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PRINCIPAL INVESTIGATOR: Stephen Rose, Ph.D.

CONTRACTING ORGANIZATION: National Neurovision Research Institute
Owings Mill, MD 21117

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14. ABSTRACT The National Neurovision Research Institute (NNRI), the clinical arm of the Foundation Fighting Blindness (FFB), proposes to establish the National Eye Evaluation Research (NEER) Network to be composed of a collaborative group of five Clinical Treatment and Evaluation Centers (CTECs). The intent of this new Network is to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD) through the conduct of clinical trials and other clinically relevant research. The scope of research to be carried out encompasses: (i) Phase I and Phase II clinical trials to evaluate the safety and efficacy of new therapeutic and preventive approaches, including devices, biopharmaceuticals, small molecules, nutritional supplements, and gene transfer approaches; natural history studies to develop standardized criteria to define disease stage, severity and progression; (iii) observational studies to enhance understanding of the natural history of these diseases for different					
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genotypes and phenotypes; and (iv) evaluations of the reliability and validity of different available treatment outcomes measures to determine those that are most appropriate for various genotypes and phenotypes as well as for specific interventions. The NEER Network will also develop standard protocols for data collection, maintain and expand patient databases, classified by genotype and phenotype, to allow for the timely identification of eligible patients and facilitate patient access for clinical trial participation, and design and conduct, in collaboration with the Department of Defense, training programs for military ophthalmologists in the latest technologies and diagnostic and treatment regimens.

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Introduction:

The National Neurovision Research Institute (NNRI), the clinical arm of the Foundation Fighting Blindness (FFB), has established the National Eye Evaluation Research (NEER) Network composed of a collaborative group of five Clinical Treatment and Evaluation Centers (CTECs) and a support Clinical Coordinating Center. The intent of this new Network is to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD) through the conduct of clinical trials and other clinically relevant research. The scope of research to be carried out encompasses: (i) Phase I and Phase II clinical trials to evaluate the safety and efficacy of new therapeutic and preventive approaches, including devices, biopharmaceuticals, small molecules, nutritional supplements, and gene transfer approaches; natural history studies to develop standardized criteria to define disease stage, severity and progression; (iii) observational studies to enhance understanding of the natural history of these diseases for different genotypes and phenotypes; and (iv) evaluations of the reliability and validity of different available treatment outcomes measures to determine those that are most appropriate for various genotypes and phenotypes as well as for specific interventions. The NEER Network will also develop standard protocols for data collection, maintain and expand standardized patient databases, classified by patient genotype and phenotype, to allow for the timely identification of eligible patients and facilitate patient access for clinical trial participation, and design and conduct, in collaboration with the Department of Defense, training programs for military ophthalmologists in the latest technologies and diagnostic and treatment regimens.

The military population mirrors the civilian population, including the incidence of retinal diseases. Soldiers and their families therefore suffer from the same sight-robbing retinal degenerative diseases as the general population. In addition, the military has an expanding retiree population that will suffer from age-related macular degeneration (AMD) and any useful preventative or treatment regimen will greatly enhance these persons lives by preventing them from losing vision.

The NEER network, in cooperation with COL Donald A. Gagliano, MD, MHA, DOD Principal Advisor for Vision, Director, DOD/VA Vision Center of Excellence, and others in DOD as appropriate will actively develop a program to include military hospitals and ophthalmologists in clinical trials for Retinal Degenerative Diseases so that military personnel and their families will directly benefit from the new preventions, treatments and cures for these sight robbing diseases. In addition, the NEER network will work with the appropriate military office to develop a fellowship and senior physician training and continuing education program for military ophthalmologists to obtain specialized training at NEER network academic centers in the latest technologies, including non-invasive imaging such as multifocal electroretinogram (mfERG), optical coherence tomography (OCT), and Adaptive Optic Scanning Laser Ophthalmoscopes (AOSLO).

Body:

The National Neurovision Research Institute (NNRI), the clinical arm of the Foundation Fighting Blindness (FFB), has established the National Eye Evaluation Research (NEER) Network composed of a collaborative group of five (5) Clinical Treatment and Evaluation Centers (CTECs). The intent of the NEER Network is to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD). This will be accomplished within the NEER Network through the conduct of clinical trials and other clinically relevant studies. Pertinent background information on the FFB, the NNRI, the retinal diseases to be studied, and the rationale underlying the need for and feasibility of this new Network are delineated below.

The FFB is the world's largest source of non-governmental support for research on inherited orphan retinal degenerative diseases and dry AMD. Since its inception in 1971, the Foundation has raised more than \$370 million and, in the current fiscal year, is providing over \$14.4 million in funding for 138 research grants to more than 100 of the leading basic and clinical research experts in this area at 76 institutions around the world. To promote collaborations between basic and clinical researchers and accelerate the advancement of promising preventive and therapeutic approaches to the clinic, the Foundation also supports 19 national and international Research Centers. This Research Center Program involves inter-disciplinary groups of investigators conducting multiple research projects with an emphasis on translational research to facilitate clinical applications and the sharing of research tools, knowledge and data.

In 2003, the Foundation established the NNRI, a non-profit entity, to capitalize on the fairly recent emergence of therapeutic and preventive products and devices that require rigorous clinical evaluation for safety and efficacy. The mission of the NNRI is to accelerate the translation of promising research on treatment and prevention approaches into clinical trials.

Inherited orphan retinal degenerative diseases are a family of inherited pathologies with the ultimate consequence of photoreceptor death and severe visual impairment usually ending in blindness. In the United States, the total number of individuals affected by retinitis pigmentosa (RP) and other forms of rare inherited retinal degenerative diseases is estimated at approximately 200,000 individuals. RP, Stargardt disease, and Usher syndrome represent the predominant forms of inherited orphan retinal degenerative diseases and are estimated to affect ~80,000 – 100,000, ~25,000, and ~20,000 individuals in the U.S., respectively. Genetic heterogeneity is a key feature of each of these predominant diseases. To date, over 200 genes with mutations causing one or more forms of inherited orphan retinal degenerative diseases have been cloned, and over 50 more have been identified based on candidate gene studies or linkage mapping.

In the majority of inherited orphan retinal degenerative diseases, visual impairment is detected in the first or second decade of life. Assuming that 30% of individuals will reach legal blindness by their third decade of life, 30% by the fourth decade of life, 30% by the fifth decade of life, while 10% never reach legal blindness, and considering just

the annual cost of blindness to the U.S. government, adjusted annually for inflation at a rate of 2.5%, then the cumulative minimal lifetime costs incurred by the U.S. government for the current civilian and military populations affected by inherited orphan retinal degenerative diseases is more than \$38 billion. This tremendous economic burden will not only continue to be incurred, but will increase unless efforts are made to define the molecular, biochemical and clinical parameters of these diseases and to advance capabilities to a point where rational, safe therapeutic strategies can be designed, tested and adopted as standard care.

While repeat evaluation and study of affected patients are vital to rigorously characterize the unique features of various diseases and the factors that cause disease progression, several obstacles, in addition to the lack of research funding, often prevent the necessary frequency and thoroughness of patient examination. First, patients are often diagnosed by ophthalmologists who have limited training in the diagnosis and management of patients with rare forms of inherited orphan retinal degenerative diseases. Second, once patients are informed of the current lack of treatment options for their disease condition, they have little incentive for engaging in repeat clinical evaluations. Third, and perhaps more rare than the diseases themselves, is the number of clinicians fully trained in both the clinical and genetic aspects of inherited orphan retinal degenerative diseases. Training of additional clinical specialists in diagnostic and genetic evaluation of patients with rare forms of inherited retinal degenerative diseases has been identified as one of the most important resources needed to ensure that therapies for these diseases reach the clinic.

While inherited orphan retinal degenerative diseases account for a small portion of all vision loss, dry age-related macular degeneration accounts for approximately 90 percent of all age-related macular degeneration (AMD), affecting over 7 million individuals in the United States alone. With dry AMD, sometimes called atrophic, nonexudative, or drusenoid macular degeneration, yellow-white deposits composed of waste products from photoreceptor cells, called drusen, accumulate in the retinal pigment epithelium (RPE) tissue beneath the macula. For unknown reasons, RPE tissue can lose its ability to process waste and drusen deposits accumulate in the RPE. These deposits are thought to interfere with the function of photoreceptors and the RPE in the macula, causing progressive degeneration of these cells.

Vision loss from dry AMD occurs very gradually over the course of many years. Central vision may even remain stable between annual eye examinations, and individuals with dry AMD do not usually experience a total loss of central vision. However, vision loss may make it difficult to perform tasks that require finely focused vision (e.g., driving or reading). Although there are extensive research efforts to identify treatments for dry AMD, at this time the only proven treatment for late-stage drug AMD is the Age-Related Eye Disease Study (AREDS) antioxidant supplement regimen and stopping smoking and eating healthfully.

Through the research programs conducted with the support of the FFB and, more recently, through the NNRI, and the National Eye Institute of the National Institutes of Health (NIH), basic scientific discoveries have shown that selected nutritional factors, neuroprotective drugs, and gene therapies are safe and can prevent visual loss or restore visual function in preclinical animal models of certain genetically defined forms

of inherited orphan retinal degenerative disease and dry AMD. While AREDS antioxidant formulation is a widely accepted treatment, clinical trials of other potentially more effective treatments are imminent.

Recent progress in the classification of mutations for various inherited orphan retinal degeneration and dry AMD genotypes and the development of treatment possibilities raise the likelihood that potential treatments will be ready for evaluation in clinical trials in the near future. Unfortunately, there are considerable obstacles to the successful conduct of these clinical trials, including:

- lack of resources for the design and conduct of effective and efficient clinical trials for inherited orphan retinal degenerative diseases and dry AMD;
- the limited number and wide geographic distribution of potentially eligible patients across the U.S., making follow up examinations at one clinical center financially and logistically problematic, if not unfeasible;
- the limited number of retinal specialists with expertise in these diseases;
- the use of diverse, non-uniform approaches to measuring disease severity, stage and progression; and
- unresolved methodologic issues, such as determination of clinically meaningful, reliable and valid outcome measures.

The development of a clinical trials network will be an efficient and valuable approach to overcome these obstacles and to maximize the resources currently available. As new interventions become available for clinical evaluation, the creation of such a network will provide the infrastructure necessary to facilitate the initiation and conduct of properly designed clinical trials of investigational therapeutic and preventive approaches and devices in a timely manner. The development of a clinical trials network in inherited orphan retinal degenerations and dry AMD will require the cooperation of an interdisciplinary team with clinical, genetic, and basic science expertise. A recently established clinical trials network for cystic fibrosis provides a paradigm for a similar network for inherited orphan retinal degenerative diseases and dry AMD.

Key Research Accomplishments:

NOTE: In 2010, the NNRI worked with TATRC to apportion the two grants it has received (-0189 and -0720) into consistent expenses. It was submitted and approved by TATRC that the -0189 grant would support the NEER infrastructure while the -0720 grant would support the actual clinical trial and natural history studies, including CTEC costs associated with these functions. The annual reports for both these grants will be the same from the Key Research Accomplishments and Reportable Outcomes perspective as these two grants support the overall operation of the NEER network.

In 2010, the NEER network finalized all CTEC contracts as well as the contracts for the EMMES Corporation, the NEER Clinical Coordinating Center and with the Oregon Health and Science University (OHSU) as the independent image Reading Center for all NEER clinical trials.

The first NEER Network Steering Committee meeting established the requirements for the online protocol submission system and this was implemented during 2010 by EMMES and is open for clinical trial concept proposal submissions for review and if approved, a full proposal may be submitted for full Steering Committee review and approval.

