STUDY PROTOCOL AND RESULTS

STUDY TITLE: AUTOMATED DETECTION OF MALARIAL RETINOPATHY IN PATIENTS DIAGNOSED WITH CEREBRAL MALARIA (ASPIRE)

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Sponsored by:
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Analyzing the performance of automated software in the identification of malarial retinopathy in digital retinal images of cerebral malaria patients.

INVESTIGATORS AND INSTITUTIONAL AFFILIATIONS

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VisionQuest Biomedical Inc.

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1. DECLARATION BY PRINCIPAL INVESTIGATORS

1. I have read and understood item 1.5.5 on page 5 and section 3 (pages 14-20) "Responsibility of the Principal Investigator (PI) and participating investigators of the HANDBOOK FOR GOOD CLINICAL RESEARCH PRACTICE (GCP) 2005 ISBN 92 4 159392 X.

2. I have thoroughly read, understood, and critically analyzed the protocol and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet and informed consent form.

3. I will conduct the trial as specified in the protocol.

5. To the best of my knowledge, I have the potential at the site. I am responsible for, to recruit the required number of suitable participants within the stipulated time period.

6. I will not commence with my role in the trial before written authorizations from the relevant ethics Committee approval have been obtained.

7. I will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.

8. I will ensure that every participant (or other involved persons, such as relatives), shall at all times be treated in a dignified manner and with respect.

9. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship which may inappropriately influence me in carrying out this clinical trial.

10. I have not previously been involved in a trial which has been closed due to failure to comply with Good Clinical Practice.

11. I will submit all required reports within the stipulated time-frames.

Signature: _____ Date: _____ / _____ / _____

Signature: _____ Date: _____ / _____ / _____

2. SUMMARY OF PROPOSALS

2.1 ABSTRACT:

The detection of malarial retinopathy (MR) in cerebral malaria (CM) patients currently requires expensive equipment and extensive training. We have developed a computerized software-based analysis of retinal images obtained by handheld fundus cameras that is >90% specific. The purpose of this study is to evaluate the performance of a software in detecting malarial retinopathy in retinal images obtained using hand-held fundus cameras by non-ophthalmologist clinicians. The overall aim of the proposed study is to collect digital retinal image data of clinically diagnosed CM patients and utilize the images to develop and test the performance of software algorithms (ASPIRE) for detecting specific signs of MR and for detecting the presence of MR. The performance of the software will be measured against the binocular indirect ophthalmoscopy (BIO) examination (if available) performed by an ophthalmologist for determining the presence of MR (reference standard) and/or against the grading of established retinal graders. Participants between the age of 6 months and 12 years who present with coma, a positive malaria test, and clinical diagnosis of CM, will be enrolled at the time of admission at the respective participating hospital(s). The imager will be masked to MR detection results. The retinal images will be graded by an ophthalmologist for the detection of specific signs of MR. The retinal images will be used to develop and test algorithms for detecting specific MR lesions and overall MR presence. The sensitivity and specificity of the software algorithms against grader's image grading will be determined to evaluate the performance of each algorithm and its usability in identifying MR. This study would be a first step in the validation of retinal image analysis software for assessment of MR. The results of the

study will be used to inform initiatives to spread the use of software-based detection of MR to preclinical settings in which CM patients are seen. Results will also be useful in planning the studies to quantify the detection of MR lesions and analyze large datasets in objective manner.

LAY SUMMARY OF RESEARCH PROTOCOL

The detection of malarial retinopathy (MR) in cerebral malaria (CM) patients currently requires expensive equipment and extensive training. We have developed a computerized software-based analysis of retinal images obtained by handheld fundus cameras that is >90% specific. The purpose of this study is to evaluate the performance of a computer software in detecting malarial retinopathy in retinal images obtained using up to three different hand-held fundus cameras in the hands of non-ophthalmologist clinicians.

The overall aim of the proposed study is to collect digital retinal color image data from 800 clinically diagnosed CM patients from the malaria endemic regions of Nigeria and Malawi and utilize the images to develop and test the performance of software algorithms (ASPIRE) for detecting specific signs of MR and for detecting the presence of MR. The performance of the software will be measured against the binocular indirect ophthalmoscopy (BIO) examination (if available) performed by an ophthalmologist for determining the presence of MR (reference standard) and/or against the grading of established retinal graders. From March 2021 or as soon as the ethics committee

approves the protocol, children aged between 6 months and 12 years who present with coma, a positive malaria test, and clinically confirmed diagnosis of cerebral malaria will be enrolled at the time of admission at the respective participating hospitals. After obtaining informed consent from the parent/guardian, both eyes will be dilated, and photos of the eyes will be collected using each of the three different cameras. There are no risks that are involved in taking part in this study. All the other procedures such as collection of samples are standard procedures in the diagnosis of malaria. Findings from this study will help in the development of a low cost system that will be integrated to a smartphone that will help clinicians in low-income countries to clearly diagnose MR.

3. INTRODUCTION.

3.1. BACKGROUND:

Cerebral malaria (CM) is a life-threatening clinical syndrome associated with malarial infection. As per the *World Malaria Report 2019*, sub-Saharan Africa experienced 213 million cases of malaria (93% of the global cases) in 2018 and an estimated 381,000 deaths that included 256,000 deaths of children under the age of five (1). Most of these mortalities were thought to be caused by CM. Because individuals in malaria-endemic areas can be infected with the malaria parasite without being symptomatic, the clinical syndrome of CM may or may not be caused by the malaria parasites detected in the blood. An incorrect diagnosis leads to incorrect treatment (2,3). Therefore, non-malarial comas which have high fatality rates may go undiagnosed and result in potentially avoidable death (4). Lewallen et al. (5) and Taylor et al. (i) found that nearly a quarter of children who died with a clinical diagnosis of CM actually had other non-malarial causes of death.

An accurate diagnostic to confirm the presence of CM is critically needed to improve clinical outcomes. Lewallen et al. (3) described a constellation of retinal lesions

associated with CM, called malarial retinopathy (MR). The characteristic features include retinal whitening, vessel discoloration, and white-centered hemorrhages (ii). Since MR was found to be greater than 90% sensitive and specific for the presence of the histologic hallmark of CM, the sequestration of parasitized red cells in the cerebral microvasculature (iii), retinal screening for MR represents an effective means for improving the specificity of CM diagnosis. In the past 2 decades, it has been demonstrated that around 60% of children in the CM research project in Blantyre, Malawi manifest MR of some degree. Children without detectable MR are significantly more likely to have another diagnosis or to be the children who respond most quickly to anti-malarial treatment. Thus, examining comatose children for the retinopathy is a useful prognostic sign, and in areas of high malaria endemicity it can help guide clinicians. It may also be useful in following the changes in the epidemiology of cerebral malaria in areas where public health interventions have been implemented.

