PIVOTAL PROSPECTIVE CLINICAL TRIAL TO DEMONSTRATE THE EFFICACY AND SAFETY OF AEYE-DS SOFTWARE DEVICE FOR AUTOMATED DIABETIC RETINOPATHY DETECTION FROM DIGITAL FUNDUSCOPIC IMAGES

Product: AEYE-DS

Protocol Number: AEYE-DS-001

Development Phase: Clinical Validation

Sponsor: AEYE HEALTH INC.

[redacted]

Protocol Approval Date:

Current protocol Version No.3.4 November 24, 2021

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonization (ICH); Israel Ministry of Health; United States (US) Code of Federal Regulations (CFR) and the Sponsor's Standard Operating Procedures (SOPs).

PROTOCOL SYNOPSIS

Protocol Number	AEYE-DS-001
Protocol Title	Pivotal prospective clinical trial to demonstrate the efficacy and safety of the AEYE-DS software device for automated diabetic retinopathy detection from digital funduscopic images.
Location(s)	5-10 primary care clinics in the US
Phase of Development	Clinical Validation, Pivotal Study
Study Population	Adult patients who are clinically diagnosed with diabetes and who have undergone a digital funduscopic examination, and have not been previously diagnosed with diabetic retinopathy.
Study Objectives	To evaluate the performance and usability of the AEYE-DS software for the detection of more than mild diabetic retinopathy (mtmDR) on digital funduscopic images from patients with known diabetes obtained from a Topcon NW400 fundoscopy device (an FDA cleared desktop camera).
Number of Patients:	A minimum of 350 and a maximum of up to 774 subjects will be enrolled in the Pivotal Study. [redacted].
Inclusion Criteria:	1. Age≥22 2. Male or female 3. Documented diagnosis of diabetes mellitus, meeting the criteria established by the American Diabetes Association (ADA) and World Health Organization (WHO): a. Elevated Hemoglobin A1c (HbA1c) ≥ 6.5% (48mmol/mol), based on repeated assessments, performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay **OR** b. Fasting Plasma Glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L), based on repeated assessments, where 'fasting' is defined as no caloric intake for at least 8 hours **OR** c. Oral Glucose Tolerance Test (OGTT) with two hour plasma glucose (2-hr PG) ≥200 mg/dl (11.1 mmol/L), using the equivalent of an oral 75 g anhydrous glucose dose dissolved in water **OR** d. Symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose (RPG) ≥ 200 mg/dl (11.1 mmol/L)

	4. Understand the study and volunteer to sign the informed consent
Exclusion Criteria:	1. Uncorrectable vision loss (e.g., with the use of eyeglasses), blurred vision, or floaters. 2. Diagnosed with macular edema, severe non-proliferative retinopathy, proliferative retinopathy, radiation retinopathy, or retinal vein occlusion. 3. History of laser treatment of the retina or injections into either eye, or any history of retinal surgery. 4. Currently participating in another investigational eye study and actively receiving investigational product for DR or DME. 5. Participant has a condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure or glycemic control, microphthalmia or previous enucleation). 6. Participant is contraindicated for imaging by fundus imaging systems used in the study: 6.1. Participant is hypersensitive to light 6.2. Participant recently underwent photodynamic therapy (PDT) 6.3. Participant is taking medication that causes photosensitivity 6.4. Participant has a history of angle-closure glaucoma or narrow anterior chamber angles
Investigational Product:	AEYE-DS
Duration of Study:	3 to 5 months. Study duration will include performing the data acquisition alongside analysis by AEYE-DS novice operators, followed by additional image data acquisition by a professional ophthalmic photographer and reading by a panel of expert readers at the Reading Center and statistical analysis.
Primary Objective	• Primary Objective: o To assess the sensitivity of the AEYE-DS software device for the detection of more than mild diabetic retinopathy (mtmDR) on digital funduscopic images in patients with known diabetes undergoing screening for diabetic retinopathy. o To assess the specificity of the AEYE-DS software device for the detection of more than mild diabetic retinopathy (mtmDR) on digital funduscopic images in patients with known diabetes undergoing screening for diabetic retinopathy. Digital funduscopic images will be acquired by the TopCon NW400 fundoscopy device based on one macula centered image obtained per eye.
Powered Secondary Objective	• Powered Secondary Objective: o To assess the sensitivity of the AEYE-DS software device for the detection of more than mild diabetic retinopathy (mtmDR)

	on digital funduscopic images in patients with known diabetes undergoing screening for diabetic retinopathy. o To assess the specificity of the AEYE-DS software device for the detection of more than mild diabetic retinopathy (mtmDR) on digital funduscopic images in patients with known diabetes undergoing screening for diabetic retinopathy. Digital funduscopic images will be acquired by the TopCon NW400 fundoscopy device based on 2 images obtained per eye, one macula centered and one optic-disc centered.
Secondary Objectives	• Secondary Objectives: o To assess the imageability of AEYE-DS, defined as the percentage of participants with a disease level output (mtmDR+ or mtmDR-) from the AEYE-DS device. o To assess the Usability of the AEYE-DS device, including User Manual comprehension and subsequent usability of the device in the hands of potential users (i.e., primary care clinicians). o To assess the sensitivity and specificity of the AEYE-DS software device for the detection of more than mild diabetic retinopathy (mtmDR) on digital funduscopic images obtained from a handheld fundoscopy device, in patients with known diabetes undergoing screening for diabetic retinopathy. Digital funduscopic images will be acquired using the Optomed Aurora handheld fundoscopy device based on one macula-centered image obtained per eye.
Study Hypothesis	In this study, we will test the following pairs of hypotheses on the primary endpoint, as well as on the powered secondary endpoint: • H0: Se ≤ 82%, H1: Se > 82% • H0: Sp≤ 87% H1: Sp> 87% Where Se and Sp are the sensitivity and specificity of the mtmDR classification of the AEYE-DS software device.
Sample Size	At least 66 positive and 265 negative subjects are required to meet the primary and powered secondary endpoints. The study will follow a sample size adaptive design with one interim analysis planned to allow for sample size increase up to at most 774 subjects, or completion per original sample size. [redacted]

	[redacted]
Statistical analysis:	Statistical analyses will be performed using SAS® V9.4 (SAS Institute, Cary NC, USA) or higher. If not specified otherwise, any statistical tests will be two-sided. The required significance level of findings will be equal to or lower than 5%. Where confidence limits are appropriate, the confidence level will be 95%. [redacted]
Acceptance Criteria	If both null hypotheses are rejected in favor of the alternative hypotheses the study will be deemed successful, and the performance goals met.

