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Protocol title: BCI and Evaluation of Visual and Task Performance in Subjects With Eye Diseases

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1. RESEARCH ABSTRACT

1. Better understand the impact of visual impairment on daily task performance in patients with eye diseases of the visual pathways, such as glaucoma and age-related macular degeneration (AMD).

2. Longitudinal study, with biannual visits, including patients with: glaucoma, suspected of having glaucoma, non-glaucomatous optic neuropathies, AMD, retinal degenerations, other diseases involving the visual pathways, besides healthy controls. Subjects will perform standard ophthalmological exams, and the following research tests: psychophysical, eye tracking, electroencephalogram, driving simulator, virtual reality, balance assessment, and questionnaires.

3. Statistical analyses will be performed by the PI using the software Stata, MATLAB, and MPLUS. Risks are low, consisting of some discomfort, fatigue, dizziness or motion sickness.

2. RESEARCH PROTOCOL

PURPOSE OF THE STUDY

The purpose of the present study is to better understand the impact of visual impairment on daily task performance in patients with eye diseases and diseases of the visual pathways, such as glaucoma and age-related macular degeneration (AMD).

BACKGROUND & SIGNIFICANCE

Glaucoma is a progressive optic neuropathy that may result in significant visual impairment. The loss of vision affects the quality of life and also has economic consequences to the patient and to society.1 The fundamental goal of glaucoma management is to prevent patients from developing visual impairment sufficient to produce disability in their daily lives and impair their health-related quality of life (HRQOL). Although investigations of glaucoma diagnostics have focused largely on conventional testing with perimetry and optic nerve evaluation, there is a compelling need to better characterize measures of functional impairment and HRQOL in glaucoma and to understand how they relate to conventional clinical tests. Our previous results have shown important relationships between subjective measures of disability obtained through patient-reported outcomes and metrics of structural and functional damage in the disease. However, self-reported evaluations are based on each individual's assessment of his or her ability to do a particular task and can be largely influenced by personal expectations, understanding of the degree of difficulty involved, personality and emotions, and may not correspond well to objective measures of performance. Therefore, an assessment of disability in glaucoma and other eye diseases necessarily involves an understanding of how the disease objectively affects patient performance on tasks, such as searching for

objects, navigating through an environment or driving. The ability to conduct such assessments, however, has been greatly limited by the difficulty in conducting real-world standardized tests that can provide meaningful and reliable information. The recent progress in virtual reality (VR) technologies has brought the opportunity of simulating daily live activities in a way that was not previously possible. Although largely confined to the gaming industry, VR techniques have the potential to transform health care by creating immersive and realistic scenarios that closely replicate difficulties faced by subjects on daily tasks, allowing quantifiable and reproducible research that can also provide insight into mechanisms leading to impairment.

The overall goal of this proposal is to improve our understanding of functional disability in glaucoma by using VR tests to investigate objective performance during simulated daily life activities. In addition, by contrasting patients with glaucoma from those of other eye conditions, such as macular degeneration, we may be able to better assess the relationship between patterns of visual damage (for example, central versus peripheral) and disability. We will conduct cross-sectional and longitudinal studies to quantify disabilities through objective VR-based tasks, study their relationship with conventional clinical measures, as well as to investigate basic vision and neurophysiologic mechanisms associated with task performance.

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DESIGN & PROCEDURES

This will be a longitudinal study in which patients will be examined with a cluster of visits biannually. We will recruit patients with:

1. Glaucoma;
2. Suspicion of having glaucoma;
3. Non-glaucomatous optic neuropathies;
4. Age-related macular degeneration (AMD);
5. Retinal degenerations;
6. Other diseases involving the visual pathways such as optic neuritis, tumors or ischemic neuropathy.

Patients with eye diseases or suspected of having eye diseases will be recruited from Dr. Medeiros's clinic by verbal communication. Staff members at the Duke Eye Center will also be invited to recommend potential participants for the study, in conformance with the Duke Human Subjects Committee Guidelines. Healthy participants will be recruited from patient’s spouses or relatives for comparison and to establish normative levels, and will also be recommended from eye doctors from the comprehensive clinic who treat this population.

