STOP RETINAL GANGLION CELL DYSFUNCTION STUDY (STOP-RGCD)

Manual of Procedures

Version 0.8
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Table of Contents

1. Introduction

1.1 Background and Significance

1.2 Objective

1.3 References

1.1 Background and Significance

Glaucoma causes progressive damage and death of retinal ganglion cells (RGCs) resulting in blindness. The prevalence of the disease will rise to a projected 3 million Americans by 2020. A central yet unresolved issue in glaucoma is determining, in individual subjects, the onset of the disease. This is defined as the stage at which retinal ganglion cells (*RGC*) have lost their autoregulatory ability in response to a chronically stressful biomechanical, vascular or molecular environment, and become increasingly dysfunctional over time until they die and are eliminated from the neuronal pool. Were the duration of the stage of RGC dysfunction preceding death known, then it would represent the ideal time window for initiating therapeutic strategies to prevent cell death and visual loss.

Recent studies pioneered by our group in human and mouse models of glaucoma showed that RGC dysfunction, measured with the Pattern Electro-retinogram (*PERG*), can be restored after intraocular pressure (*IOP*) lowering.[1-6] In addition, RGC dysfunction may be induced in susceptible eyes of mice and human in association with temporary IOP elevation during head-down body tilt (*HDT*). [4, 6, 7] Further, our group has demonstrated that patients with substantially lowered PERG amplitude in Standard Seated Position (*SSP*) undergo more rapid Retinal Nerve Fiber Layer (*RNFL*) thinning than do patients with normal PERG. [8]

If RGC function is modifiable in response to IOP modulation, then this represents both a rationale for treatment and a target to change the natural history of the disease.

1.2 Objective

The principal objective of this study is to prospectively follow glaucoma suspects (*GS*) with depressed PERG amplitude, either in SSP or upon HDT, who have been randomized either to observation or to receive either pressure lowering medicines and compare them with respect to longitudinal RNFL thinning from baseline. Further objectives include confirmation of previously published and unpublished findings suggesting that: pressure lowering medicines improve PERG amplitude in eyes with depressed SSP PERG amplitude; [3] substantially depressed SSP PERG amplitude is a risk factor for more rapid RNFL thinning in eyes not receiving pressure lowering medications; [8] and that delayed PERG phase upon HDT in combination with hemodynamic measurements is predictive of RNFL thinning in eyes not receiving pressure lowering medications.

1.3 References

1 Ventura LM, Porciatti V. Restoration of retinal ganglion cell function in early glaucoma after intraocular pressure reduction: a pilot study. Ophthalmology 2005;112:20-27.

2 Sehi M, Grewal DS, Goodkin ML, Greenfield DS. Reversal of retinal ganglion cell dysfunction after surgical reduction of intraocular pressure. Ophthalmology 2010;117:2329-2336.

3 Ventura LM, Feuer WJ, Porciatti V. Progressive loss of retinal ganglion cell function is hindered with IOP-lowering treatment in early glaucoma. Invest Ophthalmol Vis Sci 2012;53:659-663.

4 Nagaraju M, Saleh M, Porciatti V. IOP-Dependent Retinal Ganglion Cell Dysfunction in Glaucomatous DBA/2J Mice. Invest Ophthalmol Vis Sci 2007;48:4573-4579.

5 Porciatti V, Nagaraju M. Head-up tilt lowers IOP and improves RGC dysfunction in glaucomatous DBA/2J mice. Exp Eye Res 2010;90:452-460.

6 Porciatti V, Ventura LM. Adaptive changes of inner retina function in response to sustained pattern stimulation. Vision Res 2009;49:505-513.

7 Ventura LM, Golubev I, Lee W, et al. Head-down posture induces PERG alterations in early glaucoma. J Glaucoma 2013;22:255-264.

8 Banitt MR, Ventura LM, Feuer WJ, et al. Progressive loss of retinal ganglion cell function precedes structural loss by several years in glaucoma suspects. Invest Ophthalmol Vis Sci 2013;54:2346-2352.

2 Study Design

2.1 Inclusion Criteria

2.2 Exclusion Criteria

2.3 Patient Stratification

2.4 Analysis and Sample Size Calculations

2.5 Randomization

2.6 Masking

2.7 Timetable for the Study

2.1 Inclusion Criteria

All of the criteria listed below must be present in the study eye in order for the patient to be eligible for enrollment in the study.

a. Age 18 to 85 years, inclusive

b. Refractive errors within -5 to +3 diopters

c. Best corrected visual acuity (BCVA) better than or equal to 20/30 (Snellen)

d. Normal standard automated perimetry (SAP) according to the Ocular Hypertension Treatment Study (OHTS) criteria15 (reliability < 15% on all indices, normality > 5% on all global indices in two consecutive sessions 6 months apart)

e. Glaucoma Suspect Status defined as one or more of the following:

- Glaucomatous optic disc appearance (vertical cup-to-disc ratio [C/D] ≥0.5
- Cup disc ratio asymmetry ≥0.2
- Localized thinning of the disc
- Presence or history of splinter disc hemorrhage
- Moderately increased IOP (>21 to <28 mm Hg).
- Family history of vision loss for glaucoma

2.2 Exclusion Criteria

If any of the following exclusion criteria are present in the study eye, the patient may not be entered into the study.

a. Age-related macular degeneration
b. Diabetes
c. Parkinson's disease
d. Multiple sclerosis
e. Unwilling or unable to give consent, unwilling to accept randomization, or unable to return for scheduled protocol visits.
f. Pregnant or nursing women.
g. Currently using prescribed pressure lowering medicines and unwilling to be withdrawn from them.
h. An OHTS risk score high enough in the judgment of the ophthalmologist or optometrist managing the patient to recommend pressure lowering medicine to the patient and not randomization.
i. An OCT abnormal enough in a pattern consistent with glaucoma.

