THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR GLAUCOMA DETECTION STUDY, KCMC, TANZANIA

Version number: CT21 0013 CPARv2.0

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1. INTRODUCTION

A recent systematic review found Glaucoma to be the most common irreversible cause of blindness worldwide causing an estimated 2.9 million people to be blind and a further 4 million to have moderate or severe visual impairment. (1) It is the third most common cause of blindness overall, following cataracts and uncorrected refractive error. The global prevalence of glaucoma for the population aged 40-80 years is estimated to be 3.5% with over 60 million people affected. (2) In the UK it is estimated that almost 10% of those older than 75% have chronic open-angle glaucoma alone. (3) However, in low-income areas glaucoma prevalence appears to be much higher and it is a far more common cause of blindness. Recent population-based surveys from Sub-Saharan Africa found a prevalence of 4-8% in those over 40 years old with a high proportion of severe vision loss in both eyes. (1, 4-7) With an increasingly ageing population the numbers of people with glaucoma across the world are expected to show large increases in the coming years. (7)

Despite its prevalence, diagnosing glaucoma is not straightforward, and confirming or excluding the presence of the disease can be challenging. Even in developed countries up to half of glaucoma is undiagnosed, and this proportion is far lower in low-income settings. (7) Several clinical tests and imaging modalities need to be performed, often sequentially over time. (3, 8) We propose to assess and validate a combination of low-cost, portable, rapidly performed tests which can be brought together to function as a case detection system for glaucoma. The work funded by this grant will allow us to complete feasibility and reliability assessments for each of the tests in different field conditions (in the UK and Tanzania) and to optimize the glaucoma detection algorithm for maximum sensitivity and specificity.

Visual field examination is a central part of diagnosing and monitoring glaucoma. Standard automated perimetry is the current gold standard, usually performed with the Humphrey Field Analyzer (HFA). However, Humphrey Visual Fields (HVFs) are time-consuming, difficult to perform and have low patient satisfaction even in experienced test-takers, as well as requiring a trained operator to monitor the patient and ensure compliance. (9) The HFA machines are large and non-portable and are expensive to purchase and maintain, placing a financial burden on eye units and making them prohibitive in most low-income settings. This has led to an interest in developing alternatives to standard perimetry, including tablet or screen-based visual fields. Professor David Crabb's group (www.staff.city.ac.uk/crabblab), which has an impressive track record of research in visual field assessment and development, have developed a novel form of perimetry. " Eyecatcher" combines an inexpensive eye tracker with a simple portable tablet computer. Scores from Eye Catcher demonstrate a strong correlation with

HVF mean deviation scores and good concordance between corresponding visual field locations. (10) The eye-tracking technology is used to monitor and compensate for fixation and patient movement during the test. This allows variation in the distance between the patient and the screen so that a chin-rest is not needed, adding to patient comfort. Participants reported that the Eyecatcher was more enjoyable, easier to perform and less tiring. A further study assessing the use of Eyecatcher fields in clinical practice is currently ongoing in the UK with preliminary experience confirming the positive results of the earlier laboratory-based study

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The Eyecatcher visual field test will form the first key component of the proposed glaucoma case detection system. The second test to be utilized will be digital photography of the optic disc. Optic disc assessment is critical to diagnosing and monitoring glaucoma and a high-quality colour photograph of the disc will help to determine if glaucomatous damage has occurred. (3, 8) Retinal and optic disc imaging is a rapidly developing field and technological advancements are helping to drive down costs, a pattern which is likely to continue in the future. This study will use the Remidio hand-held fundus camera which can take high-quality images with the use of a smartphone. (11) We have had a good experience with this camera with diabetic retinopathy studies in Zambia. This study will use expert graders to grade the optic discs for glaucomatous damage, however, we anticipate that in the future machine learning will help to automate this process. Artificial intelligence-based automated software for detecting diabetic retinopathy from retinal images has reached an advanced stage and similar work has begun on glaucoma detection. (11-13)

