**A Multicenter, Partially-Masked, Randomized, Controlled Study of Medical Therapy vs. Medical Therapy plus Optic Nerve Sheath Fenestration vs. Medical Therapy plus Stereotactic Ventriculoperitoneal Cerebrospinal Fluid Shunting in Subjects with Idiopathic Intracranial Hypertension and Moderate to Severe Visual Loss**

***Surgical Idiopathic Intracranial Hypertension Treatment Trial ("SIGHT")***

**IND Sponsor: Michael Wall, MD**

**Version Number: 4.0**

## 11 April 2019

# KEY ROLES

| | |
|---|---|
| | |
| **Name, degree** | Michael Wall, MD |
| **Title** | Study Director |
| **Institution Name** | University of Iowa Hospitals and Clinics |
| | |
| **Name, degree** | Matthew Thurtell, MBBS, MSc |
| **Title** | Study co-Director |
| **Institution Name** | University of Iowa Hospitals and Clinics |
| | |
| **Name, degree** | Mark Kupersmith, MD |
| **Title** | Enrollment and Resource Centers Director |
| **Institution Name** | Mount Sinai |
| | |
| **Name, degree** | Stephanie DuBose, MPH |
| **Title** | Coordinator Center Director |
| **Institution Name** | Jaeb Center for Health Research (JCHR) |
| | |
| **Name, degree** | Robert Lindblad, MD |
| **Title** | Medical Monitor |
| **Institution Name** | EMMES Corporation |

# VERSION HISTORY

The following table lists versions of the protocol:

| VERSION NUMBER | AUTHOR | APPROVER | EFFECTIVE DATE | REVISION DESCRIPTION |
|---|---|---|---|---|
| 1.0 | Michael Wall, Matthew Thurtell, Stephanie DuBose | Stephanie DuBose | 04Jan2018 | Original version |
| 2.0 | Stephanie DuBose | Stephanie DuBose | 20Feb2018 | • Removed terms 'maximal' and 'initial' in reference to medical therapy and clarified that diet is part of medical therapy for all groups<br>• Replaced 'study/non-study' eye with 'eligible/non-eligible' eye throughout<br>• Modified lumbar puncture inclusion criteria to not require a repeat lumbar puncture if done within 6 weeks (instead of 28 days) and to not require grade II to V papilledema<br>• Removed 200-mile inclusion criteria and instead added criteria of good candidate for study based on investigator judgement<br>• Added note that if neurologic exam abnormalities are found, the patient should be discussed with the Study Director to determine eligibility<br>• Clarification on exclusion criterion for abnormal CT or MRI<br>• Removed breastfeeding as exclusion criterion<br>• Clarification on how visual field examinations are determined to be reliable and when they will be repeated<br>• Removed assessment of furosemide compliance by pill counts since not feasible<br>• Removed CBC and Metabolic Panel from study visit procedures at 4 and 8 weeks<br>• Clarified that Adjudication Committee will be masked to treatment group and all cases will be reviewed first by the Study Director.<br>• Added details on treatment failure criteria and moved surgery specific criteria to appropriate section<br>• Clarification on discontinuation of study drug in relation to pregnancy, birth control, and breastfeeding<br>• Removed details related to certification of study surgeons, as this will be detailed in the MOP<br>• Clarified primary outcome throughout<br>• Added clarifications and revisions to statistical chapter<br>• Corrected typos |
| 2.1 | Stephanie DuBose | Stephanie DuBose | 19Mar2018 | • Revised SMRC criteria (text and figure)<br>• Updated study design figure to match primary outcome<br>• Corrected typos and clarified text throughout<br>• Removed extraneous text throughout |