2.3 Stratification of patients

Definition: Abnormal SSP PERG amplitude is defined as ≤60% of age specific normal. The logarithm of age specific normal PERG amplitude is obtained from the regression equation published by Ventura et al (IOVS 2006; 47:3904-11)

log expected normal amplitude = 0.612 – 0.374 × log (age in years).

Definition: Susceptible to HDT is defined in the following way.

a. The effect of HDT on PERG Phase (*EPP*) is calculated as:

   $EPP = 3.433 * (Phase_{HDT} – Phase_{SSP}) – 308.465 × Phase_{HDT} ÷ Phase_{SSP}$

   where each phase variable is expressed as percent of age specific normal. The age specific normal phase is obtained from the regression equation (Ventura et al) = 1.99 – 0.0027 × age.

b. The effect of HDT on hemodynamic variables (EHV) is calculated from measurements of Systolic Brachial Pressure (SBrP) and Ocular Perfusion Pressure (OPP).

   $EHV = 24.815 × (SBrP_{HDT} ÷ SBP_{SSP}) + OPP_{SSP}$

c. These two variables are substituted into the logistic equation

   Probability = exp(EPP+EHV) ÷ (1 + exp(EPP+EHV))

   A probability so obtained which is > 0.3 is considered susceptible.

Patients eligible for inclusion in the study will be stratified into one of three groups based on the results of PERG testing at baseline.

1. Patients with abnormal baseline SSP PERG in one or both eyes (average of two measurements in different sessions) will be included in stratum 1, abnormal PERG (GS-A). Patients in this stratum will be randomized to observation or pressure lowering medicines.

2. Patients with neither eye abnormal by SSP PERG but demonstrated susceptible to HDT in one or both eyes – average of two measurements - will be included in stratum 2, HDT susceptible (GS-S). Patients in this stratum will be randomized to observation or pressure lowering medicines.

3. Patients with both eyes neither abnormal nor susceptible will be included in stratum 3 (GS-N). Patients in this stratum will be observed and not offered randomization.

2.4 Randomization

After a patient has been placed in their study stratum, the Biostatistics Center will issue them a study ID number. The Biostatistics Center will provide patients in strata 1 or 2 (GS-A, GS-S) with their randomized treatment assignment to observation or pressure lowering medicines. Randomization will be performed with in each stratum in a permuted variable block fashion to ensure approximate balance of treatment assignments within strata.

2.5 Analysis and Sample Size Calculations

Percentages of patients with RNFL thinning after four years of follow up will be compared between the observation and pressure lowering medicine groups. RNFL thinning is defined as a decrease in average RNFL of 4.0μm (Budenz, (Invest Ophthalmol Vis Sci. 2010;51:5724 –5730)).

Preliminary data suggest that about 40% of untreated patients in stratum 1 (GS-A) will have incident RNFL thinning, while about 60% of untreated patients in

stratum 2 (GS-S) will have incident RNFL thinning. These data also suggest that about 15% of patients in stratum 3 (GS-N) will have incident RNFL thinning.

If pressure lowering medicines reduce the risk of RNFL thinning in patients in strata 1 and 2 to 15%, then about 32 patients in each randomized treatment group would provide 80% power. 42 patients in each randomized treatment group would provide 90% power.

If pressure lowering medicines do not reduce the risk of thinning to 15% but only to half the risk in the untreated patients, then 66 patients in each group would provide 80% power.

These calculations assume separate independent un-corrected significance tests in each stratum. If pressure lowering medicines had similar effects in each stratum, a pooled analysis would have substantially more power.

2.6 Masking

Neither the investigator nor the patient is masked as to which treatment the patient receives.

2.7 Timetable for the Study

- **Year 1: Validate new PERG instrument, including normal control values. Complete baseline measurements, place patients into study strata and randomize GS-A and GS-S patients**
- **Year 2-4: Collect follow up visit data, monitor for pressure lowering in those patients randomized to receive pressure lowering therapy**
- **Year 5: Collect final follow up visit data and perform analyses**

3. Clinical Procedures

3.1 Visual Acuity

Visual acuity is measured before pupil dilation, tonometry, gonioscopy, or any other technique that could affect vision. Refraction is performed prior to formal measurement of visual acuity by either technique at the Qualifying Assessment and at the annual follow-up visits. Snellen visual acuity is measured at the Qualifying Assessment and at every follow-up visit.