The second NEER Network Steering Committee meeting will take place in December 2010, at which time the committee will review the UCSD/Dr. William Freeman's proposal for natural history studies for inherited orphan retinal degenerations and dry age-related macular degeneration. Dr. Freeman has been piloting this and collecting data so a standardized protocol and data collection can be developed and implemented at all CTECs. Once the Steering Committee has reviewed, commented, and approved the project, all CTECs will implement the project and development of the standardized genotype, phenotype, and imaging database will ensue.

The NEER network has submitted its first clinical trial protocol to HRPO for approval and has answered all questions (A Phase II Multiple Site, Randomized, Placebo-Controlled Trial of Oral Valproic Acid for Retinitis Pigmentosa). NNRI is awaiting final protocol review and HRPO approval for NNRI and the three enrolling clinical sites- the CTEC site at University of Utah and two recruitment sites- Retina Foundation of the Southwest in Dallas and the University of Massachusetts, Worcester. In addition, the NNRI DSMB is meeting at NNRI HQ on November 9, 2010 to review its Charter, the current VPA protocol and its monitoring plan, and discuss its role and functions in all future NEER clinical trials and natural history studies. In addition, NNRI has queried its patient registry for potential participants in the clinical trial and requesting more information from some individuals who might be eligible for this clinical trial.

In preparation for the next clinical trial, NNRI personnel and EMMES are in the process of revising an existing protocol that will be submitted for HRPO review and approval. Also, NNRI and EMMES will be reviewing the existing web-based data collection system implemented for the current about to be enrolling clinical trial to implement for the future clinical trial.

In addition to the above accomplishments, NEER:

1. has negotiated with individual investigators and some biotech companies to have access to new interventional agents to be tested in the NEER network. In addition, the NNRI is funding a gene therapy program with Oxford Biomedica to bring gene therapy for juvenile macular degeneration (Stargardt's disease). This phase I clinical trial will begin in Q1 2011 in the Paris and at the OHSU with NNRI support. The phase II clinical trials will be conducted in the NEER network.
2. Is working with Oxford Biomedica and a separate project with academic investigators on gene therapy for Usher Ib syndrome (deaf-blindness due to a gene defect in a shared gene product) that will use the NEER Network for the phase II clinical trials. The phase I clinical trial from the NNRI-Oxford Biomedica collaboration will begin no later than Q4 2011.
3. NNRI has held multiple clinical investigator meetings to define clinical trial outcomes for orphan inherited retinal degenerative diseases, using juvenile macular degeneration (Stargardt's disease) as a model. These meetings have resulted in a position paper that will guide development of clinical protocol endpoints (i.e. – measures of success) so protocol development in NEER can proceed more quickly. On November 23rd, NNRI is holding the final meeting with selected clinicians to finalize the primary endpoints to be used in the Stargardt's clinical trials. This will include Dr. Paul Sieving, the Director of the National Eye Institute of the National Institutes of Health.

Reportable Outcomes:

The NNRI NEER Network:

- has submitted its first clinical trial protocol to HRPO for approval and has answered all questions. NNRI is awaiting final protocol review and HRPO approval for NNRI and the three sites- the CTEC site at University of Utah and two recruitment sites- Retina Foundation of the Southwest in Dallas and the University of Massachusetts, Worcester. The protocol is to test a FDA approved drug (valproic acid) in individuals with autosomal dominant retinitis pigmentosa, with the ability to expand the enrollment to individuals with autosomal recessive retinitis pigmentosa.
- is working with investigators to write protocol for next NEER clinical trial, which will test an over 3000 year old Chinese medicine that has been demonstrated to be neuroprotective in retinitis pigmentosa.
- developed standard protocols for data collection that can be used in multiple studies of inherited orphan retinal degenerative diseases and dry AMD;
- established and maintains a patient databases, classified by genotype and phenotype, to allow for the timely identification of eligible patients and to facilitate patient access for participation in clinical trials for specific genotypes and phenotypes.

- executed a contract with the EMMES Corporation, a clinical research support organization (<http://www.emmes.com>) for the NEER network and Western IRB (WIRB) to be the NNRI IRB of record for all clinical trials conducted in the NEER Network.

EMMES is providing the following administrative and statistical support services for the National Neurovision Research Institute (NNRI) National Eye Evaluation Research (NEER) Network:

- Participate in NEER Network Steering Committee meetings and provide statistical and design input on Concept Proposals for clinical trials/studies.
- Develop procedures and a web-based system for submission and review of Concept Proposals.
- Assist NNRI and the NEER Network Steering Committee in the development of a complete set of network policies.
- Conduct qualification visits for the Clinical Treatment and Evaluation Centers (CTECs) which may include GCP and GLP compliance assessments and training and certification in ETDRS Visual Acuity and Refraction.
- Provide clinical study infrastructure tools such as document templates, core data elements, reporting requirements, and study procedures.

NNRI has also contracted with Western Institutional Review Board (Western IRB; WIRB) to be the NNRI/NEER IRB of record for all clinical trials and studies.

Conclusion:

While negotiations with the individual CTEC institutions took much longer than anticipated, they are concluded and all CTECs are on board for NEER participation. In addition, the NNRI has implemented infrastructure support for the network (EMMES as the NEER Network Clinical Coordinating Center [NNCCC] and WIRB as the IRB of record for the NEER Network. Also, NNRI has continued to convene working groups of clinicians to define clinical trial parameters for inclusion/exclusion and endpoints for clinical trials in inherited retinal degenerations expected to be implemented in the NEER Network within the first year. The first meeting will take place on November 23, 2010 at NNRI HQ to gain agreement on the primary endpoint and secondary endpoints to be used in clinical trials or interventions for Stargardt's disease (Juvenile macular degeneration). The NNRI and NEER, in conjunction with the National Eye Institute (NEI, NIH), will be hosting a meeting with the FDA to review the proposed endpoints. This meeting will be the example for future meetings with the FDA to educate them on the current clinical consensus on endpoints that make sense for clinical trials in inherited orphan retinal degenerations.

The most exciting development in 2010 is the impending implementation of the first NEER network clinical trial (pending final HRPO approval) and the development of the next protocol to be implemented in the NEER network. Besides these two, the NNRI is working with both academic investigators and biotech companies on very promising leads for the third clinical trial for the NEER network. It is anticipated that by the end of 2011 to the beginning of 2012, the NEER network will have three active clinical trials enrolling participants and at natural history studies ongoing at all CTECs.

References:

1. Cideciyan AV, Aleman TS, Boye SL, et al. Human gene therapy for RPE65 isomerase deficiency activates the retinoid cycle of vision but with slow rod kinetics. *Proc Natl Acad Sci U S A*. 2008;105:15112-15117.
2. Hauswirth W, Aleman TS, Kaushal S, et al. Phase I Trial of Leber Congenital Amaurosis due to RPE65 Mutations by Ocular Subretinal Injection of Adeno-Associated Virus Gene Vector: Short-Term Results. *Hum Gene Ther*. 2008.
3. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Engl J Med*. 2008;358:2240-2248.
4. Bainbridge JW, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. *N Engl J Med*. 2008;358:2231-2239.

Appendices:

- NEER web site home page
- NEER Concept Proposal Instructions
- NEER Concept Proposal application web site screen
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- NEER Full application submission web page
- VPA clinical trial abstraction
- VPA clinical trail Data Safety and Monitoring plan
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Welcome

The National Neurovision Research Institute (NNRI) of the Foundation Fighting Blindness (FFB) has established the Clinical Treatment and Evaluation Centers (CTECs) of the National Eye Evaluation Research (NEER) Network to conduct clinical trials and other clinical studies in persons with inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD).

Scope of NEER Network Clinical Research:

- single and multi-site Phase I and Phase II clinical trials to evaluate the safety and efficacy of new therapeutic and preventive strategies, including, but not limited to, the use of devices, biopharmaceuticals, small molecules, nutritional supplements, and gene transfer approaches;
- natural history studies to develop standardized criteria to define disease stage, severity and progression;
- observational studies to enhance understanding of the natural history of inherited orphan retinal degenerations for different genotypes and phenotypes;
- evaluation of the reliability and validity of the different treatment outcomes measures available to determine those that are most appropriate for various genotypes and phenotypes as well as for specific interventions;
- development of standard protocols for data collection for use across multiple clinical studies and clinical trials of retinal degenerative diseases; and
- establishment of new or expansion of existing patient databases, classified by genotype and phenotype, to allow for the timely identification of eligible patients and to facilitate patient access for participation in clinical trials for specific genotypes and phenotypes

This website serves as the central resource for attaining NEER Network Policies and Study Document Templates, submitting Concept Proposals and Full Applications to NNRI, and accessing pertinent information related to the Steering Committee. For further information about each of these, click on the links to the left.



National Neurovision Research Institute

National Eye Evaluation Research (NEER) Network

**Instructions for the Preparation and Submission of
Concept Proposals for NEER Network Clinical Trials**

**Version 1.0
December 24, 2009**

1. INTRODUCTION

1.1 Overview

A critical component of the research activities of the NEER Network involves the design and conduct of Phase I and Phase II clinical trials to evaluate the safety and efficacy of investigational products and approaches for the treatment and prevention of inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD). The NEER Network uses a two-staged process for determining the most promising clinical trials to be supported.

- Stage 1 involves the submission and review of **Clinical Trial Concept Proposals** providing NNRI with a brief description of the key study features and rationale as a basis for determining those concepts approved for further development.
- Stage 2 involves the submission and review of **Full Applications** providing the detailed information necessary to evaluate fully scientific soundness, feasibility and costs, and to determine those clinical trials that will be supported. **NOTE:** Full Applications for NEER Network clinical trials will be accepted only for Concept Proposals approved for further development by NNRI.

This document provides instructions for the preparation and submission of Concept Proposals for NEER Network clinical trials. The Clinical Trial Concept Proposal form is located on the NNRI NEER Network website (www.neernetwork.org). Separate detailed instructions and forms for Clinical Trial Full Applications are also located on the NNRI NEER Network website.

1.2 Inquiries:

Please address all inquiries regarding Clinical Trial Concept Proposals to the NNRI Project Officer, Stephen M. Rose, 11435 Cronhill Drive, Owings Mills, MD 21117-2220, 800.683.5555 or 410.568.0125, fax #: 410.363.4692, e-mail: srose@fightblindness.org.

1.3 Concept Proposal Submission:

Please complete all sections of the Clinical Trial Concept Proposal form and submit, via e-mail and in PDF format, to the NEER Network Clinical Coordinating Center (NNCCC) at neer@emmes.com.

2. INSTRUCTIONS FOR THE PREPARATION OF CLINICAL TRIAL CONCEPT PROPOSALS

To facilitate the preparation of Clinical Trial Concept Proposals, the majority of instructions provided below are also contained on the Concept Proposal form.