| VERSION NUMBER | AUTHOR | APPROVER | EFFECTIVE DATE | REVISION DESCRIPTION |
|---|---|---|---|---|
| 2.2 | Stephane DuBose | Stephanie DuBose | 04Apr2018 | • Revised titration and tapering schedule<br>• Clarified when to contact Study Director vs co-Director for questions<br>• Clarified management of non-eligible eye section to be consistent with rest of protocol<br>• Removed specification on timing of repeat perimetry |
| 3.0 | Stephanie DuBose | Stephanie DuBose | 21May2018 | • Exclusion criterion related to abnormal CSF contents changed to >8 cells, as 0-8 cells in CSF is considered within normal limits<br>• Clarified refractive error exclusion<br>• Updated AE reporting for known side effects of study drug and surgical AEs<br>• Updated details in Stored Specimens section and removed future testing that will not be done; removed duplicate text from data collection chapter<br>• Corrected typos<br>• Removed unnecessary abbreviations |
| 3.1 | Stephanie DuBose | Stephanie DuBose | 09Jul2018 | • Amended exclusion criterion related to abnormal CSF contents<br>• Corrected typos |
| 3.2 | Stephanie DuBose | Stephanie DuBose | 23Jul2018 | • Updated AE reporting for lab abnormalities<br>• Corrected typos |
| 4.0 | Nicole Foster, Stephanie DuBose | Stephanie DuBose | 11Apr2019 | • Revised exclusion criteria to allow greater monthly dosage of previous treatment with acetazolamide and methazolamide<br>• Revised exclusion criteria regarding conditions requiring steroid use and clarified that during study, steroids only permitted during ONSF surgery.<br>• Removed IOP requirement from follow up visits<br>• Clarified that size III VF test is optional at screening and not required at 26-week visit<br>• Updated amount of blood to be drawn for future research from 50 to 20 ml<br>• Revised OCT testing frequency at screening to only be required once instead of twice for all subjects<br>• Removed details on tapering schedule for participants in VPS group after shunt, to include in MOP instead<br>• Made clarifications to study procedures grid<br>• Clarified AE relatedness description to include all study procedures<br>• Revised a few analyses details in Statistical Considerations chapter to match Statistical Analysis Plan<br>• Corrected typos |

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| CC | Coordinating Center |
| CFR | Code of Federal Regulations |
| CRF | Case Report Forms |
| CSF | Cerebrospinal Fluid |
| DSMC | Data Safety Monitoring Committee |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| IIH | Idiopathic Intracranial Hypertension |
| IIHTT | Idiopathic Intracranial Hypertension Treatment Trial |
| ICH | International Conference on Harmonization |
| IND | Investigational New Drug |
| IRB/IEC | Institutional Review Board/Independent Ethics Committee |
| JCHR | Jaeb Center for Health Research |
| MOP | Manual of Procedures |
| MRI | Magnetic Resonance Imaging |
| NEI | National Eye Institute |
| NORDIC | Neuro-Ophthalmology Research Disease Investigator Consortium |
| OCT | Optical Coherence Tomography |
| OCTRC | OCT Reading Center |
| ONSF | Optic Nerve Sheath Fenestration |
| PMD | Perimetric Mean Deviation |
| PRC | Photography Reading Center |
| QoL | Quality Of Life |
| RC | Resource Center |
| RCT | Randomized Clinical Trial |
| SAE | Serious Adverse Experience |
| SIGHT | Surgical Idiopathic Intracranial Hypertension Treatment Trial |
| SMRC | Surgical Malfunction Review Committee |
| SQAC | Surgical Quality Assurance Committee |
| TF | Treatment Failure |
| VFRC | Visual Field Reading Center |
| VPS | Stereotactic Ventriculo-Peritoneal CSF Shunting |