Subjective Refraction:

Subjective refraction must be performed at the Qualifying Assessment and at the annual follow-up visits in order to determine best-corrected visual acuity. It is permissible to use a phoropter to determine best-corrected Snellen visual acuity. However, trial frames are required for testing best-corrected visual acuity. The trial frame is placed and adjusted on the patient's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupil.

The left eye is occluded first. An approximate beginning refraction may be determined by retinoscopy, automated refraction, or a subjective refraction from a prior visit. The sphere is refined first. The cylinder is then refined, first the axis followed by the power. Finally, the sphere is rechecked. If a phoropter was used in the subjective refraction, the refraction is placed in a trial frame and the sphere is refined prior to visual acuity testing. The right eye is then occluded, and the procedure is repeated for the left eye.

If the patient wears contact lenses and has glasses also, he or she is instructed not to wear the contact lenses on the day of the Qualifying Assessment. In the event that the patient either has no glasses or has forgotten the instructions and reported for the Qualifying Assessment wearing contact lenses, the contact lenses are removed and at least thirty minutes allowed to elapse before subjective refraction and visual acuity testing is performed.

Snellen Visual Acuity:

Snellen visual acuity may be measured using any standard visual acuity chart. The same type of chart must be used throughout the duration of the study. Snellen visual acuity is measured during the Qualifying Assessment and at all follow-up visits. Standardized refraction is performed prior to Snellen visual acuity testing at the Qualifying Assessment and annual follow-up examinations.

3.2 Slit Lamp Biomicroscopy

Examination of the anterior segment using slit lamp biomicroscopy is performed at the Qualifying Assessment to document the status of the eye, and at all follow-up examinations to detect any changes in the conjunctiva, cornea, anterior chamber, iris, and lens that may be attributable to the disease or treatment. Slit lamp biomicroscopy may be performed with any commercially available instrument, and it is used in a standard fashion starting anteriorly and working posteriorly. Standardizing opacities is difficult, but it is expected that subjective grading by the optometrist or glaucoma specialist is relatively reproducible. Pseudophakic eyes with uncomplicated cataract extraction are included in the study. Aphakic eyes are excluded from the study.

3.3 Tonometry

Goldmann applanation tonometry is used to measure the intraocular pressure, except when irregular corneal astigmatism, corneal scarring, or corneal edema precludes accurate readings. The intraocular pressure is measured prior to pupillary dilation. Whenever possible, the intraocular pressure should be checked at the same time of the day as the Qualifying Assessment to minimize the effect of diurnal fluctuation of intraocular pressure.

Goldmann Applanation Tonometry:

The calibration of the Goldmann applanation tonometer is checked every 3 months, as described in the Haag-Streit Goldmann Applanation Tonometer Operator's Manual. Clean the prism according to your institutional infection control policy. The right eye is always tested first. Following instillation of a drop of 0.5% proparacaine, a fluorescein strip is placed near the lateral canthus in the lower conjunctival sac. Once the lacrimal fluid has been sufficiently colored, the fluorescein strip is removed. Alternatively, one drop of premixed fluorescein and anesthetic may be instilled. The patient's head is properly positioned in the chin rest and against the forehead rest without leaning forward or straining. Any tight-fitting neckwear is loosened. The patient is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the investigator holds the eyelids open against the orbital rim taking care not to apply any pressure on the globe. The patient is instructed not to hold his or her breath. If corneal astigmatism is greater than 3.0 diopters, the prism is rotated so that the axis of the minus cylinder on the prism graduation corresponds to the red mark on the prism holder. The investigator looks through the slit lamp and gently brings the tip of the prism in contact with the center of the cornea. The mires should be well focused, centered horizontally, and positioned vertically so that they are of equal circumference above and below the horizontal dividing line. If the mires are narrower than approximately one tenth their diameter, the investigator instills additional fluorescein. The investigator adjusts the measuring drum until the inner borders of the two mires just touch each other. If pulsation is present, the measuring drum is adjusted until the mires separate a given distance during systole and overlap the same distance during diastole. The investigator removes the prism from the cornea and repeats the procedure in the right eye until two successive measurements are within 1 mm Hg. The investigator records the last two successive measurements. After testing of the right eye is complete, testing of the left eye follows the same technique.

PT100:

The PT100 (Reichert) is portable, non contact tonometer that is used to compare IOP between SSP and HDT position. The patient is positioned in either sitting

position or HDT position and instructed to fix on a distant object. Tight-fitting neckwear is loosened, and the patient is instructed not to hold his or her breath. The operator used the instrument as an ophthalmoscope and aims the light beam toward the patient's pupil. PT100 visual indicators guide the operator to correct alignment position. Once alignment is achieved the PT100 automatically takes an IOP measurement, that is perceived by the patient as an light air puff on the cornea. Three sequential measurements are required, and the instrument automatically calculates the average and the SD. The right eye is always tested first.

3.4 Gonioscopy

Gonioscopy is performed with the patient sitting at the slit lamp using either a Zeiss type four-mirror gonioprism or Goldmann single- or three-mirror lens. An examination of the anterior chamber angle for neovascularization is performed under high magnification for the purpose of excluding eyes with neovascularization from the study.

