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***Evaluation of the Effectiveness of Transcorneal Electrical
Stimulation to Improve Visual Function Following Ocular Trauma***

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SPONSOR OVERVIEW

Evaluation of the Effectiveness of Transcorneal Electrical Stimulation to Improve Visual Function Following Ocular Trauma

Department of Defense
Grant# **W81XWH-12-2-0097**

Study Design: Prospective, randomized, SHAM controlled, clinical trial

Sponsor: Department of Defense
US Army Medical Research Acquisition Activity
Defense Medical Research and Development Program
820 Chandler Street
Fort Detrick, MD 21702- 5014

Scientific Program Officer:



Principal Investigator:

Julia Haller, MD
Ophthalmologist in Chief



PROTOCOL SYNOPSIS

Name of Sponsor: Department of Defense	Proposal Number: DM120101
Investigational Device:	OkuStim®; a product of OkuVision
Protocol Title:	Evaluation of the Effectiveness of Transcorneal Electrical Stimulation to Improve Visual Function Following Ocular Trauma
Clinical Phase:	Pilot
Indication for Use:	To restore and rehabilitate vision loss as measured by improvements of visual acuity.
No. Study Sites:	One
Study Objectives:	<ul style="list-style-type: none"> • Evaluate the effectiveness of TES to improve visual function in adults with visual defects as a result of ophthalmic trauma with incidence greater than or equal to 3 months. • Evaluate the effectiveness of TES to improve visual function in adults with NAION or CIS/MS, a model of damage to optic nerve axons subsequent to trauma.
Study Design:	A prospective, randomized, SHAM-controlled clinical trial evaluating the efficacy in subjects with ophthalmic trauma, Non-arteritic Anterior Ischemic Optic Neuropathy (NAION), or Multiple Sclerosis (MS)/Clinically Isolated Syndrome (CIS).
Subject Population:	<p>The study population will consist of adults 18 years of age or older and of either gender, who have experienced:</p> <ul style="list-style-type: none"> • Ophthalmic trauma (w/ incidence greater than 3 months prior to recruitment). <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Non-arteritic Anterior Ischemic Optic Neuropathy (NAION) (w/ incidence greater than 6 months prior to recruitment). <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Multiple Sclerosis (MS) or Clinically Isolated Syndrome (CIS) (w/ diagnosis and/or incidence of acute vision loss greater than 6 months prior to recruitment). <p>And who have chosen to participate in this clinical study as evidenced by the execution of the informed consent document.</p>
Inclusion Criteria	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Age \geq eighteen (18) years • Ophthalmic trauma (w/ incidence greater than 3 months prior to recruitment).

Name of Sponsor: Department of Defense	Proposal Number: DM120101
Investigational Device:	OkuStim®; a product of OkuVision
	<p>OR</p> <ul style="list-style-type: none"> • Non-arteritic Anterior Ischemic Optic Neuropathy (NAION) (w/ incidence greater than 6 months prior to recruitment). <p>OR</p> <ul style="list-style-type: none"> • Multiple Sclerosis (MS) or Clinically Isolated Syndrome (CIS) (w/ diagnosis and/or incidence of acute vision loss greater than 6 months prior to recruitment). • Willing and able to give written informed consent. • Able to perform study during full time period of one year.
Exclusion Criteria	<p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Any other significant ophthalmologic disease or condition with relevant effect upon visual function as evaluated by study investigators (e.g. glaucoma, retinal degeneration, proliferative diabetic retinopathy, exudative age-related macular degeneration (AMD), retinal detachment, +/- six diopters of myopia). • Vision better than 20/40. • Amblyopia in affected eye, reported earlier in life. • Participation in any other interventional clinical trial. • Women who are pregnant OR women with childbearing potential and who are unwilling to use medically acceptable means of birth control for study duration OR women unwilling to perform a pregnancy test at study entry/screening and at each treatment visit prior to treatment. • Inability to detect phosphenes at the time of threshold detection • History of epilepsy or seizures and/or prescribed to anti-epilepsy or anti-seizure medication.
Treatment Outline:	<p>Following recruitment and screening, subjects will be randomized in either the treatment or SHAM group. The treatment group will undergo electrical stimulation once a week for six weeks. Subjects in the SHAM group will wear the OkuSpex® once a week for six weeks, but will not experience the electrical stimulation. After six weeks of the SHAM treatment, these subjects will undergo genuine TES electrical stimulation once a week for six weeks.</p>
Primary Effectiveness Endpoint:	<p>The primary outcomes are change in high-contrast LogMar VA and change in low-contrast LogMar VA from baseline (week 1) to initial post treatment (week 8). Each outcome will be modeled separately.</p>

Name of Sponsor: Department of Defense		Proposal Number: DM120101
Investigational Device:	OkuStim®; a product of OkuVision	
Secondary Effectiveness Endpoint:	Secondary outcomes are change in visual field mean deviation, contrast sensitivity, VEP results (peak latency, amplitude of the p100 wave), IOP, SD-OCT nerve thickness, NEI-VFQ-25 total score and subscores, and SDMT total score	
Safety Endpoints:	<ul style="list-style-type: none"> • The appearance or development of corneal abrasion. • The appearance or development of argyrosis. 	
Study Duration:	Four Years	

STUDY OVERVIEW

Treatment Group Schedule

Visit:	1	2-7	8	9	10
Time Frame	Week 1	Week 2-7	Week 8	Week 19	Week 33
	Consent Pre-treatment testing	Intervention/ Treatment	1-Week Post- Treatment Testing	12-Week Post- Treatment Testing	26-Week Post- Treatment Testing
Complete Ocular Exam	X		X	X	X
Visual Acuity ETDRS Sloan Low Contrast Sensitivity	X	6X	X	X	X
Visual Field 24-2, Static	X (3 per eye)		X	X	X
Visual Evoked Potential	X		X		X
SD-OCT	X		X		X
Fundus Photography	X		X		X
NEI-VFQ-25	X		X	X	X
Symbol Digit Modalities Testing	X		X		X
Transcorneal Electrical Stimulation		6X			
External Ocular Photography	X	6X	X		
Pregnancy Test	X	6X			

Sham Group Schedule

Visit:	1	2-7	8	9-14	15	16	17
Time Frame	Week 1	Week 2-7	Week 8	Week 9-14	Week 15	Week 26	Week 40
	Consent Pre-treatment Testing	6-week Sham Treatment	1-week Post-Sham Treatment Testing	6-week Treatment	1-Week Post- Treatment Testing	12-Week Post- Treatment Testing	26-Week Post- Treatment Testing
Complete Ocular Exam	X		X		X	X	X
VA ETDRS Sloan Low Contrast Sensitivity	X	6X	X	6X	X	X	X
Visual Field 24-2, Static	X (3 per eye)		X		X	X	X
Visual Evoked Potential	X		X		X		X
SD-OCT	X		X		X		X
Fundus Photography	X		X		X		X
NEI-VFQ-25	X		X		X	X	X
Symbol Digit Modalities Testing	X		X		X		X
Transcorneal Electrical Stimulation		6X SHAM		6X			
External Ocular Photograph	X	6X	X	6X	X		
Pregnancy Test	X	6X		6X			

LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse Event
AIC	Akaike Information Criterion
AION	Anterior Ischemic Optic Neuropathy
AMD	Age-Related Macular Degeneration
ARED	Age Related Eye Disease Study
BcL-2	B-Cell Lymphoma-2
BDNF	Brain Derived Neurotrophic Factor
BIC	Bayesian Information Criterion
CAT	Computer Axial Tomography
CDC	Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Program
CE MARK	Conformité Européenne (European Conformity)
CI	Confidence Interval
CIS	Clinically Isolated Syndrome
CLIA	Clinical Laboratory Improvement Amendments
CNTF	Ciliary Neurotrophic Factor
COT	Combat Ocular Trauma
CPEC	Cataract and Primary Eye Care
DME	Diabetic Macular Edema
DOD	Department of Defense
DRCR	Diabetes Retinopathy Clinical Research Network

DSMB	Data Safety and Monitoring Board
DTL	Diode Transistor Logic
e-CRF	Electronic Case Report Form
EEP	Electrically Evoked Phosphene
EMR	Electronic Medical Record
EP	Evoke Potential
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FGF-2	Fibroblast Growth Factor-2
HcG	Human Chorionic Gonadotropin
H&E	Hematoxylin and Eosin
HELP	Heparin-induced Extracorporeal LDL/fibrinogen Precipitation
ICD-9	International Statistical Classification of Diseases
ID	Identification
IDE	Investigational Drug Exemption
IGF-1	Insulin-like Growth Factor-1
IONDT	Ischemic Optic Neuropathy Decompression Trial
IOP	Intraocular Pressure
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LogMAR	Logarithmic Minimum Angle of Resolution
M-ERG	Multi-Focal Electroretinography
MPH	Master of Public Health
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis

NAION	Non-Arteritic Ischemic Optic Neuropathy
NEI	National Eye Institute
NEI VFQ-25	National Eye Institute Visual Function Questionnaire-25
OCT	Optical Coherence Tomography
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OSS	Open Source Software
PI	Principal Investigator
PMA	Premarket Approval Application
RCS	Royal College of Surgeons
RGC	Retinal Ganglion Cell
ROTC	Reserve Officers' Training Corps
RP	Retinitis Pigmentosa
SAS	Statistical Analysis System
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SDMT	Symbol Digit Modalities Test
SOW	Scope of Work
SPSS	Statistical Package for Social Science
TBI	Traumatic Brain Injury
TENS	Transcutaneous Electrical Nerve Stimulation
TES	Transcorneal Electrical Stimulation
TJU	Thomas Jefferson University
TON	Traumatic Optic Neuropathy
USAMRMC	United States Army Medical Research and Materiel Command
VA	Visual Acuity

VEP	Visual Evoke Potential
VF	Visual Field
WEHS	Wills Eye Health System

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Evaluation of the Effectiveness of Transcorneal Electrical Stimulation to Improve Visual Function Following Ocular Trauma

1. Introduction

1.1 Name and Indications for Use

The clinical trial will investigate whether Transcorneal Electrical Stimulation delivered by the Okuvision® Stimulation Set manufactured by Okuvision GmbH, Reutlingen, Germany, is a potentially effective therapy for the restoration and rehabilitation of vision loss as measured by improvements in visual acuity in the following three patient populations: patients with ocular trauma, patients with Non-arteritic Anterior Ischemic Optic Neuropathy (NAION), and patients with Multiple Sclerosis (MS) or Clinically Isolated Syndrome (CIS).

The Okuvision® Stimulation Set is currently marketed outside the United States under the European Medical Device Directive as a Class II a device for patients with degenerative retinal diseases.

1.2 Disease Background

Combat ocular trauma (COT), defined as an injury to the eye and/or neuro-ophthalmological pathways, has almost doubled from 8% of all injuries during the Vietnam War to approximately 13% during Operation Iraqi Freedom (OIF) (1,2). Blasts to the head, face and neck caused the majority (85%) of these injuries (3-5). Such COT injuries often result in severe vision loss and visual dysfunction (6). In fact, COT in these soldiers doubles the risk of visual impairment and poor visual outcomes, with 33% of eyes worse than best-corrected visual acuity (VA) of 20/200 (3). In addition, approximately 20% of all military personnel deployed in Iraq and Afghanistan suffered from traumatic brain injury (TBI) (3,7,8). The majority of the military personnel diagnosed with TBI also have visual dysfunction characterized by difficulty reading, strabismus, pursuit and saccade insufficiencies, accommodative and convergence insufficiencies, and diplopia (8). In addition, COT often results in injury to the retina and optic nerve, traumatic optic neuropathies (TON) and retinopathies; neither of which is amenable to medical or surgical therapies. Although, repair or regeneration of injured optic nerves and retinas is impossible, the anatomy and physiology of these structures has been very well understood for decades (Figures 1a, 1b). However only recently have clinicians been able to assess in vivo, almost real-time pathological changes in the optic nerve and retina through spectral-domain optical coherence tomography (SD-OCT), multifocal electroretinography (mERG), and visually evoked potentials (VEPs).

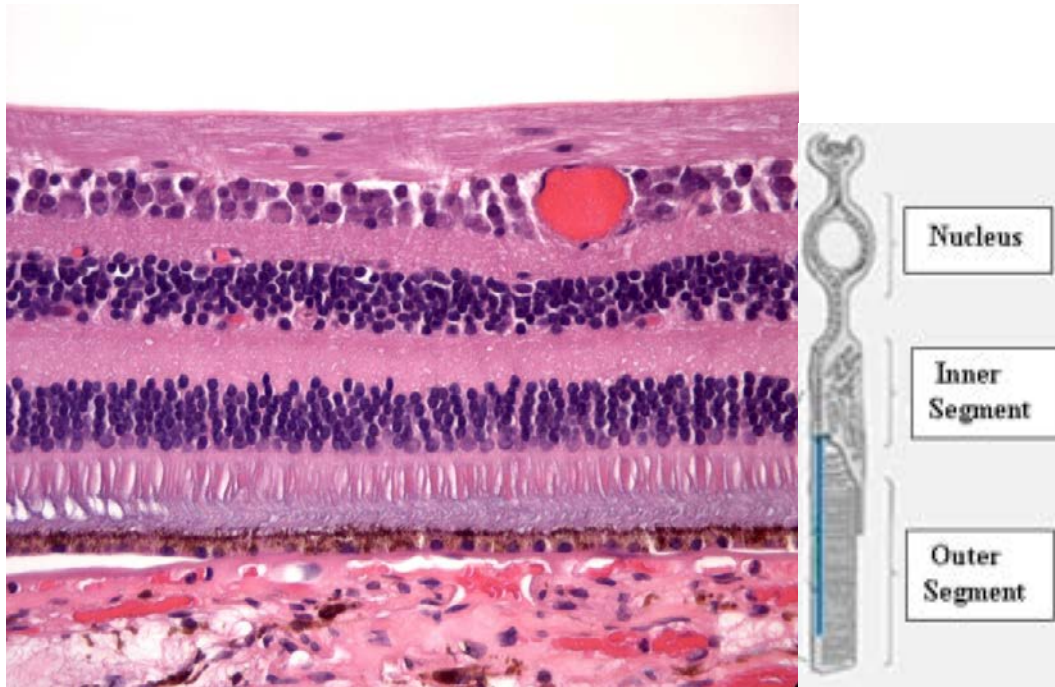


Figure 1a: Hematoxylin and eosin stain of a normal retina.