Although BIO has been the reference standard for identifying MR, it is important to recognize that it is not a true “gold standard.” Fundus photography with a modified digital camera, and even examination with direct ophthalmoscopy (DO), which both provide higher magnification than BIO, sometimes demonstrate the “abnormal vessels” of MR when they were not recognized by BIO. DO is cheaper and easier to learn than BIO but it does not provide a good alternative to BIO since it allows examination only of a narrow field of view within the posterior pole. Studies comparing the sensitivity of BIO to digital photography for detecting MR have not been carried out; in the future, such studies could

be useful to researchers seeking further understanding of the pathophysiology of CM and MR.

Now that simple, low cost fundus imaging systems such as the Pictor-Plus retinal camera (Volk Optical), VistaView, and iNview cameras are available, the possibility exists for providing digital images to clinicians in low resource settings where CM is common. This could impact the diagnosis and treatment of CM. The ability to visualize the fundus would also allow for the possibility of assessing the presence of papilledema, a valuable prognostic feature in comatose patients, irrespective of the cause of the coma. Digital retinal color image data of clinically diagnosed CM patients will be collected and utilized to develop and test the performance of software algorithms for detecting specific signs of MR and for detecting the presence of MR. The performance of the software will be measured against the binocular indirect ophthalmoscopy (BIO) examination (when available) performed by an ophthalmologist for determining the presence of MR (reference standard) or image grading from a certified retinal grader.

Handheld and easy-to-use retinal imaging systems can provide good quality color fundus images. A recent (unpublished) pilot study conducted in Malawi indicated that ophthalmic experts using handheld and smartphone based retinal cameras had sensitivity in the range of 87%-100% and specificity in the range of 75%-87% for the detection of the presence of any signs of MR, against those detected by an experienced ophthalmologist using BIO. The results of this study were encouraging and justify our efforts in moving forward to the next steps for automated analysis of retinal images for detection of MR.

Automated analysis of retinal images and a computer-assisted retinal disease diagnosis have proven to be useful in detecting number of eye diseases including diabetic retinopathy and age-related macular degeneration. An automated software for detection of MR lesions and diagnosis of MR and its integration with a portable and low-cost retinal camera will be convenient for use in non-ophthalmic, non-clinical settings, making it highly accessible and affordable to the targeted population where other CM diagnostic methods are limited.

3.2 PROBLEM STATEMENT:

Considering the malaria-endemic regions in Africa that lack adequate number of ophthalmologists, a fully automated software system for the comprehensive analysis of MR abnormalities and detecting the presence/absence of MR would be useful. This would also mitigate the challenges of training the healthcare staff to use ophthalmoscopes and/or to read and grade the retinal images. The software system can be tuned to yield high specificity, addressing the current clinical requirement to prevent deaths resulting from misdiagnosis of CM. It can also include the automated detection of papilledema, a sign of severe brain swelling and important to recognize in patients with and without CM.

3.3 JUSTIFICATION FOR THE STUDY

To date, binocular indirect ophthalmoscopy (BIO) with a 20-diopter lens by an experienced examiner (usually an ophthalmologist) is the “reference test” method for diagnosing MR. With BIO, the examiner is able to obtain a wide angle, relatively low

magnification view of the retina. BIO has been used as the diagnostic standard in all studies that demonstrate associations of MR with outcomes and other factors. BIO is inherently limited as a diagnostic tool as it depends greatly on the examiner's experience and skill. Even among experienced ophthalmologists, there may be disagreements on findings; most non-ophthalmologists do not practice enough ophthalmoscopy to be proficient in the skill. Attempts to teach non-ophthalmologist clinicians (NOC) to use BIO in CM clinical settings in Africa have generally been disappointing (with a few exceptions) due to the time required to learn the technique and the lack of personnel (particularly ophthalmologists) to provide ongoing supervision. Thus, in most settings where CM is treated in Africa, the fundus signs are not sought or missed.

Given a clear retinal image, clinicians learn relatively easily to recognize specific patterns that are common to specific diseases (e.g., diabetic retinopathy screening). Modern digital imaging techniques capture excellent images of the fundus and are used widely now for screening for eye conditions. Recently, new technologies, using handheld retinal cameras and smartphone-based retinal cameras, allow fundus imaging to be done simply and inexpensively. These open the possibility, for the first time, of providing many clinicians who treat children in malaria-endemic areas with high quality fundus photos of children with clinically defined CM. The analysis of the images is not straightforward, and unfortunately, there is a scarcity of ophthalmic experts capable of analyzing retinal images and determining the presence or absence of MR routinely in clinical settings in Africa.

3.4 GENERAL OBJECTIVE

The overall aim of the proposed study is to collect digital retinal color image data of clinically diagnosed CM patients and utilize the images to develop and test the performance of software algorithms for detecting specific signs of MR and for detecting the presence of MR. The performance of the software will be measured against the binocular indirect ophthalmoscopy (BIO) examination (if available) performed by an ophthalmologist or image grading from a certified retinal grader.

3.5 SPECIFIC OBJECTIVES

The primary objectives are:

1. To collect mydriatic retinal images of at least N= 50 pediatric subjects clinically diagnosed with CM at each of the study sites located in Nigeria, Africa. Retinal images will be collected from the participating clinics/hospitals by clinicians over a period of 2 years. The activity has been piloted and found to be within the scope of clinicians in Nigeria.
2. To determine the sensitivity and specificity of software algorithms for classifying clinically diagnosed CM patient into MR positive or MR negative using the images obtained with up to three retinal cameras, compared with retinal graders' grading (in all cases) and the clinical reference standard (BIO) when possible.

Secondary objectives are:

1. To determine the positive predictive value (PPV) and negative predictive value (NPV) of software algorithms for classifying clinically diagnosed CM patient into MR positive

or MR negative using the images obtained with up to three retinal cameras, compared with retinal graders' grading (in all cases) and the clinical reference standard (BIO) when possible.

