Adaptive Optics Retinal Imaging

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Abstract

Objective: The objective of the study is to collect and assess adaptive optics (AO) retinal images from human subjects in support of projects to demonstrate, advance, and enhance clinical use of AO technology.

Study Population: One hundred (100) healthy volunteers without eye disease and fifty (50) subjects with primary open angle glaucoma (POAG) will be enrolled.

Design: This is an interventional study protocol where participants will be imaged with investigational multimodal AO retinal imaging systems that include optical coherence tomography (OCT) and scanning laser ophthalmoscopy (SLO) channels. High resolution OCT and SLO videos will be collected while the instruments automatically detect and correct for image distortion caused by ocular aberrations. In general, videos of different retinal structures will be acquired from several retinal locations using various imaging modes.

Outcome Measures: The primary outcomes for this protocol are qualitative and quantitative assessment of the AO images and investigation of the cellular morphological and physiological changes due to glaucoma.

1.0 Introduction

Adaptive optics (AO) retinal imaging is a diagnostic technology that has the capacity to vastly aid detection and treatment of ocular diseases by providing direct visualization, quantification, and functional assessment of retinal cells [1-2]. AO works by sensing and correcting an individual's ocular aberrations providing cellular level access to the living eye. AO has for many years had the ability to routinely resolve cone photoreceptors. Recent progress includes imaging rod photoreceptors [3], retinal pigment epithelium [4-7], choriocapillaris [8], and ganglion cells [9-11]. These advances may transform the diagnosis of ocular diseases, including highly prevalent ones such as age-related macular degeneration, glaucoma, and diabetic retinopathy.

However, AO has yet to achieve full clinical translation, partially because of system complexity and cost but also because the clinical benefit to patients remains unrealized. The FDA is uniquely positioned to support translation through its mission to promote public health through regulatory science. This protocol supports a FDA/CDRH/OSEL project to develop models and methods for AO image quality assessment and standardization, discover new AO imaging-based biomarkers of retinal diseases, and develop novel modalities suited to specific cellular targets, function, and disease. For example, building on our work in developing an anthropomorphic phantom that mimics the thickness and reflectance of ten layers of the retina [12], we are currently developing a retinal phantom that simulates the structure of the photoreceptor mosaic and can be used to assess AO imaging performance [13]. In collaboration with NIH, we are also extending the multimodal scanning and averaging image modes to capture retinal pigment epithelium (RPE) and ganglion cells from subjects with normal and diseased eyes. To support these projects and others, we have built an investigational multimodal AO retinal imaging platform that will be used in a set of human subject experiments [14].

One area that will be explored in this investigation is the relationship between cell viability and blood flow and other metabolic processes, particular as it relates to disease process (often called neurovascular coupling in neurological applications). With the capability to resolve all retinal capillaries, AO allows for precise quantification of ocular blood flow [15] and the dysregulation of blood flow implicated in glaucoma pathogenesis. Previous studies have demonstrated an oxygen-induced autoregulatory effect on the retinal microvasculature [16]. Specifically, oxygen inhalation reduces the pressure gradient across capillaries, and thus decreases erythrocyte movement. More recently, studies have shown that eyes with glaucomatous damage exhibit significantly reduced retinal blood flow (RBF). However, conventional clinical imaging modalities are limited in their assessment of RBF. The advantages of AO retinal imaging will enable us to surpass these limitations for studying RBF in glaucomatous patients, which may serve as the basis of earlier detection of and more sensitive monitoring of glaucoma progression.

Other than the fact that AO imagers produces a tighter spot on the retina, which can be accounted for in the light safety analysis, AO works like any other minimally invasive, commercial, diagnostic retinal imager, of which there are dozens of manufacturers with hundreds of devices imaging millions of subjects daily. AO was invented in the late 1990s and instruments have been used in a research setting for decades, including at the University of Rochester since 1997, the University of Houston since 1998, the University of California, Berkeley since 2005, the University of California, San Francisco since 2010, and the Medical College of Wisconsin since 2011. No light-exposure-related incidents in humans have been reported at these institutions. Moreover, the Medical College of Wisconsin has established an International Adaptive Optics Consortium (IAOC) with the goal of conducting multi-center large-scale AO clinical trials. IAOC members with similar systems include the Medical College of Wisconsin, the University of Pennsylvania, the New York Ear and Eye Infirmary, Moorfields Eye Hospital (UK), the University of California, San Diego, and NIH National Eye Institute. The IAOC AO instruments have been used to screen over 1,000 patients at four sites with no light-exposure-related incidents. Commercially, Imagine Eyes has several AO instruments that have received the CE mark in Europe and have imaged thousands of patients. In the U.S., Physical Sciences Inc. has also taken some steps toward commercialization with various AO imagers. In collaboration with researchers at University of Pittsburgh Eye Center, Children's Hospital Boston, and others, their instruments have imaged hundreds of patients. In summary, adaptive optics poses risk to human subjects that is comparable to, and no more than, optical imaging devices that are already on the market.