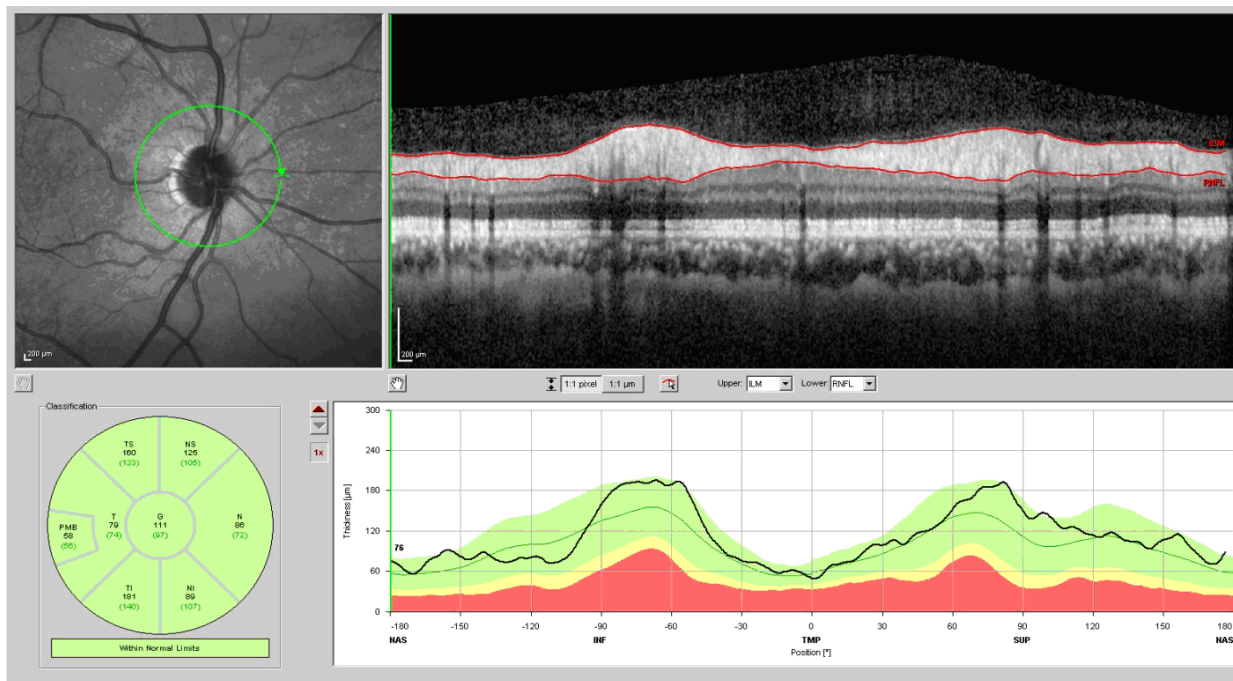


Figure 1b: Measurement of the peripapillary retinal nerve fiber layer thickness.

1.3 Mechanism of Action

The finely detailed, precise anatomy of the retina and optic nerve capture light impulses from the environment through a biochemical process and then transmit these images to the brain via electrical impulses conducted from the inner retina to the optic nerve and ultimately to the occipital cortex.

In the human eye, three types of specialized ganglion cells transmit electrical impulses to the brain. Among these three cell populations are rod and cone cells, which participate in the photo-transduction step of light perception, along with other light sensitive ganglion cells. It is a system whereby the photosensitive pigment rhodopsin (or one of its analogs) rearranges in response to light, and this change in chemical structure fires electrical impulses to the brain which in turn interprets the incoming impulses as a visual image as shown in Figure 2.

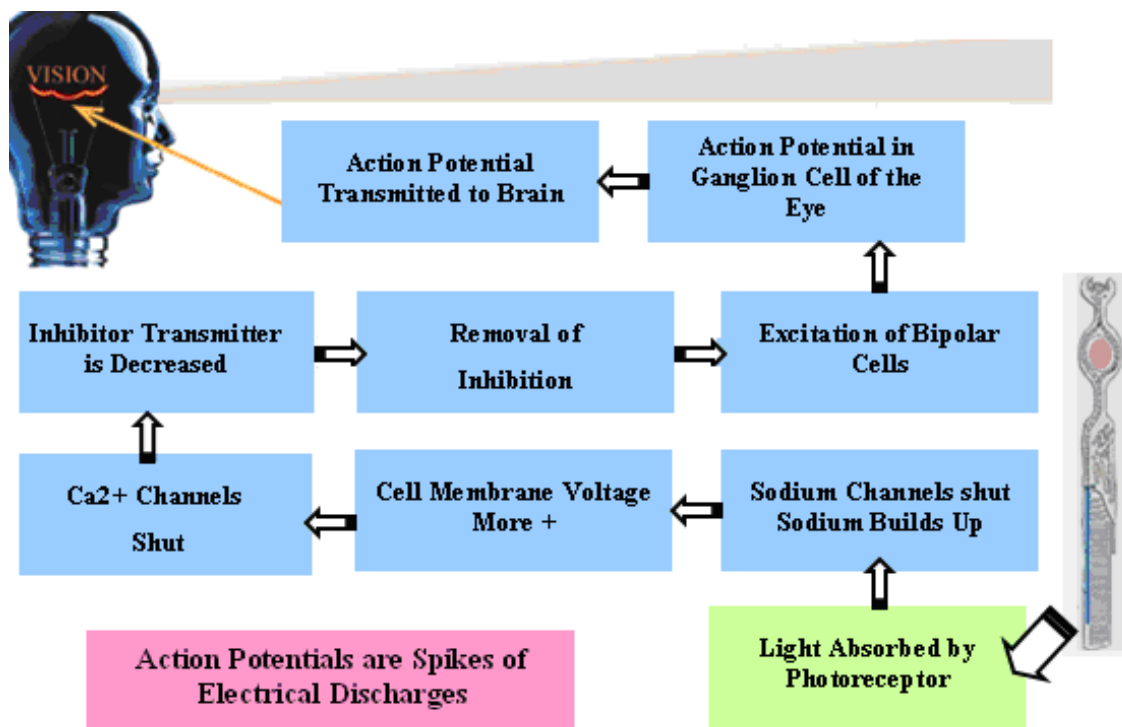


Figure 2: Photo transduction of vision and electrical response from light

Transcorneal Electrical Stimulation (TES) using the OkuStim® device delivers electrical impulses to damaged and/or diseased photoreceptor cells. This electric stimulation of the retina may help to preserve VA and/or the visual field.

1.4 Device Overview

The manufacturer of the Okuvision® Stimulation Set, Okuvision GmbH is based in Reutlingen, Germany. The Okuvision® device is one of the first out-patient treatments for degenerative retinal diseases. The Okuvision® Stimulation Set is a battery powered, electronic neurostimulator system consisting of the three components shown in Figure 3.

- OkuStim®, a reusable battery-powered, electronic neurostimulator which delivers a pulse, biphasic square output with a pulse duration of one (1) millisecond at a frequency of 20Hz;
- OkuEl®, single-use, disposable, sterile electrode; and
- OkuSpex®, glasses to properly position the OkuEl® electrode.

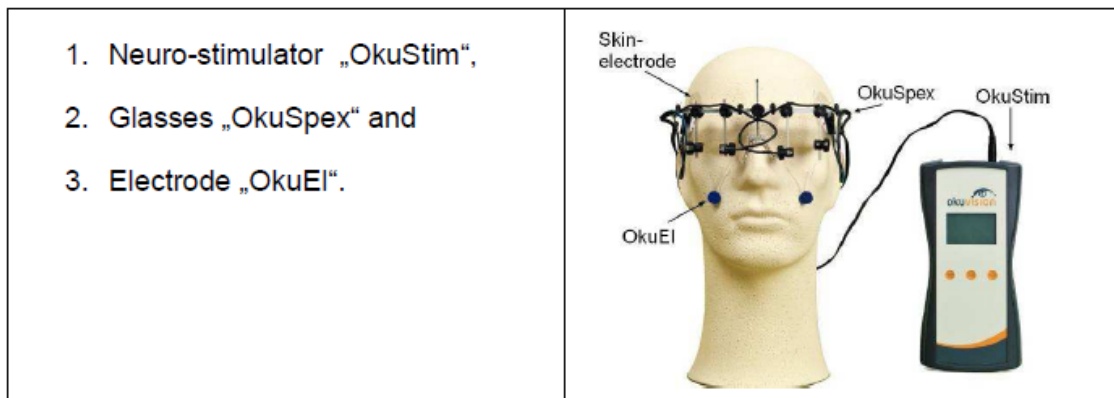


Figure 3: Okuision®-Stimulation Set

1.4.1 The OkuStim® Device

A weak electrical current is delivered by The OkuStim® device using the OkuEl® electrodes, which are held in place via the OkuSpex® glasses. The electrical output of the OkuStim® device can be adjusted by the technician exactly to the individual setting for each subject. The intensity of the electric stimulation will be evaluated and determined individually for each subject by the technicians. Settings for each subject are stored on a Mini-USB-stick and on a computer to enable investigation of the therapy over time.

After switching on the neurostimulator, the subject’s retina will be stimulated through specific electrodes worn on the face with the predetermined intensity and time period.

1.4.2 Key Components of the Device

1.) OkuStim® Device – The OkuStim® Device is a hand held battery-powered neurostimulator. As shown in Figure 4, the handheld device consists of a display screen an “On / Off / Stop” button, a “Pause” button, and a “Start” button. The handheld device and unique computer software program allows the technician to decrease or increase intensity as required by the individual subject. It is also equipped with acoustic signals indicating all substantial conditions of the device. Signals can indicate normal or abnormal settings. The power is provided by four AA type batteries placed in the back of the device.

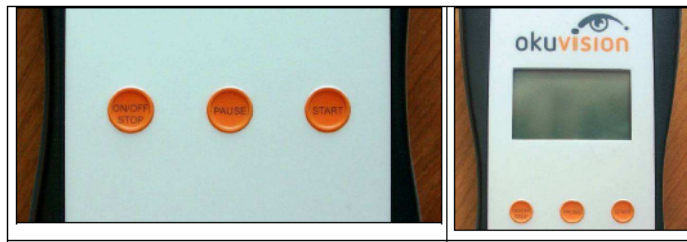


Figure 4: Key pad buttons on OkuStim® device

2.) OkuSpex® – The glasses called OkuSpex® are used as a holder for the OkuEl® electrodes. The bars on the frame can be adjusted horizontally and vertically to fit the subject’s facial contours. Figure 5 highlights the adjustment mechanism.

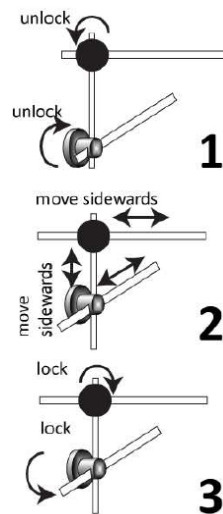


Figure 5: Adjusting OkuSpex® glasses .

3.) OkuEl® – The OkuEl® electrode is comprised of a silver threaded filament. The electrode is connected to the glasses and the filament is placed on the subject’s conjunctiva. Figure 6 provides a picture of the electrode.

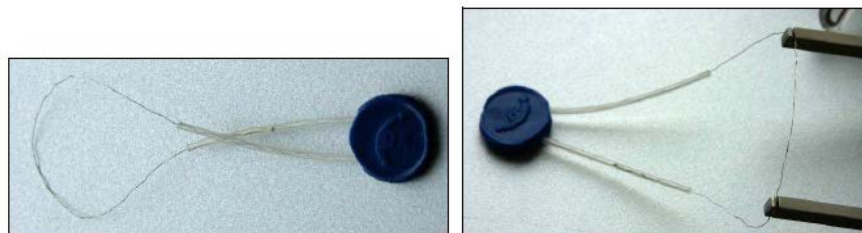


Figure 6: OkuEl® Electrode

1.5 Preclinical Studies

Among the first studies to show beneficial effects of electrical stimulation on the retina was that conducted by Morimoto et al. using the Royal College of Surgeons (RCS) rat strain which serves as a human model for retinitis pigmentosa (RP) (18,19). They demonstrated survival of ganglion cells after optic nerve injury both *in vivo* and *in vitro*. The positive results indicated that TES, an easily administered treatment via a novel, class three device (OkuStim®) developed by OkuVision GmbH in Germany, prolonged the survival of injured photoreceptor cells. These studies also specified that vision improved due to the effects ascribed to the stimulation on various growth factors and regulatory molecules on retina including insulin-like growth factor (IGF-1), enhanced release of fibroblast growth factor (FGF2) and B-cell lymphoma 2 (Bcl-2) protein, ciliary neurotrophic factor (CNTF), and brain derived neurotrophic factor (BDNF) (18,20,21). In most of the above studies, electrical currents have been applied in trans-corneal fashion using contact lens type electrodes, hence the term TES. In addition, a systematic analysis of the neuro-protective effect of different stimulus parameters of TES on axotomized retinal ganglion cells (RGCs) of the RCS rat showed that TES promoted survival of RGCs and the degree of neuroprotection depended on pulse duration (18).

1.6 Clinical Studies

The Food and Drug Administration (FDA) describes Transcutaneous Electrical Nerve Stimulation (TENS) as the use of an electric current to stimulate a target neural tissue for therapeutic purposes (10). TENS has been evaluated by the FDA as a safe, non-invasive procedure and can offer subjects effective alternative treatments to pain alleviation. In support of its treatment efficacy and safety, over one-hundred published clinical reports exist regarding the use of TENS for various types of conditions, such as low back pain, myofascial and arthritic pain, sympathetically mediated pain, bladder incontinence, neurogenic pain, and postsurgical pain (11). Furthermore, electrical stimulation of neural cells has been used for the treatment of many neurological disorders for several years. Such uses for electrical stimulation include therapy for spinal cord injuries, simulators for subjects with Parkinson's disease, cochlear implants for sensorineural hearing loss, and therapies for heart conduction abnormalities (12-15).

Therefore, electrical stimulation of neural tissues has been accepted by regulatory agencies as an effective and safe treatment for disorders of the central and peripheral nervous systems in which there is loss of normal physiological function. In addition, recent reports show potential efficacy using trans-corneal electrical stimulation (TES) to improve visual function (16-22). Therefore, the success of electrical stimulation in these neuro-degenerative disorders provides a reasonable rationale and significant precedent to investigate its potential in disorders of the optic nerve and retina, which function via an integration of biochemical and electrical interactions.

Recently, interest has been renewed by reports of efficacy and safety of TES in a small number of subjects with non-arteritic anterior ischemic optic neuropathy (NAION) and long-standing retinal artery occlusion (16,17). In addition, interest has been raised by reports that the presence of a sub-retinal implant can promote visual functions in areas distant from the implant which has been attributed to the release of neurotrophic and other growth factors (23).

In 2011, one German study assessed the safety of TES and explored its efficacy on various subjective and objective parameters of visual function in patients with RP. All 24 recruited

subjects were able to complete the study; only two subjects reported minor complaints after receiving TES treatment and no subject reported serious adverse events. One patient reported a mild foreign body sensation and showed minor irritation of the conjunctiva after IOP measurement, which was attributed to a reaction against the anesthetic eye drops used in the study. Another patient experienced a foreign body sensation after one stimulation, which resolved itself after prescription of artificial tears twice hourly for 1 day (22). No other serious adverse events were reported. In addition, electrical stimulation via DTL electrodes was reported to be tolerated well, not only for threshold determinations with short current pulses but also for continuous stimulation for 30 minutes with suprathreshold currents. General examination and blood test results were all within normal physiological ranges at all visits (22).