# PROTOCOL SUMMARY

| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| **Title** | A Multicenter, Partially-Masked, Randomized, Controlled Study of Medical Therapy vs. Medical Therapy plus Optic Nerve Sheath Fenestration vs. Medical Therapy plus Stereotactic Ventriculoperitoneal Cerebrospinal Fluid Shunting in Subjects with Idiopathic Intracranial Hypertension and Moderate to Severe Visual Loss ("SIGHT") |
| **Précis** | Randomized trial of adults (≥18 years old) with idiopathic intracranial hypertension and moderate to severe visual loss without substantial recent treatment who are randomly assigned to (1) medical therapy, (2) medical therapy plus ONSF, or (3) medical therapy plus VPS. The primary outcome is visual field mean deviation change at first of Month 6 (26 weeks) or time of treatment failure of the eligible eye(s), followed by a continuation study to assess time to treatment failure. The determination of eligible eye(s) is based on meeting the eligibility criteria at baseline. |
| **Study Objectives** | Primary objective: to determine whether the efficacy of stereotactic ventriculo-peritoneal CSF shunting (VPS) with medical therapy is superior to medical therapy alone or optic nerve sheath fenestration (ONSF) with medical therapy in reducing or reversing visual loss in subjects with idiopathic intracranial hypertension and moderate to severe visual loss.<br>Secondary objective: To assess time to treatment failure over up to 3 years. |
| **Study Design** | Multi-center randomized single-masked phase 3 clinical trial<br>• RCT is followed by a treatment failure identification phase (up to 3 years of follow-up total) |
| **Number of Sites** | ~40 sites |
| **Endpoint** | **Primary Efficacy Outcome:**<br>• Change from baseline to first of Month 6 (Week 26) or time of treatment failure in PMD (perimetric mean deviation) in eligible eye(s) with the size V stimulus.<br>**Key Secondary Efficacy Outcomes:**<br>• Time from randomization to treatment failure<br>• CSF pressure measurement by lumbar puncture<br>• Papilledema grade<br>• OCT measures<br>• QOL assessments<br>• Visual field examination ratings (improved, remained the same, or worsened)<br>**Key Safety Outcomes:** Vision loss, all reported adverse events<br>**Other Key Outcomes:** Change in weight |

| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| **Population** | **Subject Eligibility Criteria**<br>**Inclusion Criteria**<br>1. Diagnosis of IIH by modified Dandy criteria (Table 4)<br>2. Age 18 to <64 years at time of consent<br>3. Age 18 to <61 years at time of diagnosis (time of diagnosis is the time at which the patient meets the modified Dandy criteria, usually after the lumbar puncture results are reviewed)<br>4. Presence of bilateral papilledema<br>5. Lumbar puncture within 6 weeks of screening visit or completed as part of screening: Opening CSF pressure >250 mmH2O **or** 200 to 250 mmH2O, with at least one of the following:<br>• Pulse synchronous tinnitus<br>• Cranial nerve VI palsy<br>• Echography for disc drusen negative and no other disc anomalies mimicking disc edema present<br>• MRV with lateral sinus collapse/stenosis, partially empty sella turcica on coronal or sagittal views of MRI, and optic nerve sheaths with filled out CSF spaces next to the globe on T2 weighted axial MRI scans<br>*If the patient was treated with intracranial pressure lowering agents (e.g., acetazolamide) prior to obtaining a lumbar puncture, the agent(s) must be discontinued for at least 24 hours prior to performing the diagnostic lumbar puncture.*<br>6. At least one eye meeting all eligible eye inclusion criteria and no exclusion criteria.<br>7. Able to provide informed consent<br>8. Investigator believes participant is a good candidate for the study, including the probability of returning for follow-up.<br>**Exclusion Criteria**<br>1. Treatment of IIH within the past 3 months with either (1) the maximally tolerated dosage of acetazolamide for at least one week or (2) more than one month of acetazolamide with a cumulative dosage of more than 45 grams<br>*'Maximally-tolerated dose' is defined as dosage was reached where dosage could not be increased further either because of side effects or because a daily total dosage of 4 grams per day was reached.*<br>*If individual discontinued acetazolamide in the past due to side effects individual is only eligible if investigator believes that the individual is likely to tolerate acetazolamide, as it will be prescribed in the study.*<br>2. Treatment of IIH within the past 3 months with either (1) the maximally tolerated dosage of methazolamide for at least one week or (2) more than one month of methazolamide with a cumulative dosage of more than 4.5 grams<br>*'Maximally-tolerated dose' is defined as dosage was reached where dosage could not be increased further either because of side effects or because a daily total dosage of 400 mg per day was reached.*<br>3. Treatment with topiramate within two months and average cumulative dosage for the preceding month of more than 700 mg per week |

| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| | 4. Previous surgery for IIH, including ONSF, CSF shunting, subtemporal decompression, or venous sinus stenting; *gastric surgery for obesity is allowed*<br>5. Abnormalities on neurologic examination except for papilledema and its related visual loss or cranial nerve VI to VII paresis; *if other abnormalities are present, the patient will need to be discussed with the Study Director for study entry.*<br>6. Abnormal CT or MRI scan (intracranial mass, hydrocephalus, dural sinus thrombus, or arteriovenous malformation) other than findings known to occur with increased intracranial pressure. *Abnormalities on MRI that are not known to cause increased intracranial pressure are acceptable*.<br>7. Abnormal CSF contents: increased cells: > 8 cells; elevated protein: > 45 mg%; low glucose: < 30 mg% *(If the lumbar puncture produces a cell count compatible with a traumatic needle insertion, the patient does not need to be excluded if the CSF WBC after correction is 8 cells/mm$^3$ or less - see MOP for calculation. If >8 cells or >45mg% in CSF protein are documented in the CSF or calculated after conversion from a traumatic lumbar puncture, the patient can be discussed with the Study Director for possible inclusion.)*<br>8. Abnormal blood work-up indicating a medical or systemic condition associated with raised intracranial pressure<br>9. Diabetes mellitus with diabetic retinopathy<br>10. Ingestion of a drug or substance, or presence of a disorder, that has been associated with increased intracranial pressure within 2 months of diagnosis, such as lithium, vitamin A related products (e.g. Retin-A), or various cyclines *(see MOP for conditions and drugs)*<br>11. Laboratory test results showing severe anemia, leukopenia or thrombocytopenia, renal failure, or hepatic disease, based on the Site Investigator's judgment<br>12. Other condition requiring continued use of oral, I.V. or injectable steroids *(nasal, inhaled, or topical steroids are allowed since the systemic effects are small). Patients with a condition that resulted in recent or current use of steroids but may be safely tapered off will be handled on a case-by-case basis after discussion with Study Director/co-Director. See MOP for details.*<br>13. Presence of a medical condition that would contraindicate use of acetazolamide or furosemide or significantly increase surgical risk<br>14. Pregnancy or unwillingness for a subject of childbearing potential to use contraception during the first 6 months of the study<br>*Women of childbearing potential must use an acceptable form of birth control. Acceptable forms include oral contraceptives, IUDs transdermal contraceptives, diaphragm, condoms with spermicide, documented surgical sterilization of either the subject or their partner, or abstinence.*<br>15. Presence of a physical, mental, or social condition likely to affect follow-up (drug addiction, terminal illness, no telephone, homeless)<br>16. Anticipation of a move from the site area within six months and unwillingness to return for follow-up at a SIGHT study site<br>17. Allergy to pupil dilating drops or narrow angles precluding safe dilation |

| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| | 18. Presence of a condition that contraindicates general anesthesia<br>19. Participation in an investigational trial within 30 days of enrollment that involved treatment with any systemic drug therapy or therapy that affects the eligible eye(s)<br><br>**Eye-Level Eligibility Criteria**<br>Subjects must have at least one eye meeting all of the inclusion criteria and none of the exclusion criteria.<br>If both eyes meet eligibility criteria at the baseline examination, both will be included in the primary outcome analysis.<br>**Inclusion**<br>1. Visual field loss meeting the following criteria based on two full threshold 24-2 size V tests reviewed by the VFRC:<br>• PMD from -6 dB to -27 dB<br>• Reproducible visual loss present on automated perimetry including no more than 15% false positive response<br>2. Visual acuity better than 20/200 (39 or more letters correct)<br>**Exclusion**<br>1. Intraocular pressure currently >28 mm Hg or >30 mm Hg at any time in the past<br>2. Refractive error of more than -6.00 or more than + 6.00 sphere or more than 3.00 cylinder with the following exceptions:<br>• Eyes with more than 6.00 D of myopia of but less than 8.00 D of myopia are eligible if: 1) there are no abnormalities on ophthalmoscopy related to myopia that are associated with visual loss (such as staphyloma, retinal thinning in the posterior pole, or more than mild optic disc tilt), and 2) the individual will wear a contact lens for all perimetry examinations with the appropriate correction.<br>• Eyes with more than 6.00 D of hyperopia but less than 8.00 D of hyperopia are eligible if: 1) there is an unambiguous characteristic halo of peripapillary edema as opposed to features of a small crowded disc or other hyperopic change related to visual loss determined by the Site Investigator or the PRC Director (or his designate), and 2) the individual will wear a contact lens for all perimetry examinations with the appropriate correction (which can be corrected for perimetry or with the patient's own contact lens with over correction by lens at the perimeter).<br>*Note: Refractive error exclusion and exceptions refer to sphere not spherical equivalent, with cylinder expressed in plus format.*<br>3. Other disorders causing visual loss except for refractive error and amblyopia, including cells in the vitreous or iritis<br>4. Large optic disc drusen on exam or known in previous history (small drusen of the disc can occur with longstanding papilledema and are allowed if not so numerous that investigator determines they are contributing to vision loss) |
| **Sample Size** | 180 subjects entering randomized trial<br>• 90% power to detect a difference in mean change of visual field between groups assuming a true population difference between any 2 of 3 groups = 4.5dB with a two-tailed Bonferroni-adjusted significance level of 1.7%, assuming no more than 10% of subjects withdrawing. |

| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| **Treatment Groups** | Random assignment (1:1:1) to (1) medical therapy, (2) medical therapy plus ONSF, or (3) medical therapy plus VPS. |
| **Subject Duration** | ~7 months- 3 years |
| **Protocol Overview/Synopsis** | After signing the informed consent form, potential subjects will be assessed for eligibility, including eliciting medical and neurologic history, measurement of best-corrected visual acuity, visual field testing, ophthalmoscopy with optic disc edema grading, physical examination, and OCT. Questionnaires will be completed. Blood will be drawn for CBC, electrolytes, liver function tests, renal function tests, amylase if not done as part of routine care within 4 weeks and a pregnancy test will be performed (women of childbearing potential).<br>Two visual field examinations using a size V stimulus will need to be performed at the Screening/Baseline Visit. The size V fields will be sent to the VFRC to confirm eligibility or determine that testing must be repeated for the subject.<br>Eligible individuals will be randomly assigned with equal allocation to one of 3 treatment groups: (1) medical therapy, (2) medical therapy plus ONSF, or (3) medical therapy plus VPS. Acetazolamide should be started on the day of randomization. Surgery should be performed as soon as possible, ideally within 3 days of randomization, but not more than 7 days.<br>Medical therapy will consist of a low sodium weight loss diet and acetazolamide with or without furosemide. Treatment will start with acetazolamide 2 grams per day, with the dose increased as tolerated up to 4 grams per day. If there is no clinical improvement after 2 weeks of maximal dosage of acetazolamide, furosemide will be started at a dose of 40 mg per day (along with potassium) and titrated up to 160-200 mg per day. Pharmacotherapy will be tapered when there is improvement in the papilledema grade, substantial improvement in the PMD and improvement in symptoms or when there is a safety concern.<br>The primary outcome is measured at the first of 6 months (26 weeks) or time of treatment failure. During the randomized trial, follow-up visits will occur after weeks 4, 8, 16, and 26 (± 7 days). Safety visits will occur after weeks 1 and 2 (± 4 days). Additional office visits may occur as needed. Phone contacts will occur after 12 and 20 weeks (±7 days).<br>After the 6-month primary outcome visit, subjects will transition to the Treatment Failure Identification Phase for up to 3 years. Ongoing treatment will continue following the guidelines for the first six months as long as treatment failure criteria are not met at which time treatment will be at the discretion of the Site Investigator. Investigators are urged to employ treatments from another arm of the study before other treatments under these circumstances. |