Section 1: Clinical Trial Summary Information

- A. *Items 1, 2, 3 and 4:* Provide the full title of the proposed clinical trial, a short title that can be used to easily identify the trial, and identify the phase and disease indication.
- B. *Items 5 and 6:* Identify the Lead Clinical Treatment and Evaluation Center (CTEC), Lead CTEC Principal Investigator (PI), and the Clinical Trial Director (if different from the Lead CTEC PI). The Clinical Trial Director is the individual responsible for the conduct of the clinical trial at the Lead CTEC institution and for the coordination and oversight of the clinical trial at all participating clinical sites.
- C. *Item 7 – Designation of Specific Types of Clinical Trials:* Designate whether the proposed clinical trial involves any of the following:
- gene therapy
 - first in humans
 - investigational products/devices with a high risk profile
- The Department of Defense (DOD) requires a second level of review for clinical protocols in any of these 3 categories and, therefore, NNRI needs to be apprised if these types of clinical trials are being proposed.
- D. *Items 8 and 9:* Indicate the total targeted enrollment for the proposed clinical trial and the total number of proposed clinical sites.
- E. *Item 10 – Listing of Proposed Clinical Sites:*
- (a) List each CTEC institution proposed to participate as a clinical site.
 - (b) If applicable, provide a justification for the exclusion of any CTEC institutions as participating clinical sites.
 - (c) If applicable, list the name and location of each non-Network institution/organization proposed to participate as a clinical site.

NOTE: By listing proposed CTEC and non-Network clinical sites, the PI of the Lead CTEC institution affirms that (i) the proposed clinical trial has been discussed with the other CTEC PIs or lead investigators for non-Network institutions/organizations, and (ii) these individuals agree to participate in the proposed clinical trial contingent upon NNRI approval to move to the Full Application stage, NNRI approval of the Full Application, and local Institutional Review Board (IRB) approval.

- F. *Item 11 – Clinical Trial Duration:* Indicate the estimated duration of the proposed clinical trial defined as the time from initiation of recruitment to the last subject visit.

Section 2: Concept Proposal Summary Description

Briefly describe, in no more than 200 words, the rationale, objectives and significance of the proposed clinical trial.

Section 3: Detailed Clinical Trial Description

The detailed clinical trial description consists of the following 5 sections:

3.1 Scientific Rationale:

- (a) Briefly describe the theoretical and/or biological basis for the proposed clinical trial and its clinical significance, expected outcomes and anticipated benefits.
- (b) Include all available pre-clinical and clinical data used to support the scientific rationale. **NOTE:** Up to 5 references for supporting pre-clinical and clinical data may be provided in Section 4.
- (c) Provide a brief description of the investigational product(s)/device(s) proposed and their stage of development.

3.2 Study Objectives and Outcomes: Provide brief descriptions of the following:

- (a) the primary study objective, the primary study outcome, and the methods/measures for assessing the primary outcome; and
- (b) up to 2 secondary objectives and secondary outcomes, and the methods/measures to assess secondary outcomes.

3.3 Study Population: Describe and provide the rationale for the proposed study population, including any exclusions based on age, gender and/or disease stage.

3.4 Overall Study Design: Identify the key design features of the proposed clinical trial, including:

- (a) total sample size and sample size justification, including a brief description of the statistical methods or power considerations used to calculate total sample size;
- (b) randomization, if applicable;
- (c) level of masking, if applicable;
- (d) number and brief description of study arms/groups, if applicable; and
- (e) number and brief description of control group(s), if applicable.

3.5 Assessment of Serious Adverse Events (SAEs):

- (a) Briefly describe all expected, protocol-specific SAEs.

- (b) Identify the clinical evaluations to be used to diagnose each expected SAE and state how often these evaluations will be performed.
- (c) Briefly describe safety findings that would temporarily suspend enrollment and/or study intervention.

Section 4: Additional Concept Proposal Information

This section of the Concept Proposal consists of the following 4 components:

4.1 References: Provide up to 5 references for pre-clinical and clinical data supporting the scientific basis and rationale for the proposed clinical trial. Reprints corresponding to each citation **are required** to be included as attachments to the Concept Proposal.

4.2 Access to Study Subjects:

- (a) List all sources to be used to identify and recruit subjects by the proposed clinical sites.
- (b) Provide an estimate of the approximate number of eligible subjects for all proposed clinical sites combined.

4.3 Investigational Product/Device Information: Provide the following information for each investigational product/device:

- (a) name of manufacturer;
- (b) arrangements/agreements required to ensure provision of the investigational product/device for the proposed clinical trial;
- (c) IND/IDE status;
- (d) IND/IDE sponsor; and
- (e) any intellectual property issues, e.g., pending patents, patent infringements, that may prevent or delay clinical trial implementation.

4.4 Ethical Considerations: Briefly describe the potential risks and benefits for subjects participating in the proposed clinical trial.

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Concept Proposal

The NEER Network uses a two-staged process for determining the most promising clinical trials to be supported.

Stage 1 involves the submission and review of **Clinical Trial Concept Proposals** providing NNRI with a brief description of the key study features and rationale as a basis for determining those concepts approved for further development.

Stage 2 involves the submission and review of Clinical Trial Full Applications. See Full Application Submission link for further information on Stage 2.

Concept Proposal Documents

Instructions Document: The Instructions document provides instructions for the preparation and submission of Concept Proposals for NEER Network clinical trials.

Concept Proposal form: The completed form should be submitted, via e-mail and in PDF format, to the NEER Network Clinical Coordinating Center at neer@emmes.com.

[Instructions](#)

[Concept Proposal Form](#)



National Eye Evaluation Research (NEER) Network Clinical Trial Concept Proposal Form

Date Submitted:

Section 1: Clinical Trial Summary Information

1. Clinical Trial Full Title:
2. Clinical Trial Short Title:
3. Phase:
4. Disease Indication:
5. Lead CTEC Institution:
6. a. Name of Lead CTEC Principal Investigator: b. Clinical Trial Director Name, Title and Institution:
7. Designation of Specific Types of Clinical Trials: <i>(check all that apply)</i>
<input type="checkbox"/> gene therapy <input type="checkbox"/> first in humans <input type="checkbox"/> investigational products/devices with a high risk profile
8. Total Targeted Enrollment:
9. Total Number of Proposed Clinical Sites:
10. Listing of Proposed Clinical Sites:
A. CTEC Clinical Sites: 1. <i>List the name of each CTEC institution proposed to participate as a clinical site.</i>

2. *Provide a justification for exclusion of any CTEC institution as a participating clinical site.*

B. *Non-Network Clinical Sites: List the name and location of each proposed non-Network clinical site, if applicable*

11. *Clinical Trial Duration: Indicate the estimated duration of the proposed clinical trial from initiation of recruitment to last subject visit.*

Years

Months

Section 2: Concept Proposal Summary Description: *Briefly describe, in no more than 200 words, the rationale, objectives and significance of the proposed clinical trial.*

Section 3: Detailed Clinical Trial Description

Describe the following key features of the proposed clinical trial.

3.1 Scientific Rationale: *Provide a brief description of the theoretical and/or experimental biological basis for the proposed clinical trial and its clinical significance, expected outcomes and anticipated benefits. Include all available pre-clinical and clinical data used to support the scientific rationale. Also include a brief description of the investigational product(s)/device(s) proposed and their stage of development. NOTE: Up to 5 references for supporting pre-clinical and clinical data may be provided in Section 4. Reprints for all supporting data are required.*

3.2. Study Objectives and Outcomes: *Provide brief descriptions of (a) the primary study objective, the primary study outcome, and methods/measures for assessing the primary outcome; and (b) up to 2 secondary objectives and secondary outcomes, and the methods/measures to assess secondary outcomes.*

Primary Study Objective:

Primary Study Outcome:

Methods/Measures for Assessing Primary Outcome:

Secondary Study Objective #1:

Secondary Study Outcome #1:

Methods/Measures for Assessing Secondary Outcome #1:

Secondary Study Objective #2:

Secondary Study Outcome #2:

Methods/Measures for Assessing Secondary Outcome #2:

3.3 Study Population: Describe and provide the rationale for the proposed study population, including any exclusions based on age, gender and/or disease stage.

3.4 Overall Study Design: Identify the key design features of the proposed clinical trial, including: (a) total sample size and sample size justification, including a brief description of the statistical methods or power considerations used to calculate total sample size; (b) randomization, if applicable; (c) level of masking if applicable; (d) number and brief description of study arms/groups, if applicable; and (e) number and brief description of control groups, if applicable.

3.5 Assessment of Serious Adverse Events (SAEs): *Provide brief descriptions of: (a) all expected, protocol-specific SAEs; (b) the clinical evaluations to be used to diagnose each expected SAE; and (c) how often these evaluations will be performed. In addition, identify the safety findings that would temporarily suspend enrollment and/or study intervention.*

Note: A serious adverse event is defined as any adverse therapy experience occurring at any dose that meets one or more of the following criteria: 1) Death, 2) Life-threatening, 3) In-patient or prolongation of existing hospitalization, 4) Persistent or significant disability or incapacity or 5) Congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Section 4: Additional Concept Proposal Information

4.1 References: *Provide up to 5 references for pre-clinical and clinical data supporting the scientific basis and rationale for the proposed clinical trial. Reprints for all references are required.*

4.2 Access to Study Subjects: *List all sources to be used to identify and recruit subjects by the proposed clinical sites, including CTEC institutional facilities, referrals and patient registries, and provide an estimate of the approximate number of eligible subjects at all proposed clinical sites combined.*

Sources for subject identification and recruitment:

Approximate number of eligible subjects:

4.3 Investigational Product/Device Information: *For each investigational product/device, provide the following information: (a) name of manufacturer; (b) arrangements/agreements required to ensure provision of the investigational product/device for the proposed clinical trial; (c) IND/IDE status, e.g., new or amended IND/IDE required; (d) IND/IDE sponsor; and (e) identification of any intellectual property issues, e.g., pending patents, patent infringements, that may prevent or delay implementation of the proposed clinical trial.*

4.4 Ethical Considerations: *Briefly describe the potential risks and benefits for subjects participating in the proposed clinical trial.*

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Full Application Submission

The NEER Network uses a two-staged process for determining the most promising clinical trials to be supported.

Stage 1 involves the submission and review of Clinical Trial Concept Proposals. See [Concept Proposal](#) link for further information on Stage 1.

Stage 2 involves the submission and review of **Clinical Trial Full Applications** providing the detailed information necessary to evaluate fully scientific soundness, feasibility and costs, and to determine those clinical trials that will be supported.

Full Application Documents

Instructions Document: The Instructions document provides detailed instructions for the preparation of Full Applications for NEER Network clinical trials and pertains only to clinical trials for which initial Concept Proposals have been approved for further development.

Clinical Facilities and Equipment Template and Instructions: In the setting of a multi-site clinical trial, the Lead CTEC will need to obtain information from each participating site regarding the specific facilities and equipment each site has available. The template can be used by the Lead CTEC to facilitate the collection of this information.

Cover Page: For each proposed clinical site, including the Lead CTEC, the "NEER Network Clinical Trial Cover Page for a Participating Site" must be completed and signed by the CTEC PI or Lead Clinical Investigator for a non-Network clinical site (if proposed) and the institution's authorizing official. The signed Full Application Cover Pages are to be sent via e-mail, in PDF format, to the NNRI Project Officer, Stephen M. Rose, Ph.D., at srose@fightblindness.org.

[Instructions](#)

[Facilities/Equipment Template](#)

[Facilities/Equipment Instructions](#)

[Cover Page](#)

Full Application Submission System

NNRI and the NEER Network Clinical Coordinating Center have developed an electronic system for the preparation and submission of Clinical Trial Full Applications. The Full Application System is accessible via the World Wide Web using Internet Explorer 5.5 or higher. Access to this system is password protected.