3.5 Ophthalmoscopy

A dilated fundus examination is performed at the Qualifying Assessment to determine the status of the retina and optic nerve, and at all one-year follow-up examinations to detect any changes. After pupil dilation with appropriate mydriatics, the optic nerve and posterior pole are examined at the slit lamp using a Hruby lens, fundus contact lens, or Volk 90 diopter, 78 diopter, or 60 diopter lens. A head-mounted indirect ophthalmoscope and hand held condensing lens (20 diopter or 28 diopter Nikon aspheric lens) is used to evaluate the retinal periphery. At the Qualifying Assessment, particular attention is paid for signs of macular degeneration that represent an exclusion criterion.

3.6 Corneal Thickness Measurement

Central corneal thickness is measured with ultrasound pachymetry at the first baseline exam. The right eye is tested first. A drop of 0.5% proparacaine is instilled for anesthesia. The patient is asked to look straight ahead at a distant object or fixation target. The pachymeter probe is lined up with the center of the pupil and slowly advanced until it contacts the cornea. The probe is withdrawn when an audible signal is made indicating that a measurement has been

recorded. The patient is instructed to blink. The procedure is repeated to obtain three separate readings, and the investigator records the measurements. After testing of the right eye is complete, the same technique is applied to testing of the left eye.

3.7 Perimetry

Quantitative automated perimetry is performed using the Humphrey Field Analyzer . Visual field testing is performed before tonometry, gonioscopy, or any other technique that could affect vision.

A 24-2 threshold test is performed in all patients using a size III white stimulus. Visual field testing may be performed with the Swedish Interactive Thresholding Algorithm (SITA) or full threshold strategy, but the same testing strategy must be used throughout the duration of the study. The pupil diameter should be 3 mm or greater before visual field testing is undertaken, and this may require pharmacologic dilation. Standardized refraction is performed to determine the patient's distance refraction and best-corrected visual acuity prior to visual field testing. The age appropriate plus lens is added to the distance refraction. Patient education is provided, and the instrument is set up for the test. The technician should monitor the patient during testing. Visual fields are performed preoperatively (within one month of enrollment in the study) and annually thereafter. Copies of all visual fields are faxed to the Statistical Coordinating Center for evaluation.

3.8 Optical Coherence Tomography

Quantitative image analysis of the retinal nerve fiber layer (RNFL) and Ganglion Cell (GCA) is performed with Zeiss-Cirrus according to the protocol of (Mwanza et al, Ophthalmology 2012, 119:1151-1158). Cirrus HD-OCT is used to acquire 1 macular (Macular Cube 200×200 protocol) and 1 optic disc (Optic Disc Cube 200×200 protocol) scan in each qualifying eye after pupil dilation with tropicamide 1% and phenylephrine 2.5%. Only good-quality scans, defined as scans with signal strength ≥6, without RNFL discontinuity or misalignment, involuntary saccade or blinking artifacts, and absence of algorithm segmentation failure on careful visual inspection, are used for analysis. Peripapillary RNFL thickness analysis includes the average, superior, and inferior quadrant thicknesses. Parameters from the ONH analysis include the rim area, cup-to-disc area ratio, and vertical cup-to-disc diameter ratio, which were measured automatically by the Cirrus internal ONH analysis algorithm. The GCA algorithm detects and measures the thickness of the macular GCIPL within a 14.13-mm2 elliptical

annulus area centered on the fovea. The following GCIPL thickness measurements are analyzed: average, minimum, and sectoral (superior, superonasal, inferonasal, inferior, inferotemporal, and superotemporal).

3.9 Standard Seated Position (SSP) PERG

This study uses a PERG protocol optimized for glaucoma detection, which does not require topical anesthesia or pupil dilation; the recording electrodes are non-corneal (PERGLA, ref. Porciatti&Ventura Ophthalmology 2004, 111:161-168). Surface gelled cup electrodes (Grass, 9 mm diameter) are taped around the eyes with Blender surgical tape after a small patch of skin (~1 squared centimeter) on both lower eyelids, temples, and forehead is cleansed with disposable skin prep pads (Dynarex). Appropriate lenses for the viewing distance (30 cm) are mounted on a trial frame (Oculus), and the visual acuity for near is tested. This should be Jager J1 or better. Subjects look at the center of visual display pattern of moving black and white bars with both eyes for about 3 min, during which they can blink freely. PERG signal from both eyes are automatically recorded and measured for their amplitude, phase and intratest variability.

3.10 Head Down Tilt (HDT) PERG

IOP (Reichert PT100), automatic systemic blood pressure and heart rate (Vital Signs, Welch-Allyn), and PERG are first recorded with the subjects seated in SSP (Baseline). Subjects are then asked to recline on an electronically adjustable tilting bed (Skytron Elite 5001), which includes a foam-molded neck and shoulder restrainer to help the subject to maintain a comfortable position and prevent sliding in HDT (-10 deg) position. To record HDT-PERG, the PERG instrument is incorporated in a balanced, adjustable frame to align the stimulus with the subject's gaze. The frame includes a quick release handle to immediately move away the instrument from the subject's face for safety reasons. IOP, systemic blood pressure, and heart rate are measured again in the tilted position approximately 7 minutes after baseline readings.