The FDA AO devices used in this study are investigational devices that qualify for investigational device exemption (IDE) abbreviated filing requirements according to 21 CFR 812. Appendix 3a contains a summary of the relevant sections of 21 CFR 812 related to abbreviated filing requirements and the justification for the automatic IDE status for the FDA AO devices.

2.0 Study Objectives

The overall objective of the study is to collect and assess AO retinal images from human subjects in support of projects to demonstrate, advance, and enhance clinical use of AO technology.

3.0 Participants

One hundred (100) healthy volunteers (cohort 1, Non-FDA and FDA employees) and fifty (50) subjects with POAG (cohort 2, Non-FDA and FDA employees who are enrolled as UMEA patients) will be accrued for this study.

3.1 Inclusion Criteria

Participants will be eligible if they:

1. Are 21 years of age or older.
2. Have the ability to cooperate with instructions during adaptive optics imaging (similar to instructions given during a clinical eye exam).
3. Have the ability to understand and sign an informed consent.
4. Meet the criteria for POAG as defined by the American Academy of Ophthalmology Practice Patterns (cohort 2).

3.2 Exclusion Criteria

Participants will not be eligible if they:

1. Are under 21 years of age.
2. Have a condition which prevents adequate images from being obtained (e.g. unstable fixation or media opacity).
3. Have visual correction outside of the range +4 diopters (D) to -8 D.
4. Have a history of adverse reaction to mydriatic drops.
5. Have a predisposition to (i.e., narrow iridocorneal angle) or any history of acute angle closure glaucoma (AACG).
6. Do not meeting the criteria for POAG as defined by the American Academy of Ophthalmology Practice Patterns (cohort 2)
7. Have any health conditions that would contraindicate oxygen supplementation, including chronic obstructive pulmonary disease (COPD), emphysema, asthma, or any other obstructive or restrictive lung disease (RBF experiment participants only).
8. Have a dependency on oxygen support or a baseline oxygen saturation <95% (RBF experiment participants only).
9. Have tested positive for COVID-19 at initial enrollment or have acute or chronic photophobia as a result of contraction.
10. Are working under the direct supervision of Dr. Hammer.

Participants (both cohorts 1 and 2) will be screened for the exclusion criteria during the University of Maryland Eye Associates (UMEA) eye exam and after initial consent is given.

3.3 Recruitment

Participants without eye disease (cohort 1) will be recruited from FDA staff with a general email message, or through self-referral. A sample recruitment email to FDA staff is included in Appendix 4a. Healthy volunteers in cohort 1 may also be recruited from the University of Maryland Baltimore. Subjects will not participate in any aspect of the experimental study (design, conduction, or analysis). FDA staff will not be recruited who are within the work unit supervised by the PI (Dr. Hammer). POAG participants (cohort 2) will be recruited from the UMEA patient population by Dr. Saeedi (protocol medical advisor/Co-I) as described in Appendix 4b. The RBF subset will initially be recruited from UMEA patients that have undergone similar oxygen challenge experiments at UMEA and so are familiar with the tests. Gradually, we will add FDA control subjects and UMEA patients that are new to oxygen challenge experiment but have undergone AO imaging and have provided good results. In this way, we will avoid subjects that are completely unfamiliar with portions of the experiments.

3.4 Anticipated Benefit
Participants derive no direct benefit from participating in this study. However, research using data from this protocol may yield generalizable knowledge regarding methods for assessing ophthalmic variables in various eye diseases.

3.5 Consent Process
The PI (Dr. Hammer) or co-I (Dr. Liu) will consent all FDA participants (cohort 1) prior to any activity (including the UMEA eye exam) using a standard script (Appendix 5a). The PI (Dr. Hammer) or UMEA Co-I (Dr. Saeedi) will consent all non-FDA healthy volunteers (cohort 1) and POAG participants (cohort 2) using a similar script (Appendix 5b). Dr. Saeedi will recruit subjects during initial or follow-up eye exams after reviewing their medical record, POAG disease history and severity, and determining during the exam if they meet the inclusion/exclusion criteria listed above. In particular, he will judge their eligibility based upon the clarity of their anterior optics (e.g., no cataracts), their fixation ability, and their ability to keep their head motion minimal while sitting in a chin rest.