Abbreviations

Abbreviation	Description
AAO	American Association of Ophthalmologists
AMD	Age-Related Macular Degeneration
CI	Confidence Interval
CRF	Case Report Form
DR	Diabetic Retinopathy
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c (Glycated hemoglobin is a form of hemoglobin that is measured primarily to identify the three-month average plasma glucose concentration)
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
mtmDR	more than mild Diabetic Retinopathy
NPV	Negative Predictive Value
PE	Physical Examination
PI	Principal Investigator
PPV	Positive Predictive Value
SOP	Standard Operating Procedure
SW	Software
WHO	World Health Organization

1 INTRODUCTION

Diabetic retinopathy is a highly specific neurovascular complication of both type 1 and type 2 diabetes, the prevalence of which strongly correlates to both the duration of diabetes and level of glycemic control. Diabetic Retinopathy (DR) is the leading cause of vision loss in adults between ages 20-74 [Cheung et al., 2010], and ranked as one of the most common causes of preventable blindness [Bourne,2013]. Based on a recent global report [WHO, 2014], there are over 422 million people worldwide with diabetes, and over 35% have signs of DR, a third of them with vision threatening DR. Early detection of retinopathy is an important part of managing care for people with diabetes, yet many patients with diabetes are not adequately screened for diabetic retinopathy.

Retinal imaging is known to be a diagnostic tool for DR [Walker et al. 1990] as well as other known conditions, such as Age Related Macular Degeneration (AMD), Glaucoma, Papilledema, and Hypertensive Retinopathy to name a few [Wiedemann, 1997]. High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. For this reason, the AAO recommends periodic fundus examination starting at the age of 40 [AAO, 2014]. The 2017 revision of the American Academy of Ophthalmology's Preferred Practice Pattern recommends people with no or mild DR be followed annually, whereas those with more than mild DR, and/or DME (abbreviated to mtmDR), are recommended to receive evaluation and consideration for treatment.

The ability to detect the presence of DR by computer models has been demonstrated more than once in previous work [redacted] In 2018, a medical device, IDx-DR, indicated for use as a screening diagnostic tool for DR, received FDA clearance for that purpose [FDA De Novo DEN180001]. This type of device permits the availability of a novel artificial intelligence technology that can be used in a primary care doctor's office and improve patient access to needed health care.

AEYE has also developed an AI software device (AEYE-DS) to be used as a diagnostic tool to assist primary care clinicians in screening for diabetic retinopathy using digital funduscopic images. The AEYE-DS device also automatically detects more than mild diabetic retinopathy (mtmDR) in adults (22 years of age or older) diagnosed with diabetes who have not been previously diagnosed with diabetic retinopathy.

The development of artificial intelligence medical devices carries with it responsibilities as it sets precedent for use of AI applications in the medical field, especially, when used for diagnosis in a primary care setting, with less specialized medical expertise.

Consequently, the goal of this pivotal clinical study is to demonstrate the safety and efficacy of the AEYE-DS diagnostic screening tool for automatic detection of more than mild Diabetic Retinopathy (mtmDR) from digital funduscopic images.

2 DEVICE DESCRIPTION

2.1 General Device Description

AEYE-DS is a retinal diagnostic software-only device that incorporates an algorithm to evaluate ophthalmic images for diagnostic screening to identify retinal diseases or conditions. Specifically, the AEYE-DS is designed to perform diagnostic screening for the condition of more-than-mild diabetic retinopathy (mtmDR).

[redacted]

[redacted]

2.2 Device Modules

2.2.1 [redacted]

[redacted]

2.2.2 [redacted]

[redacted]

2.2.3 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The system outputs one of three possible options:

1) Insufficient image(s) quality – low quality images can be retaken immediately, while the patient is still at the camera.
2) The patient is negative for referable mtmDR (mtmDR-).
3) The patient is positive for mtmDR (mtmDR+).

2.2.4 [redacted]

[redacted]

2.2.5 [redacted]

[redacted]

3 INTENDED USE AND INDICATIONS FOR USE

The AEYE-DS is indicated for use by health care providers to automatically detect more than mild diabetic retinopathy (mtmDR) in adults (22 years of age or older) diagnosed with diabetes who have not been previously diagnosed with diabetic retinopathy. The AEYE-DS is indicated for use with the Topcon NW400.

4 PREVIOUS CLINICAL STUDIES WITH THE INVESTIGATIONAL DEVICE

[redacted]

[redacted]

5 RATIONALE FOR STUDY

Based on a recent global report [WHO, 2014], there are over 422 million people worldwide with diabetes, and over 35% have signs of DR, a third of them with vision threatening DR. With the prevalence of diabetes expected to increase 50% over the next 10 years, screening rates, detection, and treatment must be addressed in order to prevent a significant increase in unnecessary blindness across the United States. Early detection of retinopathy through periodic screening is an important part of managing care for people with diabetes, yet screening rates are low, with only 50-60% of diabetic patients properly evaluated. An automated DR screening device would allow for immediate screening results at the point of care and standardization of results.

[redacted] The current proposed study will validate the sensitivity and specificity of the AEYE-DS output by a novice operator compared to the reference standard, diagnostic determination by an independent, blinded panel of expert ophthalmologist at the reading center.

6 STUDY OBJECTIVES

6.1 Primary Objective

The primary study objective is to evaluate the performance of the AEYE-DS software for the detection of more than mild diabetic retinopathy (mtmDR) on digital funduscopic images from patients with known diabetes (acquired by the TopCon NW400 fundoscopy device based on one macula centered image obtained per eye).

6.2 Powered Secondary Objective

The powered secondary objective of the study is as follows:

To evaluate the performance of the AEYE-DS software for the detection of more than mild diabetic retinopathy (mtmDR) on digital funduscopic images from patients with known diabetes (acquired by the TopCon NW400 fundoscopy device based on 2 images obtained per eye, one macula centered and one optic disc centered).

6.3 Secondary Objectives

The secondary objectives of the study are as follows:

- To assess the imageability of AEYE-DS, defined as the percentage of participants with a disease level output (mtmDR+ or MTMDR-) from the AEYE-DS device.
- To assess the Usability of the AEYE-DS device, including User Manual comprehension and subsequent usability of the device in the hands of potential users (i.e., primary care clinicians).
- To assess the sensitivity and specificity of the AEYE-DS software device for the detection of more than mild diabetic retinopathy (mtmDR) on digital funduscopic images obtained from a handheld fundoscopy device, in patients with known diabetes (acquired by the Optomed Aurora handheld fundoscopy device based on one macula-centered image obtained per eye).

7 SELECTION OF STUDY POPULATION

The goal of the selection criteria is to identify adult patients who have undergone digital funduscopic imaging with clinical evidence of diabetes and are screened to rule out diabetic retinopathy. The study population will consist of adult patients (at least 22 years of age) with previously diagnosed diabetes, who are participating in a routine retinal screening test for diabetic retinopathy (DR) in primary care clinics, and have digital funduscopic images of sufficient quality from a specific funduscopic camera, i.e., the Topcon Model NW400. The patients referred to the screening program must be without prior diagnoses of DR. "Diabetic" patients are defined in the Inclusion Criteria (Section 7.1 below).

The AEYE-DS device will be used in the study by clinicians who represent the actual end-users. These will be clinical personnel working in primary care facilities, who perform various screening activities for patients. The users will upload the de-identified study images and simulate the generation of a clinical decision based on the AEYE-DS algorithm results.