Project Title

A Phase II Multiple Site, Randomized, Placebo-Controlled Trial of Oral Valproic Acid for Retinitis Pigmentosa Protocol #H-13371

Protocol Amendment 2, October 20, 2010

Trial Sites, Site Principal Investigators and Key Personnel

University of Massachusetts Worcester

Shalesh Kaushal, M.D., Ph.D., Principal Investigator
Chair and Associate Professor
Department of Ophthalmology
University of Massachusetts Medical Center
Biotech 5, Suite 250
381 Plantation Street
Worcester, MA 01605
Email: Shalesh.kaushal@umassmemorial.org
Phone: 508-334-8002
Fax: 508-334-4655
FWA: 00004009

Radouil Tzekov, M.D., Ph.D., Co-Principal Investigator

Senior Research Scientist
Department of Ophthalmology
University of Massachusetts Memorial Center
55 Lake Avenue
North Worcester, MA 01655
Email: Radouil.Tzekov@umassmed.edu
Phone: 508-856-8989
Fax: 508-334-4655
FWA: 00004009

George Peters, M.D., Co-Investigator

Ophthalmologist
Department of Ophthalmology
University of Massachusetts Memorial Center
55 Lake Avenue
North Worcester, MA 01655
Email: George.Peters@umassmed.edu
Phone: 508-856-8989
Fax: 508-334-4655
FWA: 00004009

George Asdourian, M.D., Co-Investigator

Ophthalmologist
Department of Ophthalmology
University of Massachusetts Memorial Center

55 lake Avenue
North Worcester, MA 01655
Email: George.Asdourian@umassmed.edu
Phone: 508-856-8989
Fax: 508-334-4655
FWA: 00004009

Retina Foundation of the Southwest (RFSW)

David G. Birch, Ph.D., Principal Investigator
Chief Scientific and Operating Officer
Director, Rose-Silverthorne Retinal Degeneration laboratory
Retina Foundation of the Southwest
Adj. Professor of Ophthalmology
Director, Visual Electrophysiology
University of Texas Southwestern Medical School
9900 North Central Expressway, Ste. 400
Dallas, TX 75231
Email: dbirch@retinafoundation.org
Phone: 214-363-3911, Ext 105
Fax: 214-363-4538
FWA: 00005004

Dr. Karl Csaky, M.D., Ph.D., Medically Responsible Investigator
Retina Foundation of the Southwest and Texas Retina Associates
9900 N. Central Expressway, #400, Dallas TX 75231
E-mail: kcsaky@retinafoundation.org
Phone: 214 363-3911, Ext 137
Fax: 214 363-3911
FWA: 00005004

Gary Edd Fish, MD, JD, Co-Investigator
Texas Retina Associates
7150 Greenville Avenue, # 400, Dallas, Texas 75231
Phone: 214-692-6941
FWA: 00005004

Neal L Sklaver, MD, FACP, Co-Investigator
Medical Specialists Associated
5461a Sierra Drive, Dallas, Texas 75231
Phone: 214-692-8541
FWA: 00005004

Dianna K. Hughbanks-Wheaton, MS, PhD, CHES, Co-Investigator
Retina Foundation of the Southwest
9900 N. Central Expressway, # 400, Dallas, Texas 75231
Phone: 214-363-3911x134
FWA: 00005004

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Amendment 2, October 20, 2010

University of Utah School of Medicine, Moran Eye Center

Paul S. Bernstein, M.D., Ph.D., Principal Investigator

Mary Boesche Professor of Ophthalmology and Visual Sciences

Moran Eye Center

University of Utah School of Medicine

65 Mario Capecchi Drive

Salt Lake City, Utah 84132

Email: paul.bernstein@hsc.utah.edu

Phone: 801- 581-6078

Fax: 801- 581-3357

FWA: 00003745

Mary Elizabeth Hartnett, MD, Co-Investigator

Moran Eye Center

University of Utah School of Medicine

65 Mario Capecchi Drive

Salt Lake City, Utah 84132

Email: me.hartnett@hsc.utah.edu

Fax: 801- 581-3357

FWA: 00003745

Judith Warner, MD, Co-Investigator

Moran Eye Center

University of Utah School of Medicine

65 Mario Capecchi Drive

Salt Lake City, Utah 84132

Email: judith.warner@hsc.utah.edu

Phone: 801- 581-6078

Fax: 801- 581-3357

FWA: 00003745

Michael P. Teske, MD, Co-Investigator

Moran Eye Center

University of Utah School of Medicine

65 Mario Capecchi Drive

Salt Lake City, Utah 84132

Email: mike.teske@hsc.utah.edu

Phone: 801- 585-6639

Fax: 801- 581-3357

FWA: 00003745

Albert Vitale, MD, Co-Investigator

Moran Eye Center

University of Utah School of Medicine

65 Mario Capecchi Drive

Salt Lake City, Utah 84132

Email: albert.vitale@hsc.utah.edu

Phone: 801- 585-6640

NNSP-CL-0510-00001-UMA-NER-VPA
Amendment 2, October 20, 2010

Fax: 801- 581-3357
FWA: 00003745

Deborah Harrison, M.S., Clinical Coordinator
Department of Ophthalmology and Visual Sciences
Moran Eye Center
University of Utah School of Medicine
65 Mario Capecchi Drive
Salt Lake City, UT 84132
Email: deborah.harrison@hsc.utah.edu
Phone: 801-585-6645
Fax: 801-587-7712

Medical Monitor and Clinical Coordination

EMMES

Robert Lindblad, M.D., Medical Monitor
401 N. Washington Street, Suite 700
Rockville, MD 20850
Phone: 301-251-1161, Ext.
Fax: 301-251-1355
Email: rlindblad@emmes.com

Paul VanVeldhuisen, Ph.D., Principal Investigator
NEER Network Coordinating Center
Phone: 301-251-1161, Ext. 143
Fax: 301-251-1355
Email: pvanveldhuisen@emmes.com

Jennifer Bacik, M.S., Co-Principal Investigator
NEER Network Coordinating Center
Phone: 301-251-1161, Ext. 2829
Fax: 301-251-1355
Email: jbacik@emmes.com

Maria Figueroa, M.B.A., Project Manager
NEER Network Coordinating Center
Phone: 301-251-1161, Ext. 156
Fax: 301-251-1355
Email: mfigueroa@emmes.com
FWA: 00000040

Trial Laboratory Facilities – Genetic Testing Laboratory

GeneDx
207 Perry Parkway
Gaithersburg, MD 20877
Phone: 301-519-2100
Fax: 301-519-2892
Sherri Bale, Ph.D., FACMG, Co-President and Clinical Director
Email: sherrib@genedx.com
Nizar Smaoui, M.D., FACMG, Associate Medical Director and Director, Division of Inherited Eye Disease
Email: Nizar@genedx.com

Trial Laboratory Facilities – Local Labs Supporting Trial Sites

Celeste Vardaman, M.D.
Lab Corp of American Clinical lab
7777 Forest Lane Suite C350
Dallas, TX 75230
Phone: 800-788-9892

UMass Memorial Medical Center
University and Hahnemann Campus Hospital Laboratories
365 Plantation Street Suite 200
Biotech 1 Department of Hospital Laboratories
Worcester, MA 01655

Edward R. Ashwood, M.D.
President and CEO,
ARUP Laboratories
500 Chipeta Way
Salt Lake City, UT 84108
Phone: 801-583-2787

Central Reading Center

Richard G. Weleber, M.D., Professor, Director, Oregon Retinal Degeneration Center
Casey Eye Institute
Oregon Health and Science University
3375 SW Terwilliger Boulevard
Portland, OR 97239
E-mail: weleberr@ohsu.edu
Phone: 503-494-8386
Fax 503-494-6864
FWA: 00000161

Peter Francis, M.D., Ph.D., Associate Professor

Casey Eye Institute
Oregon Health and Science University
3375 SW Terwilliger Boulevard
Portland, OR 97239
Email: francisp@ohsu.edu
Ph: 503-418-1627
Fax: 503-494-7233
FWA: 00000161

Total enrollment: 90 subjects
Expected initiation: Q4 2010
Expected Duration: Twenty-Four months from first-subject-in to last-subject-out.
Recruitment: 9 months (last-subject-in).
Treatment: 360 days of oral valproic acid. Follow up: 3 months after last treatment
Investigational New Drug Application Number: 106,187
Sponsor: Shalesh Kaushal, M.D., Ph.D.

Funding for this study is provided by the Department of Defense (DOD)
Telemedicine and Advanced Technology Research Center (TATRC)

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1 BACKGROUND AND RATIONALE

Retinitis Pigmentosa (RP) is a severe neurodegenerative disease of the retina characterized initially by night blindness with progression to tunnel vision and eventual loss of central vision and total blindness. Targeted therapies for RP are complicated by the identification of more than 30 genes identified being responsible for dominant and recessive forms of the disease and many more linked to RP but not identified. Further compounding this complexity is the rarity of this disorder: although RP is one of the most common inherited eye diseases with an incidence of ~1:3000, its prevalence is relatively rare. RP affects approximately 100,000 individuals in the U.S., qualifying it as an orphan disease. Given the huge costs associated with the preclinical and clinical phases of drug development, pharmaceutical companies are generally reluctant to invest in developing new therapeutics for RP. While a few new approaches for RP treatment have recently been investigated including nutritional supplementation, light reduction and gene therapy (Delyfer et al., 2004; Gaby, 2008; Hartong et al., 2006), of these, vitamin A supplementation is the most promising, but its benefits are modest and side effects are problematic. Therefore, currently there is no FDA approved therapy to substantially alter or reverse the progression of RP.

2 SCIENTIFIC RATIONALE

Recently, we have demonstrated the use of retinoids and other small molecules as pharmacological chaperones to increase the yield of properly folded RP mutant rhodopsins in heterologous cell culture (Noorwez et al., 2008). We have tested whether other known small molecules can provide similar effects. We identified valproic acid (VPA) through this screen. In vitro data supports that VPA has multiple biologic properties that make it an ideal candidate for a retinal therapeutic. First, our in vitro assay shows that VPA effectively increases yields of properly folded mutant rhodopsin (Figure 1, Appendix A. Pre-Clinical Data). Second, VPA protects cells from oxidative stress induced apoptosis (Figure 2, Appendix A. Pre-Clinical Data), most likely through upregulation of the heat shock response (not shown). Other work demonstrates that VPA is a potent inhibitor of histone deacetylase (HDAC) (Gottlicher et al., 2001) and the inflammatory response pathway via apoptosis of microglial cells (Chen et al., 2007; Draganow et al., 2006; Kim et al., 2007).

2.1 PRELIMINARY CLINICAL DATA

Seven RP patients were treated off-label with oral VPA (250 mg BID) for durations of between three and five months during a pilot study. Visual fields were measured using kinetic perimetry (Figure 3, Appendix B. Pilot clinical study). Results varied from patient to patient, however 6 of 7 patients showed no progression of their disease on VPA, one patient experienced a loss of VF and 5 patients experienced an increase in their visual field (e.g. Figure 3, Appendix B), which no other therapeutic has previously shown. Overall, we detected an average increase in visual field/month (Figure 4, Appendix B. Pilot clinical study). These results suggest that VPA has the potential to not only stop the progression but may also reverse loss of visual field.

3 STUDY OBJECTIVES

RP is an incurable and untreatable group of heterogeneous retinal degenerative diseases that cause severe visual loss. There is currently no therapeutic that substantially slows the progression of this disease, and certainly none that can restore vision in RP patients. The objectives of this study are to evaluate the efficacy of VPA to both slow the progression of visual function loss and/or to restore visual function in patients with RP and to collect safety and tolerability information.

Our specific aims are as follows:

1. To compare the degree of improvement in visual function in subjects who receive VPA versus those who receive a placebo.