Potential participants (both cohorts) will receive a verbal explanation of the purposes, procedures, and potential risks of the study. Potential participants will have the opportunity to carefully review the informed consent form (ICF) and ask questions regarding this study prior to signing, and they will be informed that they may withdraw from the study at any time without prejudice to themselves. Potential participants will also be allowed to take the ICF home overnight to carefully consider the risks prior to consent. All participants must sign an IRB-approved ICF. A signed copy of the ICF will be provided to the participant to take home.

3.6 Alternatives to Participation
Participants do not receive any treatment in this study or forego any treatment in order to participate in this study. The alternative, therefore, is not to participate.

3.7 Compensation
Participants from both cohorts will receive a $100 gift card for each visit, in accordance with relevant institutional guidance and procedures. FDA employees may not participate in an FDA research study for which compensation is offered and accepted during their FDA working hours. An FDA employee can request administrative leave to participate in an FDA research project if the employee earns no money.

3.8 FDA Staff
All study activities for FDA staff will take place during non-work hours (lunch, after-hours, on credit time, etc.) at their discretion.

3.9 Withdrawal
Participants may withdraw from the study at any time, either by oral or written notice to the PI and co-PIs. Participants will not be penalized or lose any benefits to which they otherwise qualify upon withdrawal or removal from the study. UMEA medical care will not be affected for patients that decide not to participate or end participation. The PI and co-investigators may end participation for any subject if he/she feels that participation presents any safety concern whatsoever or if a subject no longer meets eligibility requirements for inclusion in the study. Subjects will be informed if any significant new findings are discovered that may affect their participation in the study. Data collected prior to withdrawal will remain part of the study findings.

4.0 Study Design and Methods
This is an interventional study of healthy volunteers and POAG patients to develop methods for AO image quality assessment and new imaging modes suited to specific cellular targets, function, or disease (particularly glaucoma).

4.1 Adaptive Optics Imagers
The adaptive optics (AO) imagers used in the study are investigational multimodal systems that include optical coherence tomography (OCT) and scanning laser ophthalmoscopy (SLO) channels [14]. Two similar

instruments will be used in the study. The first instrument, called the FDA mAO imager, scans two near-infrared wavelength beams, one centered at ~760 nm for SLO and one centered at ~830 nm for OCT, across the retina to produce images. It also includes a visible light stimulus channel, which can deliver light at six wavelengths from 450 nm to 656 nm to the retina for functional imaging applications. The total power delivered to the retina for the mAO imager is below ANSI maximum permissible exposure limits, as described in Appendix 2a. The OCT channel in the second instrument uses a Fourier domain mode-locked laser (FDML). Therefore, the second is called the FDA AO-FDML imager, and uses three infrared beams at ~785 nm (SLO), ~850 nm (AO beacon), and ~1060 nm (OCT). The AO-FDML imager also includes a visible light stimulus channel for functional imaging experiments. The total power delivered to the retina for the AO-FDML imager is below ANSI maximum permissible exposure limits, as described Appendix 2b. The primary upgrade in the second instrument is the OCT imaging speed and pixel density, which has increased from 2.3 volumes (300×300 pixels) per second to 13.4 volumes (500×500 pixels) per second. In both instruments, ocular aberration sensing and correction is achieved with a Hartmann-Shack wavefront sensor (WS) and deformable mirror (ALPAO, DM97-08, France), respectively. Both instruments use a pupil camera and a fixation target to position the subject's head and eye for scanning a particular retinal region within 15 degrees from the fovea. Data collected include OCT, SLO, and WS videos (temporal sequences), as well as data on ocular aberrations. All patient procedures (alignment, fixation, imaging scans) and data formats used for the two FDA AO imagers are identical.

For RBF imaging, the SLO channel of the devices will be configured to scan a single line at high speed, rather than rastering over a square field. This change in scan pattern has implications for light safety. The light safety analysis in Appendix 2a and 2b considers this device mode. In summary, the SLO line scanning mode is still eye safe for the smaller field size.

4.2 Initial Eye Exam for Screening and Risk Mitigation

Prior to AO imaging at FDA, each participant will undergo a comprehensive eye exam at the University of Maryland Eye Associates (419 W Redwood Street, Suite 420, Baltimore, MD 21201, 2101 Medical Park Drive, Silver Spring MD 20902, or 5900 Waterloo Road, Suite 230 Columbia, MD 21045) to determine if they are eligible for continued participation in the study. The UMEA eye exam will be provided at no cost to the FDA employees and will be part of routine care covered by insurance for the POAG subjects. A signed IRB Authorization Agreement (IAA) between the two parties is enclosed (Appendix 8).