Evaluation of the study participant inclusion/exclusion criteria will be based on the review of clinical medical records and/or documented patient interviews conducted by the investigator or under the direction of the investigator in the application of the study inclusion and exclusion criteria, as summarized below.

To be enrolled in the study, patients must meet ALL of the inclusion criteria and NONE of the exclusion criteria designated below.

7.1 Inclusion Criteria:

1. Age ≥22
2. Male or female
3. Documented diagnosis of diabetes mellitus, meeting the criteria established by the American Diabetes Association (ADA) and World Health Organization (WHO):
   a. Elevated Hemoglobin A1c (HbA1c) ≥ 6.5% (48mmol/mol), based on repeated assessments, performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay **OR**
   b. Fasting Plasma Glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L), based on repeated assessments, where 'fasting' is defined as no caloric intake for at least 8 hours **OR**
   c. Oral Glucose Tolerance Test (OGTT) with two hour plasma glucose (2-hr PG) ≥200 mg/dl (11.1 mmol/L), using the equivalent of an oral 75 g anhydrous glucose dose dissolved in water **OR**
   d. Symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose (RPG) ≥ 200 mg/dl (11.1 mmol/L)
4. Understand the study and volunteer to sign the informed consent

7.2 Exclusion Criteria

1. Uncorrectable vision loss (e.g., with the use of eyeglasses), blurred vision, or floaters.
2. Diagnosed with macular edema, severe non-proliferative retinopathy, proliferative retinopathy, radiation retinopathy, or retinal vein occlusion.
3. History of laser treatment of the retina or injections into either eye, or any history of retinal surgery.
4. Currently participating in another investigational eye study and actively receiving investigational product for DR or DME.
5. Participant has a condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure or glycemic control, microphthalmia or previous enucleation).
6. Participant is contraindicated for imaging by fundus imaging systems used in the study:
   a. Participant is hypersensitive to light
   b. Participant recently underwent photodynamic therapy (PDT)
   c. Participant is taking medication that causes photosensitivity
   d. Participant has a history of angle-closure glaucoma or narrow anterior chamber angles

7.3 Informed Consent

Written informed consent will be obtained from each study patient prior to enrollment into the study. A written informed consent ([redacted]) must be signed and dated by the patient (or legally authorized representative, if appropriate), and the investigator. Patients will be given a copy of the signed informed consent document. The signed informed consent will be retained with the study records at the site. It is the responsibility of the Investigator to assure that informed consent is obtained from each patient in accordance with GCP guidelines. Subjects may withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject if, in his clinical judgement, it is in the best interest of the subject or if the subject cannot comply with the protocol.

8 STUDY DESIGN

The proposed study is designed to compare AEYE-DS diagnostic results obtained from fundoscopy images for the detection of more than mild diabetic retinopathy (mtmDR), to the blinded diagnostic results from expert ophthalmologists used as the reference standard.

The study is a prospective, multi-center, single-arm study. [redacted]
Study cases will be sourced from different primary care clinics in the USA. Each clinic will have its own separate staff for the acquisition of the retinal images. Staff will include a novice operator who had not previously performed ocular imaging and professional ophthalmic photographer who will be certified by the Fundus Reading Center. Each clinic will screen diabetic patients to check for potential presence of DR.

[redacted]. The study population who represent the target population for this procedure consists of stable, visually asymptomatic subjects with previously diagnosed diabetes without prior diagnoses of DR, who are participating in a routine retinal screening test for diabetic retinopathy (DR) in primary care clinics, and have digital funduscopic images of sufficient quality from a specific funduscopic camera, i.e., the Topcon Model NW400. Patients of both genders, all ethnicities, ≥22 years of age will be recruited to the study. Patients' demographics will include a comparable and representative distribution of the population of the United States and its different ethnicities, including but not limited to White, Asian, African-American and Latino populations. Investigators will screen participants based on the inclusion/exclusion criteria described above. General patient demographics, medical history, concomitant medications, fundoscopy system used, OCT system used, etc., will be obtained for each study case.

Both fundus images needed for the AEYE-DS and for the reading center (to establish ground truth) will be acquired from each eye of the patient, after the patient has signed an informed consent form.

The novice operator will obtain two fundoscopy images from each eye of the patient, after the patient has signed an informed consent form. The operator will activate the AEYE-DS system on the fundoscopy images and obtain a result of more than mild DR (mtmDR) detected, more than mild DR not detected, or insufficient quality. The results for each case will be recorded in the eCRF.

After the novice operator has generated an AEYE-DS output, but during the same visit, each participant will undergo additional retinal imaging captured by the professional ophthalmic photographer. The professional ophthalmic photographer will be masked at all times to the AEYE-DS output and will use a different, FDA-cleared camera system [redacted]) to obtain dilated four widefield stereo color fundus images, lens photography for media opacity assessment and macular optical coherence tomography (OCT) imaging. These images will all be sent to an independent Reading Center, where the severity of retinopathy and diabetic macular edema (DME) will be determined according to the Early Treatment for Diabetic Retinopathy

Study severity (ETDRS) scale. These readings will form the reference standard (ground truth) for the study. Three experienced and certified readers will review the images. If at least two readers agree, a majority voting paradigm will be implemented. [redacted] The readers will be masked to the AEYE-DS output at all times, masked to the funduscopy images when evaluating the OCT images and masked to the OCT readings when evaluating the fundoscopy images. Each participant will be categorized as mtmDR+ or mtmDR-. The worst of two eyes will be compared with the AEYE-DS output at the participant level. The results for each participant will be recorded in the eCRF.

The reference standard (ground truth) results from the Reading Center will be statistically compared to the AEYE-DS device results. The independent co-primary outcome parameters of the study will be sensitivity and specificity assessed in the Intent-to-Screen (ITS) population for whom AEYE-DS provided a diagnostic result and the Reading Center provided a usable reference standard. Furthermore, the AEYE-DS positive predictive value and negative predictive value will be determined. The imageability of AEYE-DS in terms of the percentage of readable images diagnosed successfully by the device will also be measured.

Usability of the AEYE-DS device will also be assessed including User Manual comprehension and usability of the device in the hands of potential users (i.e., primary care clinicians).

Details on the timing of all study procedures are given in the Time and Events Schedule in Attachment B of the Protocol. [redacted]
The blinding status will be maintained until the last participant has been completed in the study.

9 STUDY PROCEDURES:

9.1 Screening

Investigators will screen participants based on the inclusion/exclusion criteria described above. Diabetic patients who require fundoscopy examination, meet the inclusion criteria and do not meet any clause of the exclusion criteria and volunteer to participate will join the study. A consent form will be signed by each patient. General patient demographics (including age, gender, race and ethnicity), diabetic history (including HbA1C, FPGL, etc.), ophthalmic history (including lens status, reported light sensitivity, as applicable), medical history, concomitant medications, fundoscopy system used, OCT system used, etc., will be obtained for each study case.