Numerous other clinical studies evaluating the safety and efficacy of TES in humans and animals suffering from a diversity of various ocular pathologies (including retinitis pigmentosa, branch retinal artery occlusion, neuropathy, etc), have shown the device to be safe, fast, and reliable, with minimal occurrence of adverse outcomes. No serious adverse events were reported in any of the above studies (16, 17, 29-31). There is no evidence that leads us to believe that the study, which uses TES to treat subjects suffering from ocular trauma, would present any more risk to subjects than other clinical studies of this nature, as we are implementing TES in a near-identical fashion as other published studies. Therefore, the most probable foreseeable risk in this study is a minor adverse ocular event occurring in subjects who receive TES treatment, such as a mild foreign body sensation or minor irritation. Subjects receiving the SHAM-treatment and study personnel giving the treatment should have no foreseeable treatment-related risks.

1.7 Purpose of the Clinical Study

The purpose of this clinical study is to collect clinical data to support the hypothesis that electrical stimulation using the OkuStim® device will improve visual function. The study protocol will support a premarket approval application.

1.8 Duration of the Study

The anticipated duration for this study is four years. Enrollment is anticipated to require approximately 36 months. Treatment program and follow up will be 26 for initial treatment group and 40 weeks for Sham group.

2. STUDY RATIONALE AND OBJECTIVES

2.1 Study Rationale

As discussed in the introduction, COT, defined as injury to the globe, periocular anatomy, or neurological pathways involved with VA or ocular motility during combat operations, has increased from 8% of all injuries during the Vietnam War to approximately 13% during OIF and Operation Enduring Freedom (OEF) (27, 28). Such COT injuries often result in severe vision loss and visual dysfunction (6). The majority of the military personnel diagnosed with TBI also have visual dysfunction, difficulty reading, strabismus, pursuit and saccade insufficiencies, accommodative and convergence insufficiencies, and diplopia (8). Although the frequency of COT may be greater than ocular trauma as a result of civilian injuries, the types of ocular injuries

seen in civilian hospital general emergency rooms and eye hospital emergency rooms are similar. Civilian ocular emergencies, therefore, can be studied as a model to better understand new potential treatment modalities for individuals with COT. Taking into account these numerous findings TES reveals itself as a highly promising and beneficial therapy for subjects who have suffered from ophthalmic trauma. In addition, positive reports from subjects with TON suggest this treatment could also be used in other traumatic eye disorders (16). The pathogenesis and pathophysiology of NAION and MS/CIS represent an excellent clinical model of the vascular component of TON. Subjects with chronic visual defects resulting from NAION or MS/CIS are a model subgroup to study the effect of visual function using TES.

The administration of TES, focused on restoration and rehabilitation of vision loss resulting from ophthalmic trauma, offers the potential to significantly impact military personnel. The present study will use a portable electronic system (OkuStim®) which delivers bi-phasic pulses in subjects with traumatic visual deficits. The bi-phasic pulse model is generated into a digital processor, and is based on a healthy eye's mERG response. The intensity, time duration and repetition rate are titrated and individualized to the subject's threshold levels of response. Preliminary data from several studies have shown an improvement in subjects' VA and visual fields, and increased B wave response in standard ERG tests when TES is applied in subjects with low vision (22, 29, 30, 31). These and other researchers concluded that further studies with larger sample sizes and longer duration are needed to confirm findings and to define optimal stimulation parameters (29-31).

This clinical trial is designed as an early phase feasibility study administering TES via a novel, safe, externally applied class three (3) device (OkuStim®) focusing on restoration and rehabilitation of vision loss resulting from ophthalmic trauma, NAION, or MS/CIS. The study offers potentially significant impact to military personnel because our study population will mirror those suffering from combat-related ophthalmic trauma and injuries.

2.2 Study Objectives

Wills Eye Hospital (Philadelphia, Pennsylvania) will coordinate a prospective, randomized, SHAM-controlled clinical trial evaluating the efficacy in subjects with ophthalmic trauma, NAION, and MS or CIS.

The specific aims of the clinical trial are to:

- (1) Evaluate the effectiveness of TES to improve visual function in adults with visual defects as a result of ophthalmic trauma.
- (2) Evaluate the effectiveness of TES to improve visual function in adults with NAION, or MS/CIS, a model of damage to optic nerve axons subsequent to trauma.

Primary Hypothesis: As in the case of central nervous system strokes, in which there is a central area of irreversible infarction and a border zone of tissue that has some normal anatomic structure but does not function (so called "ischemic penumbra," akin to a state of hibernation), we postulate that some cells and axons of the optic nerve and retina are damaged by trauma but not necessarily in an irreversible manner. We hypothesize that because vision is a physiological function uniting a biochemical pathway with an electrical signal that providing a controlled, well-defined, safe

electrical stimulus has the potential to restore function to photoreceptors, glial cells, and axons that are not irreversibly damaged.

Secondary Hypothesis: Similarly, we believe that electrical stimulation of optic nerves and retinas damaged by trauma, ischemia, and multiple sclerosis may regain some function of the afferent visual system as defined by VEPs and mERGs.

3. STUDY DESIGN

3.1 Type and Design of Study

Wills Eye Hospital (Philadelphia, Pennsylvania) will conduct a prospective, randomized, SHAM-controlled clinical trial evaluating the efficacy in patients with ophthalmic trauma, NAION, and MS or CIS. Forty-two (n=42) subjects with visual defects due to ophthalmic trauma, up to seventy-five (n=75) subjects diagnosed with NAION, and forty-two (n=42) subjects diagnosed with MS or CIS will be recruited from the Wills Eye Neuro-Ophthalmology, Retina, Cataract and Primary Eye Care (CPEC), and Oculoplastic and Orbital Surgery Services. Subjects will also be identified as they present in the Wills Eye Emergency Room. Three groups of subjects will be randomized in a 2:1 ratio as follows: 28 ophthalmic trauma subjects, 50 NAION subjects, and 28 MS or CIS subjects will be included in the TES treatment group. Subjects in the SHAM-intervention (TES) group will include 14 each of the ophthalmic trauma, and MS or CIS, and 25 subjects in the NAION group. Inclusion and exclusion criteria for subject enrollment are shown in Tables 4.2.1 and 4.2.2.

Follow up visits will include measures of safety and effectiveness at one week, twelve weeks and twenty-six weeks post treatment.

Throughout the study, the Principal Investigator, Co-investigators, Project Director, ophthalmologists reviewing and reading the test results, Clinical Research Coordinator, and Biostatisticians analyzing the results will all be blinded. This prevents bias from people directly involved with the study who also review ocular examinations and test results after treatment. Furthermore, it ensures accurate and realistic interpretation of the different ocular exams and treatments, along with unbiased analysis of the results. The only non-blinded personnel are the two ocular technicians administering the treatments. Table 3.1 highlights the study design.

3.2 Study Treatments

Each potential subject will undergo screening for eligibility in the study. If eligible for the study, subjects will be randomized in a 2:1 ratio. For every two subjects placed in the treatment group, one subject will be placed in the SHAM group.

Subjects in the treatment group will undergo TES once a week for six weeks. Subjects in the SHAM group will wear the OkuStim® device, but will receive no electrical stimulation. After the initial six weeks, the SHAM group will undergo the TES treatment once a week for six weeks.

3.3 Duration of Study and Rationale

The anticipated duration for this study is 48 months. Enrollment is anticipated to require approximately 36 months. Post-treatment follow up will be for 8 months for the initial treatment group. Subjects in the SHAM group will receive treatment at week 9 and be followed for 8 months post treatment (40 weeks).

3.4 Primary Effectiveness Endpoints

3.4.1 Endpoints 1 and 2

The study's main goal is to estimate the effect of treatment for all study outcomes; it will also conduct two formal hypotheses tests for the primary outcomes. The primary outcomes are change in high-contrast LogMar VA and change in low-contrast LogMar VA from baseline (week 1) to initial post treatment (week 8). Each outcome will be modeled separately. Since this is an exploratory study with no past data available, no endpoint will be defined for high or low contrast visual acuity. The study compares the patients performance (number of letters seen on the high contrast and low contrast acuity charts) after treatment to the patient's own baseline prior to treatment.

3.5 Secondary Effectiveness Endpoint

3.5.1 Endpoints

Secondary outcomes are change in visual field mean deviation, contrast sensitivity, VEP results (peak latency, amplitude of the p100 wave), IOP, SD-OCT nerve thickness, NEI-VFQ-25 total score and subscores, and SDMT total score. The study will use a similar approach for the primary efficacy analysis. For those outcomes measured only at weeks 1 and 8, measurement will use a heterogenous compound symmetric covariance structure. Again, the study will estimate the average change from baseline to week 8 for all three arms and the difference in change between arms.

3.6 Additional Effectiveness Endpoint

Long-term Changes

Using data from all subjects, we will estimate the long-term effects of treatment. We will include all available data from the initial Treatment-Randomized group and all data from visits 8-17 from the initial SHAM-Randomized group. We will again use mixed effects linear regression to model the change in outcomes over time. Fixed effects will include time (relative to pre-treatment time) and randomization assignment (to control for possible period effects). We will use linear contrasts to estimate the change from post-treatment to week twelve and post-treatment to 6-months to estimate how much any initial improvements may have been maintained over time.

3.7 Primary Safety Endpoints

Although TES is a non-invasive procedure, there is the risk of corneal abrasion resulting from the thread scratching the cornea. And, there is a possibility for argyrosis due to the electrical impulses being delivered through the silver filament. Upon completion of TES treatments, an external photo will be taken of the cornea and conjunctiva to provide a record of the presence of silver particles/ions or any discoloration process. Should the subject have an abrasion or the presence of discoloration during the physical exam, the subject will be notified immediately.

4. STUDY POPULATION

The study population will consist of adults 18 years of age or older and of either gender, who have experienced:

- Ophthalmic trauma (w/ incidence greater than or equal to 3 months prior to recruitment)
OR
- Multiple Sclerosis (MS) or Clinically Isolated Syndrome (CIS) (w/ diagnosis or incidence of acute vision loss greater than or equal to 6 months prior to recruitment)
OR
- Non-arteritic Anterior Ischemic Optic Neuropathy (NAION) (w/ incidence greater than or equal to 6 months prior to recruitment)

and who have chosen to participate in this clinical study as evidenced by the execution of the informed consent document.

4.1 Informed Consent

Written informed consent will be obtained from all subjects (or their guardian or legal representative) before any study related procedures (including any pre-treatment screening procedures) are performed. A copy of a sample informed consent document is provided in Attachment 1. Investigators may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent. Informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research. When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the investigational study.

The investigators have both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This should be documented on a written informed consent form that should be approved by the same IRB responsible for approval of the study. Each informed consent form should include the elements required by FDA regulations in 21 CFR Part 50.

The IRB-approved informed consent form will be signed by the subject and the investigator or the IRB-designee obtaining consent. The subject will be given a copy of the signed informed consent form. The original will be kept on file by the investigator. A copy will be placed in the subject's chart.

4.2 Eligibility Criteria

4.2.1. Inclusion Criteria

All recruited subjects must demonstrate stable, impaired visual function upon screening and exam. To qualify for inclusion in study, all potential subjects must satisfy the criteria listed in Table 4.2.1 at their initial screening visit. Specifically, in addition to being able to offer adequate informed consent and being willing to remain in the study for its entire duration, potential subjects must also demonstrate acceptable proof of age of eighteen (18) years or older. Furthermore, subjects must present with ophthalmic trauma, diagnosis of MS or CIS, or a diagnosis of NAION.

Table 4.2.1: Inclusion Criteria for Subject Enrollment

Inclusion Criteria:

- Age \geq eighteen (18) years
- Ophthalmic trauma (w/ incidence greater than or equal to 3 months prior to recruitment).
 - **OR**
- Multiple Sclerosis (MS) or Clinically Isolated Syndrome (CIS)
 - **OR**
- Non-arteritic Anterior Ischemic Optic Neuropathy (NAION) (w/ incidence greater than 6 months prior to recruitment).
- Willing and able to give written informed consent.
- Able to perform study during full time period of one year.

4.2.2 Exclusion Criteria

For exclusion, subjects may satisfy any of the four specific exclusion criteria listed in Table 4.2.2 OR be unable to satisfy any one of the designated inclusion criteria. Women and minorities will be eligible to participate in the clinical trial.

Table 4.2.2: Exclusion Criteria for Subject Enrollment

<p>Exclusion Criteria:</p> <ul style="list-style-type: none">• Any other significant ophthalmologic disease or condition with relevant effect upon visual function as evaluated by study investigators (e.g. glaucoma, retinal degeneration, proliferative diabetic retinopathy, exudative age-related macular degeneration (AMD), retinal detachment, +/- six diopters of myopia).• Vision better than or equal to 20/40.• Amblyopia in affected eye, reported earlier in life.• Participation in any other interventional clinical trial.• Women who are pregnant OR women with childbearing potential and who are unwilling to use medically acceptable means of birth control for study duration OR women unwilling to perform a pregnancy test at study entry/screening and at each treatment visit prior to treatment.• Inability to detect phosphenes during threshold detection.• History of epilepsy or seizures and/or prescribed to anti-epilepsy or anti-seizure medication.

5. STUDY PROCEDURES

Upon completion of the Informed Consent Form, subjects will be randomized in a 2:1 ratio into either the treatment group or the SHAM group. Subjects in the TES treatment groups will receive TES from the OkuStim® device for 30 minutes per week for 6 consecutive weeks. Subjects in the SHAM groups will have the TES device placed over their eye each week for 30 minutes; however, electrical stimulation will not be received. These subjects will then receive TES from the OkuStim® device for 30 minutes per week for 6 consecutive weeks. All subjects will undergo electrically evoked phosphene (EEP) testing to determine their stimulation threshold for the OkuStim® device. Stimulation threshold is defined as the frequency when subjects initially sense electrically evoked phosphenes. They will then receive treatment from the OkuStim® device at 150% level threshold according to their unique threshold readings at each treatment.

Evaluation methods for all subjects during the study (including the SHAM group) will consist of complete ocular exams, VA testing (ETDRS and contrast sensitivity), visual field (VF; 24-2, static), VEP, fundus photography, external photography and SD-OCT. All subjects will be tested at baseline and will receive additional testing according to the Testing Schedules shown in Table 5.1.1a and 5.1.1b. Subjects in the intervention group will be re-tested after 6 weeks of treatment (week 8) and at 12 weeks (week 19), and at 6-month follow-up (week 33) to determine if improvements in visual function have been maintained (Table 5.1.1a). Quality of life evaluation

via the NEI-VFQ-25 will be administered on all subjects at baseline, 1-week post-treatment (week 8), 12-weeks post-treatment (week 19) and 6-month post-treatment (week 33). Cognitive function evaluation via the SDMT will also be administered to all subjects at baseline, 1-week post-treatment (week 8) and at 6-month post-treatment (week 33).