The participants will be examined by the project medical advisor/Co-I, Dr. Saeedi, who is a board-certified ophthalmologist. The participants will undergo a complete eye examination. This will include the measurement of baseline visual acuity (VA) in both eyes with a standard Snellen chart as well as slit lamp examination, intraocular pressure check, and gonioscopy to check for any predisposition to a dilation induced AACG event (narrow iridocorneal angle). Instillation of an ocular anesthetic (Proparacaine 0.5%) and topical fluorescein will be required to check intraocular pressure and perform gonioscopy as per routine office protocol for eye examination. If there is no risk for angle closure, the participant's eyes will be dilated with a mydriatic drug (Tropicamide 1%), and any possible adverse event monitored by Dr. Saeedi for 30 minutes. A dilated examination will also be completed at this time. Depending on cohort, the following testing will be performed on each subject using the following legally marketed devices:

1. Fundus photography: Topcon Fundus Camera (both cohorts)
2. OCT retinal imaging: Heidelberg Spectralis or Optovue OCT (both cohorts)
3. Biometry (eye length): Zeiss IOLMaster (both cohorts, collected at UMEA or FDA)
4. Perimetry (peripheral spatial functional testing, also known as a visual field test): Zeiss Humphrey Field Analyzer (cohort 2 only)

All four tests are standard procedures for patients with glaucoma, those suspected of glaucoma, or those undergoing intraocular lens implantation. Because the tests are standard procedures and FDA-approved or cleared devices are used, they pose no greater risk to the subject than a standard clinical eye exam. Such tests are performed on a routine basis in eye clinics across the world on both healthy and diseased eyes. These tests

are used for both screening for pathology as well as to follow patients with existing, known pathology. As they are used for screening, particularly in optometric offices, they represent minimal to no additional risk to participants, and a risk that the study subject may normally encounter in their medical care.

The tests are necessary to collect additional information on each subject's eyes that will be used to guide further AO imaging. Wide-field fundus and OCT imaging will help determine where to perform small-field AO imaging. Biometry is necessary to properly correct the AO imaging field-of-view (important for quantitative measurement of retinal cell and structure dimensions). Perimetry will only be performed on POAG subjects to locate spatial regions and severity of disease. All tests will be performed under the supervision of Dr. Saeedi at UMEA. Moreover, the test will only be performed once on each subject during the initial eye exam. Therefore, these additional tests performed during the UMEA eye exam pose very little additional risk to the patient. However, the information they provide will be extremely valuable to increase the probability of success for the research study.

Should any ocular abnormality or disease be detected on eye examination, the patient will be advised to follow up at an appropriate interval (as determined by Dr. Saeedi) with an eye care professional for monitoring or treatment. If there are no adverse events or other exclusions, as determined by Dr. Saeedi, the participant will be cleared to enter the study. Patient information from the eye exam will be kept at the eye clinic per routine office protocol and with strict confidentiality abiding by HIPAA and all relevant regulations regarding medical records. Patient records for the initial eye exam will be kept together with records from the clinical practice and destroyed seven (7) years after study termination. No patient information from the eye exam will be transferred to the FDA investigators without the participant's consent. Written consent will be obtained with a description of the exact information transferred to the FDA investigators when it is necessary to use information obtained from the clinical exam. Appendix 9 contains a copy of the HIPAA Authorization Form to be signed when clinical data is transferred to the FDA investigators.

The initial eye exam will mitigate the risk of an adverse event from mydriasis to every extent possible. It is highly unlikely that an adult study participant will have an adverse event on subsequent imaging sessions if they have not had one during the initial eye exam. However, should the participants experience eye pain after administration of dilating drops (other than the minor stinging that typically accompanies the eye drops), the participants will be brought immediately to UMEA for monitoring. Also, should the participants complain of any change in vision, they will be brought to UMEA and have their eye examined and their VA re-tested. Either circumstance will constitute an adverse event.

Dr. Saeedi has trained the PI (Dr. Hammer) and co-I (Dr. Liu) on administering dilating eye drops for the AO imaging session. Both Drs. Hammer and Liu have previously conducted human subject studies on adaptive optics and have administering dilating eye drops to patients. It is estimated that Drs. Hammer and Liu have imaged over 250 subjects with adaptive optics retinal imaging devices. It is common in eye clinics for technicians (i.e., non-MDs) to deliver dilating eye drops to patients. All FDA investigators received training on collecting biometry measurements from the manufacturer (Carl Zeiss Meditec Inc.).