2. LITERATURE REVIEW:

Cerebral malaria (CM) is a fatal neurological syndrome of malarial disease. The *World Malaria Report 2019* estimates that malaria claimed 381,000 lives in Africa in 2018, over 65% of whom were children under five years of age [iv]. CM is one of the largest contributors to pediatric malarial deaths, and approximately 23% of children are found to be misdiagnosed with CM, which leads to incorrect treatment and results in mortality or neurological disability in thousands of children in Africa [v,vi,vii,viii,ix]. There is a significant market need for low-cost and easy-to-use technology to improve CM diagnosis and save lives.

Malarial Retinopathy (MR) manifests as a series of retinal lesions highly specific (>95%) to CM and therefore can be used to improve the diagnostic accuracy of CM. VisionQuest proposes the development and clinical deployment of an artificial intelligence (AI) system, Auto Detection Software for Plasmodium Infection in Retinal Exams (ASPIRE), that offers the first AI-supported MR detection software integrated with a low-cost and portable retinal camera, a system that can be operated by minimally trained personnel such as medical technician or nurse without the need of an ophthalmic specialist.

Societal and Economic Significance. As per the *World Malaria Report 2019*, sub-Saharan Africa experienced 213 million cases of malaria (93% of the global cases) in 2018 [iv] and an estimated 381,000 deaths that included 256,000 deaths of children under the age of five. These children are particularly susceptible to severe malarial infection and its fatal syndrome, CM, which affects over 2 million children annually [6] and remains one of the major killer of children in Africa. However, up to 23% of these children's deaths are thought to be caused by nonmalarial diseases, such as pneumonia, that mimic CM

symptoms and lead to misdiagnosis of CM [v,vi,vii,viii,ix]. The high rate of CM misdiagnosis and incorrect treatment of these concurrent diseases often results in death or has long-lasting socioeconomic impacts on survivors in the form of neurologic disabilities [x]. Malaria results in a loss of USD $12 billion in GDP per year in Africa and 35.4 million disability-adjusted life years due to mortality and morbidity, to which CM is one of the major contributors [iv]. These deaths and co-morbidities could be prevented by a highly specific test for CM, such as ASPIRE, which will alleviate this economic burden by increasing the accuracy of CM diagnosis, leading to accurate treatment of underlying diseases, and saving lives [x].

Clinical Significance. CM is caused by the *Plasmodium falciparum* (*Pf*) parasite, which causes retinal abnormalities unique to MR such as retinal whitening and white-centered hemorrhages. For a comatose patient who tests positive for *Pf*, MR screening improves the specificity of CM diagnosis from 61% (World Health Organization [WHO] criteria for CM diagnosis) to 100% (WHO criteria + MR screening) [v]. However, African countries lack adequate numbers of ophthalmologists and enough ophthalmic equipment to screen for MR and to serve the affected population; for example, Malawi has only four ophthalmologists treating a population of 18 million. *ASPIRE provides an AI-supported and highly specific test that increases the positive predictive value (PPV) of CM diagnosis and can be used by a minimally trained non-ophthalmic health-care provider*. ASPIRE is designed to fulfill the clinical need in Africa with a low-cost, portable, and quick diagnostic tool, which makes it ideal for bedside diagnosis.

Clinical Benefit. The true prevalence of CM in clinically diagnosed cases is 77% (23% false positives) [v]. The use of ASPIRE (specificity = 95%) in addition to the WHO criteria

(specificity = 61%) increases the PPV of CM diagnosis from 0.89 to 0.99 and reduces the number of misdiagnosed CM patients from 11% to 1%. Based on a yearly incidence of clinically diagnosed CM patients between 2 and 2.5 million, the use of ASPIRE in addition to WHO criteria can reduce the number of misdiagnosed patients by over 200,000, leading to appropriate diagnosis, correct treatment, and saved lives.

***The proposed project will lead to the rollout of the first AI-supported bedside tool for detection of malarial retinopathy to improve accuracy in diagnosis of cerebral malaria*.** ASPIRE was *designed in response to* three major clinical needs in Africa: First, it can be operated by minimally trained (or non-ophthalmic) personnel, thus addressing the shortage of ophthalmologists in African countries. ASPIRE will thus be in demand by a variety of healthcare services from major hospitals to individual community healthcare workers that can use ASPIRE effectively. Second, ASPIRE is designed to be affordable (~USD $1,500), portable, and easily accessible to the affected population. Third, ASPIRE can be augmented with software modules to detect other equally preventable retinal diseases, such as diabetic retinopathy (DR) and hypertensive retinopathy (HTR), thus increasing its cost-effectiveness.

3. METHODOLOGY

STUDY SITE

This study will be conducted within the malaria endemic regions of Nigeria. The study population will be enrolled at each of the following study sites located within the malaria endemic region of Nigeria;

1. University College Hospital, Ibadan
2. Amino Kano University, Kano
3. General Sani Abacha Specialist Hospital, Damaturu
4. State Specialist Hospital, Sokoto
5. Massey's Children Hospital, Lagos Island

STUDY DESIGN

This will be a prospective, pivotal, multi-center clinical study.

STUDY POPULATIONS

Study participants involved in this study will be children aged between 6 months and 12-year-old who have been diagnosed with cerebral malaria.

Inclusion Criteria:

- Children aged 6 months- 12 years admitted to any one of the study sites who satisfy the standard clinical case definition of cerebral malaria

  - Blantyre coma score of ≤2
  - Known results of a positive malaria test (blood smear or malaria rapid diagnostic test)
- Consent provided by parents/caregivers of the eligible children.

Exclusion criteria:

- Children admitted who satisfy the standard clinical case definition of cerebral malaria, but when there is no clinician/nurse available to do an examination within 6 hours of admission.

SAMPLING

Sample size determination

We aim to demonstrate MR detection performance on a validation dataset collected with continuous enrollment of clinically diagnosed CM patients with or without malarial retinopathy. About 61% of CM-diagnosed patients show a manifestation of CM in retina, in form of retinal lesions, called malarial retinopathy (MR) [xi,xii,xiii]. Rest 39% of CM-diagnosed patients do not exhibit MR. So, the prevalence of MR in CM-diagnosed patients is 61%.

The study hypothesis is that the sensitivity and specificity of detecting MR using ASPIRE's MR detection algorithm is non-inferior to the clinical reference standard, which is defined as the reading of retinal images for MR detection by ophthalmic specialists such as ophthalmologists.