At the start of the study, all participants with diabetes who meet inclusion and exclusion criteria will be enrolled sequentially. To avoid excessive enrollment in any one stratum (no/mild DR or mtmDR), the totals will be monitored monthly and the study population will be enriched to ensure sufficient numbers of subjects with mtmDR. [redacted]

9.2 Data Acquisition (by Novice Operator):

The novice operator will obtain fundoscopy images from each eye of the patient, after the patient has signed an informed consent form. The novice operator is a staff personal from a primary care site, who has not previously performed ocular imaging. [redacted]

The novice operators will undergo a one-time standardized training program on how to acquire images, how to improve image quality if the AEYE-DS gives an insufficient quality output, and how to submit images for analysis to the AEYE-DS device. No additional training will be provided to the operators for the duration of the study.

9.2.1 Non-Mydriatic Fundoscopy Imaging

Fundus imaging involves photographing the fundus (i.e., the rear of an eye). Fundoscopy devices are specialized cameras which consist of an intricate microscope attached to a flash enabled camera. The main structures that can be visualized on a fundus photo are the central and peripheral retina, optic disc and macula.
The novice operator will obtain two digital fundoscopy image from each eye of the patient [redacted], using the non-mydriatic, TopCon NW400 ocular fundoscopy imaging device, according to a standardized imaging protocol with fovea/macula centered and optic-disc centered 45° images [redacted].

[redacted]

9.2.2 AEYE-DS System Operation

The operator will activate the AEYE-DS system on the fundoscopy images and obtain a result of more than mild DR (mtmDR) detected, more than mild DR not detected, or insufficient quality, [redacted]. In case the result is 'insufficient quality', fundoscopy can be re-taken for the relevant eye(s) and fixation point(s).

It is anticipated that the presence of lens opacities due to cataract will significantly increase the number of imaging attempts required to get sufficient quality images, as well as the requirement for dilation. If after three (3) imaging attempts by the operator (without pharmacologic dilation), the system still indicates that at least one image is of insufficient quality, pharmacological dilation will be performed. In this case, the participant's pupils will be dilated with tropicamide 1.0% eyedrops, until the pupil diameter is at least 5mm in each eye or 30 minutes have passed, and all 4 fundus images (1 macular centered and 1 disc centered for each eye) will be reacquired. Three (3) more attempts may be made to capture an image of sufficient quality. If the AEYE-DS system still outputs that at least one image is of insufficient quality, the AEYE-DS output of insufficient quality will be recorded as the final result.
The results for each case will be recorded in the eCRF.

The time required to process the fundoscopy images with the AEYE-DS system until a result is obtained, will also be recorded.

As this is an investigational device study, no clinical action will be taken based on the results presented by the AEYE-DS device.

9.3 Data Acquisition (by a Professional Ophthalmic Photographer)

After the novice operator has generated an AEYE-DS output, but during the same visit, each participant will undergo additional retinal imaging captured by the professional ophthalmic photographer trained by the reading center. The professional ophthalmic photographer will be masked at all times to the AEYE-DS output and will use a different, FDA-cleared camera system ([redacted] to obtain dilated four widefield stereo color fundus images, lens photography for media opacity assessment and macular optical coherence tomography (OCT) imaging.

9.3.1 Mydriatic Fundoscopy Imaging (Dilated Wide Field Stereo Color)

If the study participant is not already dilated, dilating eye drops of tropicamide 1.0% will be administered. Four (4) Mydriatic (dilated) fundoscopy imaging with Wide Field Stereo Color will be performed on each eye of the patient by the professional ophthalmic photographer, at the primary care center using the [redacted]

The four widefield stereo image pairs will be obtained to determine the severity of retinopathy according to the well-established Early Treatment for Diabetic Retinopathy Study severity (ETDRS) scale.

9.3.2 Lens Photography for Media Opacity Assessment

In the presence of media opacity, the image quality of fundoscopy devices is less satisfactory and may lead to ungradable images. For this reason, the above mentioned mydriatic funduscopy imaging capturing the red reflex ([redacted]) will be performed to evaluate lens status given that cataract and other media opacities are more prevalent in the diabetic population. Anterior segment photography for media opacity assessment will be performed according to the Age Related Eye Disease Study 2: AREDS2 Report 7 (Domalpally et al 2013).

9.3.3 Macular Optical Coherence Tomography (OCT) Imaging

Macular Optical Coherence Tomography (OCT) imaging will also be performed on each eye of the patient by the professional ophthalmic photographer, at the primary care center using the using the [redacted] to produce

a cube scan containing at least 121 B scans. A major limitation of many current DR screening programs based on fundus photography is the inability to accurately identify DME on 2-dimensional fundus photographs. [redacted]

Macular OCT images will be obtained to detect the presence of center involved DME according to the Diabetic Retinopathy Clinical Research Network (DRCR) grading paradigm.

9.4 Determining Reference Standard / Ground Truth

The four mydriatic widefield stereo color fundus images, lens photography for media opacity assessment and macular optical coherence tomography (OCT) imaging obtained with the FDA-cleared camera system ([redacted] will all be sent to an independent Reading Center, where the severity of retinopathy and diabetic macular edema (DME) will be determined according to the well-established Early Treatment for Diabetic Retinopathy Study severity (ETDRS) scale.

These readings will form the reference standard (ground truth) for the study. [redacted] All certified readers will be senior, board-certified ophthalmologists with expertise in the field of retinal diseases with at least 10 years of clinical experience and certified by the Reading Center. The readers will be masked to the AEYE-DS output at all times, masked to the funduscopy images when evaluating the OCT images and masked to the OCT readings when evaluating the fundoscopy images.

The Reading Center diagnostic grading protocol will consist of the following:
The four mydriatic widefield stereo color fundoscopy image pairs will be read by two readers (or three readers in case of disagreement using a majority voting paradigm) according to the ETDRS scale.

The macular OCT images will be read by the same readers for the presence of center involved DME according to the Diabetic Retinopathy Clinical Research (DRCR) network grading paradigm.

Because DME can be identified on the basis of retinal thickening on stereoscopic fundoscopy images, as well as on the basis of retinal thickening on OCT, performance using both definitions will be analyzed.

Stereoscopic fundus-based Clinically Significant DME (CSDME) will be identified if there is either retinal thickening or adjacent hard exudates < 600μm from the foveal center, or a zone of retinal thickening > 1 disc area, part of which is less than 1 disc diameter from the foveal center, according to the Reading Center, in any eye.

OCT based center involved DME will be identified if a participant had central subfield (a 1.0mm circle centered on the fovea) thickness that is >300μm according to the Reading Center, in any eye.

Each participant will be categorized as mtmDR+ (i.e., ETDRS level 35 or higher and /or DME present), or mtmDR- (ETDRS level 10-20 and DME absent). The worst of two eyes will be compared with the AEYE-DS output at the participant level.

In summary, the definition of mtmDR+ is defined as:

- ETDRS level ≥ 35 (determined from fundoscopy images) and/or
- CSDME (determined from fundoscopy images)

and multimodal mtmDR+ is defined as:

- ETDRS level ≥ 35 (determined from fundus photographs); and/or
- CSDME (determined from fundoscopy images); and/or
- Center-involved DME (determined from OCT).