General evaluation:

As part of the study all participants will undergo the following general exams:

1. Review of medical history;
2. Blood pressure and heart rate;
3. Height and weight;

Ophthalmological evaluation:

As part of the study all participants will undergo a comprehensive ophthalmologic examination including:

1. Low contrast sensitivity testing;
2. Best-corrected visual acuity;
3. Slit lamp biomicroscopy;
4. Serial measurement of the intraocular pressure measurement before and after drinking water;
5. Gonioscopy;
6. Corneal thickness measurement (pachymetry);
7. Corneal hysteresis measurement (Ocular Response Analyzer, Reichert, Inc.);
8. Ocular axial length;
9. Corneal curvature;
10. Anterior chamber measurement;
11. Dilated funduscopy examination;
12. Stereoscopic optic disc photography;
13. Measurement of amount of lens opacity (cataract) by the HD Analyzer system (Visiometrics, Inc.);
14. Automated perimetry with the 24-2 and 10-2 Swedish Interactive Threshold Algorithm (SITA; Carl Zeiss Meditec, Inc.) and fundus perimetry with Compass (CenterVue, Inc);
15. Spectral domain optical coherence tomography (SDOCT);
16. Swept-source optical coherence tomography (SSOCT);
17. Optical coherence tomography angiography (OCTA);
18. Macular pigment optical density (MPOD).
19. Diopsys NOVA (Diopsys, Inc.) visual evoked potentials (VEP) and electroretinogram (ERG).

The following tests are considered research related:

Questionnaires:

Patients will respond a series of questionnaires to assess quality of life as well as factors that may be associated with it. In addition, patients will answer questionnaires addressing susceptibility to motion sickness. This will be done so that patients with increased sensitivity to motion sickness may be excluded from test with a driving simulator. A study team member will read aloud the questionnaires to subjects with impaired vision who are unable to read for themselves. Team members administering the MoCA electronic test app will have MoCA certification. The questionnaires include:

1. Short structured interview to obtain information on sensitivity to motion sickness using the Motion Sickness Questionnaire;
2. Simulation sickness using the Pre- and Post-Simulation Sickness Questionnaire;
3. Depression using the Geriatric Depression Scale;
4. Physical Activity Scale for the elderly questionnaire (PASE);
5. Driving habits questionnaire using the Driving Habits Questionnaire from the American Academy of Neurology;
6. Sense of direction evaluated through the Santa Barbara Sense of Direction Scale (SBSOD);
7. Socioeconomic status information using the Socioeconomic Form;
8. History of falls and fear of falling using the University of Illinois at Chicago Fear of Falling Measure Scoring Sheet;
9. Cognitive function using the Montreal Cognitive Assessment (MoCA) using the MoCA Electronic Test app (www.mocatest.org);
10. Short structured interview to obtain vision-related quality of life information using the National Eye Institute 25-Item Visual Functioning Questionnaire (NEI VFQ-25).
11. Short structured interview to obtain glaucoma-related quality of life information using the Glaucoma Activity Limitation Questionnaire (GAL-9).

Psychophysics tests:

Patients will undergo psychophysics tests in order to better characterize their degree of visual function impairment and how it relates to performance. These psychophysics tests include investigation of visual processing speed, visual crowding and target detection under a variety of scenarios. The tests use simple LCD monitors or tablets.
The UFOV is a simple computerized test performed on a single computer touchscreen. It comprises three subtests that measure visual processing speed with increasing difficulty. The first subtest is an evaluation of central visual and processing speed and requires the identification of a central target. The second subtest evaluates divided attention by adding an addition stimulus to the central target. The last subtest evaluates selective attention by adding visual distractions (triangles) around the central and peripheral stimuli. All stages of the test are performed using a computer monitor. The stimuli are displayed for between 17 and 500 ms, and patient response is recorded.
All participants will also undergo a series of psychophysical tests on a digital tablet including visual acuity, contrast sensitivity and acuity, visual processing speed and divided