Non-Inferiority test design:

According to literature studies, the sensitivity and specificity of ophthalmologists in reading retinal images to detect retinal diseases are 89% and 87%, respectively [xiv]. We aim to demonstrate that the sensitivity and specificity of our software-based test are non-inferior to the ophthalmologist's standard, with 7% non-inferiority margin [xv]. Therefore, the lower-bound on both sensitivity and specificity will be at least equal or greater than the minimum sensitivity and specificity requirements for a diagnostic software as recommended by the FDA, of 80% and 80%, respectively.

The study will use a non-inferiority design and seek to demonstrate that the experimental method (software-based reading of retinal images) is not appreciably worse than the standard method (ophthalmologist's reading of retinal images). The reason behind using a non-inferiority design is that the proposed software-based test is not expected to be better than the standard test (ophthalmologist's reading of retinal images) on a primary efficacy end point in clinical study; but the availability, accessibility, affordability, and compliance of the proposed software-based test will be better outside the clinical study and hence efficacy will be better outside the study. Therefore, the proposed software-based test has potential to provide greater clinical benefit and/or outcome at the cost of being non-inferior in performance compared to the standard test [xvi].

In this study design, we used Blackwelder formula [xvii,xviii] to calculate sample size:

$$N_{cases} = \frac{(Z_\alpha + Z_\beta)^2}{(\pi_S - \pi_E - d)^2}\left[\pi_E(1-\pi_E) + \frac{\pi_S(1-\pi_S)}{\lambda}\right],$$

where

$$\lambda = \left(\frac{1 - Prev}{Prev}\right).$$

The conjectured accuracy (sensitivity/specificity) of the standard test is π_S, the conjectured accuracy (sensitivity/specificity) of the proposed diagnostic/experimental test is π_E. *Zα* and *Zβ* are standard values assuming 80% power and 5% Type-I error. "*Prev*" is prevalence of disease-positive patients, and "*d"* is a non-inferiority margin.

A statistical calculator developed by the National Institutes of Health - National Cancer Institute (NIH-NCI) Statistics group [xix] (that implements Blackwelder's formula) was used to perform the sample size calculations. To verify the calculations, an "R-Studio" package was used that includes a function to calculate the sample size needed for two sample non-inferiority test. The R package is *"epiR"* and the function that performs sample size calculations is *"epi.ssninfb()"* [xx]. The documentation for this function also references the Blackwelder (1982) method used by the NIH-NCI Statistics group, and contains two examples illustrating how the function is used to perform sample size calculations for a non-inferiority study with a binary outcome measure.

Input parameters:

The input parameters required for sample size calculation are the expected response rates in each group (experimental and standard), non-inferiority margin, power, alpha, and prevalence of disease-positive (MR-positive) patients.

For our study, we propose to determine a sample size required to test our software-based test for MR detection for binary classification ("MR detected" or "MR not detected"). The conjectured sensitivity of the standard test is π_S = 0.89 (ophthalmologist's sensitivity), and the conjectured sensitivity of the proposed experimental test is π_E = 0.89. At the noninferiority margin of d = 0.07, how many subjects should we include in the study to maintain 80% power and 5% Type-I error, while assuming the prevalence of Referral (MR-positive or MR detected) in the CM-diagnosed population to be 61%?

Results

The input parameters used to demonstrate the conjectured sensitivity of the experimental test of 0.89, yielded the sample size requirement as the minimum number of disease-positive "cases" of 318, and minimum number of disease-negative "controls" of 203.

Using the same method, the input parameters used to demonstrate the conjectured specificity of the experimental test of 0.87, yielded the sample size requirement as the minimum number of disease-positive "cases" of 366, and minimum number of disease-negative "controls" of 234.

Conclusion

To establish that our software-based test is non-inferior to the standard test (ophthalmologist's reading of images), with sensitivity of 0.89 and specificity of 0.87; we will require a minimum number of disease-positive (MR-positive) "cases" of 366, and minimum number of disease-negative (MR-negative) "controls" of 234. In total, we will require a minimum sample size of 600 CM-diagnosed patients to validate our proposed test.

Once we enroll the minimum number of MR-positive and MR-negative patients required, we propose to validate the software-based test performance on the collected sample and verify if the resulting sensitivity/specificity is within the margin of difference. Upon verification, it can be concluded that the experimental test is non-inferior to the standard test within a non-inferiority margin of 7%.

Sampling procedure

The procedure will be as follows:

1. Pupillary light response is checked and then pupils are dilated with 0.5% tropicamide and 10% phenylephrine, repeated after 10 minutes.
2. Ophthalmologist, clinician or nurse takes iNview photos (at least 8 photos: 4 optic disc center, 4 macula center)
3. Ophthalmologist, clinician or nurse takes VistaView photos (at least 8 photos: 4 optic disc center, 4 macula center)
4. Ophthalmologist, clinician or nurse takes Pictor-Plus photos (at least 8 photos: 4 optic disc center, 4 macula center)
5. The retinal photos captured by Pictor-Plus, VistaView, and iNview cameras may be transmitted to a laptop computer or smartphone automatically and analyzed instantaneously for image quality by a computer-based software. The software will either accept or reject each photo based on high or low image quality, respectively. A graphical display on a laptop computer or smartphone

will be shown to the imager (ophthalmologist, clinician, or nurse) that demonstrates the captured image and whether it was accepted or rejected.

6. The retinal photos captured by Pictor-Plus, VistaView, and iNview cameras will be analyzed instantaneously for detection of malarial retinopathy (MR) by a computer-based software. The imager (ophthalmologist, clinician, or nurse) will be masked to MR detection results due to non-interventional nature of this study.
7. The analysis of retinal photos for image quality and MR detection will be fully automatic and handled by a laptop computer or smartphone and will not require manual inputs or interference from the imager.
8. Ophthalmologist performs BIO when possible.

The following conditions apply to the steps above:

a) All the children will have the retinal images taken and when possible, a BIO (if available) conducted by an ophthalmologist as part of the study component.
b) Fundus examination and photography will be done as soon as the pupils are a minimum of 6 mm or not more than 1-hour post dilation.
c) The order of steps 2-4 can be interchanged or some of the steps can be omitted (depending upon camera availability) at the discretion of the ophthalmologist/clinician/nurse but once determined, efforts will be followed consistently with each patient.
d) Ideally the examinations will take place within a few minutes of each other, but if this is not possible, no more than 2 hours between examinations will be accepted

(due to possibility of changes in the clinical features). The camera images are time stamped so that this can be verified.

e) The data collection form will be the "standard form" used in previous studies of MR.

The retinal image data obtained using Pictor-Plus, VistaView, and iNview will be analyzed by an independent retinal grader masked to the ophthalmologist's findings in the BIO exam.