The reader may also classify the patient's images as "insufficient quality" for reading.
Lens status will be assessed using the following grading:

- Phakic with opacities or Cannot Grade; or
- Pseudophakic or no opacities

Phakic and pseudophakic are terms used to describe the status of an individual's lens. Phakic refers to a person with an intact natural lens while a pseudophakic individual had a lens extracted and an IOL placed.

The readers will be allowed to manipulate the images to grade subtle lesions. In the case that incidental findings unrelated to DR (e.g., optic nerve pathology, drusen, pigmented choroidal lesions) are identified by the readers, these will be recorded and the sites will be notified along with the clinical assessment, as described in section 9.6.

The results for each participant will be recorded in the eCRF.

9.5 Data Analysis

The Reading Center will enter the ETDRS result and indication of detection of macular edema in the EDC within 4 weeks of each participant's completion of the study protocol. A study participant is considered to have completed the study protocol upon completion of the AEYE-DS imaging protocol (either resulting in sufficient or insufficient quality images) and the OCT and mydriatic four wide field fundscopy imaging, according to section 10.1.

All Reading Center ETDRS results will be converted to an International Clinical Diabetic Retinopathy (ICDR) level based on the American Academy American Academy of Ophthalmology's (AAO) International Clinical Diabetic Retinopathy (ICDR) Disease Severity Scale (see table below). ICDR results will also indicate whether the Reading Center detected macular edema.

Measure	Score	Observable Findings
ICDR severity level		
No apparent retinopathy	0	No abnormalities (Level 10 ETDRS)
Mild non-proliferative diabetic retinopathy	1	Microaneurysm(s) only (Level 20 ETDRS)
Moderate non-proliferative diabetic retinopathy	2	More than just microaneurysm(s) but less than severe non-proliferative diabetic retinopathy (Level 35, 43, 47 ETDRS)
Severe non-proliferative diabetic retinopathy	3	Any of the following: > 20 intra-retinal haemorrhages in each of 4 quadrants, definite venous beading in ≥2 quadrants, prominent intra-retinal microvascular abnormalities in ≥1 quadrant, or no signs of proliferative retinopathy. (Level 53 ETDRS: 4-2-1 rule)
Proliferative diabetic retinopathy	4	One or more of the following: neovascularization and/or vitreous or preretinal haemorrhages. (Levels 61, 65, 71, 75, 81, 85 ETDRS)
Macular oedema severity level		
No macular oedema	0	No exudates and no apparent thickening within 1 disc diameter from fovea
Macular oedema	1	Exudates or apparent thickening within 1 disc diameter from fovea

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy study; ICDR, International Clinical Diabetic Retinopathy

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The following table described how the ETDES severity levels of the worst eye will be mapped and combined with fundus based DME to the dichotomous categories mtmDR- (non or mild NPDR and no DME) and mtmDR+ (more than mild DR or DME).

Worst ETDRS Level	Description	Fundus-based Clinically Significant Macular Edema	Fundus based classification
10	No or Mild NPDR	absent	mtmDR-
12, 14A, 14B, 14C,14Z, 15, 20	Mild NPDR		
10	No or Mild NPDR	a) zone of retinal thickening > 1 disc area, part < 1 disc diameter from foveal center b) retinal thickening or adjacent hard exudates < 600µm from foveal center	mtmDR+
12, 14A, 14B, 14C, 14Z, 15, 20	Mild NPDR		
35A, 35B, 35C, 35D, 35E, 35F, 43A, 43B, 47A, 47B, 47C, 47D	Moderate NPDR	absent or present	mtmDR+
53A, 53B, 53C, 53D, 53E	Severe NPDR		
60, 61A, 61B, 65A, 65B, 65C, 71A, 71B, 71C, 71D, 75, 81, 85A, 85B	PDR		

All blinded datasets will be locked after eCRF data monitoring is completed. The datasets will be merged and unblinded and the diagnostic results will be compared and analyzed. Performance for mtmDR detection will be calculated as device alone (AEYE-DS) vs. ground truth (Expert Reader committee decision) according to the data analysis plan described in Section 11 – Statistical Section.

9.6 Clinical Assessment

The converted ICDR results and corresponding American Academy of Ophthalmology management recommendations will be provided to the study investigators, who are responsible for appropriately managing study subjects. To support referral determinations based on the ICDR results provided to them, the study investigators should review the Management Recommendations for Patients with Diabetes as contained in the AAO's Preferred Practice Pattern (AAO PPP) Recommendations for Diabetic Retinopathy (See Table 6 at http://www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp-updated-2016).

TABLE 6 MANAGEMENT RECOMMENDATIONS FOR PATIENTS WITH DIABETES

Severity of Retinopathy	Presence of Macular Edema	Follow-up (Months)	Panretinal Photocoagulation (Scatter) Laser	Focal and/or Grid Laser*	Intravitreal Anti-VEGF Therapy
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	No	12	No	No	No
	ME	4–6	No	No	No
	CSME†	1*	No	Sometimes	Sometimes
Moderate NPDR	No	12‡	No	No	No
	ME	3–6	No	No	No
	CSME†	1*	No	Sometimes	Sometimes
Severe NPDR	No	4	Sometimes	No	No
	ME	2–4	Sometimes	No	No
	CSME†	1*	Sometimes	Sometimes	Sometimes
Non-high-risk PDR	No	4	Sometimes	No	No
	ME	2-4	Sometimes	No	No
	CSME†	1*	Sometimes	Sometimes	Sometimes
High-risk PDR	No	4	Recommended	No	Alternative[129,130]
	ME	4	Recommended	Sometimes	Usually
	CSME†	1*	Recommended	Sometimes	Usually

Anti-VEGF = anti-vascular endothelial growth factor; CSME = clinically significant macular edema; ME = non-clinically significant macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

* Adjunctive treatments that may be considered include intravitreal corticosteroids or anti-VEGF agents (off-label use, except aflibercept and ranibizumab). Data from the Diabetic Retinopathy Clinical Research Network in 2011 demonstrated that, at two years of follow-up, intravitreal ranibizumab with prompt or deferred laser resulted in greater visual acuity gain and intravitreal triamcinolone acetonide plus laser also resulted in greater visual gain in pseudophakic eyes compared with laser alone.[131] Individuals receiving the intravitreal injections of anti-VEGF agents may be re-examined as early as one month following injection.

† Exceptions include hypertension or fluid retention associated with heart failure, renal failure, pregnancy, or any other causes that may aggravate macular edema. Deferral of photocoagulation for a brief period of medical treatment may be considered in these cases.[132] Also, deferral of CSME treatment is an option when the center of the macula is not involved, visual acuity is excellent, close follow-up is possible, and the patient understands the risks.

‡ Or at shorter intervals if signs approaching those of severe NPDR appear.

