APPLICATION FORM

Research Proposal

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RESEARCH FIELD – GLAUCOMA

Longitudinal assessment of visual field using iPad tablet computer for patients with glaucoma

RESEARCHERS

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Study Protocol:
Longitudinal assessment of visual field using iPad tablet computer for patients with glaucoma

1. OVERVIEW

Glaucoma is one of the leading causes of irreversible blindness worldwide, affecting more than 60.5 million people[1]. Optic nerve damage in glaucoma causes visual field deficits that are often asymptomatic and unnoticeable by patients until late[2]. Current standard visual field testing machines are not easily portable and come at a high cost. To provide glaucoma care to remote and rural communities with inadequate resources and to allow for development of future home-monitoring of visual field there is a need for visual field testing using light weight portable device such as the Apple ® iPad tablet computer.

Recent collaborative work between Chief investigator (Dr Yu Xiang Kong) and external researchers from the United States and Nepal showed promising results in the use of an early prototype of iPad visual field testing app in screening for visual field deficits [3]. Chief investigator has conducted a cross-sectional study in Melbourne Australia in 2015, where he found an more refined software (MRF, Melbourne Rapid Fields) has a high level of correlation with the Gold Standard (Humphrey Visual Field, HVF) test.

For visual field testing with MRF on iPad to be useful for monitoring visual field changes it is important to examine the longitudinal repeatability and validity of the test over time. The aim of this study is to examine the degree of repeatability and validity of the MRF test on iPad against Humphrey visual field test over a duration of 6 months.

2. AIMS AND HYPOTHESIS OF RESEARCH

2.1 Aims

The aim of this study is to examine the longitudinal repeatability and the degree of correlation of MRF field test compared to the current standard Humphrey Visual Field test.

2.2 Hypothesis

Hypothesis is visual field test using MRF software on iPad will be able to produce output measures that matches visual field test performed on the gold standard Humphrey visual field test.

3. BACKGROUND AND RATIONALE

Glaucoma is one of the leading causes of irreversible blindness worldwide, affecting more than 60.5 million people[1]. Optic nerve damage in glaucoma causes visual field deficits that are often asymptomatic and unnoticeable by patients until late[2].

Recent collaborative work between principal investigator (Dr Yu Xiang Kong) and external researchers from the United States and Nepal showed promising results in the use of an early prototype of iPad visual field testing app in screening for visual field deficits [3]. Chief investigator has conducted a cross-sectional study in Melbourne Australia in 2015, where he found an more refined software (MRF, Melbourne Rapid Fields) has a high level of correlation with the Gold Standard (Humphrey Visual Field, HVF) test (See Table 1, Manuscript in Review). Results showed a high level of correlation for Mean Deviation (Pearson's R =0.90, 95% Limits of Agreement= -7.2 to 4.4dB) and Pattern Deviation (R=0.7, 95% Limits of Agreement=-6.5 to 4.9dB) outcomes from iPad visual field test and Humphrey Visual field test from the same patient for a single time point.

For visual field testing on a portable device to be useful for monitoring visual field changes it is important to examine the variability of the test over time. A test with low variability will be able to detect change in visual field with less number of tests compared to a test with high variability. This study will examine visual field using MRF software on iPad at 4 time points over 6 months: at baseline, at 1 month, at 3 month and at 6 months. This study will give information on the degree of correlation of the MRF iPad software outcomes against Humphrey visual field test over time.

	Mean Deviation			**Pattern Deviation**			**Visual Capacity**		
	R,(m)	Bias dB	95% LoA	R, (m)	Bias dB	95% LoA	R, (m)	Bias %	95% LoA
Overall	0.9 m=0.8	-1.4	-7.2, 4.4	0.7 m=1.0	-0.8	-6.5, 4.9	0.9 m=1.0	1.8	-18.0, 20.6

Table 1: Outcome relationships between visual field test using Melbourne Rapid Fields software on iPad and Humphrey Visual Field test for the main summary indices (MRF-HFA: Pearson's correlation R, linear regression slope (m), bias and Limit of Agreement (LoA)).

4. METHODOLOGY

4.1 Investigator Obligations

Our primary obligation is to the health and well-being of our subjects. If requested, a participant's data would be withdrawn from the study.

4.2. Study Design

40 patients will be recruited as part of this project.

Consent will be obtained at the end of the patient's usual consultation. Patient information sheets will be sent out 1 week prior to the appointment.

Each patient will be examined at 4 time points over 6 month period: at baseline, at 1 month, 3months and 6 months. At each visit, patient will be have standard Humphrey Visual field test (Humphrey Visual Field SITA-Fast) performed as part of their usual consultation. This is followed by visual field test performed using iPad.