3.11 Disc Photos

Digital optic disk stereo photographs will be obtained at the qualifying visit and at every annual follow up visit.

4. Pressure Lowering Medical Therapy

4.1 Introduction

The principal study intervention is lowering of intraocular pressure in the group randomized to receive this therapy.

4.2 Goal of pressure lowering therapy

The goal is 20% reduction in intraocular pressure from the average of the Baseline IOP, hereafter called treatment baseline. The 20% reduction is not necessary if IOP ≤ 15 mm Hg. Medical therapy is changed and/or added until both goals are met or until the participant is receiving maximum tolerated topical medical therapy. Participants not meeting treatment goals despite maximum tolerated topical medical therapy continue to be followed in the trial.

4.3 Medications to reduce eye pressure

─Prostaglandin analogs include Xalatan®, Lumigan®, and Travatan Z®, and they work by increasing the outflow of fluid from the eye. Side effects are possible changes in eye color and eyelid skin, stinging, blurred vision, eye redness, itching, burning.
─Beta blockers such as timolol are the second most often used class of medication and work by decreasing production of fluid.: side effects are low blood pressure, reduced pulse rate, fatigue, shortness of breath; rarely: reduced libido, depression.
─Carbonic anhydrase inhibitors (CAIs) reduce eye pressure by decreasing the production of intraocular fluid. These are available as eye drops (Trusopt®, Azopt™) as well as pills [Diamox® (acetazolamide) and Neptazane® (methazolamide)].Side effect of eye drops are stinging, burning, eye discomfort.

Side effects of pills are: tingling hands and feet, stomach upset, memory problems, depression, frequent urination.
–Combined medications can offer an alternative for patients who need more than one type of medication: side effects may include any of the side effects of the drug types they contain.

5 Study Organization

Introduction

This single center randomized trial of glaucoma suspects is organized as follows:

- Project Chairman (Vittorio Porciatti, DSc)
- Clinical Center (John McSoley, OD, Steven Gedde, MD, Luis Vazquez MD, Pedro Monsalve, MD, Giacinto Triolo, MD)
- Biostatistics Center (William Feuer, MS, Joyce Shiffman, MS)

Since the patients being treated do not have manifest glaucoma at baseline and risks of treatment are well understood and minimal, no Safety and Data Monitoring Committee was created. However, a Safety and Data Monitoring Plan is created (details in section 5.5).

5.1 Project Chairman

Dr Porciatti, the project chairman, is responsible for ensuring that PERG measurements are completed for each patient and, with the study's clinical coordinator, ensuring integrity of data collection and entry. He is also responsible for obtaining approval for the study and consent form from the local Institutional Review Board.

5.2 Clinical Center

Clinical center personnel include

- A fulltime clinical coordinator (Marlene Colon) who is responsible for
  - Patient scheduling
  - Patient flow in the clinic (ie from ophthalmic examining room to locations of testing for visual field, OCT, photography, PERG),
  - Ensuring completeness of study forms (ie data collection),
  - Data entry.

- Treating optometrist (John McSoley) and ophthalmologists (Steven Gedde and Luis Vazquez) whose responsibilities include:
  - Assessing the eligibility of patients for the Stop-RGCD Study.
  - Enrolling patients in the study through informed consent.
  - Managing each patient in accordance with the randomized treatment assignment.
  - Examining patients using the techniques and schedules established for the study.
  - To work with the clinical coordinator to complete the proper forms and obtain visual fields, OCT scans, and optic disc photos at the appropriate follow-up visits.
  - To promote patient satisfaction and commitment to the trial.

- Research Fellows (Pedro Monsalve, MD, Giacinto Triolo, MD) whose responsibilities include:
- Recording PERG in SSP and during HDT
- Measuring IOP in SSP and during HDT
- Measuring Blood Pressure in SSP and during HDT
- To work with the study coordinator to complete the proper forms and data entry in the Access database.

5.3 Biostatistics Center

The study statistician for the Stop-RGCD study, William J Feuer and Ms. Joyce Schiffman, has the following responsibilities:

- Creation of the variable permuted block randomization lists for the GS-A and GS-S strata.
- Running interim edit checks of study data.
- Performing data analyses and preparing manuscripts with the project chairman.
- Ensuring security of patient data transmitted to the biostatistics center.

5.4 Data Safety and Monitoring Plan (DSMP)

The University of Miami IRB has established that this study is of minimal risk, and the NIH-NEI SRG has established that a formal data safety and monitoring board is not required. However, a complete Data and Safety Monitoring Plan (DSMP) will be used.
The individuals responsible for data safety and monitoring will be the principal investigator Dr. Porciatti, the clinical co-investigators Dr. Gedde MD, Luis Vazquez MD, the optometrist Dr McSoley OD, the research fellows Dr Monsalve MD and Dr Giacinto Triolo MD, the study coordinator Ms. Colon, and the biostatisticians William Feuer MS and Joyce Shiffman, MS. None of these individuals has conflict of interest. Quality control will include regular data verification and protocol compliance checks. The above individuals will meet quarterly to analyze study progress, any new issues, data entry verification, data safety and any protocol deviations. Throughout the study, the clinical co-investigators will monitor the participants for adverse events. Events determined to be unanticipated problems involving risks to subjects or others will be reported by the PI to the IRB within 10 days. Any other adverse events will be reported by the PI to IRB at the time of continuing review. All study staff members will be promptly informed about any unanticipated problems involving risks to subjects or others. If any protocol changes are needed, the PI will submit a modification request to the IRB. Protocol changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB will be promptly informed of the change following implementation (within 10 working days).