We hypothesize that subjects who receive VPA will have a greater degree of improvement in visual function than those who receive a placebo. The primary outcome measure is the change in visual field area (VFA) at 52 weeks as compared to baseline. We will compare mean change in VFA between the two groups. Secondary

outcome measures used to address this aim include change between baseline and 52 weeks in the following measures:

- a. Static perimetry volumetric measurements of the full field, including the central 30° field
 - b. Best corrected visual acuity as measured by EVA-ETDRS
 - c. Color contrast sensitivity as measured by the Chroma Test
 - d. Peak ERG amplitude
 - e. Central macular thickness and macular volume as measured by SD-OCT
 - f. Fundal appearances
 - g. Total score on vision-related quality of life as measured by the NEI-VFQ25
2. To assess the safety profile of a one-year course of VPA.
We will address this aim by evaluating the incidence of adverse events and changes from baseline in clinical chemistry and physical examinations in subjects who receive VPA compared to those who receive a placebo.

4 STUDY DESIGN AND METHODS

This is a three-site, interventional, prospective, randomized, placebo-controlled, double-blinded study of 90 subjects undergoing 12 months of therapy with oral VPA. The study population will be comprised of male and female patients who have been diagnosed with autosomal dominant retinitis pigmentosa (adRP) and who meet the inclusion/exclusion criteria outlined in section 4.3. Patients who have been genotyped autosomal dominant for RP prior to their baseline visit will undergo clinical examinations and evaluations of retinal function and structure to determine whether the subject is eligible. Clinical examinations will include refraction, static and kinetic perimetry, fundus photography and visual acuity. Measures of visual function will include full-field electroretinography. Spectral-Domain Optical Coherence Tomography (SD-OCT) will be used to measure retinal structure. Methods of these measures are detailed below. During these evaluations, medical and ophthalmic histories will be elicited from subjects and their families to ensure that there are no comorbid medical or ocular genetic conditions that may prevent study participation. While the equipment proposed for use in this trial is state of the art and as such will provide the highest level of quantitation available, the quasi-subjective nature inherent in many standard ocular tests make day-to-day variation an important confounder to our analysis. All diagnostic measures will be calibrated and standardized such that intervisit and interocular variances for each outcome measure will be quantified and included in our analysis. This will involve sequential repeated measures for the same patients on these machines.

The study design flow chart can be found in Appendix C. Study Schedule Flow-chart.

4.1 STUDY POPULATION

It is likely, given the vastly different nature of the proteins involved in RP, that certain therapies will have varying beneficial effects on patients with different genetic mutations. Indeed our preliminary clinical analysis suggests a varied response to VPA among the 7 RP patients treated (Figure 4, Appendix B. Pilot clinical study), and indicates that certain individual or patient populations may preferentially respond to this medication. Patients included in this preliminary clinical analysis were not well characterized in regards to their RP genotype. Current evidence suggests VPA may be beneficial to patients with an autosomal dominant pedigree. Therefore, enrollment will be restricted to genotyped autosomal dominant RP until there is substantial preclinical evidence to expand treatment into other subpopulations of RP (e.g., X-linked or autosomal recessive). A protocol amendment and IRB approval would be needed prior to redefining the population of RP patients being studied.

The genotyping in families with autosomal dominant pedigrees will be done through a qualified CLIA-certified laboratory (e.g. GeneDx). Genotyping of autosomal dominant patients is a prerequisite for this study. If prior documentation does not exist documenting the subject's genotype, blood samples will be collected after informed consent is obtained and will be shipped to a qualified CLIA-certified genotyping laboratory where they will be screened for the most common RP mutations. Due to the rarity and sporadic nature of the many mutations associated with RP, it is likely that specific

mutation information will not be identified for over half of the screened patients. If the genotyping does not definitely confirm that the subject is autosomal dominant for RP, the subject will not be eligible for the study.

DATA AND SAFETY MONITORING PLAN

**"A Phase II Multiple Site, Randomized, Placebo-Controlled Trial
of Oral Valproic Acid for Retinitis Pigmentosa Protocol #H-13371"**

DRAFT

July 9, 2010

Version 0.3

Prepared and distributed by:
The NEER Coordinating Center
The EMMES Corporation
Rockville, Maryland

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DATA AND SAFETY MONITORING PLAN

The data and safety monitoring plan for the study "A Phase II Multiple Site, Randomized, Placebo-Controlled Trial of Oral Valproic Acid for Retinitis Pigmentosa Protocol #H-13371" is intended to describe processes in place to ensure both the safety of study participants and the validity and integrity of data collected and reported in this NNRI-sponsored clinical trial. More detailed information on the processes in place for the protocol can be found in the Manual of Operations.

1 SAFETY MONITORING

1.1 Data and Safety Monitoring Board (DSMB) Responsibilities

An independent NNRI-appointed DSMB will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data by examining accumulating data to assure protection of patients' safety while the study's scientific goals are being met. Following a review, the DSMB will determine whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Adverse event data and other data intended for safety monitoring will be reported via reports from the Coordinating Center through NNRI to the DSMB. After each DSMB meeting, recommendations will be communicated to NNRI in a summary report and this report in turn will be provided to the Principal Investigators at each participating site so that evidence of a DSMB review can be conveyed to each IRB involved in the study.

Because the Valproic Acid has been associated with serious hepatotoxicity, rapid progression of pancreatitis, and birth defects, guidelines have been developed such that if any of the following conditions are met, enrollment would be suspended and a detailed data review by the DSMB would be performed:

- Liver Function Tests greater than 5 times the normal limit without an infectious disease etiology
 - 2 cases within the first 10 study participants or 5 cases overall
- Grade 3 Pancreatitis using Common Terminology Criteria for Adverse Events v3.0
 - 2 cases within the first 10 study participants or 5 cases overall
- Pregnancies while on study medications
 - 2 cases within the first 10 female study participants of child-bearing potential or 5 cases overall

Given the relatively small sample size, short duration of the study and needs for precise estimation of multiple outcome measures, no formal interim efficacy inspection that would suggest early termination of the study is planned.

Details on the membership of the DSMC, the frequency of meetings, and the processes describing the decisions of the DSMC are provided in a separate DSMC charter.

1.2 Participating Site Principal Investigator (PI) Responsibilities

Each participating site's PI is responsible for study oversight, including ensuring human research protections by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

1.3 Coordinating Center Medical Monitor Responsibilities

A central Medical Monitor at the Coordinating Center will continuously monitor safety information provided by each site throughout the trial. All serious adverse events will be reviewed at the time they are reported. The medical monitor will also indicate concurrence or not with the details of the report provided by the site principal investigator. Reviews will be conducted in AdvantageEDCSM data management system and will be a part of the safety data base. All adverse events will be MedDRA coded according to a current MedDRA coding dictionary by the Coordinating Center and will be reviewed on a regular basis to observe trends or unusual events.

1.4 Participant Protection Monitoring

In order to maintain participant confidentiality throughout the conduct of the trial, all assessments, eCRFs, reports and other records will be coded using alphanumeric identifiers only. All research and clinical records will be stored in a secure location with limited access. Only research staff will have access to the records. Other parties with access to study data, such as local or central institutional review boards, will be specified to the participants, per HIPAA regulations.

Participant information will not be released without their written permission, except as necessary for monitoring. By participating in this protocol, each site investigator agrees that within local regulatory restrictions and ethical considerations, any regulatory agency may consult and/or copy study documents in order to verify study data.

By participating in this protocol, the site investigator affirms that information furnished to the investigator by the Sponsor will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committees, affiliated institutions, and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

1.5 Informed Consent

Participants will be provided with an IRB-approved informed consent form that will include a description of all significant elements of the study. The consent form will include assurances of confidentiality and a statement that participation is entirely voluntary, that the decision to participate will in no way influence other aspects of the participant's treatment, and that the participant is free to withdraw participation at any time. 100% of the informed consent documentation will be reviewed via on-site monitoring by Coordinating Center staff.

1.6 Participant Eligibility

Eligibility criteria will be verified 100% for all enrolled participants. Verification will include ensuring that each protocol-specified inclusion and exclusion criterion has been met (review of lab data, medical history, etc.). This review will be performed against source documentation during on-site during monitoring visits by Coordinating Center staff.

1.7 Safety Assessments

All Adverse Events (AEs) and Serious Adverse Events (SAEs) will be carefully monitored and reported throughout the study by site staff. These events will be subject to ongoing monitoring by the Coordinating Center and will be presented for DSMB review.

The site investigator or designee will review all AEs and SAEs for seriousness, severity and relatedness during each participant visit, and will consult with other research personnel as needed. This review of AEs and SAEs will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The site investigator will also provide advice for decisions to exclude, refer, or withdraw participants as required.

The study staff will be trained to monitor for and report adverse events and serious adverse events under the direct supervision of the site investigator.

1.7.1 Reportable Adverse Events, including Serious Adverse Events

All adverse events and serious adverse events observed while conducting this protocol will be reported through the data system for the duration of the study.

As noted in the protocol, an adverse event is defined as a new, undesirable medical event or occurrence or worsening of an existing condition (including an abnormal laboratory finding) in a study participant whether or not it is considered to be study related. Adverse events or medical events and toxicities are treatment emergent signs and symptoms. For the purposes of this protocol, a pregnancy will not be considered an adverse event but will be reported on a pregnancy specific form and will be followed until resolution of the pregnancy.

A serious adverse event is defined as any adverse therapy experience occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution. This includes, but may not be limited to any of the following events: (This terminology is from Section B.2 on the FDA MedWatch form. For a copy of the current MedWatch Form 3500A, see the list of PDF forms on the Web at: <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>).

1. **Death:** A death occurring during the study, or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy whether or not considered treatment related, must be reported.
2. **Life-threatening:** Any adverse therapy experience that places the subject or subjects, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death).
3. **In-patient hospitalizations (>24hrs) or prolongation of existing hospitalization.**
4. **Persistent or significant disability or incapacity.**

5. Congenital anomaly/birth defect.
6. Other important medical event: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, it may jeopardize the subject's well-being or it may require medical or surgical intervention to prevent one of the outcomes listed above.

1.7.2 Eliciting and Monitoring Adverse Events

Adverse events will be captured from the time consent is signed until the final study visit (approximately 13 weeks after the last study medication dose is administered). Follow up information will be evaluated from the onset of the event until the time the event is resolved or medically stable, or until the final study visit, whichever comes first.

AEs may be discovered through any of these methods:

- Observing the subject
- Questioning the subject, which should be done in an objective manner
- Receiving an unsolicited complaint from the subject
- Review of medical records/source documents

All adverse events must be documented in the source record first and then recorded on an AE eCRF in the electronic database. A multi-page adverse event form within AdvantageEDCSM, the Coordinating Center's data capture system, will be used allowing all adverse events to be submitted through a single reporting mechanism. Serious adverse events will require additional information reported on additional pages within AdvantageEDCSM. Source documents, when required, will be scanned and attached to the adverse event form within AdvantageEDCSM. Only the participant study ID should be provided on the source documentation, and all other personally identifying information should be redacted.

The site investigator will treat participants experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

Each of the participating sites are staffed by trained medical professionals, associated with full-service accredited hospitals, have emergency treatment equipment (crash cart) on site or immediately accessible, and are located close to full-service hospital emergency rooms.

A site investigator will review all AEs reported at the site for the determination of seriousness, severity, and relatedness. A site investigator will further classify each AE as serious or non-serious and follow appropriate reporting procedures.