4.3 Study Procedures

The exposure time limits and restrictions outlined in Appendix 2a and 2b will be followed in order to ensure that there is minimal risk of retinal damage. In particular, the output power level at each wavelength will be recorded with a calibrated power meter (Newport Power Meter Model 1918-C with 918D-ST-IR head) for every imaging session day prior to subject imaging.

Some participants may be asked to be re-imaged multiple times to characterize test-to-test variability or other measures related to system performance or physiological changes over time. The maximum number of imaging sessions for any participant in a year will be five and the time between imaging sessions will be no less than one week. Either or both eyes may be imaged in a given session. Each imaging session will take ~2 hours and no patients will undergo more than one imaging session a day. The exact duration will depend upon the subject themselves (ability to hold fixation, number of rest stops, etc.) and also on attributes of the experimental design

(the scanning mode, number of retinal locations imaged, number of eyes imaged, etc.), and will be known (approximately) and communicated to the participant prior to any given session. Subjects will consent to participation as described above. They will be informed of the approximate session duration and that they may ask for a rest period at any time. They will be offered rests frequently during testing and between test blocks, and a rest will be required any time a participant shows sign of fatigue.

Each subject's pupils will be dilated with Tropicamide 1%. One drop will be delivered to the eye(s) at least 20 minutes prior to imaging by the PI (Dr. Hammer) or co-I (Dr. Liu). Two additional drops of Tropicamide may be administered for insufficient dilation. Adverse reaction to the mydriatic agent will be monitored for 30 minutes following administration by the PI or co-I. After pupillary dilation, the following procedures will be performed:

1. Alignment: The subject will be instructed to sit at the instrument and place their chin in the chin-rest while their head is positioned to align their eye to the imaging beams.
2. Closed-loop AO operation (aberration measurement and correction): The subject will be instructed to look at a specific fixation target. The instrument will measure the wave-front aberrations of the subject's eye and the AO control system will correct ocular aberrations to allow acquisition of high-resolution images.
3. Retinal image acquisition: The subject will be instructed to look at a specific fixation target. Image sequences, with various durations depending on scanning mode, will be acquired at different retinal locations. The patient will be allowed to take periodic breaks during imaging as needed.

A subset of subjects in both cohorts will undergo AO RBF imaging concurrent with oxygen inhalation to investigate autoregulation of blood flow in glaucoma:

4. Following acquisition of baseline measurements while breathing room air, subjects will be placed on oxygen via non-rebreather face mask for up to two hours. Procedural steps 1-3 will then be performed for acquiring images during continuous oxygen supplementation.
5. Pulse oximetry, Blood Pressure, and ECG: Standard pulse oximetry, blood pressure, and ECG monitoring will be applied throughout all procedures to monitor heart rate, rhythm, and blood oxygen saturation.

A subset of subjects from the healthy control cohort will undergo photoreceptor stimulation experiments concurrent with AO-OCT imaging. This involves delivery of a sequence (5-10) of short duration (5-100 ms) pulses of visible light stimulation to the eye. The visible light pulse duration is precisely controlled with a shutter and synchronized to the image acquisition. Sets of AO-OCT volumes will be collected as usual. The visible light stimulus is included in the light safety analyses (Appendix 2a and 2b) and introduces no additional risk of retinal injury.

A subset of subjects will also be imaged with the FDA Heidelberg Spectralis high resolution OCT system, an investigational device that uses a wide bandwidth source to increase the axial resolution of the OCT images. This device has not yet received market clearance by the FDA for human subject use. In addition to a different source, it will also be modified to increase the scan pixel density to allow for cellular-scale retinal imaging. Otherwise, the device is identical in form and function to the FDA-cleared Heidelberg Spectralis OCT device. These changes do not render any additional safety risk to the participant, particularly with respect to light safety (Appendix 2c). A non-significant risk assessment by the company, which additionally lists all standards to which the device conforms, is attached to this protocol (Appendix 3b).

4.4 Location

The AO imagers and Heidelberg Spectralis high resolution OCT system are housed in the FDA/CDRH/OSEL laboratory space on the White Oak Campus, Building 62, Room G238.

4.5 Study Duration
The duration of the study, including data collection, analysis, and dissemination, is expected to last five years.

5.0 Data Management Plan
5.1 Storage of Data and Samples
No blood, tissue or other samples will be collected or stored in this study. Patient records from the initial UMEA eye exam will be kept at the eye clinic as described in Section 5.3. Clinical retinal images and data will be transferred on an external hard drive to the FDA investigators with subject consent (Appendix 9). De-identified images (that contain only the subject number but no personal information) will be stored only on an external hard drive (i.e., not transferred to an FDA computer) and stored in a locked file cabinet in the FDA PI's office (WO62.1106). The clinical data and images will be de-identified by Dr. Saeedi.