5.1 Schedule of Assessments at Each Study Visit

All treatment and diagnostic procedures will take place at Wills Eye Hospital, Philadelphia PA, on the 11th Floor in the Wills Eye Diagnostic Center. Table 5.1.1a provides an overview of the subject screening and baseline evaluations, treatment plan and follow-up.

Table 5.1.1a: Testing Schedule: Initial Treatment-Randomized Group

Visit:	1	2-7	8	9	10
Time Frame	Week 1	Week 2-7	Week 8	Week 19	Week 33
	Consent Pre-treatment testing	Intervention/ Treatment	1-Week Post- Treatment Testing	12-Week Post- Treatment Testing	26-Week Post- Treatment Testing
Complete Ocular Exam	X		X	X	X
Visual Acuity ETDRS Sloan Low Contrast Sensitivity	X	6X	X	X	X
Visual Field 24-2, Static	X (3 per eye)		X	X	X
Visual Evoked Potential	X		X		X
SD-OCT	X		X		X
Fundus Photography	X		X		X
NEI-VFQ-25	X		X	X	X
Symbol Digit Modalities Testing	X		X		X
Transcorneal Electrical Stimulation		6X			
External Ocular Photography	X	6X	X		
Pregnancy Test	X	6X			

Subjects in the SHAM group will be re-tested after 6-weeks of SHAM treatment (week 8) and after 6-weeks of treatment (week 15) and at 12-week follow-up (week 26) and 6-month follow-up (week 40) to determine if improvements in visual function have been maintained (Table 5.1.1b).

All subjects in the SHAM-intervention group will have VA evaluations at each visit during weeks 2-7 before the SHAM treatment. Quality of life evaluation via the NEI-VFQ-25 will be administered on all subjects in the SHAM group at baseline, 1-week post-SHAM treatment (week 8), 1-week post-treatment (week 15), 12-week post-treatment (week 26), and at 6-month post-treatment (week 40). Cognitive function evaluation via the SDMT will also be administered to all subjects at baseline, 1-week post-SHAM treatment (week 8), 1-week post-treatment (week 15) and at 6-month post-treatment (week 40). Outcome measures will be based on the results of these tests as well as the rate of wound healing in acute trauma subjects and the ability to restore visual function in subjects with chronic visual impairment. Evaluation of visual outcomes will help develop possible predictive diagnostic criteria in adults with acute and visual deficits due to ophthalmic trauma or TBI.

Table 5.1.1b: Testing Schedule: Initial Sham-Randomized Group

Visit:	1	2-7	8	9-14	15	16	17
Time Frame	Week 1	Week 2-7	Week 8	Week 9-14	Week 15	Week 26	Week 40
	Consent Pre-treatment Testing	6-week Sham Treatment	1-week Post-Sham Treatment Testing	6-week Treatment	1-Week Post-Treatment Testing	12-Week Post-Treatment Testing	26-Week Post-Treatment Testing
Complete Ocular Exam	X		X		X	X	X
VA ETDRS Sloan Low Contrast Sensitivity	X	6X	X	6X	X	X	X
Visual Field 24-2, Static	X (3 per eye)		X		X	X	X
Visual Evoked Potential	X		X		X		X
SD-OCT	X		X		X		X
Fundus Photography	X		X		X		X
NEI-VFQ-25	X		X		X	X	X
Symbol Digit Modalities Testing	X		X		X		X
Transcorneal Electrical Stimulation		6X Sham		6X			

External Ocular Photograph	X	6X	X	6X	X		
Pregnancy Test	X	6X		6X			

5.2 Recruiting/Pre-screening

It is anticipated that recruiting will require a large pool of potential subjects. Therefore, recruiting will be broken out in three phases. Phase I (Years 1-4) will focus on recruiting subjects within the Wills Eye Health System. Because this is a complex study with three different study arms, an assessment will be made on which subjects are easily recruited and which subjects require more effort. After this assessment is made, we will reach out to develop collaborations with both Thomas Jefferson University Hospital and the Philadelphia and Wilmington Veterans Administration. Phase II (Years 2-4) will focus on recruiting subjects from Thomas Jefferson University Hospital. Phase III (Years 2-4) will focus on recruiting subjects from the Philadelphia and Wilmington Veterans Administration.

Phase I – Wills Eye Health System

We will recruit subjects from the various subspecialty departments of WEHS, as well as identify potential subjects that have been seen at the Wills Eye Emergency Room (ER). We feel that subjects that had been patients in the Wills Eye ER and still require follow-up will provide an adequate, representative population. It is important to note that subjects will not be recruited while they are in the Emergency Room. The Wills Eye ER is the only 24 / 7 ophthalmic trauma center on the East Coast. Its large volume of acute ocular trauma patients provides a pool of subjects with a variety of ophthalmic and orbitofacial injuries, including blunt and penetrating trauma. Many of the injuries result from electrical, construction, and industrial accidents. The ophthalmic and orbitofacial injuries experienced by populations in the electrical, construction, and industrial fields are often similar to the traumas suffered by combat veterans. The age and gender of patients most represents those most likely to be in combat units, as the most common ER subject is male between the ages of 18-30 years old.

Subjects will be recruited by reviewing electronic medical records (EMR) or be identified by Wills Eye physicians. If the research coordinator identifies a subject through EMR, he / she will then call the potential research subject. A phone script has been developed and is attached. (Attachment 3)

For potential subjects fitting the inclusion/exclusion criteria that are identified by their physician at Wills Eye, the physician notifies the research coordinator that day. The research coordinator will meet with the potential subject to inform and educate him/her about the study. In both instances, the subject then consents to the study with the physician after allowing sufficient time for the subject to read the consent form and ask questions.

Subjects will also be recruited from a network of affiliated general ophthalmologists, neuro-ophthalmology specialists, and retina specialists practicing in the Tri-State Area including those practicing at the Philadelphia Veterans Administration Hospital and Cooper University Hospital,

using email, letters, and flyers addressed to physicians during medical education conferences. Wills Eye Hospital staff involved in the clinical trial will schedule site visits to inform the affiliated with the site about the clinical trial details, provide IRB-approved study flyers and letters for physician and patient use, and review medical charts of potential participants for future correspondence and scheduling.

In order to reach additional potential subjects in the tri-state area, a newspaper advertisement will be published in a free, local newspaper, Metro Newspaper. The advertisement will be addressed to people who have vision problems who have experienced trauma or have been diagnosed with NAION, or Multiple Sclerosis/ Clinically Isolated Syndrome and will also specify that the study is for patients 18 and older. Contact information for the study coordinator will be included in the advertisement. Direct to patient/caregiver advertising will benefit recruitment and enrollment due the relatively small network of physicians and patients at Wills Eye Hospital and the limited treatment options for patients with trauma, NAION, and MS/CIS.

Phase II – Thomas Jefferson University Hospital (Grant Years 2-4)

We plan to utilize the collaboration between Thomas Jefferson University Hospital (TJUH). Wills Eye serves as the Department of Ophthalmology for TJUH and its clinicians often see patients with head injuries that present at the TJUH. Wills Eye will work with TJUH to recruit potential subjects.

Phase III – Philadelphia and Wilmington Veterans Administration (Grant Years 2-4)

Wills Eye will seek to include patients referred from the Philadelphia and Wilmington Veterans Administration Hospital. The inclusion of the Philadelphia and Wilmington VA increases the potential of recruiting actual combat veterans.

5.3 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (i.e. subject signs an informed consent form), but in whom treatment with the investigational device is not used because it is determined that the subject does not meet all of the eligibility criteria, after signing the informed consent. Screen failure subjects will not be counted towards the total enrollment of 126 subjects

5.4 Screening and/or Baseline Evaluation

All subjects will receive the following tests/evaluation at screening. The results of the tests will serve as the data for the baseline visit. No wash out of period from other treatments is required.

5.4.1 Complete Ocular Exam

A complete ocular exam consists of an array of tests conducted by an ophthalmologist assessing vision and ability to focus on and discern objects, as well as other tests and examinations relating to the eyes. The complete ocular exam will include an external examination, followed by specific tests for pupil function (normal/abnormal), extraocular muscle motility (normal/abnormal), and measure of intraocular pressure (IOP). The complete ocular exam will also document the subjects' current symptoms, health problems,

medications, and ocular co-morbidities. VA and visual fields will be tested and are described below.

5.4.2 Visual Acuity - Early Treatment Diabetic Retinopathy Study (ETDRS)

VA is referred to as acuteness or clarity of vision, which is dependent on the sharpness of the retinal focus within the eye and the sensitivity of the interpretative capability of the brain. ETDRS acuity testing has become the worldwide standard for VA testing. It was developed to aid in evaluating the changes in vision following panretinal photocoagulation in subjects with diabetic retinopathy. The ETDRS test incorporates specific design criteria to be more accurate than the Snellen or Sloan acuity tests. These include: 1) same number of letters per row (five letters per row) 2) equal spacing of the rows on a log scale (the rows are separated by 0.1. log unit) 3) equal spacing of the letters on a log scale, and 4) individual rows balanced for letter difficulty. To prevent memorization, different versions of the ETDRS test chart are available. The three standard versions of the ETDRS chart are R, 1 and 2. Sloan low contrast sensitivity is a component of the ETDRS. Data will be reported, quantified, and analyzed for changes in VA after converting to LogMar scales.

5.4.3 Symbol Digit Modalities Test

The SDMT, developed by Aaron Smith, PhD, is a simple, practical measure of information processing speed presented visually (33). The SDMT involves a simple substitution task. Using a reference key pairing unique symbols with numbers, the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses can be written or oral, and for either response mode, administration time is just 5 minutes. Advantages of the SDMT include the lack of need for academic skill and the rapidity of the test. The SDMT has demonstrated remarkable sensitivity in detecting not only the presence of brain damage, but also changes in cognitive function over time and in response to treatment. Because it involves only geometric figures and numbers, the SDMT is relatively culture free as well, and can be administered to people who do not speak English. Response can be written or spoken, so the test can be used with almost anyone, including those with motor disabilities or speech disorders.

The SDMT been used in many disorders including head injury, stroke, brain tumor, reading difficulties, learning disorders, and dementia. Previous research in Subjects with MS has shown the SDMT to be reliable, sensitive, and strongly associated with brain magnetic resonance imaging (MRI) metrics (34-38). It has been proposed as a screening test for MS-associated cognitive disorder and poor performance on the SDMT is associated with work disability (39,40). Unemployed subjects scored more poorly on several cognitive tests including the SDMT (41). It was also the best predictor of numerous tests for behind the wheel driving performance in MS subjects (42). Data will be reported, quantified, and analyzed for each subject and changes over time will be tracked.

5.4.4 National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25)

The NEI-VFQ-25 includes a series of 25 questions pertaining to vision, or feelings about a vision condition, and quality of life. Answers are selected among a numbered list of possible responses, the values of which are ultimately recorded and converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. Items within each subscale are averaged together to create 12 subscale scores (32). An

overall composite score will be calculated by averaging the vision-targeted subscale scores, excluding the general health rating question. The 12 sub-scales for the NEI-VFQ-25 includes: 1) general health 2) general vision 3) ocular pain 4) near activities 5) distance activities 6) social functioning 7) mental health 8) role difficulties 9) dependency 10) driving 11) color vision, and 12) peripheral vision. The sub-scales 6 to 9 are vision specific. Data will be reported, quantified, and analyzed for these good subscores for each subject and changes over time will be tracked.

5.4.5 Visual Field 24-2, Static

The automated perimeter maps the peripheral and central vision using a computerized algorithm. Threshold static perimetry will be used for this study. A series of lights of varying size and intensity are randomly presented to the subject. The responses are used to create a map of the visual field and the obtained results are compared to a normative database where age and gender is matched. Data will be reported, quantified, and analyzed according to the change in mean deviation from visual field using the normal standards.

5.4.6 Spectral-Domain Optical Coherence Tomography

SD-OCT is used for diagnosis, and management of optic neuropathies and retinal diseases. In SD-OCT, low coherence near-infrared light is split into a probe and a reference beam. The probe beam is directed at the retina while the reference beam is sent to a moving reference mirror. The probe light beam is reflected from tissues according to their distance, thickness, and refractive index. It is then combined with the beam reflected from the moving reference mirror. When the path lengths of the two light beams coincide (known as constructive interference) it provides a measure of the depth and reflectivity of the tissue that is analogous to an ultrasound A scan at a single point. A computer then corrects for axial eye movement artifacts and constructs a two dimensional B mode image from successive longitudinal scans in the transverse direction. A map of the tissue is then generated based on the different reflective properties of its components, resulting in a real-time cross-sectional histological view of the tissue. SD-OCT is a relatively new non-invasive imaging modality that uses reflected light in a manner analogous to the use of sound waves in ultrasonography to create high-resolution (10 micron) cross-sectional images of the vitreoretinal interface, retina and subretinal space, analogous to histological sections seen through a light microscope. SD-OCT also gives quantitative information about the peripapillary retinal nerve fiber layer thickness, retinal architecture and structure. Data will be reported according to the change in the thickness of the retinal nerve fiber layer and compared to baseline measurements

5.4.7 Fundus Photography

A fundus camera or retinal camera is a specialized low power microscope with an attached camera designed to photograph the interior surface of the eye, including the retina, optic disc, macula, and posterior pole (i.e. the fundus). Fundus cameras are used by optometrists, ophthalmologists, and trained medical professionals for monitoring progression of a disease, diagnosis of a disease (combined with retinal angiography), or in screening programs, where the photos can be analyzed later. Baseline fundus photograph data about the condition of the retina will be reported.

5.4.8 External Ocular Photography

External ocular photography is the term used by ophthalmic photographers to describe pictures of the eye made with conventional and slit lamp cameras. External photographs are used by ophthalmologists to document ocular conditions in the conjunctiva, cornea, iris, sclera, and the eyelids. Images will be filed and compared each week before and after the treatment and at the one week post treatment exam.

5.4.9 Visual Evoked Potential

VEPs are electrophysiological signals extracted from the electroencephalographic activity in the visual cortex recorded from the overlying scalp in response to a visual stimulus. VEPs depend on functional integrity of central vision at any level of the visual pathway including the eye, retina, optic nerve, optic radiations, and occipital cortex. However, they are most sensitive to optic nerve dysfunction. In the test, the subject sits comfortably in front of a monitor with a checkerboard pattern on the screen. The screen reverses the black and white pattern which stimulates the visual system. The electrical activity generated is measured with wire electrodes over the posterior scalp. Data will be reported, quantified, and analyzed by measuring the peak latency and the amplitude of the p100 wave of the VEP. Obtained results will be compared to the baseline

5.5 Treatment

Subjects will be assigned to the appropriate study group based on their ocular disability. Prior to the first treatment, the subject will undergo a complete ocular examination, visual acuity (ETDRS), SDMT, NEI-VFQ-25, visual field 24-2 static, SD-OCT, fundus photography, slit lamp external photographs and VEP testing. If all inclusion and exclusion criteria are met the subject will be scheduled for treatment. The same diagnostic testing procedures will be followed at post-treatment testing visits with the exception of fundus photography, SD-OCT, VEP, and slit lamp external photographs at the 3-month follow-up visit.