Coordinating Center staff will routinely monitor the clinical sites to review the study data for any unreported or unidentified AEs and SAEs discovered during visits and ensure these events are promptly reported by the site in the data entry system and to the IRB per local IRB requirements, and will be reported on the monitoring summary report. Staff education, re-training or an appropriate corrective action plan will be implemented at the participating site when unreported or unidentified AEs or SAEs are discovered, to ensure future identification and timely reporting by the site.

AEs and SAEs will be followed through resolution, stabilization or study end, and any serious and study-related AEs will be followed until resolution or stabilization, even beyond the end of the study.

1.7.3 Assessment of Severity/Toxicity and Relatedness

The site investigator will review all AEs and SAEs for seriousness, severity and relatedness during each visit with the participant, and will consult with other research personnel as needed. Per the Protocol, the site Investigator must assign the severity grade and make the initial determination of the relatedness of the event to the study intervention or study procedure. The site Investigator may not delegate someone other than a listed study physician the responsibility for reviewing the accuracy of the adverse event report.

The severity/toxicity of the experience refers to the intensity of the event. The relatedness of the event refers to causality of the event to the study. Toxicity grades are assigned by the study site to indicate the severity of adverse experiences and toxicities. This study will use the NCI-CTCAE v3.0 for application in adverse event severity grading. The NCI-CTCAE has been reviewed specifically for this protocol and is appropriate for this study population. The purpose of using the NCI-CTCAE system is to provide standard language to describe toxicities and to facilitate tabulation and analysis of the data and assessment of the severity of treatment-related toxicities.

The NCI-CTCAE provides a term and a grade that closely describes the adverse event. Copies of the grading scales and event descriptions will be provided to each participating site.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE website, <http://ctep.cancer.gov/reporting/ctc.html>.

Adverse events not included in the NCI-CTCAE listing should be recorded and graded 1-5 according to the General Grade Definition provided below:

Grade 1	Mild	Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., non-aspirin pain reliever for simple headache, acetaminophen for post-surgical pain).
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required, hospitalization or hospice care probable.
Grade 5	Death	Death.

Relatedness: Relatedness requires an assessment of temporal relationships, underlying diseases or other causative factors, and plausibility. Their assessment is critical as only those events felt to be related to study participation by the site Investigator are required to be reported.

Relationship to therapy is defined according to the following:

Associated: There is a reasonable possibility that the AE may have been caused by the study drug. This definition applies to those adverse events that are considered definitely, probably or possibly related to the study drug.

1. **Definitely related:** An AE that follows a temporal sequence from administration of the study drug and/or procedure; follows a known response pattern to the study drug and/or procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the study drug (positive dechallenge; and by reappearance of the reaction after repeat exposure [positive rechallenge]); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.
2. **Probably related:** An AE that follows a reasonable temporal sequence from administration of the study drug and/or procedure; follows a known response pattern to the study drug and/or procedure, is confirmed by improvement after rechallenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or other therapies.
3. **Possibly related:** An AE that follows a reasonable temporal sequence from administration of the study drug and/or procedure and follows a known response pattern to the study drug and/or procedure, but could have been produced by the participant's clinical state or by other therapies.

Not associated: An AE for which sufficient information exists to indicate that the etiology is not related to the study drug.

1. **Unrelated:** An AE that does not follow a reasonable temporal sequence after administration of the study drug and/or procedure and most likely is explained by the participant's clinical disease state or by other therapies. In addition, a negative rechallenge to the study drug and/or procedure would support an unrelated relationship.

1.7.4 AE Reporting Procedures

Adverse events are to be reported within 7 days of the site becoming aware of the event using the Adverse Event eCRF in the EDC system. All reported AEs must be followed to resolved or medically stabilized and the reports updated in the EDC system, as appropriate.

1.7.5 SAE Reporting and Management Procedures

Serious adverse events will be recorded on the adverse event case report form (CRF). All sites are obligated to report SAEs within 24 hours of their occurrence and/or the sites knowledge of the event to the Coordinating Center via the EDC system. Additional information may need to be gathered to evaluate the SAE and to complete the AE and SAE eCRFs. This process may include obtaining hospital discharge reports, physician records, autopsy records or any other

type of records or information necessary to provide a complete and clear picture of the SAE and events preceding and following the event. The following attributes will be assigned:

- Description
- Date of onset and resolution (if known when reported)
- Severity
- Assessment of relatedness to study drug
- Action taken

When reporting an adverse event, the site Investigator must assign a severity grade to each event and also make an initial determination of the relatedness of the event to the study drug.

The site Investigator will apply his/her clinical judgment to determine whether an adverse event is of sufficient severity to require that the subject is removed from treatment. If necessary, an investigator will suspend any trial procedures and institute the necessary medical therapy to protect a participant from any immediate danger.

Serious adverse events will be followed until resolved or considered medically stable. The site must actively seek information about the SAE as appropriate until the SAE is resolved or medically stabilized or until the participant is lost to follow-up and terminated from the study. The Medical Monitor at the Coordinating Center may also request additional and updated information. Details regarding remarkable adverse events, their treatment and resolution, should be summarized by the site Investigator in writing upon request for review by the Sponsor, Medical Monitor, local ethics Committee/IRBs or regulatory authorities.

The Medical Monitor at the Coordinating Center is also responsible for reviewing all serious adverse event reports. The Medical Monitor will report events to the sponsor and the DSMB. The DSMB will receive summary reports of all adverse events at a frequency requested by the DSMB, but at least annually. Serious adverse events that are considered unexpected and associated with the treatment or intervention will be reported within 15 days and deaths and life-threatening events meeting these criteria will be reported within 7 days of the sponsor, or sponsor representatives, learning of the event. The IND Sponsor, Shalesh Kaushal, M.D., Ph.D., will be responsible for submitting reportable SAEs to the regulatory authorities.

Subsequent review by FDA, the DSMB, ethics review committee or IRB, or the sponsor(s) may suspend further trial treatment or procedures at a site. The study sponsor(s), FDA and DSMB retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

Questions regarding the reporting of safety events for this protocol may be directed to the protocol assigned Medical Monitor and Safety Monitor.

<p>Medical Monitor: Robert Lindblad, MD Phone: 301-251-1161, Ext. 205 Fax: 301-251-1355 Email: rlindblad@emmes.com</p>	<p>Safety Monitor: Nilay Shah, MD Phone: 301-251-1161, Ext. 2941 Fax: 301-251-1355 Email: nshah@emmes.com</p>
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2 Data and Trial Monitoring

2.1 Data Management

The Coordinating Center is responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site staff on applicable data management procedures. A web-based distributed data entry model will be implemented. This system is developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management process associated with this protocol. A detailed description of the data system and form-by-form completions instructions are provided in the study's AdvantageEDCSM Users' Guide and Data Management Handbook.

The data collection process consists of data entry at the study sites into the EDC system(s). Data entry into the eCRFs should be completed according to the instructions provided and project specific training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant. The Coordinating Center is not responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

The Principal Investigator and Clinical Coordinator of each clinical center are responsible for the integrity of the information entered into the EDC system.

The Coordinating Center will (1) define the process by which data are to be entered at the clinical sites; (2) conduct ongoing data monitoring activities on study data from all participating sites; (3) monitor any preliminary analysis data cleaning activities as needed, and (4) rigorously monitor final study data cleaning.

Data entry into electronic CRFs (eCRFs) shall be performed by authorized individuals. Electronic CRFs will be monitored for completeness, accuracy, and attention to detail throughout the study.

Completed data will be entered into the Coordinating Center's automated data acquisition and management system. If incomplete or inaccurate data are found, a data clarification request will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into the Coordinating Center's automated data acquisition and management system.

The training for site staff includes training on assessments, GCP, eCRF completion guidelines, data management procedures, and the use of computerized systems, as required.

Quality measures that cover both Coordinating and Reading Centers' activities will be routinely evaluated by the Coordinating Center and NNRI to evaluate the performance of clinical sites. Specific measures are displayed below. Clinical sites performing poorly in any of these measures will be provided additional training until the improvement to acceptable levels is achieved.

The study DSMC will be provided summaries of the data quality measures at DSMC meetings for review.

Participant Accrual

- Total number of participants enrolled since study first opened, overall and by site
- Number of participants enrolled during the last reporting period

Participant Retention

- % of enrolled participants who have discontinued study treatment
- % of enrolled participants who are lost to long-term follow-up

Electronic Case Report Forms (eCRFs) Submission

- % of required eCRFs that are past due
- % of required eCRFs that are more than 30 days past due
- % of submitted eCRFs with one or more required items missing

Data Completeness/Accuracy

- % of missing forms that are excepted (not available, e.g., missed visits)
- % of missing items that are excepted (not available, e.g., test not done)
- % of submitted forms with data queries (requires to confirm or correct data)

Reading Center Data

- % of images with borderline photo quality or ungradable
- % of images queries
- Timeliness from image date to receipt at reading center

2.2 Protocol adherence

Adherence to the protocols, policies and procedures is crucial, as the validity of a clinical trial can be compromised if the protocol is not adhered to. Areas of protocol adherence that will be monitored in the study include (1) eligibility violations, (2) off-protocol treatments, (3) examination procedures not specific by the protocol; (4) out of window scheduled visits; (5) examinations done by uncertified staff; and (6) improper or delayed consenting procedures.

Serious violations, such as failure to obtain informed consent, enrollment of ineligible participants, treatment errors, etc., require prompt remediation and are resolved with the sites as soon as they are observed, and sites will be required to provide an action plan to prevent future violations. These violations will be documented on eCRFs and presented to the DSMC at face-to-face meetings.

2.3 Site Monitoring

Monitoring in the study is critical to ensure the safety of participants and the validity and integrity of the data. The Clinical Research Associate (CRA) designated for monitoring the trial will be the day-to-day 'go-to' person for the clinic coordinator for questions and issues that arise during the conduct of the study. The CRA will provide telephone and e-mail coverage to immediately answer any questions or issues that arise during a participant visit.

To ensure the highest level of compliance, the CRA will conduct regular calls with the study coordinator to discuss general study issues and to assure the site is up to date with all study document requirements, including data completion and image submission. In the event that a new study coordinator is assigned to the study, comprehensive training will be provided by the CRA.

All sites will undergo a site initiation visits by the study CRA prior to participant enrollment. These visits are intended to ensure compliance with all Federal regulations governing human subjects research, GCP, ICH and Good Laboratory Practice guidelines and to ensure the adequacy of the staff and facilities. Further, investigators will host periodic visits by Coordinating Center's CRAs during the conduct of the trial to cover the following aspects of clinical trial conduct and site operations, including but not limited to (1) the accuracy and completeness of reportable data on eCRFs; (2) adherence to inclusion and exclusion criteria; (3) reporting of protocol violations; documentation and reporting of all AEs and SAEs; (4) documentation of informed consent and adherence to informed consent procedures; (5) test article accountability including pill count and review of disposition records on an ongoing basis; and (6) adherence to other protocol-specific requirements, including the collection and reporting of clinical laboratory and other tests, and storage of clinical specimens and other test results.

A detailed monitoring plan covering aspects of site initiation, routine, for cause, and close-out visits is provided in the study's Manual of Operations.

The Coordinating Center will create a site visit summary report at the end of each visit. Summary of these reports, with major findings, will be reviewed with the DSMC. All site monitoring reports will be made available for review if requested by the DSMC.