Visual field test on iPad will be conducted using an iPad generation 3, running iOS 8.0. Software to be used is Melbourne Rapid Fields. Patient testing will be performed in a quiet room free of distractions. The background lighting in the room will be dimmed to below 10 lux, the iPad screen will be cleaned and we ensured no glare was evident in the screen as glare can cause reductions in contrast sensitivity.[2] Full field thresholding (Using 24-2 Grid Pattern) will be performed.

Testing will be performed using natural pupils. Each eye will be tested separately. The fellow eye will be patched and the patient seated comfortably at a table with the iPad tablet placed on a typing stand that accompanies the Bluetooth™ keyboard, 33cm from the patient. The angle of the typing stand ensured that the screen is viewed at right angles. Testing is performed in free space with no constraints to head movement apart from initial check at the start to ensure the proper viewing distance. Care will be taken to ensure that the iPad screen is not tilted with respect to the viewing plane as tilt has been shown to reduce target luminance and contrast.[2] iPad screen brightness is set to maximum (100%) for every test by the software and the iPad is turned on for at least 10 minutes prior to patient testing to ensure stability of luminous output.[2]

Patients are asked to wear their habitual reading glasses (single vision, bifocal or multifocal) as required for normal near viewing. The clinician administering the test ensured that the viewing distance is maintained during the test and paused the test if a change in viewing distance was noted. In these cases patients were repositioned to the 33 cm viewing distance and the test was restarted.

Data analysis will be performed by examining the correlation of both outputs of visual field test using MRF iPad software and that performed on the standard Humphrey visual field test machine. Output measures include point-wise threshold deviation and also global indices such as Mean Deviation and Pattern Deviation.

4.3 Other data collection

Clinical information about each patient will also be collected, these include age of patient, treatment history, visual acuity, visual field loss and type of glaucoma (Open angle or close angle or secondary glaucoma). The results will be de-identified and entered into a database, and will be analysed for significant association.

4.4 Number, age range and source of participants

The study will involve 40 patients with glaucoma of varying severity (mild, moderate and severe). The eligibility criteria are a diagnosis of glaucoma (either angle open or closed angle) in one or both eyes (based on characteristic optic disc changes or glaucomatous visual field loss). Patients with any significant non-glaucomatous conditions affecting visual function such as cataract, macular degeneration, retinal detachment, diabetes, non-glaucomatous optic neuropathy and ocular surgery in the past 3 months will be excluded. Patients with significant non-visual impairment (eg mobility, verbal communication) preventing the completion of the objective testing will be excluded.

4.5 Informed consent

Consent will be obtained by chief investigator for the study. Participants suitable for the study will be identified by chief investigator from glaucoma clinic prior to appointment. Patient information forms will be posted to patient 1 week prior to their appointment. All participants are fully informed of the reasons for the study, the nature of the study and the process of anonymous storage and analysis of the information. The full rights of participants are explained and participants are asked if they fully comprehend. They are invited to ask any further questions, and then sign the consent form.

4.6 Means by which participants will be recruited

This will be a longitudinal study, consecutively enrolling appropriate patients attending Glaucoma subspecialty clinics. Participants will be recruited for a period of 6 months, with 6 months of subsequent follow-up. Every eligible patient attending the practice is offered the opportunity to participate, but only once. A confidential list of enrolled patients is kept by the practice staff to prevent multiple entry. There will be no advertising for patients, and they will be recruited during routine visits.

Patients will be recruited in the glaucoma research clinic which will on average able to recruit 6 patients for this study every 2 weeks. Therefore this study is likely to complete recruitment of 40 patients over 14 weeks (approximately 3 months).

4.7 Proposed plan for statistical analysis

Data analysis will be performed by Prof Keith Martin.

Point-wise retinal threshold will be calculated by reflecting all left eye data in the vertical to produce equivalent right eye fields. Mean Deviation (MD) was calculated from the average point-wise deviations using the age-adjusted expectation. Pattern Deviation (PD) was calculated using standard formulae as the average residual after allowing for the patient's MD.[16] Visual Capacity (VC%) was determined by normalizing the patient's MD against the age-expected value, similar to the VFI index of the Humphre Visual field test.

Linear regression correlation will be performed using a least squares method (SigmaPlot version 10.0; Systat Software, Inc., San Jose, CA, USA) and fixing the intercept at the origin. The slopes of the best fitting lines will be calculated and Pearson coefficients will be determined to gauge the strength of these associations. A Bland-Altman analysis will be used to consider bias and 95% Limits of Agreements (LoA) when

comparing Humphrey visual field versus iPad visual field data and the test-retest data. Group comparisons will be performed using SPSS for Windows (SPSS version 15.0, SPSS Inc., Chicago, IL) with t-tests or ANOVA as appropriate with an alpha of 0.05.