Subjects will be randomized into either treatment-initial or SHAM-initial groups prior to their scheduled appointment. Trained technicians will administer OkuStim® stimulation to subjects according to the treatment schedule. Preservative-free, artificial tears (i.e. GenTeal) will be applied on the surface of the prior to the application of the OkuEl® fiber on the corneal surface at the time of each treatment. Additionally, the technicians will prepare and administer SHAM treatment for subjects, as appropriate.

Subjects randomized to the treatment-initial group will undergo OkuStim® treatment once a week for a 6-week period of time. Each session will consist of 30 minutes of TES at 150% threshold levels, which will be individualized for each subject using EEP testing. The settings will be stored on a password protected computer in order to provide consistent and appropriate stimulation across the six-week trial period and to enable investigation of the therapy over time.

Subjects randomized to the SHAM-initial group will similarly be configured with an OkuStim® device, but the device in such case will provide no electric impulses and subjects will receive no TES. 30 minute sessions will be held once a week for six weeks. Following the 6-week SHAM trial, SHAM-initial subjects will return once a week for six additional weeks of genuine TES, during which they will receive full OkuStim® stimulation according to the same schedule and procedure as the treatment-initial group.

Subjects in the intervention groups will receive TES from the OkuStim® device for 30 minutes per week for 6 consecutive weeks. Subjects in the SHAM groups will have the TES device placed over their eye each week for 30 minutes; however, electrical stimulation will not be received. After that, the SHAM group will receive TES from the OkuStim® device for 30 minutes per week for 6 consecutive weeks.

After completion of each TES treatment or TES SHAM treatment the eyes will be flushed with a saline solution and all subjects will have slit lamp corneal photography of the treatment eye to record the potential of discoloration, presence of corneal abrasion and/or the presence of silver particles and/or ions. External photos will also be performed at the one week post treatment visit.

All subjects will undergo Electrically Evoked Phosphene (EEP) testing to determine their stimulation threshold for the OkuStim® device. Stimulation threshold is defined as the frequency when subjects initially sense electrically evoked phosphenes. They will then receive treatment from the OkuStim® device at 150% level threshold according to their unique threshold readings.

5.6 Administering TES through the OkuStim® device

After undergoing the EEP testing and prior to using the OkuStim® device on the subject, the skin electrodes must be placed on the subject. To ensure a good electric contact zone, the skin on the subjects' temple will be cleaned with alcohol prep at each treatment and SHAM session, followed by applying time to air dry. After cleaning, a skin-electrode will be placed onto the temple (Figure 7). Once a small amount of electrode gel is applied in the center of the skin-electrode, it can be placed on the temple with gentle pressure.

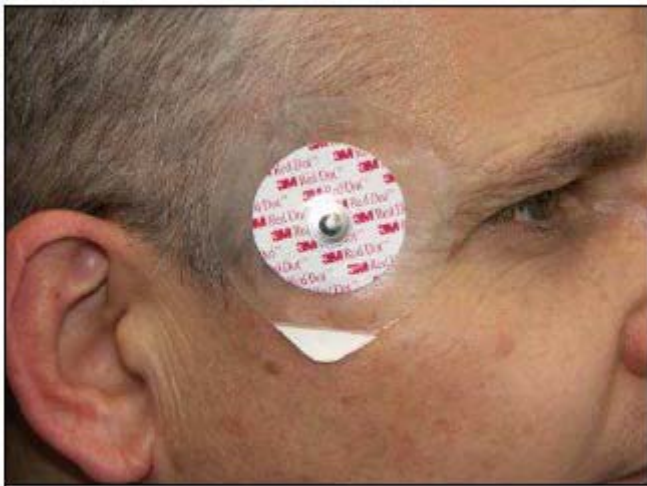


Figure 7: Position of the skin electrode on the temple

After the skin electrode is applied on the subject, the technician will adjust the bars on the frame of the OkuSpex® glasses horizontally and vertically to fit the subjects' facial contours (Figure 8). The thick screws at the joints of the bars of the OkuSpex® glasses will be slightly opened in order to adjust the vertical and horizontal bars easily. The OkuSpex® glasses will then be carefully put into position on the subject, while the subject's eyes are closed. The vertical bars will be adjusted to a suitable height, and if required, the nose pad of the OkuSpex® glasses can

be adjusted in height, as well. The horizontal bars will be positioned at the edges of each eye, on top of the skin exactly to the right and left of each eye.

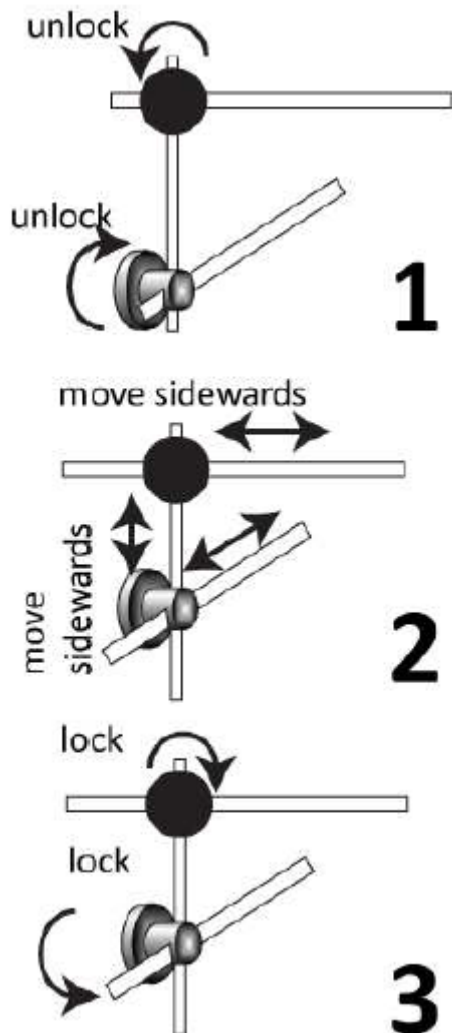


Figure 8: Adjustment of the bars on the OkuSpex® glasses

Because only one eye will be stimulated over the course of this study, only one OkuEI® electrode and one skin electrode are required per subject per visit (Figure 9). The OkuEI® electrode will be placed onto the bars of the OkuSpex® glasses and gently pulled to slide the filament into its final position within the slit in the horizontal bar of the OkuSpex® glasses (Figure 10).

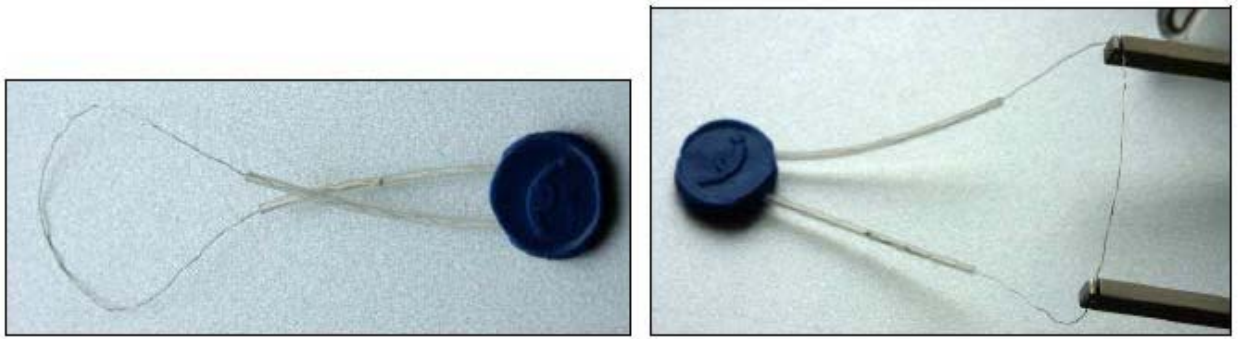


Figure 9: OkuEI® electrode

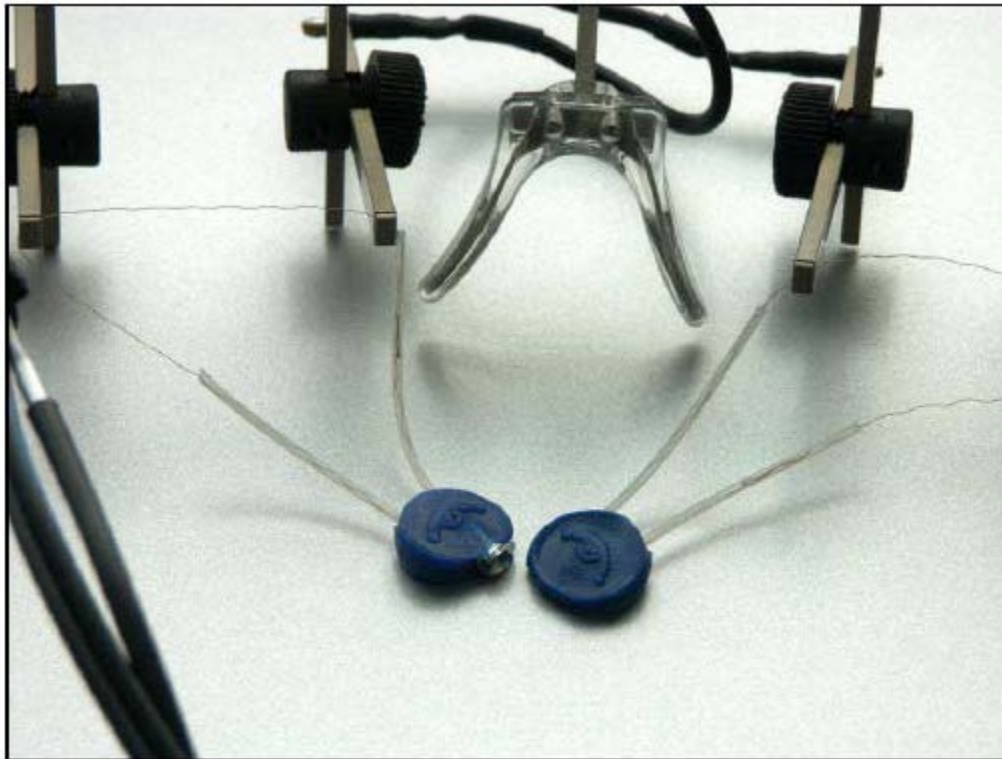


Figure 10: Pull OkuEI® filament over both bars to position within slit

Before placement of the OkuEI® electrode (Figure 11) preservative-free, artificial tears will be applied, then the horizontal bars of the OkuSpex® glasses will be carefully moved towards the eye. The OkuSpex® glasses will be correctly fitted to the subject as soon as the OkuEI® filament contacts the conjunctiva underneath the pupil without tension. The subject may not sense the filament at all. The OkuStim® technicians will then take the OkuSpex® glasses in hand and carefully tighten the thick screws on the joints of the glasses.

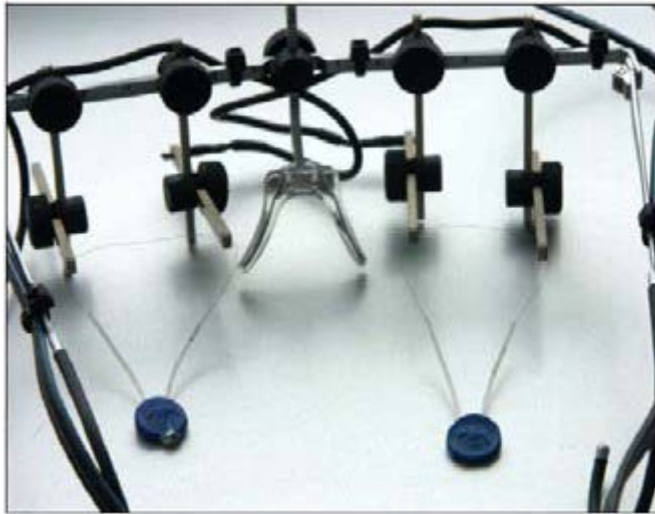


Figure 11: OkuSpex® shown with two OkuEI®

The OkuSpex® glasses will then be replaced on the subject, ensuring that the bars do not contact the eyes directly (Figure 12). Instead, the OkuEI® electrode-filament should contact the conjunctiva above the lower eyelid. While putting on the OkuSpex® glasses, small movement of the eyes will facilitate proper contact of the OkuEI® electrode-filament on the eye.

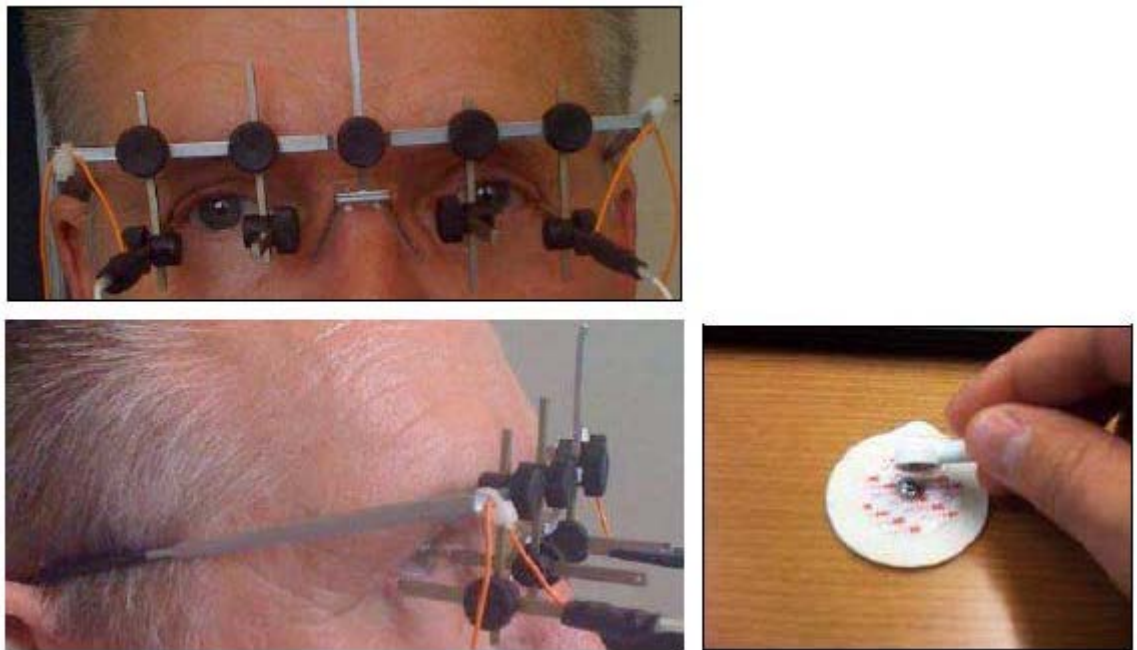


Figure 12: OkuSpex® glasses in position with correctly adjusted bars

The OkuEI® electrode-filament should be positioned directly above the lower eyelid and below the pupil, contacting the conjunctiva (Figure 13). The skin-electrode at the temple should be connected to the snap-fastener on the cable of the OkuStim® glasses only after the device is turned ON.