Name	Role	Institution
Stuart Fine, MD	Chair	University of Pennsylvania
Marie Diener-West, PhD	Statistician	Johns Hopkins University
Jacque Duncan, MD	Clinician	University of California, San Francisco School of Medicine
Karen Rothenberg, JD	Ethicist	Univeristy of Maryland School of Law
Dean Bok, PhD	Retinal Cell Biologist	David Geffen School of Medicine at UCLA
Gary Ingenito, PhD	Neurologist	CATASYS, Inc.

NATIONAL EYE EVALUATION RESEARCH (NEER) NETWORK

DATA SAFETY MONITORING BOARD

CHARTER

**Version 1.0
July 16, 2010**

The National Eye Evaluation Research (NEER) Network is sponsored by the National Neurovision Research Institute (NNRI), through a grant from the Department of Defense (DOD).

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1. Purpose

It is the policy of the National Neurovision Research Institute (NNRI) to promote the safety of participants and the validity and integrity of the data by implementing a system for the appropriate oversight and monitoring of NNRI-supported clinical trials. The establishment of a Data Safety Monitoring Board (DSMB) is a key component of the system, and is integral to ensuring ongoing review of safety and efficacy data in order to provide guidance to NNRI on continuing, discontinuing, or modifying clinical trials. The DSMB is composed of a group of individuals with pertinent expertise and it is the DSMB's responsibility to weigh risks and benefits throughout the study's duration. These data and safety monitoring functions are distinct from the requirement for review and approval of human subjects research protocols by local Institutional Review Boards (IRBs).

2. Responsibilities of the DSMB

The initial responsibility of the DSMB is to review proposed research protocols and plans for data and safety monitoring and oversight prior to study initiation, and at planned intervals during the course of each clinical trial. The overall DSMB responsibilities are to:

- Promote the safety of the participants.
- Review the research protocols, informed consent documents, and plans for data and safety monitoring.
- Review proposed modifications to the protocols prior to implementation.
- Review the statistical analysis plan for interim data analysis proposed by the Principal Investigator (PI) and, where appropriate, the NEER Network Clinical Coordinating Center (CCC) in advance of the study initiation.
- Evaluate study progress reports, including periodic assessments of data quality and timeliness, participant accrual and retention, participant risk versus benefit, overall study performance and the performance of individual participating sites, and other factors potentially affecting study outcome.
- Prepare reports on the study safety and progress for NNRI and IND/IDE sponsors (hereinafter referred to as "sponsor"). To assure participant safety in each clinical trial, the DSMB monitors adverse events. The CCC provides to the DSMB, on a regular schedule determined by the needs of the clinical trial, reports of adverse events among trial participants. Deaths or other serious events are reported to the DSMB Chair and appointed Medical Monitors at the CCC as soon as they occur.
- When appropriate, review interim analyses of efficacy and cumulative toxicity data that are clearly defined in advance of data analysis and have the approval of the DSMB in accordance with interim monitoring plans. These reviews will assist NNRI and the sponsor to determine whether clinical trials will continue as originally designed, be changed, for example as a result of the implementation of a protocol established adaptive design, or be prematurely terminated.
- On a schedule determined prior to data collection, the DSMB may examine outcome data provided by the CCC for early evidence of either efficacy or futility. Throughout the clinical trial conduct, the DSMB will monitor study assumptions about incidence rates and sample size. The DSMB will also evaluate, as appropriate, outcome data according to guidelines for interim data monitoring outlined in published procedures (e.g., Pocock, O'Brien and Fleming, and Lan and DeMets). Based on data reviewed at these interim evaluations, the DSMB may recommend early termination of the clinical trial either

because of established efficacy of treatment or because of the unlikelihood that a meaningful assessment of treatment effect could be established by the planned end of the clinical trial. The DSMB may also recommend extensions in clinical trial length or increases in sample size, as well as other relevant modifications to the protocol or protocol-related documents.

- Make written recommendations to NNRI and the sponsor, and others designated by the sponsor, concerning any problems with study conduct, enrollment, sample size and/or data collection.
- Provide written comments to NNRI, the sponsor, sponsor's designee, the PI, and, if required, the U.S. Food and Drug Administration (FDA), non-U.S. regulatory authorities, as appropriate, and involved IRBs/Institutional Ethics Committees (IECs) concerning continuation, termination or other modifications of the studies based on the observed beneficial or adverse effects of any treatment(s) under study, or low probability of achieving study objectives.
- Consider factors external to NNRI-supported clinical trials when relevant information becomes available, such as scientific or therapeutic developments, and including such factors as the relevant comments from the IRBs that approve, disapprove, or alter the protocol that may have an impact on the safety of the participants, the ethics of the study, or the need to continue the study.
- Maintain the confidentiality of the overall DSMB process.

It is important to note that the decision to terminate or substantially alter a study rests with NNRI and the sponsor, although the DSMB-recommended actions are considered key to this decision.

3. DSMB Membership and Term of Appointment

Membership on the DSMB will be decided by NNRI.

The DSMB will be composed of a core membership that will review all studies funded or managed by NNRI, and *ad hoc* members for specific studies to provide drug- and/or indication-specific expertise. Core and *ad hoc* DSMB members will be selected for their relevant medical experience and expertise, knowledge of clinical trial methodology, and absence of conflicts of interest (see **Conflict of Interest** section below). Voting members of the DSMB should be free of conflicts of interest in the trial(s) to be monitored; principal investigators involved in the trial are ineligible. In exceptional circumstances, a voting member may be from an institution participating in the trial but not of the same department as the investigator involved in the study. In this situation, the member should view his or her role as representing the interests of the participants enrolled in the trial and not those of the institution.

Core DSMB members will be appointed for a term of two (2) years, renewable upon mutual agreement between NNRI and the core DSMB member.

DSMB members for a given clinical trial shall not include investigators participating in the conduct of that clinical trial. NNRI, with assistance from the CCC if applicable, shall be responsible for the logistical management and support of the DSMB.

Any member absent for at least three DSMB meetings (conducted in person or via teleconference) in one year may be replaced by NNRI.

3.1. Core Membership

Chairperson

The DSMB Chair will be a board-certified medical doctor with documented expertise and experience in the diagnosis, treatment and management of patients with inherited retinal degenerations, including inherited orphan retinal degenerative diseases, and dry age-related macular degeneration (AMD), and in conducting clinical trials for these diseases. Previous experience in serving as a member of a DSMB is highly desirable. The Chair will be responsible for overseeing the meetings/teleconferences, and for developing the agenda in consultation with NNRI's Chief Drug Development Officer or designee and the CCC. The Chair is the contact person for the DSMB.

NNRI Representatives

The Chief Drug Development Officer and Chief Research Officer will serve as the non-voting NNRI representatives to provide scientific/clinical expertise in the development of therapeutic and preventive interventions and in clinical trial design, as well as represent the patient community. As non-voting members, the NNRI representatives will remain blinded and are not permitted to participate in any closed DSMB sessions.

Biostatistician

The DSMB biostatistician will have an advanced degree in Applied Mathematics, Statistics, or Biostatistics, experience in clinical biostatistics, and at least ten (10) years of experience in statistical methodology for evaluation of clinical outcomes. Experience in the statistical analysis of clinical trials in ophthalmology is highly desirable. The DSMB biostatistician shall not be involved in performing the interim statistical analyses.

Specialist

This member will be an experienced board-certified retinal specialist with expertise in conducting clinical trials.

Ethicist

The ethicist will have an advanced degree in bioethics and/or related disciplines with extensive experience in the ethical issues involved in the conduct and monitoring of human subjects research and in the interpretation of clinical trial safety and efficacy data, including previous experience serving on DSMBs.

3.2. Ad Hoc Members

These voting members will be added for each protocol for the study of a specific drug and indication.

Ad hoc members of the DSMB will be physicians, board-certified in a subspecialty, or appropriate non-physician specialists. The qualified individual(s) should have over ten (10) years of experience in the appropriate subspecialty (both in clinical practice and in the performance of clinical trials). If there are two indications for a specific drug, subspecialists with expertise in each indication will be selected. Further, expertise providing insight into the clinical care over a broad range of patients (outpatient and inpatient) is also needed on the board, and if the core membership lacks this expertise, a generalist physician as an ad-hoc member can be added.

3.3. Ex Officio Members

The study Chair and representatives from the CCC may also serve as non-voting *ex officio* members at the discretion of the DSMB Chair.

In addition, a CCC staff physician will serve as the Medical Monitor for each clinical trial and will review and report all adverse events to the DSMB Chair. Procedures for notifying the Chair of the DSMB and the sponsor will be discussed at the first DSMB meeting.

4. DSMB Review of Final Draft Clinical Protocols

The DSMB will review final drafts of clinical protocols and protocol-related documents and advise NNRI on design and safety monitoring prior to study initiation. This shall include primary and secondary outcomes and outcome measures, statistical analysis plans, and Data and Safety Monitoring Plans (DSMPs).

NNRI will be responsible for communicating any DSMB recommendations for protocol modifications to the study PI and the sponsor, and for approving modifications based on DSMB advice.

5. DSMB Review of Ongoing Clinical Trials

In accordance with approved, study-specific DSMPs, the DSMB will review safety and efficacy data for ongoing clinical trials. The following policies and procedures will be used in carrying out this function.

5.1. Interim DSMB Reports

Interim reports are prepared by the CCC study statistician(s) and distributed by the CCC to DSMB members at least ten (10) days prior to each scheduled meeting. These interim reports are numbered and provided either in hardcopy or via secure DSMB web page. The contents of these reports are determined by the DSMB. Interim reports will generally consist of two parts:

- Part 1 (Open Session Report) provides information on study aspects such as data quality and timeliness, participant accrual and retention, baseline characteristics, and other general information on study status.
- Part 2 (Closed Session Report) may contain data on study outcomes, including safety and efficacy data. Interim analyses of efficacy data are performed only if they are specified and approved in advance and if criteria for stopping are clearly defined. The Closed Session Report is considered confidential and will be collected and destroyed by the DSMB Executive Secretary at the conclusion of each meeting. When the meeting is held via teleconference, DSMB members must certify in writing that all materials have been destroyed. Data files to be used for interim analyses will have undergone established quality control procedures to the extent possible to ensure accuracy of data presented in interim reports.

5.2. DSMB Recommendations

The DSMB may recommend continuation, modification or termination of ongoing clinical trials. The applicable provisions and procedures are delineated below. DSMB recommendations should be based on results from the clinical trials being monitored, as well as on published data from other studies. It is the responsibility of the Study PI, participating investigators, sponsor staff, and individual DSMB members to ensure that the DSMB is kept apprised of non-confidential outcome results from other related studies as they become aware of any relevant findings. It is the responsibility of the CCC, NNRI, and sponsor staff to keep the DSMB apprised

of any significant programmatic issues related to the clinical trial being monitored, such as changes in clinical center personnel (e.g., Principal Investigator).

All discussions and any written communications pertaining to decision-making on DSMB recommendations for protocol modification/termination are considered confidential and may not be shared with individuals/organizations outside of NNRI, the DSMB, sponsors and Study PIs.

- **Voting Provisions**

Recommendations for study continuation or modification will be made by formal majority vote. In the event of a split vote, majority vote will rule and a minority report shall be appended. Recommendations to terminate an ongoing clinical trial for safety reasons require a unanimous vote of the DSMB.