6. Policy Matters

6.1 Patient Consent

6.2 Authorship Policy

6.1 Patient Consent

The Stop Retinal Ganglion Cell Dysfunction (Stop-RGCD) Study requires that written consent be obtained from each patient enrolled in the study. The patient is requested to sign the consent form only after patient education is completed. The signed consent form is kept with the study records at the Clinical Center. A copy of the signed consent is given to the patient, and a second copy is sent to the Biostatistics Center.

INFORMED CONSENT FORM [We will ask for official translation in Spanish as the English version is approved]

BASCOM PALMER EYE INSTITUTE
University of Miami
CLINICAL INVESTIGATION CONSENT FORM

TITLE:

Monitoring Early Glaucoma with Pattern Electroretinogram.

PURPOSE:

Glaucoma causes progressive death of cells within the eye that build up the optic nerve. If glaucoma is not diagnosed and treated with eye drops, damage to the optic nerve can result in progressive loss of vision and eventually blindness. You do not have glaucoma, but have suspicious signs in one on both of your eyes that may indicate that you have the disease at a very early stage or you are at risk of developing it in the near future. It is important to check at regular intervals how many optic nerve fibers are present in your eye and how they are functioning. This is possible by means of two noninvasive techniques called pattern electroretinogram (PERG) and Optical Coherence Tomography (OCT). The PERG is the electrical response of the eye when you look at a pattern of moving stripes on a TV monitor. OCT yields an image of the thickness of the retina, from which we can evaluate the amount of optic nerve fibers. We ask you to participate in a research study which will be monitoring the number and the function of your optic nerve fibers over the course of four years. For the duration of the study, you may be asked to use eye drops to lower the intraocular pressure (IOP). This will enable the study to understand if eye drop medication is effective to prevent loss of optic nerve tissue and function over time. This study has been reviewed for its scientific merit and is sponsored by U.S. Government (National Institute of Health, Bethesda, MD). A total of 500 subjects will participate in this research study.

PROCEDURES:

The PERG is recorded from small metallic buttons taped on the skin similarly to an electrocardiogram, with the difference that the electrodes are around the eyes. The only physical

contact you will experience is a gentle cleaning of the skin with an alcohol prep pad. During the test you must look with both eyes at a TV display for about 3 minutes. During the follow up period you may be asked to take one more PERG test lying down in a bed. This will cause a momentary increase of your eye pressure similar to the one that occurs during your normal sleep. This may help to understand whether or not your optic nerve functions normally when the pressure in your eye increases. For OCT evaluation, the pupil has to be dilated with drops as you did before for your eye exam. You have to briefly look at a mark inside the instrument one eye at a time. PERG and OCT will be performed during the same day of your visit with the eye doctor. If you have already done these tests in the past, as part of another study or as part of your standard treatment, the results of these tests will be obtained from your record, and be included in this study.

If you are a participant in the Observation Group, you will be monitored with PERG, OCT, and standard clinical examinations every six months until close of study. If you are a participant in the Medication Group you will be also treated with eye drop medicines.

RISKS:

There are certain risks and discomforts that may be associated with this research. You should be aware that you are at risk of developing glaucoma whether you participate in the study or not. It is not known whether the risk of developing glaucoma is reduced by eye drops to lower eye pressure; the study will attempt to answer this question. If you are include in the Medication Group, another risk is the development of a side effect to one of the prescribed medications:

Prostaglandin analog (include Xalatan®, Lumigan®, and Travatan Z®,) : possible changes in eye color and eyelid skin, stinging, blurred vision, eye redness, itching, burning.

Beta blockers such as timolol: low blood pressure, reduced pulse rate, fatigue, shortness of breath; rarely: reduced libido, depression.

Alpha agonists (Alphagan®P, iopidine®) : burning or stinging, fatigue, headache, drowsiness, dry mouth and nose, relatively higher likelihood of allergic reaction.

Carbonic anhydrase inhibitors (CAIs) as eye drops (Trusopt®, Azopt™): stinging, burning, eye discomfort.

Combined medications can offer an alternative for patients who need more than one type of medication: side effects may include any of the side effects of the drug types they contain.

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For the PERG, the only significant risk to you is a small chance of a rash to the cleansing agent for skin electrodes, which should go away without treatment. For OCT, there is a rare risk to you of an allergic reaction to the drops used to dilate your pupils. The risk is even lower if you did not have any reaction during your previous eye exams. In case of an allergic reaction, your eye

doctor will immediately treat it. If you had previous problems with pupil dilation, you may wish to speak to your eye doctor about the option of doing this additional test.

BENEFITS:

There is no benefit to you in participating in this study.