EXAMINATION PROCEDURE FOR RETINAL CAMERAS (Pictor-Plus, VistaView, iNview)

The right eye will be examined first with slow "panning" in image mode of the disc, the macula, the horizontal raphe, along all four main vascular arcades, and a 360-degree survey outside the arcades. The left will be examined the same way. These procedures may have to be modified if the eyes are deviated or the head position is restricted due to intravenous catheter. Images collected by Pictor-Plus, VistaView, and iNview will be transmitted to a laptop computer or smartphone automatically and analyzed instantaneously for image quality by a computer-based software. The software will either accept or reject each photo based on high or low image quality, respectively. A graphical display on a laptop computer or smartphone will be shown to the imager (ophthalmologist, clinician, or nurse) that demonstrates the captured image and whether it was accepted or rejected. Further, the images will be analyzed instantaneously for detection of malarial retinopathy (MR) by a computer-based software. The imager (ophthalmologist, clinician, or nurse) will be masked to MR detection results. The images will be independently graded by a retinal grader masked to the BIO exam and clinical status. The user will

record his/her feedback on each retinal camera device, its ease of use, view on the quality of the images and suggestions for improvements to the computer

CLINICAL CARE

The children in this study will all be patients at one of the participating clinics or hospitals. They will all receive standard medical treatment for their acute illness. Clinical care will be provided according Nigeria's MOH guidelines for the treatment of malaria and standard guidelines at each site. Briefly, children with presumed CM may receive intravenous artesunate followed by a full course of artemether-lumefantrine. Anticonvulsants, antipyretics, antibiotics and blood transfusions will be administered as necessary. If specific ophthalmic problems are identified, an appropriate treatment or referral will be initiated to a local ophthalmic unit, following recovery from the child's acute illness.

TYPE OF DATA TO BE COLLECTED

Data will be collected on clinical and laboratory report forms, and retinal images with their interpretations. All study participants will be assigned a unique identification number (UNID) that will be used to link the information gathered over the course of the study.

Demographic data collected will include age, village location and home, sex, bed net use, and occupation. Clinical assessment data collected will include recent past history of malaria infections or malaria medications, general health information, temperature, respiratory rate, heart rate, and physical exam findings. Laboratory data to be collected

includes presence and density of malaria parasites (by blood smear and RDT) and hemoglobin.

Retinal images, retinal image interpretation in the form of grading and annotations of the images by an independent retinal grader, as well as the results of the indirect ophthalmoscopy (BIO) examination performed by an ophthalmologist (when possible). Images and other data will be stored in the portable storage devices such as hard-drives or jump-drives. The data will be transferred from each device on a daily basis to a secure computer at the hospital and backed up on a portable hard drive or to a Cloud-based server. The image data will be transmitted to the retinal graders using portable storage devices or through online storage facilities such as “Dropbox” or Cloud-based server in a secure manner. The retinal grader’s image interpretations done off-site will be indexed with the images and stored in a secure computer and backed up on a portable hard drive. Data will be entered into case report forms for archiving and then double-entered from the report forms into password-protected spreadsheets using predetermined metafile coding values (and internal error-checking protocols) in order to minimize coding errors prior to analysis. Data entry and cleaning will occur in institutional research offices**.** The data of retinal images and their interpretations will be cleaned, stored, and imported to VisionQuest Biomedical’s research team for analysis.

PROVISIONS FOR DATA VERIFICATION AND VALIDATION IN FIELD AND LABORATORY

We have developed a detailed data verification scheme that includes checking digital data against original data sheets, double data entry, and algorithms designed to identify data

collection or entry errors. A key component of this system is immediate data entry and revision to provide immediate feedback to field teams in the case of systematic errors in data collection.

DATA MANAGEMENT

All written forms (i.e., consent and data collection forms) will be stored in locked cabinets at institutional research offices. All forms will be labeled and filed in filing cabinets with the Study Protocol Number, Principal Investigators' name and collection dates. These cabinets will be metal and have functioning locks. Keys will be kept with local PI. The database will be password protected and access to password will be authorized by the local Principal Investigators. Electronic data files will be stored on VisionQuest-operated and-dedicated server laptop or smartphone. The paper forms will be stored for the duration of the study plus three years per IRB protocol for primary data storage. The electronic database will be stored indefinitely by the Principal Investigators. Retinal images and relevant interpretation data will be stored in encrypted portable storage devices such as hard-drives or jump-drives and/or on Cloud-based servers. The data will be transferred from each device on a daily basis to a secure computer at the hospital and backed up on a portable hard drive or to a Cloud-based server. The image data will be transmitted to the retinal graders in a secure manner. The retinal grader's image interpretations done off-site will be indexed with the images and stored in a secure computer and backed up on a portable hard drive. The data will be cleaned, stored, and exported to VisionQuest Biomedical's research team for analysis.

DATA ANALYSIS

To address *study question #1,* the data include both images and the interpretations, grading and annotations of the images by an independent retinal grader, as well as the results of the indirect ophthalmoscopy (BIO) performed by an ophthalmologist (when possible). Images are stored in the portable storage devices such as hard-drives or jump-drives. The image data will be transferred from each device on a daily basis to a secure computer at each hospital and backed up on a portable hard drive or on Cloud-based servers. The image data will be transmitted to the retinal graders using portable storage devices or through online storage facilities such as “Dropbox” or “Cloud” in a secure manner. The retinal grader’s image interpretations done off-site will be indexed with the images and stored in a secure computer and backed up on a portable hard drive. At the end of the study, data will be cleaned and imported into Stata for analysis.

To answer *study question #2*, sensitivity and specificity with 95% CI will be calculated for each of the following:

- presence or absence of MR (any hemorrhage, whitening or abnormal vessels) between:

To answer *study question #3*, positive predictive value (PPV) and negative predictive value (NPV) will be calculated to evaluate software algorithm’s performance in classifying a retinal image for presence or absence of each of the following MR lesions, against retinal grader’s grading for the presence of respective lesions.

The analyses described above will be performed for subgroups determined by malaria test results as well. It is not possible to mask the malaria status from the examining clinicians. The analysis results will be presented in form of tables.

DISSEMINATION OF THE RESULTS

Results of the study will be provided to VisionQuest Biomedical and NHERC in the final report, presented locally in Nigeria, and submitted to an international journal for publication. Standard rules for authorship on a final publication will apply.