attention. The tests include the presentation of visual targets on the screen of an iPad (Apple, Inc.) or similar tablet, such as letters, images or Gabor patches. The targets may be presented in isolation or with additional targets. The time of presentation is shortened over time in order to obtain a threshold for target detection.
Visual crowding tests will also be performed. This test investigates the ability to detect targets in cluttered visual environments. Test is conducted on an LCD monitor where targets are shown in isolation or in situations of crowding (with flankers). Ability to detect the targets is then assessed. Visual crowding sets a fundamental limit on the peripheral vision. Therefore, its study may provide fundamental insights on how loss of vision in diseases such as glaucoma may affect task performance.
Duration of psychophysical testing is expected by be approximately 45 to 60min.

Eye Tracking:

Eye tracking will be used to monitor patient eye fixations and eye movements during the visual tests. The eye tracking consists of glasses (ETG, SMI Sensorimotor instruments), Tobii eye tracking monitor (Tobii instruments) and virtual reality goggles equipped with eye tracker (FOVE and HTC Vive).

Depending on the specific visual task performance, a different type of eye tracker will be used. Monitoring eye movements is essential in order to better evaluate where the patient is looking during the visual tests. In addition, investigations of eye movements may provide insight on how different eye diseases affect patterns of gaze and their impact on task performance. The SMI eye tracking glasses are similar to a regular pair of glasses. Eye movement is monitored by cameras and data is transmitted to a computer. The Tobii eye tracking is coupled to a regular LCD monitor and can be used to monitor eye gaze while allowing for complete freedom of head and eye movement. Depending on the task being performed, we may also use virtual reality goggles equipped with eye tracking to monitor eye movements.

Electroencephalogram (EEG) and Visual Evoked Potentials (VEP):

Electroencephalogram will also be obtained while patients perform visual tasks. This will allow us to understand the relationship between visual and brain functioning and their interplay in task performance. The electroencephalogram (EEG) is a well-established procedure for measuring the surface electrical potentials on a patient's scalp. The procedure involves the use of sensors placed on the surface of the skin and is generally considered safe and non-invasive for both clinical and research use. Participants will undergo the EEG test (Cognionics, Inc.) when performing visual tasks presented on a standard LCD display or tablet. Visual evoked potentials (VEP) will be evaluated with Diopsys NOVA (Diopsys, Inc.), which is a well-established conventional multifocal VEP device to assess brain functioning following visual stimuli from a computer screen. It is a

non-invasive, safe testing and patient is prepared in a similar fashion than EEG: three small areas in the scalp are cleaned and dried and then sensory pads are placed on the cleansed areas.

Driving simulator:

Participants will be tested on a driving simulator. The simulator system consists of a panel of screens, a wheel drive, and a foot pedal, similar to a real car, all connected into a computer. Participants are asked to perform simple tasks such as follow a vehicle, keep up with the speed limit and avoid obstacles. Data collection includes several variables such as speed, lane deviation, time of reaction, vehicle control and obstacle avoidance. If a patient feels dizzy the exam can be interrupted at any time. The duration of testing with the simulator is about 15 minutes. As this is an experimental procedure, no results will be reported to the DMV with regard to driving ability.

Virtual Reality Tests:

Virtual reality tests will be conducted using virtual reality goggles (HTC Vive, Samsung Gear VR or FOVE). The tasks include scenarios replicating daily activities such as driving through a road, walking through a virtual environment or searching for objects. In order to navigate through the environment, subjects will use a steering wheel or joystick. The estimated duration of the test is 30 minutes. In the task of navigation, the subject will find him or herself near a wall in a rectangular room with colored walls, different objects on each wall, and different objects (couch, table statue, etc.) at various locations. The subject will be asked to move to and step upon a green tile that is displayed at some random location in the room. Once the target location is attained, the display is turned off for a short period. The task will then begin again, but with a different starting position. These initial tests are designed to assess the subject's ability to move from one location to another in a virtual environment. Subjects that can achieve sufficient proficiency in the target-visible protocols will then be instructed that the next series of tests will require them to find a hidden target tile and that they will be asked to remember its location. In these protocols, the subjects will be given a limited amount of time (2 minutes) to locate the target, which will become visible when it is reached, and their path and time to target discovery recorded. Path length and path topology will be measured in real time. The test will be repeated, from the same starting location, at least 5 times or until no improvement in time/distance to target is observed by the experimenter, who is analyzing the test outcomes on a tablet in real time. After a 5-minute rest period with no visual stimulus, the subject will be asked to repeat the task for a "probe" trial. This time the search will be limited to 30 seconds or to the shortest time attained in the prior trials, without the target becoming visible. The outcome measurement will be time spent and path length in the vicinity of the target, as a measure of spatial memory and spatial navigation strategy. Depending on the data obtained in this set of trials, the subject will be asked to continue with further tests of increasing difficulty,

as for example with reduced numbers of distinct landmarks or with random starting locations for a constant target position. Visual search task will consist of a virtual environment (e.g., an apartment) and the patient will be given a specific task of object finding. The time and path to complete the task will be obtained. For driving tasks, the subject will use a driving wheel to guide a car through a virtual environment and complete a simple task of wayfinding, following a car or negotiating a curve.

Balance Assessment:

During this test subjects will stand on a force platform while different visual stimuli will be presented. The force platform (AMTI Optima Human Performance System, Advanced Mechanical Technology, Inc., Watertown, MA) is used to evaluate the posture and balance by recording pressure changes at the four corners of the platform that change as the subjects stabilize themselves. For this test we will use virtual reality goggles (Oculus Rift, Oculus VR, LLC, Irvine, CA) to deliver the visual stimuli. Such a system is appealing since it provides whole-eye coverage allowing a controlled environment for the visual input. The subject will be required to fixate the gaze at the center of the scene, while different visual stimuli will be presented, such as rotating rings. A harness system (Handrail and Harness Safety Structure, Bertec Corp., Columbus, OH) will be used to prevent subjects from falling. The experiment will consist of a number of short (approximately 1 minute) sessions with pauses to rest in between. The total duration of the test will be approximately 20 minutes.

Retinal metabolic analysis:

The OcuMet Beacon is a novel medical device that non-invasively assesses retinal mitochondrial dysfunction. The device takes an infrared fundus image that highlights the acquisition area for the retinal metabolic image, takes a retinal flavoprotein fluorescence (FPF) metabolic image, and provides quantitative analysis of the retinal mitochondrial function and patient report printout.

Assessment of intraocular pressure (IOP) with Tono-Vera:

Tono-Vera measures IOP by analyzing acceleration changes of a light-weight, plastic-tipped probe as it briefly contacts the cornea. The motion of the probe generates a voltage, which is recorded during the measurement process. The IOP value, which is displayed in the device, is intended to be a “Goldmann- equivalent” (Highly correlated to the gold-standard Goldmann applanation tonometer). The process described above takes only a few milliseconds and the sensation of the probe contacting the patient’s cornea is so light many patients cannot notice it. As such, the device is used without topical anesthesia. Probes are single-use, disposable.

Scheduled Visits

Subjects will be scheduled for 1 visit every six months for a period of 5 years. The duration of each visit is expected to be 2 hours and 30min. Subjects may also elect to complete the tests in 2 separate visits, which will be scheduled within 4 weeks. A subgroup of participants will be scheduled to have visits every 2 months to assess short-term visual function changes. In addition, a subgroup of participants will have 6 visits within a two-month period to assess test-retest reproducibility. Patients who elect to perform only a subset of the tests may still be included as long as the Principal Investigator decides that their inclusion is in line with the goals of the study and in maintaining the highest standards for research quality.