# Chapter 1: Introduction

## 1.1 Background

Idiopathic intracranial hypertension (IIH), previously called pseudotumor cerebri, is a disorder of elevated intracranial pressure of unknown cause. Its incidence is rising with the obesity epidemic, with about 22.5 new cases each year per 100,000 overweight women of childbearing age. It affects at least 100,000 Americans. Because of pressure on the optic nerve (papilledema), 86% have visual loss and 10% develop severe visual loss.[1]

We recently completed the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), a multicenter, randomized, double-masked, placebo-controlled study of 165 subjects with IIH and mild visual loss. We showed that the acetazolamide-plus-diet regimen was significantly superior to placebo-plus-diet for improving perimetric mean deviation (PMD), papilledema grade, quality of life measures (QoL) and intracranial pressure.[2]

In patients with IIH who have moderate to severe visual loss at presentation, no intervention, neither medical nor the various surgical treatments, has been verified as efficacious by well-designed clinical trials. The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) Network has identified management of moderate to severe visual loss in IIH as an investigational priority. The NORDIC Executive Committee has provided the guidance for the development of a second prospective IIH treatment trial, the Surgical IIHTT (SIGHT– pronounced "Sight"). NORDIC will provide the infrastructure to accomplish the proposed study, consisting of experienced study leadership, ~40 sites (most of whom had successfully executed the IIHTT), Coordinating Center, Reading Centers, and an Enrollment Center. The goals of the proposed study are: (1a) to establish evidence-based treatment strategies to restore and protect vision in IIH patients with moderate to severe visual loss; (1b) to compare currently used treatment strategies with respect to the cumulative probability of treatment failure over time to determine long-term outcomes; (2a) to determine how interventions that purportedly lower intracranial pressure affect deformation of the peripapillary retinal pigment epithelial – Bruch's membrane layer (ppRPE/BM layer) using optical coherence tomography (OCT) imaging; and (2b) to determine the predictive value of OCT retinal ganglion cell layer (GCL) thickness at baseline for visual outcome.

To address these aims, we will enroll 180 newly diagnosed* IIH patients with a perimetric mean deviation (PMD) between -6 and -27 dB in at least one eye, as determined by full threshold standard automated perimetry using the size V stimulus. We will compare the efficacy of 1) medical therapy alone, 2) surgical intervention via optic nerve sheath fenestration (ONSF) with medical therapy, and 3) surgical intervention via ventriculo-peritoneal cerebrospinal fluid (CSF) shunting with medical therapy. Subjects will be followed for an initial 6-month intervention phase, followed by transition to the treatment failure identification phase with clinical follow-up at 12 months, 24 months, and 36 months. After one year, there will be quarterly telephone contact to determine the subject's clinical status.

* Nearly all subjects will be "newly diagnosed;" however, if a patient was previously diagnosed but not treated, they will undergo another evaluation for IIH and visual loss to assess eligibility. We expect this situation to be rare.

## 1.2 Clinical Experience

### 1.2.1 Visual Loss in IIH

IIH has four stages based on severity of visual loss. The first stage (20% of IIH patients) exhibits papilledema and symptoms, but no visual field loss. The second stage (40% of cases), the target for the IIHTT, is characterized by mild visual field defects and prompts effective intervention. The third stage (30% of cases), a target for the SIGHT, is characterized by moderate visual loss. Stage three patients have symptomatic vision loss and current thinking, without class I or II evidence, suggests that aggressive intervention is required to prevent blindness. In the fourth stage (10% of cases), also a target for the SIGHT, severe visual loss occurs, which can worsen rapidly to blindness.

Medical treatments, including diet, acetazolamide, and furosemide, are the interventions usually employed for the first two stages of IIH. Several retrospective studies of obese patients with IIH suggest that weight loss may be associated with reduction in papilledema grade. The IIHTT demonstrated that acetazolamide-plus-diet led to a statistically significant improvement in vision and significant improvements in papilledema grade, CSF pressure, and quality of life measures at 6 months compared to placebo-plus-diet in patients with mild visual loss.

