified as not deteriorating.
Subjects will be matched to the demographics and disease spectrum of the UKGTS cohort. Recruitment of these patients will be based on the diagnosis of glaucoma. Patient recruitment and all new data collection will be undertaken at the Research and Treatment Centre of the National Institute for Health Research (NIHR) Biomedical Research Centre, at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology. STARD guidelines will be followed.

Written information will be provided with no potential subject being coerced into participation. Potential participants will be given at least 24 hours to decide whether to take part in the study. If the individual chooses to participate he/she will give written consent to the investigator. Alternatively the volunteer may contact the chief investigator directly for further information on the study and/or request an appointment.

Inclusion Criteria:

- Open angle glaucoma (OAG; including primary OAG, normal tension glaucoma and pseudoexfoliation glaucoma) in either eye
- Age over 18 years
- Snellen visual acuity equal to or better than 6/12
- Able to give informed consent and attend at the required frequency for the duration of the study.

Exclusion criteria:

- Visual field loss worse than -16 dB or paracentral points with sensitivity < 10dB in both the upper and lower hemifields in either eye
- IOP > 30mmHg
- Unable to perform reliable visual field testing (false positive rate > 15%)
- Poor quality OCT (quality score < 15 for FD-OCT and < 7 for SD-OCT)
- Previous intraocular surgery (other than uncomplicated cataract extraction with posterior chamber lens implantation)
- Cataract extraction with posterior chamber lens implantation within the last year
- Diabetic retinopathy

Informed consent will be required before any subject is included in the study. Since there may be doubt that the procedures involved in the project (as described in the consent form and patient information leaflet) will be fully understood by a non-English speaking individual, it is considered prudent to exclude such potential participants. Potentially eligible patients will be identified in the glaucoma clinics of MEH.

Summary of testing:

1. All VF tests will be performed with the Humphrey Field Analyzer (HFA) Mark II (or II-*i*) and the SITA Standard 24-2 programme. A glaucomatous VF defect, for study inclusion (see below), will be defined as a reproducible (in at least 2 consecutive reliable post-screening VFs) reduction in sensitivity at two or more contiguous points with P < 0.01 loss or greater, or three or more contiguous points with P < 0.05 loss or greater, or a 10-dB difference across the nasal horizontal midline at two or more adjacent points in the total deviation plot. A reliable VF is one with <15% false positives. Unreliable tests will be repeated on the same day (with a break of at least 30 minutes).

2. Optical coherence tomography (OCT) imaging we be conducted using the Stratus OCT (Carl Zeiss Meditec, Dublin, CA, software version 5.0), the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) and the DRI OCT-1 Atlantis (Topcon, Japan).
   Patients' pupils will be dilated to ensure the pictures are of a suitable quality; pupils will be dilated using Tropicamide 1% eye drops (the drops used in routine hospital visits).

   a. Stratus images will be acquired through dilated pupils with the 'Fast RNFL thickness (3.4)' scanning protocol and using the 'landmark' function. Signal strength of ≥7 will be required to ensure images are reliable.
   b. Spectralis images will be acquired through dilated pupils with the and with the eye tracker and the retest function engaged; a signal strength >15 will be considered acceptable.
      i. A radial pattern of 24 angularly equidistant high-resolution 15-degree B-scans with the scan pattern centred on the ONH (data for each B-scan averaged from 20 to 30 individual B-scans, with 768 A-scans per B-scan).
      ii. Peripapillary circular scans (16 averaged consecutive circular B-scans; diameter of 12 degrees, 1536 A-scans)
      iii. A 'Dense' Volume Scan (20° x 20°) of the macula
   c. Atlantis images will be acquired through dilated pupils with the '12 x 9 wide' scanning protocol

Scheduling of testing:

Eligibility visit: subjects will be screened for eligibility from their clinical records and clinic examination at the time of a scheduled visit for monitoring (no additional investigations).

First study visit:

1. Visual acuity measurement with a Snellen chart at 6m. Approximately 3 minutes.
2. Autorefraction. Approximately 3 minutes.
3. Axial length measurement with IOL Master. Approximately 5 minutes.
4. VF testing twice. Approximately 15 minutes each with 30 minute break between tests. Pupil dilatation. Approximately 20 minutes.
5. Optic nerve head imaging with optical coherence tomography (Stratus, Spectralis and Atlantis). Approximately 40 minutes

First visit investigations will take approximately 2 hours.