The only site of AO data and image collection will be the optical diagnostics devices laboratory of FDA/CDRH/OSEL/DBP on the White Oak Campus. The acquired data will be initially stored on the AO system computer, which is password protected. Because of the potential size of volumetric image datasets, which can be tens of gigabytes for a single subject for a single imaging session or more, de-identified data will be transferred to a shared network drive, which is password protected and accessible only from FDA scientific computers.

5.2 Privacy
All research activities will be conducted in a private setting, with only the subject and investigators in the imaging laboratory.

5.3 Confidentiality
All records will be kept confidential and will only be reviewed by Drs. Hammer, Liu, and Saeedi. Printed, signed informed consent forms will be stored in a locked file cabinet in the PIs office (WO62.1106). The Certificate of Confidentiality issued by the FDA in accordance with new requirements under the 21st Century Cures Act is included in Appendix 10.

For the initial UMEA eye exam, records will be kept at the eye clinic in the same manner as records from patients in the clinical practice. Most patient information is recorded in paper files that are kept in locked cabinets. Some information is collected in encrypted electronic records, which are stored on password protected computers. Except de-identified clinical data and retinal images discussed above in Section 5.1, all patient information remains on-site at the UMEA eye clinic and is accessible only by trained staff and maintained with confidentiality abiding by HIPAA and all relevant regulations regarding medical records. Records for the initial eye exam will be kept together with records from the clinical practice and destroyed seven (7) years after initial collection.

FDA staff are considered a vulnerable population because of their close working relationship with the FDA investigators. Therefore, confidentiality of potentially sensitive and private information about co-workers requires heightened vigilance. To mitigate risk of a confidentiality breach, this study is designed to minimize personal identifiable information (PII) and private health information (PHI) data collection and to consolidate PII and PHI data storage in only one electronic location kept by the PI (Dr. Hammer). Furthermore, all study staff have been instructed not to discuss any study patient information with co-workers or in a regular work environment.

For the FDA imaging session, the only PII collected from the subjects will be name and age. A participant's age and sex will be collected to ensure a diverse population is represented and also potentially to compare retinal images across different age groups. A subject number will be assigned to each participant and all information collected during the imaging session (image videos and ocular aberration data) will be coded using their subject number. The only link between patient number and PII (name and age) will be a single cross-referenced list, which will be kept in a password-protected excel spreadsheet. Any data publicly disclosed cannot be linked back to the subject. Only the study investigators will have access to this electronic document.

5.4 Analysis Plan

De-identified data, particularly OCT and SLO videos will be analysed with custom software written by the investigators in LabVIEW and MATLAB or commonly available image processing (ImageJ, Photoshop) and statistical programs. Examples of image processing and analysis code for AO applications include image registration, montaging or mosaic generation, capillary tortuosity and flow, and photoreceptor, RPE, and ganglion cell identification and quantification (cone packing, tessellation, Voronoi analysis). Because only de-identified information will be processed, a direct breach of confidentiality is not possible. Moreover, because high resolution AO images of only a small patch of the retina will be acquired in one video, it is not possible to reconstruct patient identifiable vascular patterns.

De-identified images from the study will be made public in the form of presentations, peer-reviewed publications, and other scientific and educational interactions with internal and external professional colleagues, students, and other trainees. Confidentiality will be maintained through-out the reporting process.

5.5 Study Conclusion

At the conclusion of the study, all data will be removed from shared drives and archived on external hard drives. Documents containing any PII or documents that link the subject's identification to the de-identified data will be destroyed 5 years after study termination.

6.0 Patient Risks

6.1 Summary of Potential Risks

In general, there are four potential risks to the participants in this imaging study:

1. The participant has an allergic reaction or other complication to the mydriatic agent (increase in intraocular pressure),
2. The participant is exposed to a light level that exceeds the maximum permissible exposure (MPE) limit that damages the retina,
3. The participant becomes injured during imaging from their presence in a research laboratory setting near scientific instrumentation, and
4. The participants experience side effects from continuous oxygen supplementation.

Mydriatic drugs work by inhibition of the parasympathetic (i.e., contractive) response of the eye by blockage of muscarinic acetylcholine receptors or by stimulus of the sympathetic response of the eye by blockage of the re-uptake of noradrenaline. Side effects and complications associated with mydriatic drugs include photophobia, and in extremely rare cases, an increase in intraocular pressure leading to acute glaucoma. Mydriatic drugs are necessary for this investigation because the benefit from adaptive optics is optimal for dilated pupils larger than 6 mm. Only those subjects known (from clinical administration conducted by Dr. Saeedi) not to have severe adverse reactions to mydriatic agents will be enrolled in the study. All participants will experience some level of photophobia similar to that associated with a routine visit to their ophthalmologist. The effect of the drugs usually lasts 4-6 hours.