The third test to be evaluated is contrast sensitivity. There is good evidence that contrast sensitivity can differentiate between glaucomatous and healthy eyes and should be used much more in standard clinical practice. (14-17) PEEK contrast sensitivity is a newly developed test, which can be performed on a smartphone or tablet computer, is a repeatable and rapid test and is highly comparable to Pelli-Robson contrast sensitivity. (18)

Each of the three proposed tests is rapid, easily performed and requires relatively low-cost equipment (especially considering future advances) with a portable set-up. They can be performed by allied healthcare workers without the need for extensive training. A single electronic device, such as a tablet computer, can currently be used to perform two of the tests, the Eyecatcher fields and contrast sensitivity. Recent technological advancements strongly point to such a device also being able to obtain high-quality optic disc images in the future. This device can be used to securely store all of the data collected, including relevant patient demographic parameters, and could also potentially contain software helping to interpret and analyse this data.

We also plan to retrospectively gather clinical data from ophthalmology patients which is of relevance.

1.1. Rationale of the study

This study would form an important part of a wider body of glaucoma research being undertaken by the London School of Hygiene and Tropical Medicine. A key aim of this work is to promote the development of a low-cost system for glaucoma detection for use in communities that are poorly resourced in areas difficult to reach. Equipment and a diagnostic protocol will be developed that can be used by non-medical personnel. The work put forward in this grant proposal will play a foundational role in taking this work forward. The ongoing research work will be able to test the glaucoma detection system developed in this study and validate its usefulness in ongoing studies in the community. Our long-term aim is for a single device to be used to perform all the clinical tests, analyse the data according to an optimized algorithm, and give a likelihood ratio score for the presence of glaucoma.

1.2. Study details

Clinical Trial Registration number	TZ22CT0009
Title of the study	Glaucoma Detection Study, KCMC, Tanzania
Protocol Identification Number/code	GDS / v.1.2
Ethical Clearance Number/ Date of Approval	NIMR/HQ/R.8a/Vol.IX/3669 dated 29th April 2021
TMDA Approval Date	01-03-2022
Name of Investigational Product or Intervention	GDS System
Dosage Form(s) and Strength(s) (where applicable)	N/A
Route(s) of Administration (where applicable)	N/A
Name (s) of Comparator Product (where applicable)	N/A
Name and address(es) of the Sponsor	London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK
Name and address(es) of the Principal Investigator (PI)	Dr. Einoti Matayan, Principal Investigator, Department of Ophthalmology, Kilimanjaro Christian Medical Centre (KCMC), P.O. Box 3010,

	Moshi. **E-mail:** blessednai23@gmail.com
Name and address(es) of Study Site(s)	Kilimanjaro Christian Medical Centre, Department of Ophthalmology, PO Box 3010, Moshi, Tanzania.
Name and address of the manufacturer of Investigational medical product (IMP) if applicable	Peek Vision Limited, We Work @ Moor Place, 1 Fore Street, London, EC2Y 9DT, UK
Name and address of the manufacturer of the comparator product (if applicable	N/A
Phase of Trial	Phase 3
Duration of the study	4 years
The primary purpose of the study (*Screening, Diagnosis, Prevention, Treatment*)	Diagnosis
Condition or diseases under study	Glaucoma
Number of participants intended to be enrolled in the study	200-300

1.3. Assessment procedure

The application for authorization for a clinical trial of Glaucoma Detection Study, KCMC, Tanzania submitted on 04-08-2021. The assessment was completed in three (3) rounds of evaluation. The trial was approved on 01-03-2022

2. TRIAL INFORMATION

2.1. Study Objectives

Primary Objective

To determine whether the 3 proposed tests (Eyecatcher visual fields; PEEK contrast sensitivity; optic disc photography) can be used as a case detection system for glaucoma.

Secondary Objective

a) Measure the repeatability of each of the tests.
b) Determine the utility of each test to differentiate glaucomatous damage from normal, and the optimum combination of tests for this purpose.
c) Measure the patient acceptability of each test.