Subsequent study visits:

1. Visual acuity measurement with a Snellen chart at 6m. Approximately 3 minutes.
2. VF testing once. Approximately 15 minutes.
   Pupil dilatation. Approximately 20 minutes.
3. Optic nerve head imaging with optical coherence tomography (Stratus, Spectralis and Atlantis). Approximately 30 minutes

Subsequent visit investigations should take less than 90 minutes.

Sample size:
The sample size was determined as a pragmatic solution to balance precision of estimates and feasibility. A sample of 80 subjects was deemed sufficient to approximate between individual differences in test-retest variability. The sample size estimate was based on a previous study investigating 30 patients tested 12 times.

Setting:
Patients will be seen in the Clinical Research Facility in the NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology.

Data Handling

All information will be stored and processed in accordance with the Data Protection Act 1998. All personal information collected will be stored in locked, secure-access filing cabinets and/or password protected computers on NHS premises (Moorfields Eye Hospital). Once enrolled, all participants will be allocated a study number, this being used throughout the study for all data collected. Access to the data collected will be limited to the Chief Investigator and each of the named collaborators. Participants may at any time request to see any data pertaining to them.

Data Analysis

This work will draw together a number of different statistical strands. We will establish statistical tools to analyse glaucomatous disease progression in clinical practice **and** for future clinical trials:

1. **'Trend' analysis for clinical trials:** the potential of linear mixed models (also termed hierarchical models or multi-level models) to increase trial power will be explored. We anticipate that multivariate linear mixed models for longitudinal data of the sort utilised, for example, by Beckett and colleagues for modelling different facets of cognitive decline in Alzheimer's disease and by Wilson and colleagues

for jointly modelling Parkinsonism and cognitive decline in Alzheimer's Disease are most appropriate here. The properties of our new joint 'VF with OCT' model (Index Test) will be compared to approaches based on ordinary least-squares (OLS) estimates of change of each outcome separately (Reference Test).

The 'VF with OCT' Index Test will be compared with the same statistical techniques applied to 'VF only' data (Reference Test); the Test providing the more significant treatment effect, shorter trial duration and smaller sample size will be the superior Test.

2. **'Trend' analysis for clinical practice**:
    a. For clinical practice, we are not concerned with analysing repeated measures data from multiple subjects (as we do in a clinical trial), and instead need to analyse progression within an individual subject. Thus, linear mixed modelling is not appropriate. As part of this research, we will continue to develop Bayesian techniques to monitor VF deterioration velocities, in clinical practice, using structural OCT measurements as a 'prior' in the linear regression model. The accuracy of each Test to estimate the 'true' rate of deterioration will also be assessed. There is no gold-standard by which to measure true change. Thus, in order to compare the accuracy of the methods, the prediction error (residual) associated with each Test will be calculated when forecasting the final measurement by extrapolation from linear regression on initial measurements. The superior Test will have a lower prediction error.

3. 'Event' analysis for clinical practice and clinical trials: the criteria for significant VF deterioration using a change from baseline analysis will be modified so that the Index and Reference Tests have the same specificity (according to the number of patients identified as not deteriorating in the Stable Patient Cohort). The Tests will be formally compared, in the UKGTS data, using a log-rank test, with hazard ratios determining the effect size. We will also explore Bayesian approaches and joint models of longitudinal and survival data, and compare these with the Reference Test.

Report and dissemination of results

Results will be communicated to academic audiences, policy makers and healthcare providers. The findings will be disseminated to the scientific community through publications in peer-reviewed scientific journals and presentations at scientific meetings. Furthermore, D. Garway-Heath will directly report the results to NHS management since the proposed work has very important implications for service delivery that could lead to enhanced public service and community engagement. We also anticipate a special interest group meeting as part of the annual UK and Eire Glaucoma Society meeting in December 2013 or 2014. In addition, patients will be consulted on how they would like to see the findings disseminated; patients groups including Friends of Moorfields and the International Glaucoma Association will take an important role in propagating the information. We also aim to present our findings at the annual National Glaucoma Awareness week and in the International Glaucoma Association (IGA) Newsletter.

Insurance/NHS Indemnity

This research study is organised and sponsored by Moorfields Eye Hospital NHS Foundation Trust and the NHS Indemnity scheme will apply.