The second risk, light exposure to focused (ANSI) Class II or higher laser power levels, has to do with the interaction between imaging beams that are directed to the participant eyes and their retina (the only reason the device is minimally invasive rather than non-invasive). The light safety analyses in Appendix 2a, 2b, and 2c describes the technical details of the risk. Given the mitigation strategy, this risk has a very low likelihood of occurring but moderate severity if it does occur.

The third risk involves injuries that can occur when a participant unfamiliar with research enters a laboratory. The optics laboratory is not a wet lab, and so does not have harmful chemicals. The patient has one ingress/egress path to the AO imaging systems. Therefore, this risk has a very low likelihood of occurring and low severity if it does occur. This protocol and the imaging procedures described, as well as the eye exam, have been examined by the CDRH safety officer and found to be acceptable (Appendix 6).

A fourth risk for the subset of subjects that undergo oxygen supplementation includes restriction of facemask air-flow leading to hypoxia, and possible side effects from continuous oxygen inhalation (dry nose, bloody nose, fatigue, or headaches). The side effects are dependent on the duration and intensity of the oxygen delivery. Oxygen supplementation will be set to a rate of 10-15 L/min for delivery via the non-rebreather face mask. Oxygen saturation levels will be closely monitored using standard pulse oximetry. Therefore, this risk has a very low likelihood of occurring. If the subjects exhibit any side effects, we will terminate the experiment immediately. If an adverse event occurs, the subject will be monitored on-site for an hour until symptoms resolve. If any issues persist, Dr. Saeedi will be contacted (if not already present) and the subject will be taken to UMEA. For an adverse event that is deemed by the investigators to be serious or potentially serious, 911 will be called. As per normal laboratory safety practice, oxygen cylinders will be kept away from heat sources and electrical hazards to ensure the safety of the laboratory setting.

6.2 Risk Mitigation Strategy

We will recommend that each subject avoids sunlight and wears sunglasses outside to mitigate photophobia. More severe complications (allergic reaction to mydriatic drugs) will be monitored by the Medical Advisor for 30 minutes after administration during the initial UMEA eye exam and by the PI and co-Is during the imaging sessions. The eye exam is designed to provide significant reduction in risk of reaction by screening subjects with a predisposition or history of AACG.

The primary mitigation for the second risk is to maintain power levels that are below ANSI MPE limits. The power at the cornea will be measured each day an imaging session takes place and recorded in a logbook. The SLO and OCT illumination sources are superluminescent diodes (SLD), the output power of which are controlled from the computer. The SLD electronic drive boards have current limits that prevent excessive output power being delivered to the participant's eye. When SLDs fail, their power output will drop significantly or altogether (i.e., the power never increases for device failure). Scanner failure will direct a focused beam to the retina but also stop imaging, which will be nearly immediately noticed by the operator (within seconds), who can tell the subject to sit back from the instrument. The visible light stimulus source delivery is controlled with a shutter that precisely sets the illumination timing (pulse duration, etc.). The SLO line-scanning mode (for RBF imaging) will be configured to interleave line and raster frames so that the line scan is only stationary for 37 ms.

The third and fourth risks are mitigated by common laboratory safety practices that are in place at DBP and described in our BSC safety manual, which contains the emergency response plan as well as a description of procedures for dealing with chemical safety, biosafety, laser safety, and issues related to hazardous waste. OSEL complies with all Occupational Safety and Health Administration (OSHA) regulations and conducts routine safety training for its staff. Additionally, the fourth risk will be mitigated by having a dedicated technician monitor airflow, pulse oximetry measurements, blood pressure, ECG, and patient status for signs of fatigue or discomfort continuously during imaging. The participant will be queried through-out to check for side effects of oxygen supplementation.

6.3 Classification of Risk

The FDA IRB has classified this protocol as a greater than minimal risk study.

7.0 Participant Monitoring and Adverse Event Reporting

7.1 Participant Monitoring

Participants will be monitored for adverse events by the study investigators during all imaging sessions.

7.2 Adverse Event Reporting

The PI is responsible for detecting, documenting, and reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs), suspensions, terminations, adverse events (AEs), including serious adverse events (SAEs), and non-compliance with FDA policy, IRB requirements, and federal regulations. Adverse event can include conditions that affect either or both eyes (e.g., pain) or the whole body (e.g., dizziness). Unanticipated problems, as defined by the FDA SOP [17], will be reported, including death, regardless of

whether the death is expected and/or unrelated to the research. Unanticipated adverse device effects will also be reported to the FDA within 10 working days after the effect per 21CFR812.150(b)(1). The PI will report all such events to the FDA IRB and provide any additional information which the committee may require to evaluate the severity of the event.