4.8 Other ethical, legal or management issues

The major ethical issues are a potential breach in patient confidentiality, loss of patient morale due to inability to perform the test and patient physical harm during testing.

Breach in confidentiality is avoided by the use of a private consultation room for ophthalmic consultation and iPad visual field test, the recording and storing of de-identified data, and the use of a password-encrypted computer to store the information. Visual field testing is an integral part of normal clinical care for glaucoma patients. Performing visual field test using an iPad tablet computer does not put patients at any further risk compared to their usual eye test. The main burden for the patient is the slightly extended consultation. The iPad visual field test averages 5 minutes per eye, therefore for the patient it is expected that visual field test using iPad will extend clinic visit by 10 minutes. Participating in the study does not alter the standard high quality care that all patients receive through the Addenbrooke's Eye Unit.

Participants are not expected to gain additional benefit directly from performing the iPad visual field test, although it is known that more practice in doing visual field test can improve reliability of performing Humphrey Visual Field test. Benefits to the patients also include comprehensive eye examination and contribution to medical research.

5. LAY DESCRIPTION

Glaucoma is a common disease, known to impair vision and quality of life. Patients with glaucoma frequently have problems with peripheral vision (otherwise known as the visual field) that effects their ability to drive, walk, venture from home, read, see objects at night or coming from the side.

Visual field testing is an important part of early diagnosis of glaucoma and monitoring change in the visual field is important to its management. Current standard visual field testing machines are not easily portable and come at a high cost. To provide glaucoma care to remote and rural communities with inadequate resources and to allow for development of future home-monitoring of visual field there is a need for visual field testing using light weight portable device such as the Apple ® iPad tablet computer.

Chief investigator has shown that a software on the iPad can be useful for screening for moderate and severe glaucoma in Nepal. Chief investigator also conducted a cross-sectional study in Melbourne Australia, where he found an more

refined software (MRF, Melbourne Rapid Fields) has a high level of correlation with the Gold Standard (Humphrey Visual Field, HVF) test. The aim of this study is to examine how closely does MRF software on Apple iPad compares with current Gold Standard in a longitudinal study over duration of 6 months.

Participants must be able to comprehend English. People with any other form of eye disease or eye surgery within the last 3 months are excluded. People with significant non-visual impairment (eg mobility, verbal communication) preventing the completion of the objective testing will be excluded.

Research questions:
What is the correlation between iPad MRF visual field test and Humphrey Visual Field test results over time?
What is the longitudinal repeatability of MRF visual field testing over time compared to Humphrey Visual Field test?

Plan
The participants will be patients attending an ophthalmology clinic. This study will be discussed with appropriate candidates. The candidates will be given time to consider the elements of the study and informed consent obtained before participating in this study. Each patient will be examined at 4 time points over 6 month period: at their first visit, at 1 month, 3months and 6 months. At each visit, patient will have their usual medical consultation which includes the standard Humphrey Visual field test. This is followed by visual field test performed using MRF on iPad.

The outcomes of the MRF software will not be used in any clinical decision making process in patient consultations. This is because the software is designed for conducting scientific study of visual field and is not designed for providing any clinical diagnosis. All clinical decision making will be based on test outcomes on the standard Humphrey visual field test.

Benefits and Costs
There are no costs for the patient, apart for a little more time prior to the consultation. All patients can accept or refuse to take part in the study; this will not effect the clinical care received from the Ophthalmic team. The benefits of the study may lead to improved glaucoma in the future, especially for people in resource poor areas with lack of access of standard visual field testing.

Ethical Implications
There are no ethical implications or conflict with the patients' interest. Patients can withdraw from the study without compromise. Should they require further explanation and counselling, this will be offered. The patients' identity will remain anonymous, and the de-identified data will be kept confidential in a password-protected computer.

7. General Information

7.1 DISSEMINATION OF RESULTS

Once the data is collected and de-identified, it will be stored on the NHS computer under password protection. The investigators intend to publish the findings in an ophthalmic journal. Participants will be welcome to contact the investigators as to the final outcomes of the study.

7.2 OTHER APPROVALS REQUIRED?

IRAS (UK NHS ethics committee) approval for these studies has been undertaken .

7.3 FINANCIAL AND LEGAL AGREEMENTS INVOLVING INVESTIGATORS AND PARTICIPANTS

The investigators have obligation is to the health and well-being of the subjects. There will not be any financial gain or cost to the patient from participation in the project. If requested, a participant's data would be withdrawn from the study.

7.4 RESEARCHERS

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