* * Amendment Protocol version 1.21:
Normal subjects will be invited to complete all tests and questionnaires listed in the section above only once, over 2 separate visits (visits "1" and "2"), within 4 weeks from enrollment. The duration of each visit is expected to be 2 hours. Subjects may also elect to complete the tests in 1 additional separate visit, which will be scheduled within 4 weeks. Normal subjects will not be followed longitudinally. All new subjects enrolled in the pathologies arms (glaucoma, AMD, and others) will be invited for a 7-visit regimen every 6 months for the first 2 years of the study (months 0, 6, 12, and 24 -- but not month 18). All visits in each cluster will be completed within a two-month period to reduce test-retest variability and provide better estimates of change. Over visits "1" and "2", subjects will complete all tests and questionnaires listed in the section above (i.e, each item only once, distributed over visits "1" and "2"). Visits "1" and "2" have an expected duration of 2 hours each and are the same for the normal group. Visits "3" through "7" will include only visual field testing, OCT testing, and IOP check (items 4, 14, 15, and 17 in the "Ophthalmological evaluation" subsection above). The duration of visits “3”, “4”, “5”, “6”, and “7” is expected to be of 1 hour each. After month 24 of follow-up, subjects will continue a regular schedule of 2 visits (visits "1" and "2" only) every 6 months until the 5 years of the study are completed. Subjects already enrolled in the study will be invited to transition to a 7-visit schedule for 2 years, if not completed yet as part of the test-retest variability preliminary assessment. All active subjects will be re-consented.
Patients who elect to perform only a subset of the tests or visits may still be included as long as the Principal Investigator decides that their inclusion is in line with the goals of the study and in maintaining the highest standards for research quality.

Unscheduled visits

An unscheduled visit may be any visit to the Investigator other than the specific visits requested in the protocol as possibly required for the subject’s ophthalmic condition. The Investigator will perform all procedures necessary to evaluate the study participant at these visits and record any adverse events in the source document.

SELECTION OF SUBJECTS

Inclusion criteria:

1. Subjects must be between the ages of 40 and 90 years old;
2. Both males and females will be included.
3. Be able and willing to provide signed informed consent and follow study instructions

Exclusion criteria:

1. Subjects will be excluded if they present with any systemic or ocular conditions that in the opinion of the Principal Investigator may prevent them from completing the tests (e.g. history of seizures or pathologies affecting the vestibular system or lower limbs).
2. Women of child-bearing potential will be excluded from tests that require pupil dilation, unless they have already received dilating drops as part of their standard of care. Pregnant women may self- report pregnancy testing and not undergo formal pregnancy testing since the SOC in ophthalmology is to not test for pregnancy or dilate the eyes of women who are of childbearing age.

Glaucoma Arm

To be considered glaucomatous, patients will be required to have at least two consecutive and reliable standard automated perimetry (SAP) examinations with either a pattern standard deviation (PSD) outside the 95% normal limits or a glaucoma hemifield test (GHT) result outside the 99% normal limits. Patients considered suspects for glaucoma must have an IOP greater than 21mmHg or suspicious appearance of the optic nerve head but with reliable normal visual fields, defined as a PSD within 95% confidence limits and a GHT result within normal limits. To be considered healthy, subjects have to have IOP<22mmHg with no history of elevated IOP and with at least two reliable normal visual fields, defined as a PSD within 95% confidence limits and a GHT result within normal limits.

Age-related macular degeneration (AMD) Arm

Patients will be considered as having AMD if one or more of the following are present on posterior biomicroscopy (fundoscopy), indirect ophthalmoscopy or Optical Coherence Tomography (OCT) exams:
1. Presence of at least intermediate-size drusen (63µm or larger in diameter)
2. Retinal pigment epithelium (RPE) abnormalities such as hypopigmentation or hyperpigmentation
3. Reticular pseudodrusen (also called sub retinal drusenoid deposit)

4. Presence of any of the following features: geographic atrophy of the RPE, choroidal neovascularization (exudative, wet), polypoidal choroidal vasculopathy, or retinal angiomatous proliferation.