The risk probability of adverse events is expected to be extremely low. Participants will be asked at the end of imaging if they notice any changes in vision, apart from those normally experienced during pupil dilation. Participants will be provided with the contact information of the PI (on the IFC) to report any delayed effects of imaging. In the event of an injury, medical treatment will not be provided at WO, and the participant or his or her insurer will be responsible for the payment of any medical treatment for research related injuries.

8.0 Investigator Roles and Qualifications

Daniel X. Hammer, Ph.D., is the Principal Investigator and is responsible for the conduct and oversight of all aspects of the study. He has 25 years of experience in biomedical research and has been the PI on many human subject protocols, including for AO imaging. He will consent the subjects and operate the AO systems during a portion of the imaging sessions.

Zhuolin Liu, Ph.D., is a Co-Investigator and will be the primary operator of the AO systems during the human subject tests. She is first author on several seminal AO-OCT papers and has participated in several human subject investigations. With Dr. Hammer, she designed and built the FDA mAO and AO-FDML systems.

Osamah Saeedi, M.D., is the Director of Clinical Research in the Department of Ophthalmology and Visual Sciences at the University of Maryland School of Medicine. He will perform the initial ophthalmic exam, train personnel in the administration of eye drops, and provide oversight. Dr. Saeedi is an active clinician and ophthalmic surgeon. He oversees several clinical trials in his current position at the University of Maryland.

Anant Agrawal, Ph.D., is a research scientist in FDA/CDRH/OSEL/DBP and will participate in many of the AO imaging studies, both those that involve human subjects and others. He will operate the AO systems occasionally. He is leading the AO retinal phantom development effort and has over 12 years of experience with OCT instrumentation, phantom development, and data analysis.

Johnny Tam, Ph.D., is a staff scientist at NIH/NEI and is an active collaborator with the FDA team. He has an AO imaging system in the NIH clinical space, where he has a human subject protocol to image subjects with retinal degeneration and other diseases.

Achyut Raghavendra is a staff fellow in FDA/CDRH/OSEL/DBP. He will assist with AO subject image collection, particularly for the retinal blood flow experiments, as well as data analysis and interpretation.

Swetha Ravichandran is a post-doctoral fellow at the University of Maryland School of Medicine. She will assist with AO image collection, image processing, data analysis, and data interpretation, particularly for the glaucoma study. Havish Gadde and Priya Agrawal are research assistants at the University of Maryland School of Medicine. They will assist with glaucoma patient recruitment, collection of participant information and demographics, and some data analysis and statistics.

8.1 Conflicts of Interest

No investigator has a conflict of interest according to FDA and NIH guidelines on conflicts of interest.

9.0 References

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[17] FDA IRB SOP, "Unanticipated Problems Involving Risks to Subjects or Others, Serious or Continuing Noncompliance, and Suspension or Termination of IRB Approval," Office of the Commissioner, Office of the Chief Scientist, Version 1, February 19, 2019.

10.0 Appendices

1. Informed consent form
2. Light safety analysis for:
    a. mAO imager
    b. AO-FDML imager
    c. Heidelberg High Resolution Spectralis OCT
3. IDE abbreviated filing requirements documents
    a. Justification for FDA AO systems
    b. NSR assessment for Heidelberg High Resolution Spectralis OCT
4. Recruitment documentation
    a. Example FDA staff recruitment e-mail message
    b. UMB SOM recruitment strategy description
5. Consenting scripts:
    a. Version for FDA employees
    b. Version for UMEA patients
6. CDRH Safety Officer recommendation memo
    a. Original 62.G238 lab safety survey, 11/30/2017
    b. 62.G238 lab safety survey including oxygen tank setup, 01/21/2020
7. CDRH Laser Safety Officer recommendation memo
    a. mAO imager light safety analysis review for amendment 4 (8/2/19) and amendment 5 (7/15/20)
    b. AO-FDML imager light safety analysis review for amendment 6
    c. Heidelberg High Resolution Spectralis OCT light safety analysis review for amendment 9
8. IRB authorization agreement with University of Maryland
9. HIPAA Authorization Form
10. Certificate of Confidentiality
11. FDA map and security checkpoint instructions for non-FDA employees
12. Oxygen Training Plan
13. Investigators' CV and CITI training certifications (provided only upon request)