COSTS:

PERG testing will be provided at no expense to you. OCT, visual fields, and eye drops medications will be billed to your insurance and, just as for visual fields, may require authorization before OCT is performed. You should be aware that you may be expected to travel and park at your own expense to and from our facility. PERG and OCT testing will be scheduled on the same day as your visit to the doctor.

ALTERNATIVES:

You have the alternative not to participate in this study

COMPENSATION for INJURY:

Although risks are unlikely, if injury should occur, treatment will in most cases be available. If you have insurance, your insurance company may or may not pay for these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be expected to pay. Funds to compensate for pain, expenses, lost wages and other damages caused by injury are not routinely available.

CONFIDENTIALITY:

Your consent to participate in this study includes consent for the investigator and her assistants to review all your medical records as may be necessary for the purpose of the study. The investigator and his assistants will consider your records confidential to the extent permitted by law. Your records and results will not be identified as pertaining to you in any publication without your expressed permission. The U.S. Department of Health and Human Services (DHHS) or the Food and Drug Administration (FDA) may request to review and obtain copies of your research records. Your records may also be reviewed for audit purposes by authorized University of Miami employees or other agents who will be bound by the same provisions of confidentiality.

RIGHT TO WITHDRAW:

Your participation is voluntary. You have the right to withdraw or refuse to participate. Your withdrawal or lack of participation will not prejudice your future care. The principal investigator can remove you from the study without your consent either because of your failure to follow the study, if he/she feels it is in your best interest medically, or for administrative reasons.

OTHER PERTINENT INFORMATION:

The principal investigator will answer any questions you may have regarding the investigation. If you have any questions about your rights as a research subject you should contact the Human Subjects Research Office at (305) 243-3195, Fax (305) 243-3328

_____ _____

Signature of subject Date

_____ _____

Signature of witness Date

_____ _____

Signature of Person Obtaining Consent Date

_____

Print Name of Person Obtaining Consent
Principal Investigator's Name: Vittorio Porciatti, Dsc
Telephone Number: Day_305-326-6050; Night_ Cell: 786-543-1766

6.2 Authorship Policy

Authorship of Stop-RGCD will be determined at the discretion of the project chairman.

Clinical Center Procedures

7.1 Qualifying Assessment

7.2 Assignment of Patient Identification Number

7.3 Randomization Procedure

7.4 Schedule of Visits

7.1 Qualifying Assessment

The Qualifying Assessment establishes whether the patient satisfies Stop-RGCD Study eligibility criteria. If the patient appears to be eligible for the study, the Clinical Center completes the Qualifying Assessment Form and faxes it to the Statistical Coordinating Center, along with a copy of the consent form. Informed consent is an eligibility criterion because it is an agreement by the patient to be randomized and complete follow-up in their treatment group. The SCC reviews each of the inclusion and exclusion criteria to ensure that the patient is eligible. **It is vital to the scientific validity of the study that every eligible patient be offered enrollment.**

7.2 Assignment of Patient Identification Number

Any patient who is confirmed by the Statistical Coordinating Center to meet the eligibility criteria and is enrolled in the study is assigned a patient identification number.

7.3 Randomization Procedure

Randomization takes place at the time the patient is enrolled in the study. After patient eligibility is confirmed and a patient identification number is provided, the Statistical Coordinating Center assigns treatment by saying, “Treatment” or “No Treatment”. The Clinical Center then repeats the assigned treatment. The treatment/no treatment date is the study entry date, and the dates for all follow-up visits are computed from this date.

The randomization schedule is constructed using a computer pseudo-random number generator. The allocation ratio is equal between the two treatment groups. The randomization is blocked by clinic and study stratum using a scheme with small variable blocks. This procedure ensures that there is an equal number of patients in each treatment group even early in the trial, and that the CC is not able to predict the next treatment assignment.

7.4 Schedule of Visits

All study investigators must be familiar with the schedule of visits to ensure that required data is collected and that future visits are scheduled within the appropriate time windows. The need for continued follow-up and timely visits should be stressed to the patient during the informed consent process and throughout the study. An appointment schedule is generated for each patient by the Statistical Coordinating Center and sent to the patient’s Clinical Center. Table 1 summarizes the required data at each of the scheduled visits.

Year of Study Study Visit	Baseline 1	Baseline 2	Month 6	Year 2 FUp Yr 1	Year 3 FUp Yr 2	Year 4 FUp Yr 3	Year 5 FUp Yr 4	Year 5 FUp Yr 4 repeat
Medical History	**x**							
Ocular History	**x**							
Refraction	**x**			**x**	**x**	**x**	**x**	
Visual Acuity	**x**		**x**	**x**	**x**	**x**	**x**	
Visual Field	**x**	**(x) If not done on the first visit**		**x**	**x**	**x**	**x**	
PERG		**x**	**x**	**x**	**x**	**x**	**x**	**x**
Eye Examination	**x**		**x**	**x**	**x**	**x**	**x**	**x**
IOP	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Corneal Thickness	**x**							
Gonioscopy	**x**							
Dilated Fundus	**x**			**x**	**x**	**x**	**x**	**x**
Ophthalmoscopy	**x**		**x**	**x**	**x**	**x**	**x**	**x**
Disc Photos	**x**	**(x) If not done on the first visit** **x**		**x**	**x**	**x**	**x**	
OCT Randomization/ treatment onset	**x**	**(x) If not done on the first visit** **x**		**x**	**x**	**x**	**x**	**x**