Other pathologies Arm

Patients with other retinal degenerations such as retinitis pigmentosa or with other diseases affecting the visual pathways such as tumors, ischemic neuropathy or optic neuritis may also be included. Their diagnosis will be extracted from their clinical visits.
Subject Recruitment and Compensation

SUBJECT RECRUITMENT AND COMPENSATION

Subject recruitment will be done at the Duke University Eye Center clinics. The study will also utilize D.E.D.U.C.E (Duke Enterprise Data Unified Content Explorer) an on-line research tool providing Duke investigators with access to clinical information collected as a by-product of patient care. The study will apply for a waiver of consent to identify potential subjects for the study. The PI will introduce potential eligible subjects to the study during their visit to the eye clinics, and if they are determined eligible a delegated key personnel will obtain consent from the subject. If the subject is not available for immediate consenting the PI will obtain the patient's permission to be contacted by telephone at a later date. A telephone script will then be used for the conversation. In addition, once the subject has the consent signed we will request access to their medical records through a medical records release form to obtain the participant's general medical history, previous use of systemic medications, previous use of ophthalmological medications, previous ocular examinations, previous ocular procedures, and results of other medical tests.
There will be no additional costs as a result of being in this study. Subject will be compensated $30 for each visit. Additional $30 per visit will be provided for participants to additional visits, up to a maximum amount of $450/year (two scheduled visits plus a maximum of 13 extra visits per year). Extra visits may be necessary to assess short-term and changes reproducibility (test-retest variability) of the results obtained by different tests. This compensation is for expenses related to subject participation (parking, gas, and time).

**Amendment, Protocol version 1.21:
All subjects will be compensated with $30 for each scheduled or additional visit.
Normal subjects will undergo 2 scheduled visits. An additional $30 will be provided for participants who need 1 additional visit to complete all the tests.
Subjects in the pathologies arms will undergo 14 visits in the first year of the study, 9 visits in the second and third years of the study, and 4 visits per year (2 visits every 6 months) until the end of the study, up to 5 years of participation. Additional $30 per visit will be provided for participants who need additional visits to complete all the tests, up to a maximum amount of $450/year.

CONSENT PROCESS

We will use protected health information to screen for possible/eligible subjects. No PHI will leave Duke. A member of the eye care team will approach the potential participant to introduce the study. Knowledgeable key personnel will explain the study to the potential subjects and the Principal Investigator will be available during the consenting process to answer any questions the potential subjects may have about the study. The consenting process will occur in a private room and no study related activities will begin until the subject's consent is obtained. Only delegated key personnel can consent potential subjects.

A waiver of consent and HIPAA authorization will be filed with the Duke IRB to allow us to review PHI and health information to screen potential participants.
A telephone script will be submitted to schedule potential subjects in Maestro Care for study screening prior to full consent, and in case subjects are interested in participating and they cannot discuss the study in person when they are initially seen, after the PI introduces the study and key personnel to them.

Subject's Capacity to Give Legally Effective Consent: Adult subjects able and willing to participate will sign the consent forms. If the vision of the potential subject is severely impaired enough to affect reading the consent document, the person obtaining consent, a study team member or a witness will read aloud and a witness will be required to sign the consent.

RISK/BENEFIT ASSESSMENT

Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant women, prisoners or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

Risks:
Risks from participating in the study are very low. The primary risks for all participants are some discomforts, which are similar to those encountered in any complete eye examination. Participants will undergo non-invasive procedures used for diagnostic purposes that are used in standard clinical care. The software for Macular pigment optical density analysis is currently undergoing FDA review and is not currently approved. The software for measurement of the trabecular meshwork stiffness (OCT/iFEM) from OCT is not currently approved. The OcuMet Beacon and Tono-Vera devices are currently undergoing FDA review and are not currently approved. The subject may experience mild discomfort due to drying of the eye during the study. Should a patient note drying, a drop of