2.2. Outcome Measures

2.2.1. Primary Outcome

The primary outcome measures of the study are:

a. To establish the diagnosis of glaucoma versus healthy control. Researchers want to establish whether the proposed system can differentiate those who have a definite diagnosis of glaucoma from those with no disease.
b. Mean deviation on HVF testing: this is well-established means of assessing glaucoma severity and we will measure how well this can be predicted by the case detection system.

2.2.2. Secondary Outcome Measure

The secondary outcome is the patient acceptability of the three proposed tests

2.3. Investigational Plan

This is a phase 3 Prospective, observational, non-interventional study aiming to detect glaucoma using low-cost, portable and easy-to-perform tests. This is by testing the feasibility and reliability of several diagnostic tests which can be combined to form a novel glaucoma case detection system. Participants will be recruited from patients who are attending ophthalmology appointments in outpatient departments. This is a heterogenous population and will allow us to include patients ranging from those with established glaucoma and clear visual field defects, early glaucoma, glaucoma suspects, ocular hypertension and also healthy controls (for example, new referrals with no disease). The overall plan is to investigate whether the 3 proposed tests (Eyecatcher visual fields; PEEK contrast sensitivity; optic disc photography) can be used as a case detection system for glaucoma.

2.4. Type and number of the study participants

The study will be conducted among the age group above 18 years old who are both healthy and well-established with a diagnosis of glaucoma. The study plans to enroll about 200-300 participants.

2.5. Selection of Study Population

Inclusion criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply to meet all

a. Age group above 18 years old who are both healthy and established with a diagnosis of glaucoma
b. Giving informed consent.
c. The ability to understand and cooperate with the tests

Exclusion criteria

A subject is not eligible for inclusion in this study if any of these criteria apply

a. Not meeting the inclusion criteria.
b. Previous participation in the study

2.6. Drug Formulation or Device Description in Case of Devices

Brief description of the study drug(s) and formulation to be used in the clinical trial:
The study is using the glaucoma case detection system (GSD System).
Instructions for safe handling:
The GDS tests will be performed by trained research assistants in the Eye Department.
State the accounting procedures for the investigational product(s), placebos and comparator(s) and disposal:
The GDS equipment will be maintained and kept securely by trained research assistants in the Eye Department.

2.7. Treatments

Treatments administered in case of biologicals or medicines.
The study involved the medical devices system

2.7.1. The name(s) of all the product(s):
2.7.2. Dose(s): N/A
2.7.3. The dosing schedule(s): N/A
2.7.4. The route/mode(s) of administration: N/A
2.7.5. The treatment period(s): N/A
2.7.6. Follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial: N/A
2.7.7. Concomitant Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial: N/A
2.7.8. Procedures for monitoring participant's compliance: N/A
2.7.9. Wash-out period (Description for pre-, during- and post-trial, as applicable) N/A

2.8. Pre-Study Screening and Baseline Evaluation

Participants will undergo an informed consent process. We would like to recruit a range of participants from those with no disease to those with advanced disease. Therefore, potential participants only need to fit the inclusion criteria to be suitable for participation.

The tests which will be performed for the study have been outlined above, with the summary diagram: This is by the clinical study protocol.

2.9. Efficacy and Safety Measurements to be Assessed

Efficacy measurements

a) Eyecatcher visual fields: the protocol for this is well established and has shown a good correlation with HVF results, as above. A tablet computer or laptop screen can be used, with a clip-on eye tracker such as the Tobii EyeX. The diagnostic test is done similarly as follows: a quick, screening field test is done with supra-threshold light intensity, taking 1-2 minutes. Participants who can perform this initial test will go on to be tested with light-intensity stimuli equivalent to ~10 dB on the HFA. The subsequent analysis allows pointwise concordance with HFA locations to be computed with an equivalent sensitivity, for example, of 25 dB. This will take around 5 minutes, but the patient experience compared to HVF is improved as the eye-tracking technology can compensate for patient movement and fixation. Patient acceptability will be measured. Participants will be asked if they are willing to repeat the Eyecatcher fields before leaving the department so that we can assess the retest variability. The Eyecatcher field analysis will be graded as indicating glaucomatous damage or no damage

b) Contrast sensitivity: Peek Contrast Sensitivity will be measured on a handheld device. The screen presents the letter “E” in random orientations and the subject indicates the correct orientation. The test starts with maximal contrast which then decreases until the subject’s contrast detection threshold is determined. A logarithm score of between 0.00 and 2.25 log units is generated. The test takes less than a minute complete. Other tests of the Peek platform, e.g. the visual acuity test will be performed as well.