Figure 13: OkuEI® electrode on eye, contacting the conjunctiva below the pupil

The subject should not make any change on the adjustment of the OkuSpex® glasses once the proper setting of the horizontal and vertical bars has been achieved. The thick screws at the joints of the OkuSpex® glasses should remain locked. Following configuration of the OkuSpex® glasses and proper positioning of the OkuEI® electrode-filaments on the subject, the OkuSpex® plug will be positioned into the OkuStim® female connector on the upper side of the OkuStim® device (Figure 14). The Mini-USB-stick will be positioned within the port of the OkuStim® device to provide the subjects' personal therapy settings for transcorneal electrical stimulation (Figure 15).



Figure 14: Plug of OkuSpex® Sitting in OkuStim® female connector



Figure 15: USB port for physician and Mini USB stick port (right side)

When switched on by the technician, the OkuStim® device will begin the therapy session. The subject's closed eye will be stimulated with weak electrical pulses guided to the subject's retina, according to the setting determined by the technician (time and intensity). Subjects undergoing SHAM treatment will not receive any electrical stimulation. The subject should remain stationary throughout the duration of the 30-minute treatment session.

After 30 minutes of treatment, either the OkuStim® device will self-terminate or the technician will terminate the stimulation by pressing the "STOP" button on the OkuStim® device and the treatment session will end. The plug of the OkuSpex® glasses will be carefully removed. The subjects' eyelid will be opened widely while carefully removing the OkuSpex® glasses to allow for an easier withdrawal of the OkuEl® electrode from the eye. The OkuEl® electrode and skin electrode will then be removed from the OkuSpex® glasses and discarded. OkuEl® electrodes and skin-electrodes are single-use medical devices; there are technical, functional, and hygienic reasons for non-reusability.

5.7 Follow-up

Subjects in the Initial Treatment Randomized Group will be asked to return to the sites for follow-up at one week post treatment, twelve weeks and 26 weeks post treatment.

Subjects in the SHAM group will be re-tested after 6-weeks of SHAM treatment (week 8) and after 6-weeks of treatment (week 15) and at the 12-week follow-up (week 26) and 6-month follow-up (week 40) to determine if improvements in visual function have been maintained.

5.7.1 One week post treatment (Week 15)

Repeat all testing performed at baseline with the exception of repeating visual field. Visual field testing is required to be performed once per eye.

5.7.2 Twelve weeks post treatment (Week 26)

Repeat complete ocular exam, visual acuity with ETDRS and Sloan low contrast sensitivity, visual field and NEI-VFQ-25.

5.7.3 6 months post treatment (Week 40)

Repeat all testing performed at baseline with the exception of slit lamp external photography and of repeating visual field. Visual field testing is required to be performed once per eye.

5.8 Withdrawal Criteria and Procedures

All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue any subject at any time if medically necessary. The reason for the subject's withdrawal should be documented on the appropriate case report. The subject should undergo the recommended follow-up specified for the last study visit, including evaluation of disease signs and symptoms, unless contraindicated due to a medical condition. Withdrawn subjects will not be replaced.

5.9 Protocol Deviations

This study should be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of a subject requires a protocol deviation, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). If the deviation from the protocol is necessary to protect the physical well-being of a subject in an emergency, such protocol deviations must be reported to the sponsor and the reviewing IRB as soon as possible, but no later than 5 working days after the emergency occurred. In the event of a significant deviation from the protocol due to an accident or mistake, the investigator or designee must contact the sponsor at the earliest possible time by telephone to discuss the deviation and its impact on the study and subject continuation in the study. These discussions will be documented by the investigator and the sponsor, and reviewed by the monitor.

5.10 End of Study (Completion)

All subjects who have signed an informed consent, except for screen failures, will be considered enrolled in the study. Subjects who complete the study duration will be considered to have completed the study. Any subject who does not return for scheduled follow-up visits will be contacted at least twice by telephone to determine the cause for the missed visit. A new visit will be scheduled as soon as possible. All subjects should be followed until completing the study follow-up or until study discontinuation (withdrawal) for other reasons. The reason for study discontinuation should be documented for each subject. For subjects who discontinue the study early, an effectiveness evaluation should be conducted at the last study visit to document the signs and symptoms of the disease prior to study exit.

6. EFFECTIVENESS AND SAFETY VARIABLES

6.1 Primary Effectiveness Variable

6.1.1 ETDRS Visual Acuity

Standardized visual acuity measurement procedures will be implemented for the examinations. Incorporating a standard will minimize the effects technician variability and subject bias. In this study visual acuity testing is performed by the standard ETDRS Visual Acuity protocol.

Visual Acuity Chart: Modified Bailey-Lovie: The ETDRS visual acuity charts 1 and 2 are used for standardized measurement of visual acuity. Acuity testing of all subjects, regardless of visual acuity, begins at four meters. Two ETDRS Visual Acuity Charts are used for the measurement of visual acuity, each with a different letter sequence. The right eye will always be tested with Chart 1 and the left eye with Chart 2.

Illumination of Visual Acuity Charts and Room: The light box will be hung on the wall or placed on a stand at a height such that the top of the 3rd row of letters (0.8 LogMAR) is 49 + 2 inches (124.5 + 5.1 cm) from the floor. Room lighting should be approximately 50 foot-candles and should be uniform between the subject and the light box. The distance from the center of the exam chair to the Visual Acuity Chart should be 4.0 meters.

Best-Corrected Visual Acuity Measurements: The right eye is tested first and then the left eye. The subject is seated 4.0 meters from the center of the exam chair to the ETDRS Visual Acuity Chart. This testing distance is always used first even if the subject could not be refracted at four meters. With the lens correction obtained by subjective refraction in the trial frame, the subject is asked to read ETDRS Visual Acuity Chart 1 from the top with the right eye. It is emphasized to the subject that each answer will be scored so adequate time should be allowed for each letter in order to achieve the best identification. The subject is instructed that all of the figures to be read are letters and that there are no numbers. The examiner records each letter identified correctly by the subject as he/she reads the chart by circling the corresponding letter on the ETDRS score sheet (or study form). Letters read incorrectly, or for which no guesses are made, are marked by placing a "X" through the letter on this form. Each letter read correctly is scored as one point. The score for each line (including zero if no letters were read correctly on that line) and the total score for the eye are recorded on the form, as soon as the four meter testing has been completed. If the number of letters read correctly at four meters is less than twenty, the test should be repeated at one meter and both the four-meter and one-meter totals should be recorded on the ETDRS score the one-meter test distance. It is strongly advised that the total number of letters correctly read at our meters be calculated as soon as the four meter testing has been concluded in order to identify subjects who require one meter testing. The subject must sit for testing at the one-meter distance. The same procedure for obtaining visual acuity for the right eye is used for the left eye, except that ETDRS Visual Acuity Chart 2 is used. Chart 1 should never be exposed to the left eye and chart 2 should never be exposed to the right eye, even when switching charts and occlusion.

Poor Vision Testing: Follow the procedures described above, Visual Acuity Testing using the EVA System.

Calculating the Visual Acuity Score: After each measurement of visual acuity the score for the visit is calculated. The visual acuity score is defined as follows:

If twenty or more letters are read correctly at the four-meter test distance, the visual acuity score is equal to the number of letters (N) read correctly at four meters.. If one or more but less than twenty letters are read correctly at four-meter distance, the visual acuity score is equal to the number of letters read correctly at one meter in the first six lines. If no letters are read correctly at either the four-meter distance or the one-meter distance, the visual acuity score is 0, and testing for counter fingers or worse should be performed.

6.2 Secondary Effectiveness Variable

6.2.1 Contrast Sensitivity

Contrast sensitivity will be evaluated by Sloan Low Contrast Sensitivity charts. A standardized chart comprises 14 lines of letters with constant contrast. Each line has 5 letters decrease downward from line to line. The size of the letters is 4.9×4.9 cm (2×2 inches). There are different sets of letters on each chart, depending on the percentage of contrast being tested. The manufacturer recommends a testing distance of 2.52 m from patient when using the translucent 1.25% low contrast symbols chart and 2 m from patient when using the translucent 2.5% low contrast symbols chart, which corresponds to a spatial frequency of about 1 cycle per degree. The logarithmic contrast sensitivity value of the last triplet of which at least 3 letters are correctly seen is marked as the result.

Illumination and Mounting of the chart: The light box will be hung on the wall or placed on a stand at a height such that the top of the 3rd row of letters (0.8 LogMAR) is $49 + 2$ inches ($124.5 + 5.1$ cm) from the floor. Room lighting should be approximately 50 foot-candles and should be uniform between the subject and the light box.

Testing of the subject: Subjects will be tested before dilating their pupils or applying any other drugs. The subject should sit directly in front of the chart so that the distance from the eyes to the chart is 2.52 meters (100 inches).

Recording the subject performance: Full study ID of the subject, the date and the technician's name will be recorded on the scoring sheet. A subject will make a single attempt to name each letter on the chart, starting with the letters on the first line, then reading downward line by line. On the scoring sheet, correctly read letter will be circled or underlined and incorrect letter will be stroked through.

Patient Effort: Subject will be made to guess even when they believe that the letters are invisible. (Several seconds should be allowed for the faintest letters to appear, but subject should not give up until he or she has guessed incorrectly 2 of the 3 letters in a triplet).

Testing the other eye: Each eye will be tested separately; always testing the right eye first while the left eye is occluded, then alternating to test the fellow eye. The technician will begin with the translucent 1.25% low contrast sensitivity chart at 2.52 m, then changing the chart to the translucent 2.5% low contrast sensitivity chart.

Life and care of the chart: The chart will not be used if it is marred by visible marks, e.g. fingerprints. Chart will be wiped using soft cloth with diluted solution of mild soap and rinsed with clean water.

Explaining the test: The subjects will learn about the chart and the procedure. 'Try reading just one letter at a time'. 'Try blinking', or 'Do you see something against the white blackboard?'

Standardization: These instructions accompanying a chart have been designed to achieve the highest possible comparability of results among different users. The chart follows the luminance, font, and letter spacing recommendations of the Committee on Vision of the National Academy of Sciences and National Research Council (1980).

6.2.2 Visual field mean deviation

In this study, we will evaluate visual field with the Humphrey threshold static perimeter map. In static threshold perimeter we map the island of vision using a different technique. In the classic "30-2" test on the Humphrey Field Analyzer, 76 points are tested over the patient's central 30° of vision. The technician then determines a threshold of light sensitivity for each of these points. This intensity of the stimulus is seen 50% of the time, and it can be likened to the depth or thickness of an island at each of these points. The mean deviation (MD) calculates the mean of the deviation in the patient's results from the age-corrected normal database. The calculation is center-weighted so that central points contribute more to the overall score than peripheral points. In other words, the MD is the average measure of how depressed the patient's visual field is compared with a normal person of the same age.

Instruction to the subjects: The subjects will be explained that the test is a computerized machine test. The subject will be instructed to look straight ahead and informed to look at the steady white light inside the machine all the times. They will be informed to push the button when they see the flash of light and blink after they push the button. They will be informed about the bright and dim light and the need to have them to test for sensitivity of your eyes. The test will take around 5 minutes for each eye. Each eye will be tested separately while the other eye is covered. The subject will be seated comfortably with their forehead pushed forward into the machine as far as possible and allowed rest in between. Only at the screening visit is Visual Field, 24-2 static performed on each eye three times. All other post-treatment follow-up visits each eye is tested a single time.

6.2.3 Visual Evoked Potential

The measurement that results from the recordings of an electroencephalogram from the occipital area of the scalp as the result of retinal stimulation by a light flashing at quarter-second intervals, as given by a computer that averages the electroencephalogram response of 100 consecutive flashes.

Prior to test instructions: Subjects will be asked to wash their hair and avoid hair chemicals. Also, to take a good night sleep and bring their corrective eye wear with them.

Test duration: The average test takes 30-45 minutes to complete.

Description of the test method: The test will be done by scrubbing spots on the scalp and placing metal disc electrodes on those spots with conduction cream. Both eyes will be tested individually. One eye will be covered and with the other eye, which is being tested, subject will watch a screen.

6.2.4 Intraocular Pressure Measurement (IOP)

In this study the intraocular pressure will be measured by the Applanation (Goldmann) Tonometry method. This type of tonometry uses a small probe to gently flatten part of your

cornea to measure eye pressure and a microscope called a slit lamp to look at your eye. The pressure in your eye is measured by how much force is needed to flatten your cornea.

Subject Preparation: The subject will be asked to remove contact lenses before the test. They will be instructed to remove or loosen any tight clothing around their neck, as pressure on neck veins can increase the pressure inside eyes and asked to stay relaxed.

Duration for the test: The test will take few minutes to complete.

Test description: The subjects will be asked to rest their chin on a padded support and stare straight into the microscope (slit lamp). A bright light will shine in subject's eyes and the tonometry probe will be gently touched to the examining eye. The subjects will be instructed, to not rub eyes 30 minutes until the numbing medicine has worn off. Avoid blinking or squeezing eyes. There is a very slight risk that the cornea may be scratched during the methods that involve touching a tonometer to the eye.

6.2.5 Spectral Domain - Optical Coherence Tomography

In this study, technicians using the Heidelberg Spectralis will capture one 20°x20° volume scan at high speed with a 5/frame rate and 97 B-scans. Additionally, a 20°x20° high resolution cross hair scan is performed at a 10/frame rate.

OCT Technician Certification: All technicians performing OCT will be certified for the relevant study procedure before submitting actual study subject scans. Only certified OCT technicians are allowed to take baseline (screening visit scans). The baseline measurements for a subject are critical since all follow up measurements are compared to this point to determine the study outcome.

Subject Preparation: The subject will be asked to sit comfortably and look straight ahead to the beam of light and avoid blinking. The chin and forehead will be rested against support.

6.2.6 National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25)

The subjects in the study will be answering a questionnaire of 25 questions pertaining to vision as per the National Eye Institute version 2000.

- The subjects can take as much as time needed and should try to complete the forms on their own. If they need any assistance they could ask for assistance.
- If the subjects have glasses/ contact lens, they should answer the questions as though they are wearing them.
- The subjects will be assured about confidentiality and the information will be used only for the study purpose.
- The scoring data will be analyzed by the standard method, by Rasch analysis, and by use of an algorithm created by Massof to approximate Rasch person measure.