A copy of the final report and any published paper(s) or abstracts of papers read at conferences out of the research findings will be submitted to each of the following:

1. VisionQuest Biomedical Inc.
2. University College Hospital, Ibadan, Nigeria
3. Amino Kano University, Kano
4. General Sani Abacha Specialist Hospital Damaturu
5. State Specialist Hospital Sokoto -
6. Massey's Children Hospital, Lagos Island

A copy of the data (including photos) will be distributed to all of the above institutions, if necessary, for use in future analysis upon agreement of the main investigators.

ETHICAL CONSIDERATIONS

Study personnel trained in human ethics will obtain informed consent from parents of study participants. The Principal and co-investigators will conduct on-site training sessions for Nigerian study staff who will be collecting study information and obtaining

consent from study participants. The study will be explained in detail to the local study staff. The basic principles of informed consent process, documentation of informed consent, protection of subjects' rights, confidentiality, and handling of data will be covered in these training sessions. All training sessions will be documented, and study staff monitored by the on-site project manager on a regular basis to ensure compliance with the principles of informed consent.

A discussion of the minimal risk and possible benefits of this study will be provided to caregivers of subjects. Consent forms describing in detail the study interventions/products, study procedures, and risks will be provided to the caregiver and written documentation of informed consent will be required prior to instilling mydriatic eye drops and obtaining fundus images.

Consent forms will be IRB-approved and the caregiver will be asked to read and review the document. Upon reviewing the document, the nurse initiating informed consent will explain the research study to the subject and answer any questions that may arise. Caregivers will sign the informed consent document prior to any procedures being done specifically for the study. If the parent/guardian is illiterate, the consent will be explained verbally. If the parent/guardian is unable to form a signature, a thumb print will be obtained instead, and a witness who has observed the process will sign the form see attached patient information/ consent form. In all cases the pertinent material will be supplied in both oral and written form. Forms will be available in English and the local language. The caregiver will be supplied with a copy of the consent form and given ample time to ask

questions regarding specifics of the study. A study clinician or study nurse will review the study consent with the parents or guardians accompanying the child.

Although all subjects will be minors under the age of eight, the subjects will not be capable of providing assent to participate because all will be, by definition, comatose. They will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Caregivers may withdraw consent at any time throughout the course of the data capture. A copy of the informed consent document will be given to the caregivers for their records. The rights and welfare of study subjects will be protected by emphasizing to caregivers that the quality of their child's medical care will not be affected if they decline to participate in this study.

The decision to approach the parent/guardian for screening will only be made after the participant has been stabilized clinically and anti-malarial therapy commenced. In the context of obtaining informed consent, the wide spectrum of CM disease presentation will be explained and our desire to collect funduscopic images will be presented. The fact that this does not represent treatment will be explained.

If the parent/guardian consents to the study, mydriatic eye drops will be added to the participant's eyes and fundus photos will be collected as explained in patient information and consent form.

Although all subjects will be minors under the age of twelve, the subjects will not be capable of providing assent to participate because all will be, by definition, comatose. They represent a vulnerable population by virtue of being unconscious, hence the importance of securing consent from the caregivers.

SAFETY REPORTING:

Any adverse events associated with this study will be immediately reported to the IRBs.

RISKS

This study does not introduce any invasive procedures into the routine care provided for children with CM. Dilation of the pupils with short acting drugs (0.5% tropicamide and 10% phenylephrine) is essential to proper fundoscopy and it is a routine practice of ophthalmologists. Fundus photography is non-invasive and not harmful. Data collected will not include patient identifiers.

Direct Benefit

There is no direct benefit to the individual other than involvement in the study may result in the development of an automated system that can be integrated to a smartphone and low-cost retinal camera for the detection of specific signs of MR and for detecting the presence of MR. This system will be convenient for use in non-ophthalmic, non-clinical settings, making it highly accessible and affordable to the targeted population where other CM diagnostic methods are limited.

Indirect Benefits

The study as designed presents no potential direct benefit to the participants because this is an observational not interventional study. However, an indirect benefit of participating in the study is that the retinal images obtained from this study will be used to develop and refine a software system for the comprehensive analysis of MR abnormalities and detection of the presence/absence of MR. This would also mitigate the challenges of training healthcare staff to perform ophthalmoscopy and/or interpret retinal images. The software system can be tuned to yield high specificity, addressing the current clinical requirement to prevent deaths resulting from misdiagnosis of CM. The algorithm can also include detection of a number of eye diseases including diabetic retinopathy and age-related macular degeneration.

COMPENSATION:

No monetary compensation will be offered to study participants. All study activities will take place during the acute illness episode, there is little to no risk, and no pain at all.

METHOD OF MAINTAINING CONFIDENTIALITY

Privacy of Participants: Privacy will be maintained by assigning a Unique Identifying Number (UNID) to each participant enrolled in this study. This number will be used to label the retinal images. The database linking personal identifiers to this study number will be kept by the Principal Investigators. Original data collection forms, such as consent forms and CRFs will be stored in a locked filing cabinet at designated study offices. All study personnel will be required to complete training for the ethical conduct during human

investigation research. Since these field assistants have either direct contact with our study participants or may be privy to protected health information, it was deemed important for them to understand the history behind the rights of study participants in order to protect their privacy and confidentiality.

Confidentiality of data: Risks to confidentiality are protected by codifying all personal information except for a single master file linking the subject's name to the UNID. This file is maintained and updated by the PIs. The Principal Investigators, Co-investigators will use the results of this study for publications, presentations at scientific meetings or preliminary data for subsequent grant applications. Confidentiality of study participants will be maintained by not using names or personal identifiers. The PI will permit access to all documents and records that may require inspection by the respective funding agencies, governmental regulatory agencies, institutional review boards or its authorized representatives.

EXPECTED APPLICATION OF THE RESULTS:

This study would be a **first step** in the validation of retinal image analysis software for assessment of MR and CM. The results of the study will be used to inform initiatives to spread the use of software-based detection of MR to preclinical settings in which CM patients are seen. Results will also be useful in planning studies to quantify the detection of MR lesions and analyze large datasets in objective manner. In the long term, the development of automated algorithms that will be integrated to a smartphone could prevent widespread misdiagnosis of cerebral malaria in low-income countries, helping more children receive accurate diagnoses of CM.