artificial tears will be placed over the eye by the study key personnel. In very rare cases, artificial eye tear drops may cause irritation or allergy. There are no known risks associated with the psychophysics tests, EEG and eye tracking other than discomfort and fatigue. Subjects might become bored, fatigued or distressed while participating in the virtual reality and driving simulator tests. To minimize these potential effects, the tasks will be kept short and subjects will be instructed that they may request to interrupt the test anytime. The driving simulator, virtual reality tests, and balance assessment may cause dizziness or motion sickness in susceptible patients. Every precaution will be taken to minimize this possibility of motion sickness (e.g., by limiting the speed of linear or rotational motion). For the balance assessment task, falls will be prevented by the use of a harness system. All assessments, software, instruments that are not FDA approved will be used as tools to assess disability and device efficacy, and will not be used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. There is, however, the potential risk of loss of confidentiality. Every effort will be made to keep the information confidential; however, this cannot be guaranteed. Some of the questions that will be asked as part of this study may make the patients feel uncomfortable. Patients may refuse to answer any of the questions and may take a break at any time during the study. Patient may stop their participation in this study at any time.

Unknown/Unforeseeable Risks

In addition to the risks and discomforts listed here, there may be other risks that are currently not known. Subjects will be informed if any other potential risk becomes known through the duration of the study. Also, the risks and discomforts may occur more often or be more severe than have been seen before and written in this form.

Benefits:

Subjects will be referred from the Duke Eye Center care providers after a comprehensive clinical eye examination from a routine visit. If the last clinical eye examination is not within 6 months of the study visit, the participant will be examined by the PI, with no additional cost to the patient. Participants will also undergo other tests that will allow a better understanding of the relationship between potential visual impairment caused by their diseases and the ability to perform daily tasks. The results of the study are likely to provide important information on how eye diseases are associated with visual impairment, task performance and quality of life. This may lead to development of better tests to predict patient performance and visual loss, which could benefit patients with these diseases.

COSTS TO THE SUBJECT

All procedures described here, including both visits, will be free of charge to patients. There is no additional cost for the subject if they participate in the study. Study related activities/procedures will be paid by the study.

DATA ANALYSIS & STATISTICAL CONSIDERATIONS

Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

For all test results and variables, an extensive data preparation will be performed, with analysis of distributions, error checking and cross-tabulation. We will investigate differences in the results of the tests between diseased and healthy participants. Normality of variables will be assessed using histograms and Shapiro-Wilk tests. Student t tests will be used for comparison of means of normally distributed variables, whereas Mann-Whitney tests will be used for non-normally distributed variables. Generalized estimating equations (GEE) will be used to take into account potential correlations between tests results from the two eyes of the same subject.
Mixed models will be used for analysis of longitudinal data collected over time. These methods can successfully take into account longitudinal correlations among observations as well as correlations of results of eyes nested within patients. We will also use methods such as survival analysis (Weibull and Cox models) to assess prediction and joint longitudinal survival models.
All statistical analyses will be performed by Dr. Medeiros and associates using commercially available statistical and mathematics software Stata (version 15; StataCorp LP, College Station, TX, USA), MATLAB (Mathworks, Inc.), and MPLUS (Muthen & Muthen). Additional analysis and image processing from de-identified data will be performed by GA Tech's PI Dr Ethier, and Dr Farsiu and associates. An alpha level will be generally set at 0.05, unless there is a need to correct for multiple comparison testing which will then be performed by procedures such as false discovery rate.

3. DATA & SAFETY MONITORING

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), and all reportable adverse events (AEs) will be submitted per the DUHS IRB policies.
All examinations will be performed by appropriately trained personnel. If any incidental findings are discovered during the routine examination, during visual field testing or during the driving simulator testing, the patient will be verbally informed and referred to a physician of the appropriate specialty, and eligibility to the study will be reassessed. If responses to the Depression questionnaire appear to indicate a significant level of

depression (below 20 on the Geriatric Depression Scale), patients will be offered referral to a psychiatric clinic.