6.2.7 Symbol Digit Modalities Test

The **Symbol Digit Modalities Test (SDMT)** detects cognitive impairment in less than 5 minutes. This simple, economical test is an ideal way for busy clinicians to screen for organic

cerebral dysfunction in both children (8 years and older) and adults. In this study, this test will be performed with standardized method.

Instructions for administration: The test can be taken by individuals or groups. If it is given to groups, the papers should be given out face down, so that everyone turns over at the same time when instructions are given. The following are the principal instructions that all subjects will receive.

- Look at the Key at the top of the page. Each of the shapes goes with its own number, shown in the box beneath.
- Practice giving each shapes the right number in the second line – stopping at the vertical double line.
- After the practice is completed and checked, do them one at a time, starting at the vertical double line.
- When you finish a line, go to the next. Don't stop to correct a mistake – just write over it. Do as many as you can in a minute and a half. Work quickly.
- Be prepared to stop immediately when you are told.
- After **90 seconds** make sure that all copying ceases.

6.3 Safety Variables

The development of corneal abrasion will serve as the primary safety end point this study. For subjects that experience a corneal abrasion, drops will be administered initially. If the irritation continues for more than two days, the subject will be examined by an ophthalmologist.

7. STATISTICAL ANALYSIS

7.1 Primary Effectiveness Endpoint

While our main goal is to estimate the effect of treatment for all study outcomes, we will also perform two formal hypotheses tests for the primary outcomes. The primary outcomes are change in high-contrast LogMar VA and change in low-contrast LogMar VA from baseline (week 1) to initial post treatment (week 8). Each outcome will be modeled separately within each cohort. We will use mixed effects linear regression to model all available VA measures from week 1 to week 8. Fixed effects will be randomization assignment (treatment vs. SHAM), time, and randomization assignment x time interaction. We will treat time as a categorical variable to allow for the most flexibility in modeling the shape of the VA trajectories over time. Correlation among repeated measurements will be modeled using an appropriate within subject covariance structure. Unstructured, compound-symmetric, heterogeneous compound symmetric and first-order autoregressive structures will be considered with the final choice being determined using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics. Satterthwaite's approximation will be used to estimate denominator degrees of freedom. We will examine the distribution of the residuals to assess the reasonableness of the normality assumption, and will apply appropriate transformations as needed.

It is important to note that the three cohorts (ophthalmic trauma, MS or CIS, and NAION) cannot be pooled as they are clinically distinct populations and the natural history is different in the groups. Ophthalmic trauma results in both anterograde and retrograde degeneration of the afferent visual system. This degeneration continues after the initial insult and further degeneration may be

preventable or even reverse early damage with intervention(s) instituted between 3 to 6 months post-trauma. The degeneration from ophthalmic trauma occurring 6 months or greater is thought to be complete, though occult cell damage may continue, and the visual loss is generally thought to be unrecoverable.

Within this model, we will use linear contrasts to estimate average change from baseline to week 8, and we will estimate the difference in these change scores as our primary measure of treatment effect. Our primary hypothesis is that subjects randomized to initial treatment will have greater improvement in VA at 8 weeks compared with those randomized to initial SHAM. For each outcome, we will perform a two-sided test with $\alpha=0.05$.

7.2 Secondary Effectiveness Endpoints

Secondary outcomes are change in visual field mean deviation, contrast sensitivity, VEP results (peak latency, amplitude of the p100 wave), IOP, SD-OCT nerve thickness, NEI-VFQ-25 total score and subscores, and SDMT total score. We will use a similar approach for the primary efficacy analysis. For those outcomes measured only at weeks 1 and 8, we will use a heterogenous compound symmetric covariance structure. Again, we will estimate the average change from baseline to week 8 for all arms and the difference in change between arms.

7.2.1 Additional Effectiveness Endpoints

Within-subject Estimate of Efficacy

Since the initial SHAM-Randomized group will also receive the active treatment, we will calculate an additional estimate of treatment efficacy for each outcome using only data from this arm. A similar mixed effects regression analysis will be performed using study period (SHAM vs. active TES) rather than randomization assignment. Study time will be entered as pre-sham, post-sham, and post-active TES. The secondary estimates of treatment efficacy will be calculated as change from post-sham to post-active TES minus change from pre-sham to post-sham.

7.2.2 Long-term Changes

Using data from all subjects, we will estimate the long-term effects of treatment. We will include all available data from the initial Treatment-Randomized group and all data from visits 8-17 from the initial SHAM-Randomized group. We will again use mixed effects linear regression to model the change in outcomes over time. Fixed effects will include time (relative to pre-treatment time) and randomization assignment (to control for possible period effects). We will use linear contrasts to estimate the change from post-treatment to week 12 and post-treatment to 6-months to estimate how much any initial improvements may have been maintained over time.

7.3 Sample Size

We have based our sample sizes on efficacy data reported in a similar study of patients with RP (22). In that study, average improvement in LogMAR VA for the SHAM group was 0.017 (SD=0.05) and for the active treatment (150% of threshold) group was .067 (SD=0.05) for a difference in change scores of 0.05 and an effect size of 1. To have 80% power to detect a true effect size of 1 using a two-sided t-test with a Type-I error rate of 5% requires 39 subjects (26 initial treatment; 13 SHAM). Allowing for roughly 5% attrition during the initial treatment period, we will aim to randomize 42 subjects for each study.

While we will have sufficient power to detect a fairly large effect size, our main goal in this project is to estimate the effect size for all study outcomes. With 39 subjects we will have reasonable precision to estimate the effect size with a 95% CI of width +/- 0.69. That is, if the observed effect size were 0.8, the 95% CI would extend from 0.11 to 1.49. If the observed effect size were 0.4, the 95% CI would extend from -0.29 to 1.09. In terms of the LogMAR VA, assuming a standard deviation of 0.05, if the observed average difference in change scores is 0.07, the 95% CI would extend from 0.036 to 0.10.

7.4 Datasets

7.4.1 Full Data Set

This data set is the “intent-to-treat” data set and includes all randomized subjects with baseline and/or follow-up data for the primary and secondary outcomes. Subjects are analyzed as they are randomized, regardless of the amount of treatment received. This data set will be analyzed for primary and secondary efficacy outcomes.

7.4.2 Per-protocol Data Set

This data set includes all randomized subjects with baseline and/or follow-up data for the primary and secondary outcomes who received at least 3 treatments during the initial study period. Subjects randomized to either arm who received fewer than 3 treatments will be excluded. In addition, any subjects receiving the incorrect treatment (SHAM instead of initial treatment or vice versa) will be excluded. Any subject found to be ineligible after randomization will also be removed from this data set. Analyses specified under section 7.1 will be repeated using the data set.

7.4.3 Missing Data

While we anticipate that the rate of attrition will be low, there is likely to be at least some incompleteness in data over time. We will include all available outcome data from all randomized subjects in our initial analysis of primary and secondary outcomes. The mixed effects approach to modeling allows for missing data and will yield unbiased estimates of treatment effects under the assumption that the data are missing at random. To evaluate sensitivity to this assumption, we will repeat the primary and secondary efficacy analyses including only subjects with complete data at baseline and post-treatment.

7.5 Primary Hypothesis

As in the case of central nervous system strokes, in which there is a central area of irreversible infarction and a border zone of tissue that has some normal anatomic structure but does not function (so called “ischemic penumbra,” akin to a state of hibernation), we postulate that some cells and axons of the optic nerve and retina are damaged by trauma but not necessarily in an irreversible manner. We hypothesize that because vision is a physiological function uniting a biochemical pathway with an electrical signal that providing a controlled, well-defined, safe electrical stimulus has the potential to restore function to photoreceptors, glial cells, and axons that are not irreversibly damaged.

7.6 Secondary Hypothesis

We believe that electrical stimulation of optic nerves and retinas damaged by trauma, MS or CIS, and ischemia may regain some function of the afferent visual system as defined by VEPs and mERGs.

7.7 Analysis of Safety

Rates of adverse events will be calculated by randomization assignment and study period along with exact binomial confidence intervals. Rates between arms during the initial treatment period will be compared using Fisher's exact test. Safety evaluation issues are described in detail in Attachment 2, Human Subjects Recruitment and Safety Procedures.

8. RESTRICTIONS

8.1 Prohibited Medications

History of epilepsy or seizures and/or prescribed to anti-epilepsy or anti-seizure medication.

8.2 Other Restrictions

Subjects cannot be participating in any other interventional clinical trial.

Women who are pregnant or women with childbearing potential and who are unwilling to use medically acceptable means of birth control for study duration or women unwilling to perform a pregnancy test at study entry/screening and at each treatment visit prior to treatment.

Subjects cannot have history of epilepsy or seizures and/or prescribed to anti-epilepsy and/or anti-seizure medication.

9. EVALUATION OF ADVERSE EVENTS

9.1 Definitions

An adverse event (AE) is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered device-related by the investigator.

9.2 Relationship to the Investigational Device

The investigator should assess the relationship of the adverse event to the investigational device. The relationship should be assessed using the categories in Table 8.2-1 below.

Table 9.2 Possible Relationship Between Adverse Events and Investigational Device

Probably Related	It is more likely than not that there is a reasonable causal relationship between treatment with the investigational device and adverse event.
Possibly Related	There is a reasonable relationship to the device treatment, but the causal relationship is unclear or lacking.
Not Likely Related	There is a temporal relationship to the device treatment, but there is not a reasonable causal relationship between the study device and

	the event. For example, the adverse event occurs in a time relation to the device treatment, which makes relation improbable.
Unrelated	No relationship between treatment with the investigational device and the adverse event exists.

9.3 Unanticipated Adverse Device Effects (Events)

An unanticipated adverse device effect is defined as "any serious adverse effect on health or safety, or any life-threatening problem, or death caused by, or associated with, a device; if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or application (including supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

If an unanticipated adverse device effect occurs, the investigator should promptly notify the sponsor of such an event, within 48 hours of first learning of the event. The investigator must promptly notify its reviewing IRB of such an event in accordance with its policies and requirements. In the United States, the investigator must notify its IRB within 10 working days after first learning of the event.

9.4 Serious Adverse Events

Each adverse event should be assessed for its seriousness. The definition below should be used for this assessment. Please note that the term serious adverse event is not synonymous with a "severe" adverse event, which may be used to describe the intensity of an event experienced by the subject. (Please refer to Section 9.6 for severity definitions.)

An adverse event should be classified as serious if it meets any of the following criteria:

- Results in, or contributes to, a death;
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at risk of death at the time of the event, but it does not include an event that, had it occurred in a more severe form, might have caused death);
- Results in permanent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure);
- Requires in-patient hospitalization or prolongs hospitalization;
- Necessitates medical or surgical intervention to prevent death or a life-threatening condition, or to preclude a permanent disability or incapacity; and,
- Results in a congenital anomaly or birth defect.

Non-serious adverse events are all events that do not meet the criteria for a "serious" adverse event.

9.5 Reporting Requirements for Serious Adverse Events

Serious adverse events must be reported to the Wills Eye IRB as soon as possible. The adverse event must be recorded on the subject's case report form. The Wills Eye IRB will conduct an

investigation. If the sponsor determines that the investigation presents an unreasonable risk to subjects, they will terminate all investigations or parts of the investigation presenting that risk as soon as possible. The investigator must report serious adverse events to his/her IRB according to the IRB requirements at the study site.

9.6 Severity

Each adverse event should be assessed for its severity, or the intensity of an event experienced by the subject, using the following.

- 1 = Mild - Discomfort noticed, but no disruption to daily activity
- 2 = Moderate - Discomfort sufficient to reduce or affect normal daily activity
- 3 = Severe - Inability to work or perform normal daily activity

9.7 Deaths

The investigator must notify the sponsor as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of subject's death, regardless of whether the death is related or unrelated to the investigational device. The investigator should attempt to determine, as conclusively as possible, whether the death is related to the device. The cause of death and the investigator's discussion regarding whether or not the death was device-related should be described in a written report. The investigator must report death to their IRB according to the IRB regulations at the study site.

9.8 Pre-existing Conditions

Pre-existing conditions should not be reported as an adverse event unless there has been a substantial increase in severity or frequency of the problem that has not been attributed to natural history.

9.9 Clinical Laboratory Changes

The investigator should review the results of all laboratory tests as they become available. For each laboratory test result, the investigator needs to ascertain if this is an abnormal (i.e., clinically significant) change from baseline for that individual subject. (This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests.) If this laboratory value is determined to be an abnormal change from baseline for that subject, this should be considered an adverse

9.10 Independent Study Oversight (Data Safety Monitoring Board)

WEHS will establish a Data Safety and Monitoring Board (DSMB) for this research project. These groups will assure protocols are being followed properly, case reports match the source documents, inclusion/exclusion criteria are being followed, and all subjects are consented properly. In addition, the DSMB will review safety data and visit after we have enrolled ten subjects after which we will initiate site visits every six months. The DSMB will meet with the research team on a quarterly basis.

9.10.1 Data Safety Monitoring Board Chairperson Roles and Responsibilities

Byron Lam, MD is appointed the DSMB Chairperson and will also serve as the Research Monitor for this study. Byron Lam will be responsible for:

- Reviewing and evaluating accumulated study population data, analyzing patient safety, and study conduct and progress
- Overseeing the assurance that the study protocols are being followed properly
- Ensuring all participants meeting the eligibility criteria are consented properly and thoroughly
- Organizing and developing a monitoring plan in collaboration with the members of the DSMB, which will begin after ten subjects have been enrolled into the study by an initial site visit after which site visits will initiate every six months
- Track and report to the IRB factors that might affect overall study outcomes and compromise confidentiality of study data, such as violations of protocol, randomization, or masking procedures
- Observing consistency and accuracy of case report forms and source documents
- Monitoring the transfer and analysis of de-identified participant results and other case sensitive study material between the research team members involved in the study
- The chairperson “has the authority to stop the research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well being of human subjects until the IRB assesses the independent Research Monitor's report.”
- The chairperson is "required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the research monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The research monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO."

9.10.2 DSMB Reporting Requirements to the local IRB

The DSMB will develop a monitoring plan and provide procedures for transmitting the DSMB’s summary reports to the IRB. The DSMB will issue a written summary report to the IRB and the study’s Principal Investigator. The report will provide individual findings, overall safety assessment and recommendations. The summary report will reflect familiarity with the study’s protocol, proposing appropriate analyses of participant enrollment, site visits, study procedures, study documents completion, data quality, and losses to follow-up. The report should also inform study investigators of the DSMB members’ conclusions with respect to the study’s progress or need for modification of the protocol.

10 RISK ANALYSIS

10.1 Potential Risks

10.1.1 Corneal Abrasion

The OkuStim® device may result in mechanical irritation of a subject's cornea, which may be observed together with red eye and/or dry eye sensation. In this case, conventional eye drops (contact lens saline solution) or artificial tears can alleviate the irritating sensation. In case the irritation does not disappear within 1-2 days, subjects will be examined by one of the ophthalmologists for evaluation. In addition to TES treatment administration risk, another inherent risk of study participation is the potential, inadvertent loss of confidentiality of subject data. Inadvertent disclosure of subject identifying information and the accompanying breach in confidentiality can contribute significantly to psychological and social risk in addition to physical and legal risk. This risk of loss of confidentiality will be protected against by assigning a unique identifier to the patient.