- **DSMB Recommendations for Protocol Modifications**

If the DSMB recommends a protocol modification for participant safety or efficacy reasons, or recommends that the clinical trial be closed early due to slow accrual or other reasons (e.g., the availability of substantially better alternative therapy, numerous compliance issues that would ultimately jeopardize the interpretation of the data, or new information that has become available that would impact clinical endpoints, patient health, and overall well being), NNRI and the Study PI, in collaboration with the sponsor, must act to implement the change as expeditiously as possible if there is concurrence with the DSMB recommendation. If NNRI, the Study PI and/or sponsor do not concur with the DSMB's recommendation, it will be the responsibility of NNRI, the sponsor and the DSMB Chair to reach a mutually acceptable decision. The ultimate decision rests with NNRI and the sponsor. The DSMB may also make other recommendations for protocol modifications such as increasing sample size or delaying the proposed timing of interim analyses for safety and efficacy. All DSMB recommendations for protocol modifications must be accompanied by adequate rationale.

In the absence of disagreement with DSMB recommendations for protocol modifications, the CCC will be responsible for amending the protocol and notifying the Study PI and participating investigators as expeditiously as possible. It is the responsibility of the Study PI and the participating investigators to notify their local IRBs of any protocol changes.

NNRI is responsible for making final decisions on terminating its involvement in a clinical trial based on DSMB recommendations for protocol modifications or early termination due to slow accrual or, for the NEER Network, based on recommendations from the DSMB and the Department of Defense (DOD).

- **DSMB Recommendations for Study Termination**

If the DSMB recommends termination of an ongoing clinical trial, the written recommendation will provide a detailed rationale based on interim reports reviewed to date. NNRI and the Study PI, in collaboration with the sponsor, must act to implement study termination as expeditiously as possible if there is concurrence with the DSMB's recommendation. If NNRI, the Study PI and/or sponsor do not concur with the DSMB's recommendation, it will be the responsibility of NNRI, the sponsor and the DSMB Chair to reach a mutually acceptable decision. The ultimate decision rests with the sponsor.

In instances where a mutually acceptable decision cannot be reached and the sponsor decides to continue the clinical trial, NNRI will make the final decision about continuing its involvement in the study.

- **Communications with IRBs**

To assist local IRBs in the annual review of ongoing clinical trials, summaries of recommendations resulting from each DSMB review will be provided by the CCC to each Clinical Site Principal Investigator, who will then be responsible for providing to the appropriate IRBs. In addition, a DSMB member will be available to attend IRB meetings by phone, if necessary, for discussion of any safety issues or DSMB recommendations for study protocol modifications.

The Study PI will be responsible for sending all IRB communications related to participant safety to the CCC.

5.3. Critical Issues and Special Actions

The NNRI-designated DSMB Executive Secretary will work with the DSMB to discern and assess critical issues such as:

- failure to comply satisfactorily with recruitment goals, including those related to the participation of females and minorities;
- increased or decreased morbidity and/or mortality related to the study interventions;
- adverse reactions to therapy;
- unsatisfactory performance on the part of the CCC and/or study centers;
- suspicion of fraud;
- any other issues that would lead to important protocol changes;
- unblinding of a subject enrolled in a double-blinded study;
- implementation of an adaptive design monitoring strategy; and
- breach of confidentiality.

If such issues arise, the DSMB Chair and the NNRI-designated DSMB Executive Secretary will discuss the situation with NNRI. Approaches for responding to such issues may include: (i) expanding the number of enrolling centers; (ii) extending the period of recruitment; (iii) stopping recruitment because of inadequate rate of acquisition; (iv) modifying the protocol (in collaboration with the Study PI and participating investigators); or (v) discontinuing participation of a study center with poor performance. NNRI may also elect to establish an *ad hoc* committee to provide assistance in these matters. Such *ad hoc* committees may include representation from DSMB members, and members of the relevant scientific community.

6. DSMB Meetings

Provisions for the type, purpose and frequency of DSMB meetings are delineated below.

6.1. General Provisions for DSMB Meetings

- DSMB meetings may be convened in person or via teleconference with the exception of the face-to-face Inaugural DSMB Meeting, as specified in section 6.2 below, and one of the two Semi-Annual DSMB Meetings, as specified in section 6.3 below.

- It is expected that all DSMB members will attend every meeting/teleconference. However, it is recognized that this may not always be possible. For open DSMB sessions, as specified in section 6.4. below, a quorum of the DSMB is considered to be at least the Chair, biostatistician, one physician member, and the NNRI representatives. Sponsor officials will be invited to participate at every open meeting/teleconference, schedules permitting. A quorum for closed DSMB sessions is considered by be at least the Chair, biostatistician and one physician member.
- The DSMB Chair will be responsible for overseeing meetings/teleconferences, and for developing the agenda in consultation with NNRI's Chief Drug Development Officer or designee and staff of the CCC.
- NNRI will be responsible for all logistical arrangements for DSMB meetings/teleconferences, for reimbursing DSMB members for associated travel expenses, and for providing honoraria for the services of DSMB members.

6.2. Inaugural DSMB Meeting

The Inaugural DSMB meeting, following acceptance of the DSMB Charter, will be convened in person and should attended by all core members. Acceptance of the charter will be based on each DSMB member completing and a signed DSMB Member Signature Page (Appendix 1). If exceptional circumstances preclude the participation of any DSMB member in person, NNRI may agree to allow participation via teleconference.

The purposes of the Inaugural DSMB Meeting are to:

- review the roles and responsibilities of the DSMB Chair and other core members, *ad hoc* members, NNRI representatives, and *ex officio* members;
- review the schedule and discuss the format for meetings/teleconferences;
- review specific DSMB operating procedures/policies, including: (i) definition of what constitutes a quorum; (ii) specification of who may attend all or part of DSMB meetings/teleconferences; (iii) specification of who has access to interim data; and (iv) study monitoring guidelines and stopping rules when appropriate;
- discuss the format for presentation of interim reports of clinical and laboratory data from ongoing clinical trials, i.e., summary tables and data listings, and the timing for delivery of interim reports to DSMB members prior to each meeting/teleconference;
- discuss plans to keep the DSMB blinded to treatment group assignment (e.g., Treatment A vs. Treatment B rather than identifying the actual treatment) and the process by which DSMB members are unblinded in the event critical safety concerns arise; and
- present NNRI policies and procedures for disclosure of financial and personal interests on the part of DSMB members, identification of real and potential conflicts of interest, and methods to remove or mitigate identified real or potential conflicts of interest.

6.3. Semi-Annual DSMB Meetings

Meetings of the DSMB will be held at least two (2) times each year at the call of the Chair, with advance approval of NNRI, or at the call of NNRI. At least one (1) face-to-face meeting will be held annually. All DSMB meetings will be closed to the public because discussions may address confidential participant data.

In accordance with study-specific DSMPs, the DSMB may be required to meet more frequently to review interim safety and efficacy data for ongoing clinical trials. In addition, the DSMB may also require *ad hoc* meetings to address unexpected or exigent safety events.

6.4. DSMB Open, Closed and Executive Sessions

DSMB meetings and teleconferences will be organized into open, closed and executive sessions.

Open sessions of DSMB meetings/teleconferences will include the NNRI representatives and the CCC study statistician(s) and may be attended, when appropriate, by the study PI. In addition, sponsor officials may participate in open sessions, schedules permitting. Issues discussed at open sessions will include study conduct and progress, including participant accrual, protocol compliance, and problems encountered. Participant-specific data and treatment group data shall not be presented in the open session.

Closed sessions of DSMB meetings/teleconferences will be attended **only** by voting DSMB members, the NNRI-designated DSMB Executive Secretary, and the relevant unblinded statisticians from the CCC. The DSMB may request others to attend part or all of the closed session. All safety and efficacy data must be presented during the closed session, and all such data and closed session DSMB discussions are considered confidential.

The DSMB may elect to hold **executive sessions** in which the DSMB members and a CCC representative responsible for taking minutes are present in order to discuss study issues independently and to review unblinded study data. If the executive session occurs via teleconference, steps will be taken to ensure that only the appropriate individuals participate, and to invite others to re-join the call only at the conclusion of the executive session. Under some circumstances (at the discretion of the DSMB Chair), CCC representatives may also be included in executive sessions. At the conclusion of the executive session, the DSMB Chair will discuss any DSMB recommendations resulting from the discussions with the NNRI representatives.

7. DSMB Minutes and Formal Recommendation Reports

7.1. Minutes

Draft minutes of all DSMB meetings/teleconferences will be prepared by the NNRI-designated DSMB Executive Secretary and reviewed, modified if necessary, approved and signed by the DSMB Chair. Copies of all signed minutes will be distributed to the DSMB members prior to the next meeting.

When important issues, such as complications of therapy, protocol violations, or other major issues affecting clinical trial conduct are discussed during DSMB meetings, the NNRI-designated DSMB Executive Secretary will document the discussions and the outcome.

7.2. Formal Recommendation Reports

A formal report containing recommendations for continuation, modification or termination of ongoing clinical trials will be prepared by the CCC study statistician, with concurrence from the DSMB Chair, and will be sent to the full DSMB for review and approval within two (2) weeks of each meeting/teleconference. If no changes are recommended, the report may simply state "The DSMB recommends that the study continue as designed." Formal recommendation reports shall also include a summary of discussions held in open session, and shall document any information provided orally to sponsors that was not included in the formal DSMB written report. Once approved by the DSMB, formal recommendation reports will be forwarded to the study PI by NNRI. It is the responsibility of the PI to distribute the formal DSMB

recommendation report to all co-investigators and to assure that copies are submitted to all local IRBs associated with the study. These recommendations will also be available on the secure CCC website to those with approved access.

8. Access to Interim Data

Access to the accumulating endpoint data will be limited to as small a group as possible. Limiting access of interim data to the DSMB members relieves the investigator of the burden of deciding whether it is ethical to continue to randomize participants and helps protect the study from bias in patient entry and/or evaluation.

In addition, blinded safety data will be communicated to all DSMB members and to the CCC Medical Monitor on a scheduled basis or as agreed upon by the DSMB.

9. Release of Data

Confidential data should not be made available to individuals outside of the DSMB. Any release of confidential data to individuals outside of the DSMB must be reviewed and approved by the DSMB, NNRI, the sponsor, and the study PI.

10. Confidentiality Procedures

No communication, either written or oral, of the deliberations or recommendations of the DSMB will be made available outside of the DSMB except as provided for in these guidelines. Study results are strictly confidential and must not be divulged to any individual or organization that is not a member of the DSMB. Each member of the DSMB, including non-voting members, must sign a statement of confidentiality.

In addition, the CCC, which is responsible for preparing confidential interim reports to the DSMB, shall maintain all meeting/teleconference records in order to best ensure continued confidentiality of interim data. The FDA may request copies of these records.

11. Conflict of Interest

Individuals invited to serve on the DSMB, as either a voting or non-voting member, will disclose any potential conflicts of interest, whether real or perceived, to the CCC on an annual basis. Conflict of interest can include financial interest, professional interest (in the sense of the trial outcome benefiting the individual professionally), proprietary interest, institutional and miscellaneous interest as described in 45 CFR Part 94. NNRI will make decisions regarding service by individuals with potential conflicts of interest or the appearance of conflicts of interest collaboratively.

Appendix 1: DSMB Member Signature Page

**National Neurovision Research Institute
National Eye Evaluation Research (NEER) Network**

DSMB MEMBER SIGNATURE PAGE

Member Information

Role: Chair Member

Voting Rights: Yes No

Name: _____

Affiliation: _____

Phone: _____ Fax: _____

E-mail: _____

Re: DSMB Charter Version 1.0 Dated: July 15, 2010

I have reviewed the NEER Network DSMB Charter and approve it as written. I understand my role as a member of this DSMB.

Signature: _____ Date: _____

Please sign and return to National Neurovision Research Institute (NNRI) via fax at (410) 363-4692.