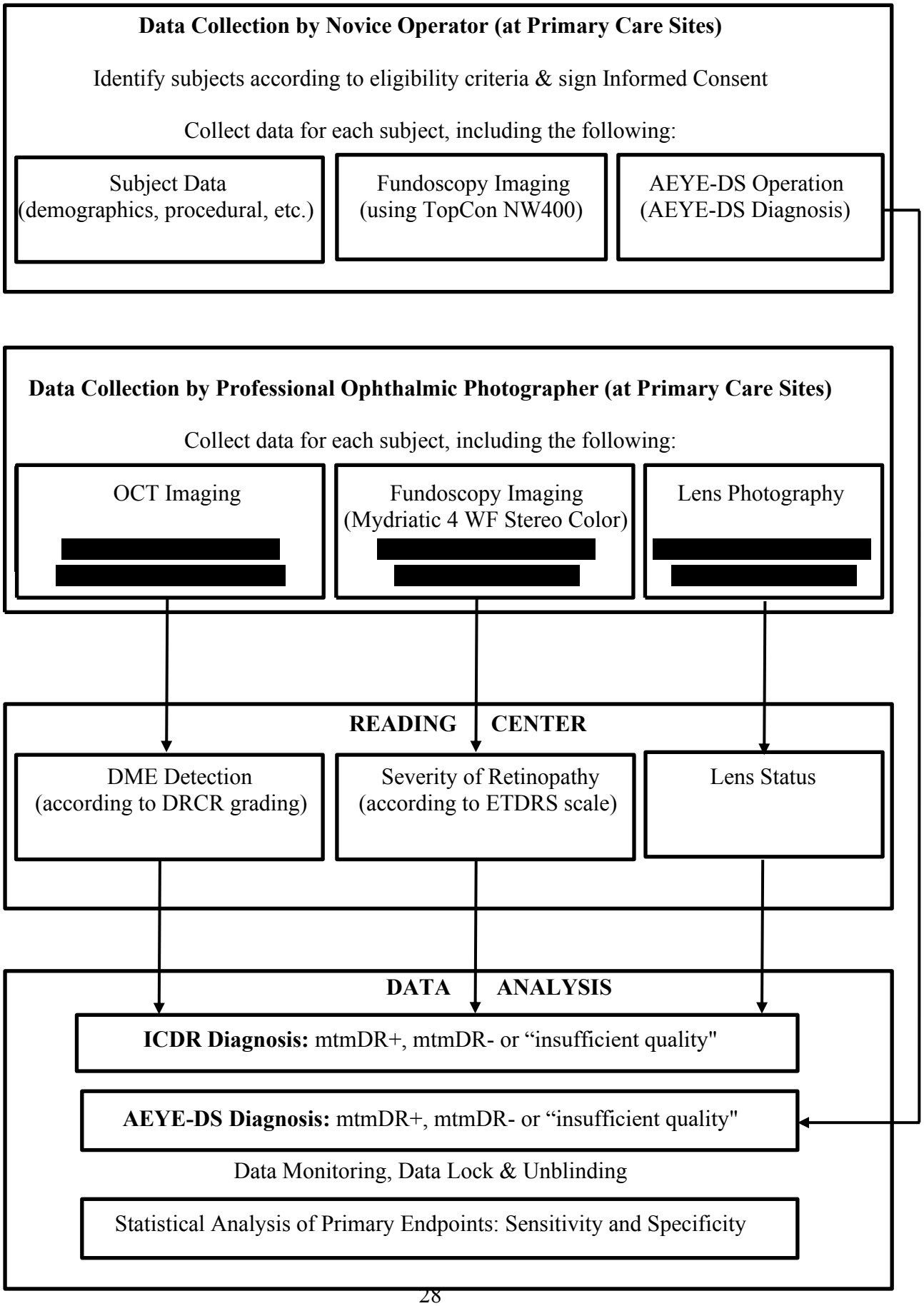
In correspondence about Reading Center results, clinicians will also be provided with the following notes regarding the PPP:

- The AAO PPP recommends a 12-month follow-up for patients with normal, minimal non proliferative diabetic retinopathy (NPDR) or mild NPDR when there is no presence of macular edema (ME).
- The AAO PPP recommends that it may be appropriate for patients with moderate NPDR to receive follow-up examination by an eye care professional in an interval less than 12 months.
- Based on the AAO PPP, those patients with severe NPDR, Non-high risk PDR, or High Risk PDR – as well as those with macular edema – may be indicated for treatment based on evaluation by an eye care professional. These subjects should be referred.

On the basis of Reading Center ICDR results and AAO PPP Recommendations, physicians will be able to provide appropriate eye care referrals for study participants.

Furthermore, in the case that incidental findings unrelated to DR (e.g., optic nerve pathology, drusen, pigmented choroidal lesions) are identified by the readers, these will be recorded and the sites will be notified of these findings, along with the clinical assessment.

9.7 Flow Chart



[redacted]

9.8 Non-Mydriatic Fundoscopy Imaging with a Handheld Device

In selected sites, additional fundus imaging using an FDA cleared, handheld fundoscopy device may also be performed and processed using the AEYE-DS device. The handheld fundoscopy device is a specialized camera which consists of an intricate microscope attached to a flash enabled camera, only much smaller in size. Various handheld devices may be used for the purpose of this sub-study. The type of handheld device used will be recorded on the CRF.

The novice operator will obtain two digital fundoscopy images (one from each eye of the patient)[redacted], using the non-mydriatic, handheld fundoscopy imaging device, according to a standardized imaging protocol. Images will be fovea/macula centered [redacted].

The novice operator will activate the AEYE-DS system on the fundoscopy images obtained from the handheld device and obtain a result of more than mild DR (mtmDR) detected, more than mild DR not detected, or insufficient quality, in the same manner described in section 9.2.2 above. The 'software upload client' will be modified for the data collection (as only one image per eye is submitted for analysis) and installed at the applicable participating sites.

9.9 Human Factors Testing

The human factors testing will be performed in accordance with the FDA Guidance *Applying Human Factors and Usability Engineering to Medical Devices*, dated February 3, 2016, as well as IEC 62366 *Medical devices – Application of usability engineering to medical devices*.

Human factors testing will include preliminary, iterative evaluation of the workflow, device training and labeling materials and device use, followed by interviews with probing

questions during feasibility and simulated studies. The standardized workflow, training program, and operator materials developed by this process will be implemented and tested as part of this pivotal study as described below.

Human factors testing will be performed as part of the clinical study to demonstrate that the instructions for use and training are sufficient for users to operate AEYE-DS, as intended. The human factors testing will validate the setting in which the device is intended to be used. A list of critical tasks associated with the use of the device will be provided to the novice operators including uploading the fundoscopy images, operating the AEYE-DS device and obtaining the diagnostic results from the device.

A post-use questionnaire will be administered to the novice users for feedback, and recorded and documented as part of the eCRFs. A similar observer questionnaire will be used to capture and record any confusion or user errors and documented as part of the eCRFs, as well.

The human factors testing to be conducted as part of the AEYE-DS pivotal study will validate the fundoscopy use and imaging protocol and the standardized labeling materials which enable the capture of at least two medical grade image by previously untrained fundoscopy operators for at least 80% of the subjects imaged who will complete the full imaging protocol on a fundoscopy device intended for use with AEYE-DS device.