8. Data Management And Security

8.1 Data Management
8.2 Data Security
8.3 Data Forms

8.1 Data Management

A master log is kept of each patient enrolled in the STOP-RGCD Study. An appointment schedule is made for each patient and sent to the patient's Clinical Center. When a data form is received at the Statistical Coordinating Center, it is processed for filing and data entry. Each form is data entered by a data entry clerk and then verified by double entry by the SCC Research Coordinator. Edit checks, such as missing data and out-of-range values, will be clarified within the CC.

The statistical package SPSS is used for data entry, management, and analysis. Each of the study's two statisticians has a personal computer and one more is dedicated to data entry. The Research Coordinator also has a personal computer to use for data management, study correspondence, reports, and manuscripts. Each computer, except the one dedicated to data entry, has access to the University of Miami's network for e-mail, Internet access, and data file transfer.

8.2 Data Security

The paper data forms for the STOP-RGCD Study are kept in file cabinets in the Biostatistics facility in the McKnight Research Building. The building is locked and access is by card key entry. A security guard is present during working hours. The computer files for the study are kept on computers in the same location. These rooms are kept locked when not in use, and the study computer files are password-protected. The data is backed up weekly, and monthly backups are stored at a remote facility. Computer data files used for publication are saved and stored as separate files.

8.3 Data Forms

The data forms were designed to be self-explanatory. Their completion should not require reference to separate information manuals. The data forms contain information to be collected at a given point in time during the study. Information collected at another date is incorporated into a separate form. Data forms are faxed to the Statistical Coordinating Center for data entry. Forms will be reviewed periodically and revised as dictated by protocol changes. The various data forms are provided at the end of this section.

BASCOM PALMER EYE INSTITUTE
Monitoring Glaucoma Subject Data Sheet (Standard Seated Position)

Visit Date	**Last Name**	**First Name**	**BP #**

Enroll Date	*Birth Date*	*Gender* *1 M 2 F*	*Ethnicity* *1 Hisp 2 non-Hisp*	*Race* *1 C 2 AA 3 As* *4 Other*	*Fam. History Glaucoma* *1 Absent 2 Present*	*CCT*	
						OD	
						OS	

Distance Refraction	**Sphere**	**Cylinder**	**Axis**	**Snellen acuity**	**Cataract**
OD				/	
OS				/	
Near Refraction (30cm)	**Sphere**	**Cylinder**	**Axis**	**Jaeger acuity**	**Contact lenses**
OD				**J**	
OS				**J**	

Severity		**Medical Treatment**				
OD	1 GS 2 HRGS 3 Control	1 β-block	2 α_2-ago	3 CAI	4 Prost	5 Other
OS	1 GS 2 HRG 3 Control	1 β-block	2 α_2-ago	3 CAI	4 Prost	5 Other

	IOP	**SAP Reliability**	**GHT**	**MD**	**PSD**
OD		1 Normal 2 Low	1 WNL 2 BL 3 ONL 4 GRS 5 AHS		
OS		1 Normal 2 Low	1 WNL 2 BL 3 ONL 4 GRS 5 AHS		

Optic Disc	**Clinical Vertical C/D**	**Localized Thinning**	**Splinter Hemorrhage**	**Disc Photos**	**OCT today**
OD		1 Absent 2 Present	1 Absent 2 Present	1 Not Done 2 Done	1 Yes 2 No
OS		1 Absent 2 Present	1 Absent 2 Present		

PERG	**Amplitude**	**Phase**	**Noise**
OD			
OS			

Notes:

_____
Obtained Data (Signature)

BASCOM PALMER EYE INSTITUE
Monitoring Glaucoma and Control Subject Data Sheet (Head-down Tilt procedure)

Visit Date	Last Name	First Name	BP #

Birth Date	Gender 1 M 2 F	Ethnicity 1Hisp 2 non-Hisp	Race 1CC 2AA 3A 4Other	Family History Glaucoma 1 Absent 2Present

Diagnosis (severity)		Medical Treatment				
OD	1 GS 2 HRGS 3 Control	1 β-block	2 α2-ago	3 CAI	4 Prost	5 Other
OS	1 GS 2 HRGS 3 Control	1 β-block	2 α2-ago	3 CAI	4 Prost	5 Other

Distance Refraction	Sphere	Cylinder	Axis	Snellen acuity	Cataract
OD				/	
OS				/	
Near Refraction	**Sphere**	**Cylinder**	**Axis**	**Jaeger acuity**	**Contact lenses**
OD				**J**	
OS				**J**	

B/P (seated)	IOP OD (seated)	IOP OS (seated)	PERG (seated)	Amplitude	Phase	Noise
			OD			
			OS			

B/P (HDT)	IOP OD (HDT	IOP OS (HDT	PERG (HDT)	Amplitude	Phase	Noise
			OD			
			OS			

Notes:

Signature _____