TIME FRAME/DURATION OF THE PROJECT

This study is anticipated to take a duration of 2 years to complete. Study participants will be in the study for the period they are admitted to the hospital. Recruitment of subjects will occur over the two years. A summary of the study timeline and data analysis is presented below:

Benchmarks	**Performance Site**	**Y1**	**Y2**
Develop SOPs (Aims 1-4)	VisionQuest, Nigeria	X	
Develop Clinical Protocols, IRB approvals for study	VisionQuest, Nigeria	X	
Enroll CM cases and Collect Retinal images	Nigeria	X	X
Data analysis	VisionQuest, Nigeria	X	X
Manuscript preparation	VisionQuest, Nigeria		X
Report preparation and dissemination	Nigeria		X

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7. LIST OF ABBREVIATIONS

CM - Cerebral Malaria

MR - Malaria Retinopathy

BIO - Binocular indirect ophthalmoscopy

AI - Artificial Intelligence

GDP – Gross Domestic Product

8. INFORMED CONCENT

IRB Research approval number: ####

This approval will elapse on: dd/mm/yyyy

Title of the research: Analyzing the Performance of Automated Software in the Identification of Malarial Retinopathy in Digital Retinal Images of Cerebral Malaria Patients

Sponsors of the research: This study is sponsored by VisionQuest Biomedical Inc., USA

Purpose(s) of research:

The overall aim of the proposed study is to collect digital retinal color image data of clinically diagnosed Cerebral Malaria patients and utilize the images to develop and test the performance of software algorithms for detecting specific signs of Malaria Retinopathy and for detecting the presence of Malaria Retinopathy. The performance of the software will be measured against the binocular indirect ophthalmoscopy (BIO) examination (if available) performed by an ophthalmologist or image grading from a certified retinal grader.

Procedure of the research, what shall be required of each participant and approximate total number of participants that would be involved in the research:

The overall aim of the proposed study is to collect digital retinal color image data from 800 clinically diagnosed Cerebral Malaria (CM) patients from the malaria endemic regions of Nigeria and utilize the images to develop and test the performance of software algorithms (ASPIRE) for detecting specific signs of Malaria Retinopathy (MR) and for detecting the presence of MR. The performance of the software will be measured against

the binocular indirect ophthalmoscopy (BIO) examination (if available) performed by an ophthalmologist for determining the presence of MR (reference standard) and/or against the grading of established retinal graders. From March 2022 or as soon as the ethics committee approves the protocol, children aged between 6 months and 12 years who present with coma, a positive malaria test, and clinically confirmed diagnosis of cerebral malaria will be enrolled at the time of admission at the respective participating hospitals. After obtaining informed consent from the parent/guardian, both eyes will be dilated, and photos of the eyes will be collected using each of the three different cameras. There are no risks that are involved in taking part in this study. All the other procedures such as collection of samples are standard procedures in the diagnosis of malaria. Findings from this study will help in the development of a low-cost system that will be integrated to a smartphone that will help clinicians in low-income countries to clearly diagnose cerebral malaria.

Expected duration of research and of participant(s)' involvement:

In total, we expect the study to last for two years, you or your ward\child will be involved in the study for the period that your child/ward is on admission for treatment of cerebral malaria (1 to 4 weeks), to be involved in this research for 1 year.

Risks

This study does not introduce any invasive procedures into the routine care provided for children with CM. Dilation of the pupils with short acting drugs (0.8% tropicamide and 5% phenylephrine) is essential to proper fundoscopy and it is a routine practice of

ophthalmologists. Fundus photography is non-invasive and not harmful. Data collected will not include patient identifiers.

Costs to the participants, if any, of joining the research:
Your participation in this research will not cost you anything.

Benefit(s):
Direct Benefit

There is no direct benefit to the individual other than involvement in the study may result in the development of an automated system that can be integrated to a smartphone and low-cost retinal camera for the detection of specific signs of MR and for detecting the presence of MR. This system will be convenient for use in non-ophthalmic, non-clinical settings, making it highly accessible and affordable to the targeted population where other CM diagnostic methods are limited.

Indirect Benefits

The study as designed presents no potential direct benefit to the participants because this is an observational not interventional study. However, an indirect benefit of participating in the study is that the retinal images obtained from this study will be used to develop and refine a software system for the comprehensive analysis of MR abnormalities and detection of the presence/absence of MR. This would also mitigate the challenges of training healthcare staff to perform ophthalmoscopy and/or interpret retinal images. The software system can be tuned to yield high specificity, addressing the current

clinical requirement to prevent deaths resulting from misdiagnosis of CM. The algorithm can also include detection of a number of eye diseases including diabetic retinopathy and age-related macular degeneration.

Confidentiality:

Privacy of Participants: Privacy will be maintained by assigning a Unique Identifying Number (UNID) to each participant enrolled in this study. This number will be used to label the retinal images. The database linking personal identifiers to this study number will be kept by the Principal Investigators. Original data collection forms, such as consent forms and CRFs will be stored in a locked filing cabinet at designated study offices. All study personnel will be required to complete training for the ethical conduct during human investigation research. Since these field assistants have either direct contact with our study participants or may be privy to protected health information, it was deemed important for them to understand the history behind the rights of study participants in order to protect their privacy and confidentiality.

Confidentiality of data: Risks to confidentiality are protected by codifying all personal information except for a single master file linking the subject's name to the UNID. This file is maintained and updated by the PIs. The Principal Investigators, Co-investigators will use the results of this study for publications, presentations at scientific meetings or preliminary data for subsequent grant applications. Confidentiality of study participants will be maintained by not using names or personal identifiers. The PI will permit access to all documents and records that may require inspection by the respective funding

agencies, governmental regulatory agencies, institutional review boards or its authorized representatives.

All information collected in this study will be given code numbers and no name will be recorded. This cannot be linked to you in anyway and your name or any identifier will not be used in any publication or reports from this study. As part of our responsibility to conduct this research properly, officials from NAFDAC, NHREC and ethics and food and drugs regulators from the United States may have access to these records.)

Voluntariness:
Your participation in this research is entirely voluntary.

Alternatives to participation:
If you choose not to participate, this will not affect your treatment in this hospital in any way.

Due inducement(s):
No monetary compensation will be offered to study participants. All study activities will take place during the acute illness episode, there is little to no risk, and no pain at all.

Consequences of participants' decision to withdraw from research and procedure for orderly termination of participation:
You can also choose to withdraw from the research at any time. Please note that some of the information that has been obtained about you before you chose to withdraw may have been modified or used in reports and publications. These cannot be removed

anymore. However, the researchers promise to make good faith effort to comply with your wishes as much as is practicable.