10.1.2 Corneal Argyrosis

Subjects may experience argyrosis as a side effect. To date, as recorded in previous studies, no subject has experienced discoloration of the cornea or the conjunctiva as a result of silver particle deposition. Investigators will take precautions to minimize the particle deposition and record any progression of discoloration.

Immediately after receiving TES, subjects' eyes will be flushed with a buffered saline solution to reduce the presence of silver particles. In addition, an external photo will be taken of the subjects' conjunctiva and cornea. If any discoloration appears, the subject will be notified immediately.

10.2 Manner in Which the Potential Risks Have Been Minimized

The WEHS employs adequate risk management plans and emergency response personnel. In the case of adverse ophthalmic outcomes, the WEHS will offer subjects any necessary treatment to correct the adverse finding. Nevertheless, as adverse events were rare in previous clinical studies implementing TES, we anticipate the risk of emergency or adverse outcomes to be equally low, if not lower since we have a successful human study to model our protocol and gain OkuStim®-specific knowledge from. In addition, the WEHS will take all necessary precautions to minimize the risk of an adverse event to the best degree possible. Only personnel who are trained on how to properly use the device by OkuStim® technicians will be able to administer it, regardless of whether treatment administered is SHAM or authentic. Since all TES administration will take place on site at the WEHS, subjects will have access to immediate ophthalmic care if an adverse event or emergency arises. In addition, all members of the research team will be educated on the device, including its risks, hazards and commonly encountered problems, in order to prepare for an emergency scenario. During the treatment period, and for nine months afterwards, subjects will be able to contact the WEHS and consult an ophthalmologist if an adverse ophthalmic event occurs as a result of TES intervention. Though an emergency is highly unlikely, the WEHS will instruct all study personnel on how to operate and handle emergency scenarios should they arise. Furthermore, in the event of physical injury or illness resulting to the subject as a direct result of the treatments used in this investigation, comprehensive medical and/or surgical care (including hospitalization) to the extent needed and available will be

provided. However, Wills Eye Health System cannot assure that this comprehensive medical and/or surgical care will be provided without charge, and the costs incurred for this care may ultimately be the subject's responsibility. In this regard, our study thoroughly minimizes risks to subjects to the best of our capability.

10.3 Potential Benefits

The largest potential benefit available to subjects participating in the study is the rehabilitation and restoration of vision after having endured debilitating ocular trauma. If the proposed TES treatment can be shown to significantly improve VA in our subjects (improvement by 2 lines or more upon re-evaluation) then we may be able to adapt these findings to improve overall visual function in our wounded military personnel, and in doing so alleviate some of the anxiety of their straining careers.

10.4 Justification for the Clinical Study

Reports show potential efficacy using transcorneal electrical stimulation (TES) to improve visual function (16-22). Therefore, the success of electrical stimulation in these neuro-degenerative disorders provides a reasonable rationale and significant precedent to investigate its potential in disorders of the optic nerve and retina, which function via an integration of biochemical and electrical interactions.

11. DEVICE MANAGEMENT

11.1 Accountability

The investigator, or designee, must maintain an inventory record of investigational devices received, used for treatment, otherwise discarded, and returned to the sponsor to ensure that the investigational new device will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol.

12. REGULATORY AND ETHICAL REQUIREMENTS

This clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and in accordance with applicable local and federal regulatory requirements and the laws in the country in which the study is being conducted, and in accordance with the standards of good clinical practice. In the United States, the study will be conducted in accordance with the Protection of Human Subjects Regulations, including Subpart B Informed Consent of Human Subjects (21 CFR Part 50); the Institutional Review Board Regulations (21 CFR Part 56); the Financial Disclosure by Clinical Investigators Regulations (21 CFR Part 54); and the Investigational Device Exemptions Regulations (21 CFR Part 812).

12.1 Informed Consent

A copy of an example informed consent document is provided in **Attachment 1**. Informed consent will be obtained from all subjects prior to study participation.

12.2 Institutional Review Board/Ethics Committee

Prior to initiation of any study procedures, the protocol, informed consent and device labeling will be submitted to a duly constituted IRB for review and approval. In addition, any

amendments to the protocol or informed consent form will be reviewed and approved (if necessary) by the IRB. The sponsor must receive a letter documenting the IRB approval at the clinical site prior to the initiation of the study.

The investigator is responsible for providing the appropriate reports to its reviewing IRB during the course of the clinical study. The investigator should refer to his/her site-specific requirements. In the United States, this will include the following at a minimum:

- Informing the IRB of the study progress periodically as required, but at least annually;
- Reporting any unanticipated adverse device effects within 10 working days of first learning of the event;
- Reporting any deviations from the clinical protocol to protect the life or well-being of a subject in the case of an emergency within 5 working days after the emergency occurred;
- Reporting the use of the device without obtaining informed consent from a subject within 5 working days of the event; and,
- Providing any other reports requested by the IRB.
- Notifying the IRB of study completion within 30 days of the final visit of the last subject and providing a summary of the results of the study by the investigator.

12.3 Confidentiality of Patient Records

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the sponsor. Authorized regulatory officials and sponsor personnel (or its representatives) will be allowed full access to inspect and copy the records. All investigational devices and/or other materials collected should be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects should be identified only by initials and unique subject numbers in case report forms. If necessary, their full names may be made known to a regulatory agency or other authorized officials.

13. REPORTS AND RECORDS MANAGEMENT

This investigational study will follow the investigator report and record keeping requirements specified below and in accordance 21 CFR Part 812. These requirements are summarized below.

13.1 Investigator Records

Prior to participation in the investigation, the investigator must provide the following documentation to the sponsor:

- Investigator Agreement, signed by the investigator, which lists any physicians who will be involved in conducting the investigation under the direction of the primary investigator.
- A copy of the investigator's curriculum vitae (CV) as well as copies of CVs for any co-investigators.
- A letter signed by the chairperson of the IRB of the institution at which the investigation will be conducted indicating that that the IRB has reviewed and approved this investigational plan.
- A copy of the IRB approved informed consent document.

During the study, investigators are required to maintain on file the following accurate, complete and current records relating to this study as described in 21 CFR § 812.140. A summary of these records is described below:

- All correspondence and required reports which pertain to the study;
- Records of receipt, use or disposition of the investigational device, including the type and quantity of the device, the dates of receipt, the lot number, the names of all persons who received, used or disposed of each device, and why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed;
- Records of each subject's case history and exposure to the device;
- Signed and dated consent forms;
- Relevant observations, including records concerning adverse events, condition of each subject upon entering and results of diagnostic tests;
- Case report forms and corrections to the forms;
- Protocol, amendments and case report forms;
- Subject recruiting materials; and, investigator curricula vitae.

13.2 Investigator Reports

Investigators are required to prepare and submit to the sponsor the following complete, accurate, and timely reports on this investigation when necessary. These reports, which follow, include all of those described 21 CFR § 812.150, and some additional reports requested by the sponsor:

- The investigator will notify the sponsor of a subject death occurring during the investigation, as soon as possible preferably within 1 day of learning of the subject's death, but in no event later than 3 days. The investigator will notify the reviewing IRB of a subject death as specified by the IRB.
- The investigator will notify the sponsor of any unanticipated adverse device effects within 5 days after the investigator first learns of the effect. The investigator will notify its reviewing IRB of any unanticipated adverse device effects, as soon as possible, but no later than 10 working days after the investigator first learns of the effect.
- The investigator will notify the sponsor of the withdrawal of IRB approval, as soon as possible, but no later than 5 working days after the investigator first learns of the withdrawal.
- The investigator will provide current progress reports to the sponsor and reviewing IRB at regular intervals and at least on an annual basis.
- The investigator will notify the sponsor and reviewing IRB of any deviation from the investigational plan to protect the life and physical well-being of a subject in an emergency, as soon as possible, but no later than 5 working days after the emergency occurred.
- The investigator will notify the sponsor and reviewing IRB that an informed consent was not obtained from a subject, as soon as possible, but no later than 5 working days after such an occurrence.
- The investigator will provide a final summary report within 3 months after termination or completion of the study to the sponsor and reviewing IRB.
- The investigator will provide any other information upon the request of an IRB, regulatory authorities, or the sponsor.

13.3 Data Collection

During each subject's visit to the clinic, an investigator participating in the study will record progress notes to document all significant observations. In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

For transmission to the sponsor, information from the study progress notes and other source documents will be promptly transcribed in black ink to case report forms. **Attachment 2** contains the case report forms.

Any changes to information in the study progress notes, other source documents, and case report forms will be initialed and dated in ink on the day the change is made by a site study staff member authorized to make the change. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

13.4 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, computer printouts, screening logs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons.

13.5 Records Retention at the Study Site

The investigator is responsible for retaining the necessary records. This includes a copy of the protocol, the device labeling, case report forms, medical records, original test result reports, all study related correspondence, a record of written informed consent, and any other documents pertaining to the conduct of this study.

FDA regulations require all investigators participating in investigational device studies to maintain detailed clinical records during the investigation and for a period of at least 2 years after the latter of the following two dates:

- The date on which the investigation is terminated or completed; or,
- The date the records are no longer required for purposes of supporting a premarket approval application.

The investigator must not dispose of any records relevant to this study without either (1) written permission from the sponsor or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor and the FDA.

14. MONITORING PROCEDURES

14.1 Monitoring

Wills Eye has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and FDA regulations. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the

progress of the study), Wills Eye will hire a data safety monitoring board to visit the site during the study in addition to maintaining frequent telephone and written communication.

The following guidelines are provided to describe the Wills Eye's procedures for monitoring the clinical studies. If the investigator is not complying with the signed Investigator Agreement, the protocol, or any condition of the study (e.g., incomplete data forms), the sponsor has the right to terminate the investigator's participation in the study. Wills Eye will seek highly respected and qualified ophthalmologists and scientists with training and experience to conduct monitoring of the trial, and for ensuring the quality of the study monitoring visits by the monitor.

14.2 Pre-Study Monitoring Procedures

14.2.1 Selection of Monitors

There will be an overall study monitor, as well as two other monitors, for the investigational study. Wills Eye will determine the total number of monitors for its investigational studies based on the size and complexity of the study, the number and location of sites, the number of subjects, and the scope of the contractual obligations at each site. All monitors are to be qualified by education, training, and experience.

14.2.2 Clinical Investigators

Upon receipt of a signed Investigator Agreement, and IRB approval letter, investigators will be sent the appropriate clinical study materials.

14.3 Pre-Investigation Visit

A monitor will be responsible for determining and documenting that each investigator clearly understands and accepts the responsibilities and obligations incurred in conducting a clinical study. The monitor will ensure prior to study initiation that the investigator:

- Understands the requirements for a well-controlled study;
- Understands the nature of the clinical protocol;
- Understands his/her reporting obligations;
- Understands the requirements for device accountability;
- Understands and accepts the obligations to obtain informed consent in accordance with 21 CFR Parts 50 and 56;
- Understands and accepts the obligation to obtain IRB review and approval of the clinical investigation before it is initiated and to ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56, and to keep the sponsor informed of all IRB actions concerning the study;
- Understands and accepts the requirements regarding financial disclosure of clinical investigations, 21 CFR Part 54;
- Has adequate facilities and access to an adequate number of suitable subjects to conduct the investigation; and,
- Has the required documentation on file, including IRB approval and a signed investigator agreement.

14.4 Periodic Monitoring Visits

Monitoring visits will be conducted in accordance with the FDA Guideline for the Monitoring of Clinical Investigations, January 1988. The monitor should visit each site frequently to ensure the following:

- Facilities continue to be adequate and acceptable.
- The protocol is being properly followed.
- The IRB has approved or been notified of any protocol changes.
- Accurate, complete and current records are being maintained, and the information recorded and submitted to the sponsor is representative of the subject's record and other supporting documentation.
- Accurate, complete and timely adverse event reports are being submitted to the sponsor.
- Informed consent has been obtained.
- The reason for a subject's withdrawal from the study has been documented.
- Reports are being submitted to the IRB and sponsor.
- The appropriate staff is carrying out study activities.

The investigator or designee must, upon request, provide to the sponsor or FDA investigator the necessary study records for a thorough review of the study's progress. These records include, but are not limited to, case report forms and original documents and records such as hospital and clinic charts, consent forms, and operative reports.

All case report forms and other documentation related to the study will be reviewed upon receipt, and the site will be promptly notified of any deficiencies.

14.5 Frequency of Monitoring Visits

The frequency of monitoring visits will be determined on the basis of several factors, including:

- Duration of the study;
- Number of outstanding issues from previous visits;
- Number of subjects enrolled;
- Number of investigators/sites; and,
- Complexity of the study.

Each site will undergo a monitoring visit at least monthly.

14.6 Study Termination

All routine monitoring functions must be performed prior to the study termination visit; the study termination visit may be combined with a monitoring visit. The following tasks should be completed at the last visit by the monitor.

- Ensure that all forms have been sent to the sponsor.
- Remind the investigator of the obligation to retain the records.
- Prepare final monitoring report for sponsor and IRB.

14.7 Reports of Monitoring Visits

Monitoring reports must be completed for all visits. Reports must include the following information:

- Date of the visit;
- List of study site personnel present; and,
- A summary of the findings, problems, and actions taken to correct any deficiencies.

14.8 Additional Auditing

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact the sponsor immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

15. CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the sponsor. Authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All investigational devices, subject bodily fluids, and/or other materials collected should be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subject names and identifiers will be coded for privacy and subjects will be identified only by unique subject numbers in case report forms. If necessary, their full names may be made known to a regulatory agency or other authorized officials.

16. AMENDMENT POLICY

The investigator will not make any changes to this protocol without prior written consent from the sponsor and subsequent approval by the IRB, except if the deviation from the protocol is necessary to protect the life and physical well-being of a subject in an emergency. Such protocol deviations must be reported to the sponsor and the reviewing IRB as soon as possible, but no later than 5 working days after the emergency occurred.

Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed by the investigator(s) and the sponsor. If agreement is reached regarding the need for an amendment, the sponsor will write it. The written amendment must be submitted to the chairman of the IRB identified with this responsibility. Except for "administrative amendments", investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol; the scientific soundness of the investigational plan or protocol; and, the right, safety or welfare of the human subjects involved in the investigation.

When, in the judgment of the chairman of the local IRB, the investigators and/or the sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written informed consent form will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before continued participation.

STUDY SITES AND INVESTIGATORS

This clinical study will be conducted at Wills Eye Hospital, 840 Walnut Street, Philadelphia PA 19107. Julia Haller, MD is the Principal Investigator.

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