9.10 Repeatability & Reproducibility Testing

Adequate validation will be performed and controls implemented to characterize and ensure consistency (repeatability and reproducibility) of the diagnostic output. The reproducibility (variability between different devices) and repeatability (variability between results from the same operator) analysis will be performed in a separate validation sub-study, under a separate sub-study protocol, but on subjects who will have participated in the pivotal study. Half of the participants will have been diagnosed as mtmDR- based on the original Expert Reader grading and half of the participants will have been diagnosed as having mtmDR+.

Each participant in the sub-study will have completed the entire AEYE-DS imaging protocol 10 times, imaged by three different novice operators on two different Topcon NW400 fundoscopy devices. [redacted]

The binary output of AEYE-DS will be used to assess repeatability and reproducibility and compute the percent complete agreement of the AEYE-DS outputs across repeats, novice operators and fundoscopy devices. Full details of the study design and analysis will be provided in the Repeatability and Reproducibility Study Protocol.

10 PATIENT COMPLETION / WITHDRAWAL

10.1 Completion

A subject will be considered to have completed the study if the required, fundoscopy imaging and AEYE-DS operation are completed by the novice operator as described in section 9.2 and the mydriatic fundoscopy imaging, OCT imaging and lens photography has been completed by the professional ophthalmology photographer as described in section 9.3 and all imaging files have been received at the Reading Center.

10.2 Withdrawal from the study

A subject will be withdrawn from the study for any of the following reasons:

- Withdrawal of consent
- Subject is not compliant with requirements of the study, including inclusion and exclusion criteria.
- The investigator believes that for safety reasons (e.g. an adverse event) it is in the best interest of the patient to stop the study.
- The study is prematurely stopped or halted (e.g. clinical halt)

10.3 Analyzable Subjects

A subject will be fully analyzable if all of the following conditions are met:

1. Subject is eligible to participate in the study according to the study eligibility criteria specified in section 7.0.
2. FPRC Reading:
   - Subject completed the professional ophthalmic photography imaging protocol and met all minimal requirements according to section 9.3.
   - Subject received a positive or negative diagnosis by the FPRC.
3. AEYE-DS Imaging Protocol
   - Subject completed the AEYE-DS imaging protocol and met all minimal requirements according to section 9.2.
   - Subject received a positive or negative diagnosis by the AEYE-DS System.

Subjects who are non-analyzable due to "insufficient quality" or "missing output" by the AEYE-DS imaging, will be considered in the study imageability analysis as well as sensitivity analyses as described in the statistical section below.

11 STATISTICAL CONSIDERATIONS

11.1 Study Design and Objectives

The study is a blinded, single arm cohort study, designed to evaluate the performance of the AEYE-DS software device for the detection of more than mild diabetic retinopathy (mtmDR) on digital funduscopic images in patients with known diabetes undergoing screening for diabetic retinopathy. [redacted].

11.2 Study Endpoints

11.2.1 Primary Efficacy Endpoints

The primary efficacy endpoints are the sensitivity and specificity of the AEYE-DS device to detect mtmDR on digital funduscopic images (acquired by the TopCon NW400 fundoscopy device based on 1 macula centered image obtained per eye). The ground truth will be determined by a panel of expert ophthalmologist readers at the Reader Center.

11.2.2 Powered Secondary Efficacy Endpoint

Powered secondary efficacy endpoint includes:

- Sensitivity and specificity of the AEYE-DS device to detect mtmDR on digital funduscopic images (acquired by the TopCon NW400 fundoscopy device based on 2 images obtained per eye, one macula centered and one optic-disc centered).

11.2.3 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- The percentage of cases with a disease level output (mtmDR+ or mtmDR-) from the AEYE-DS device.
- Device Usability
- Sensitivity and specificity of the AEYE-DS device to detect mtmDR on digital funduscopic images ([redacted]

11.3 Study Hypotheses

In this study, we will test the following pairs of hypotheses on the primary endpoint, as well as on the powered secondary endpoint:

- H_0: Se ≤82%,
  H_1: Se > 82%

- H_0: Sp≤87%,
  H_1: Sp >87%

Where Se and Sp are the sensitivity and specificity of the mtmDR classification of the AEYE-DS software device.

[redacted]

11.4 Sample Size

The two null hypotheses will be evaluated independently, therefore sample sizes will be calculated for both and the maximum sample size will be chosen. A sample size is calculated such that the lower limit of the one-sided 97.5% exact binomial confidence interval for sensitivity and specificity are greater than 82% and 87% respectively with over 90% power, using the SAS POWER procedure.

[redacted]

[redacted]

[redacted]

[redacted]

11.7 Randomization

This is a single arm, non-randomized study, no randomization will be performed.

11.8 Blinding

The clinician who will assess the DR score with the AEYE-DS will be blinded to the committee decision.

The expert ophthalmologists in the Reading Center will be blinded to the AEYE-DS.

11.9 Statistical Analysis

11.9.1 General Considerations

Statistical analyses will be performed using SAS®V9.4 (SAS Institute, Cary NC, USA) or higher.
If not specified otherwise, any statistical tests performed will be two-sided. The required significance level of findings will be equal to or lower than 5%. Where confidence limits are appropriate, the confidence level will be 95%.

Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage. Confidence intervals will be provided where relevant.

11.9.2 Significance level and handling of Type I error

The primary efficacy endpoints will be assessed with confidence intervals, using a one-sided confidence level of 97.5%. [redacted]
The null hypotheses will be rejected if the lower limits of the confidence interval of the sensitivity and specificity are greater than 82% and 87%, respectively. These are two independent hypotheses. [redacted]

11.9.3 Demographic and Baseline Characteristics

Demographic and clinical history variables will be tabulated. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage, such as:

- Age
- Ethnicity
- Race
- HbA1C level

11.9.4 Disposition of Subjects

The numbers of subjects who were enrolled will be provided. A list of discontinued patients, protocol deviations, and patients excluded from the efficacy analysis will be provided as well.

11.9.5 Analysis of Primary Endpoint

A 2x2 table of the results of all subjects who had valid results on both AEYE-DS and the Reader Center comparing the positive/negative results obtained from the AEYE-DS versus the reference values will be presented.

The primary efficacy analysis will present the estimation of sensitivity and specificity of the of the AEYE-DS device to detect mtmDR on digital funduscopic images (acquired by the TopCon NW400 fundoscopy device based on one macula centered image obtained per eye) together with their lower limit of their respective one-sided exact 97.5% confidence intervals. If the lower limits of the one-sided 97.5% confidence intervals of the sensitivity and specificity are greater than or equal to 82% and 87% respectively the null-hypotheses will be rejected. If both null hypotheses are rejected in favor of the alternative hypotheses the study will be deemed successful, and the performance goals met.

The positive and negative predictive values (PPV and NPV respectively) of the diagnosis together with their respective exact 95% confidence intervals will be presented as well.

Analyses will be performed on both ground truth modalities, fundus-only and multi-modality (using fundoscopy and OCT).