Modality of providing treatments and action(s) to be taken in case of injury or adverse event(s):

If you suffer any injury or adverse events highly (unlikely) as a result of your participation in this research, you will be treated at the Hospital where the study is conducted and the research will bear the cost of this treatment.

What happens to research participants and communities when the research is over:

The researchers will inform you of the outcome of the research through a news bulletin. During the course of this research, you will be informed about any information that may affect your continued participation or your health.

Statement about sharing of benefits among researchers and whether this includes or exclude research participants:

If this research leads to commercial products, the sponsors and researchers shall jointly own it. There is no plan to contact any participant now or in future about such commercial benefits.

Any apparent or potential conflict of interest:

None of the researchers own shares in Vision Quest Biomedicals Inc or its associated companies. We are not aware of any other information that may cause the researchers not to do their work with fear or favour.

Statement of person obtaining informed consent:

I have fully explained this research to _____ and have given sufficient information, including about risks and benefits, to make an informed decision.

DATE: _____ SIGNATURE: _____

NAME: _____

Statement of person giving consent:

I have read the description of the research or have had it translated into language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form and additional information sheet to keep for myself.

DATE: _____ SIGNATURE: _____

NAME: _____

WITNESS' SIGNATURE (if applicable): _____

WITNESS' NAME (if applicable): _____

Detailed contact information including contact address, telephone, fax, e-mail and any other contact information of researcher(s), institutional HREC and head of the institution:

This research has been approved by the Health Research Ethics Committee and the Chairman of this Committee can be contacted at ….. The phone and fax numbers are …… In addition, if you have any question about your participation in this research. In addition, if you have any question about your participation in this research, you can contact the principal investigator at the Hospital your child is admitted.

9. ACCENT FORMS

Title of Study: Analyzing the Performance of Automated Software in the Identification of Malarial Retinopathy in Digital Retinal Images of Cerebral Malaria Patients

Study Coordinator:

Dr Vinayak Joshi, VisionQuest Biomedical Inc., USA

We want to tell you about a research study we are doing. A research study is a way to learn more about something. We would like to find out more about the Performance of Automated Software in the Identification of Malarial Retinopathy in Digital Retinal Images of Cerebral Malaria Patients

You are being asked to join the study because your ward has been suspected to have cerebral malaria.

If you agree to join this study, you will be asked to allow us take a use this device to take a picture by placing over the eyes for about 30 seconds to 1 minute each only once.

There is absolutely no risk or damages involved. It is not painful.

We expect that the study will help you by *accurately diagnosing of you have Cerebral Malaria*

This study will help us learn more about Performance of Automated Software in the Identification of Malarial Retinopathy in Digital Retinal Images of Cerebral Malaria Patients

You do not have to join this study. It is up to you. You can say okay now and change your mind later. All you have to do is tell us you want to stop. No one will be mad at you if you don't want to be in the study or if you join the study and change your mind later and stop.

Before you say **yes or no** to being in this study, we will answer any questions you have. If you join the study, you can ask questions at any time. Just tell the researcher that you have a question.

If you have any questions about this study, please feel free to contact PI's name and contact here

☐ Yes, I will be in this research study. ☐ No, I don't want to do this.

Child's name	Signature	Date

Person obtaining Assent	Signature	Date

10. APPENDIX

Appendix 1: Technical specifications of study devices:

Technical specifications for Pictor-Plus:

Volk's Pictor-Plus is a hand-held fundus camera with interchangeable modules. The four imaging modules include posterior and anterior segment, dermatoscopic, and otoscopic. The Pictor Plus provides 5-megapixel image (1536 X 1152 pixels) resolution and incorporates Wi-Fi technology for image transfer to a PC. An easy-access micro SD card slot may be used as a temporary storage unit for images. LED illumination is available in white or blue. The cobalt blue LED light allows for fluorescent imaging to detect dry eye, cuts, or rashes on the anterior segment of the eye. The white LED is used for fundus imaging. There are three focus modes: Auto, Auto Focus (AF) Assist, and Manual.

Specifications	Pictor-Plus
Resolution	5 Megapixels
Image dimensions	1536 X 1152
Image Format	JPEG and Video
Field of View	40 Degree
Pixel footprint	27 microns
Focus Range	-20 to +20D

Minimum Pupil Size	3 mm
Fundus Lighting	White LED
Weight	400g (~1 lb)
Power Supply	Rechargeable NI-MH Battery (3 hours)
Connectivity	Wi-Fi, USB

Technical specifications for iNview:

The Volk iNview is an ophthalmic camera used to acquire wide-angle digital color images of the retina (fundus) using an Apple iPhone or iPod. It is a combination product comprised of a mobile application (Apple App Store) and an indirect ophthalmoscopic lens attachment that fits for an Apple iPhone/iPod. The iNview device used in the proposed study is a simple adapter currently used on iPhone smartphone (http://www.volk.com/index.php/volk-products/ophthalmic-cameras/volk-inview.html).

This aligns the optics of the phone's camera with a light source. iNview camera obtains a wide 50-degree field of view to visualize the entire posterior pole in one image. Images taken with Volk iNview are stored with patient data and can be easily exported to a PC or Mac. iNview's user guide can be referred here: http://www.volk.com/media/ifu/im088/im088english.pdf

Technical specifications for VistaView:

The Volk VistaView is an ophthalmic camera used to acquire wide-angle digital color images of the retina (fundus) using a smartphone. The VistaView device used in the proposed study is a simple adapter used on smartphone (https://www.volk.com/products/vistaview%E2%84%A2). This aligns the optics of the phone's camera with a light source. VistaView is a mydriatic camera with following specifications:

• VOICE-ACTIVATED IMAGE CAPTURE for when you need an extra hand!

• RED-FREE FILTER to help enhance vascular visualization

• USB-C CHARGING - no external batteries needed!

• WIRED EXPORT TO PC VIA USB-C - just drag and drop your files to your computer

• INSTANT REPORT GENERATION WITH CASE NOTES so you can see your next patient sooner

• DICOM FILE EXPORT to easily connect your patient images to your EMR

• PASSWORD PROTECTED DATA EXPORT to provide a layer of protection during data sharing

• ON-BOARD PATIENT DATA SEARCH AND SORTING - all your patient data in one place

• AUTOFOCUS & MANUAL FOCUS WITH -15D TO +15D ADJUSTMENT - choose your level of control

• ILLUMINATION ADJUSTMENT TO HIGH, MEDIUM OR LOW SETTINGS - comfort for your patients.

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