c) Optic disc photo: the Remidio hand-held fundus (or comparable) camera can take good quality optic disc images without pupil dilation in a dim room or with the use of a small gown. Image acquisition takes around 2-3 minutes. The camera has a well-developed software package which allows easy extraction and transfer of images. Images will be graded by experts e.g. using the disc damage likelihood scale and graded as indicating glaucomatous change or not

Safety measurements

Serious Adverse Events (SAEs) should be reported to the study coordination centre within 24 hours of the local site being made aware of the event.

An SAE form should be completed and submitted to the study coordination centre with as much detail of the event that is available at that time.

If awaiting further details, a follow-up SAE report should be submitted promptly upon receipt of any outstanding information. Any events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

3. ETHICAL CONSIDERATIONS

3.1. Ethical Clearance

The study has approved by the National Health Research Ethics Committee on 29th April 2021 with ethical clearance. No NIMR/HQ/R.8a/Vol.IX/3669 dated 29th April 2021

3.2. Insurance

The study participants will be insured through Travelers Insurance Co. Ltd via the study titled Glaucoma Detection Study, KCMC, Tanzania which has protocol No. GDS / v.1.2 The validity is from 01.06.2021 to 30.05.202 with the policy cover no. UCCMK5565295 and amount of premium insurance of £10,000,000.

3.3. Informed Consent

Informed consent version 2.0 dated 01.03.20 20 was approved by the ethics committee on 29th April 2021.

3.4. Patient Information Leaflet

Patient information leaflet version 2.0 dated 01.03.2020 was provided by the ethics committee on 29th April 2021.

3.5. Payment

The study participants will not receive any remuneration

4. WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

The study participants will benefit from being screened for Glaucoma detection.

5. ARE THERE ANY POTENTIAL BENEFITS TO OTHERS THAT MIGHT RESULT FROM THE STUDY?

We cannot promise the study will help you but the information we get from the study will help our knowledge and understanding of this research area in glaucoma.

6. WHAT ARE THE RISKS OF THE STUDY?

There are no known risks. The tests are non-invasive and do not involve any bright or harmful light. If you enter the study as it does not involve any change in your routine care

Details on treatment and/or management of participants and their disease condition(s) after completion of the trial (post-trial medicine access) if provided

N/A

7. PRE-CLINICAL STUDIES (IF APPLICABLE)

N/A

8. HUMAN EXPERIENCE (CLINICAL STUDIES) IF APPLICABLE

N/A

9. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION OF THE INVESTIGATIONAL MEDICINAL PRODUCT OF DRUG SUBSTANCE (VACCINES AND DRUGS ONLY)

N/A

9.1. Drug Substance(s)

9.1.1. Description

N/A

9.1.2. Name(s)

N/A

9.1.3. Structural Formula and Molecular Formula

N/A

9.1.4. Physical-Chemical Properties

N/A

9.1.5. Drug Substance Stability

N/A

9.2. Drug Product

9.2.1. Drug Product Formulation

N/A

9.2.2. Placebo Formulation (In case applicable)

N/A

9.2.3. Drug Product Stability

N/A

9.2.4. Drug Product Storage

N/A

10. BENEFIT-RISK ASSESSMENT AND CONCLUSION

Based on the data provided, the current state of knowledge regarding an investigational product, including the non-clinical and clinical information that is currently available, is sufficient to support the proposed clinical trial and compliance with Good Clinical Practice (GCP), and the anticipated benefits of conducting the trial justify the risks associated with its use when done by the approved protocol and ethical principles that have their origin in the Declaration of Helsinki.

11. POST-APPROVAL UPDATES

11.1. Amendment applications

Reference number	Date submitted	Change Requested	Recommendation	Granting date

PART 5: CHANGE HISTORY

Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**