[redacted]

The percent of participants requiring pharmacologic dilation and not requiring dilation to obtain an AEYE-DS disease level output will be calculated.

Sensitivity and specificity, analyses will be carried out on the combined cohorts. [redacted]

[redacted]

11.9.6 Analysis of Secondary Endpoints

The powered secondary efficacy analysis will present the estimation of sensitivity and specificity of the AEYE-DS device to detect mtmDR on digital funduscopic images (acquired by the TopCon NW400 fundoscopy device based on 2 images obtained per eye, one macula centered and one optic disc centered) together with the lower limit of their respective one-sided exact 97.5% confidence intervals. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.9.7 Safety Assessments and Adverse Events

[redacted]

11.9.8 Poolability

[redacted]

11.9.9 Handling of Missing Data

Subjects with missing data will be compared to those with complete data, with respect to demographic and perhaps other baseline characteristics.

As a sensitivity analysis, the primary and powered secondary endpoints will be analyzed considering a non-analyzable result of the AEYE-DS as “negative” for the calculation of sensitivity, and “positive” for the calculation of specificity.

12 RISK / BENEFIT ANALYSIS

12.1 Risks

The risks to patients resulting from potential device hazards have been analyzed using the Risk Management Standard - ISO 14971. The different types of hazards were identified and evaluated using risk assessment numerical parameters. Applicable controls for the risks were analyzed. [redacted]

12.2 Benefits

Diabetic Retinopathy (DR) is the leading cause of vision loss in adults between ages 20-74 [Cheung et al., 2010], and ranked as one of the most common causes of preventable blindness [Bourne, 2013]. Based on a recent global report [WHO, 2014], there are over 422 million people worldwide with diabetes, and over 35% have signs of DR, a third of them with vision threatening DR. With the prevalence of diabetes expected to increase 50% over the next 10 years, screening rates, detection, and treatment must be addressed in order to prevent a significant increase in unnecessary blindness across the United States.

Early detection of retinopathy is an important part of managing care for people with diabetes, yet many patients with diabetes are not adequately screened for diabetic retinopathy. A 1990 program launched by the American Academy of Ophthalmology (AAO), known as Diabetes 2000, was designed to increase nationwide DR screening rates. However, after 20 years of implementation, screening rates continue to stagnate, with only 50-60% of diabetic patients properly evaluated.

A DR screening solution at the point of primary care is expected to help address the unmet need, lack of access, and racial and ethnic disparity issues that have persisted for decades. An automated screening device would allow for immediate screening results at the point of care and standardization of results. Ophthalmic key opinion leaders state that an automated diabetic retinopathy screening device in the hands of primary care healthcare providers would increase screening rates and detect more treatable vision threatening DR.

The current proposed study will validate the sensitivity and specificity of the AEYE-DS output by a novice operator compared to the diagnostic determination by an independent, blinded panel of expert ophthalmologist at the reading center.

13 ETHICAL ASPECTS

13.1 Study-Specific Design Considerations

Subjects/cases will be carefully screened using the study eligibility criteria prior to enrollment in the study.

13.2 Regulatory Ethics Compliance

13.2.1 Investigators Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

13.2.2 Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and if applicable, amendments
- Informed consent form
- Investigator's Brochure (or equivalent information) and amendments
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, and other potential conflicts of interest
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after IEC/IRB has given full approval of the final protocol, amendments (if any), and informed consent and after the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the documents being approved.

During the study the investigator will send the following documents to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IEC/IRB)

- Reports of any serious adverse events, if applicable
- Deviations from or changes to the protocol
- Notification if new investigator is responsible for the study at the site
- Any other requirements of the IEC/IRB

At least once a year the IEC/IRB will be asked to review and re-approve this clinical study. This request and approval should be documented in writing.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

13.2.3 Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles set forth in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before entry into the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment for his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally they will be told that their records may be accessed by health authorities without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject is authorizing such access.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by name of the subject, subject's signature and date of signature. After having obtained the consent, a copy of the informed consent form must be given to the subject. If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written explanations) and should personally date and sign the inform consent form after the oral consent of the subject or legally acceptable representative is obtained.

13.2.4 Privacy of Personal Data

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study. This data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

14 ADMINISTRATIVE REQUIREMENTS

14.1 Protocol Modifications

The investigator will not modify this protocol without a formal amendment. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the patients in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

The investigator or other physician in attendance will contact the appropriate sponsor representative by fax or telephone regarding any situations requiring a departure from the protocol. If possible, contact will be made before implementing any departure from the protocol. In all cases contact with the sponsor must be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source document will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

14.2 Regulatory Documentation

14.3 Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated at a site until all local regulatory requirements are met.

14.3.1 Required Pre-study Documentation

The following documents must be available and maintained during the study:

- Approved Study Protocol and amendment(s)
- A copy of the dated and signed written IEC/IRB approval of the protocol and any amendments. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- An approved informed consent form
- Regulatory authority approval or notification, if applicable
- Documentation of investigator qualifications (e.g., curriculum vitae)
- Completed financial disclosure form
- Signed and dated clinical trial agreement, which includes the financial agreements
- Other documentation required by local regulations

14.3.2 Patient Identification Register and Patient Screening Log

The investigator agrees to complete a subject/case identification register to permit easy identification of each subject/case during and after the study.

The subject/case identification register will be treated as confidential. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the study will identify subject/case by initials and assigned number only.

The investigator will also complete a subject/case enrollment log, which reports all subject/case who were determined eligible for inclusion in the study.

14.3.3 Case Report Form Completion

All data relating to the study will be recorded on source documents and then entered into an EDC with electronic CRFs (eCRFs). Data will be collected in English. The source documents and eCRFs are to be completed at the time of the data collection. Every effort should be made to ensure that all measures are recorded on the source documents and eCRFs. The investigator must verify that all data entries on the source documents and in the eCRFs are accurate and correct.

14.3.4 Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all source documents and eCRFs that support the data collected from each patient, as well as all study documents as specified in ICH/GCP Section 8, Essential, Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

[redacted]

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

[redacted]

14.3.5 Use of Information and Publication

[redacted]

[redacted]

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APPENDIX A – TIME AND EVENTS SCHEDULE

Study Procedure	Primary Care Site (by Novice Operator)	Primary Care Site (by Professional Ophthalmic Photographer)	Reading Center	CRO
Informed Consent	√			
Eligibility Criteria	√			
Patient Demographics	√			
Diabetic History	√			
Ophthalmic History	√			
Medical History	√			
Concomitant Medications	√			
Procedural Information	√			
Fundoscopy Images Acquisition with TopCon NW400	√			
Fundoscopy Images Acquisition with handheld device (Optomed Aurora)	√			
AEYE Operation & mtmDR Diagnosis with TopCon NW400 images	√			
AEYE Operation & mtmDR Diagnosis with handheld fundoscopy images	√			
Mydriatic Fundoscopy Images Acquisition		√		
Macular Optical Coherence Tomography (OCT) Imaging		√		
Lens Photography		√		
ETDRS Results			√	
Detection of Macular Edema			√	
Lens Status Determination			√	
ICDR Results				√