Surgical treatments, such as ONSF and CSF shunting, with or without medical therapy, are commonly employed in the third and fourth stages of IIH.

### 1.2.2 Optic Nerve Sheath Fenestration for IIH

Hayreh,[3] using a primate model, demonstrated efficacy of ONSF for relief of experimental papilledema. Later, Smith et al.[4] reported successful relief of papilledema in a human after ONSF. ONSF consists of either creating a window or making a series of slits in the optic nerve dural sheath just behind the globe in one eye. This treatment has been used for patients with progressive visual loss, and over 50% of patients with IIH have post-operative headache relief.[5]

Several hypotheses exist as to the mechanism of action of ONSF. The demonstration of fistula formation[6,7] and some improvement of papilledema in the unoperated eye suggest that ONSF efficacy may be due to local decompression of the subarachnoid space with filtration of CSF into the orbit.[8] CSF pressure may be modestly lowered post-operatively, but the duration and magnitude of this effect is unknown. Another possible long-term mechanism of action of ONSF may be secondary closure of the subarachnoid space via fibrosis at the surgical site, thereby preventing transmission of pressure to the optic nerve head.[9,7] The success of surgical decompression of the optic nerve, however, may be limited by several factors that are not yet fully understood. Trabeculations within the retrobulbar subarachnoid space may contribute to resistance of bidirectional CSF flow between the optic nerve sheath and the intracranial subarachnoid space; this compartmentalization of CSF, demonstrated in vivo by Killer et al.,[10] may be responsible for the occasional failure of the fellow eye to improve after ONSF.[11] On the other hand, there may be free flow from the fenestration site to the full CSF space and a generalized pressure lowering effect may occur. It is not known which if either of these mechanisms prevails.

A meta-analysis of large case series suggests efficacy of ONSF in IIH. Post-operative visual acuity or visual field results were equal to, or better than, pre-operative results in 87% of patients

reported; however, 13% of patients had worse vision in the post-operative period. A report on 75 eyes from 54 patients undergoing ONSF suggested that patients undergoing ONSF may have substantial long-term failure rates.[12] This study defined perimetric mean deviation worsening as > 2 dB deterioration in PMD post-operatively on a single visual field exam. By this criterion, 68% of eyes improved or stabilized and 32% worsened. However, these results are suspect since a 2 dB or greater mean deviation worsening is within observed individual retest variability in patients with moderate to severe visual field damage and a confirming visual field should have been required.[13] Although ONSF appears to be helpful in the short term for visual loss, other interventions, such as weight loss or acetazolamide, may have a delayed, but long-term benefit. There are no quality of life (QoL) studies of ONSF in IIH. The uncertainties concerning the short- and long-term efficacy and safety of ONSF in moderate to severe IIH can only be addressed with a prospective, randomized, controlled trial.

#### 1.2.3 CSF Shunting for IIH

Various CSF shunting procedures have been employed for the treatment of IIH, including lumbo-peritoneal (LP), ventriculo-atrial (VA), ventriculo-jugular, and ventriculo-peritoneal (VP) shunting.[14-17] In general, the indication for a CSF shunting procedure has been failed medical therapy or intractable headache. Most series document efficacy in preserving vision in most cases, but there was a high rate of shunt failure and shunt revisions were often required.[14-18] While shunting preserved vision in many patients, long-term headache relief was achieved in only 50% over 36 months.[19] Many of the shunts inserted were lumbo-peritoneal; these are now out of favor due to a high complication rate, which includes frequent shunt occlusion, infection, and intracranial hypotension. Stereotactically inserted ventriculo-peritoneal shunts (VPS) have a lower failure and complication rate, and are easier to monitor and adjust.[19-22]

There is no consensus regarding strategies for therapeutic intervention for IIH patients with moderate to severe visual loss. Furthermore, the mechanisms of action of the treatments and their effectiveness remain uncertain.[23] Various therapies have been used to treat IIH, but prior to the IIHTT, their safety and efficacy had not been adequately evaluated in prospective, randomized, controlled trials. Although there are large variations in practice, most physicians wait until there is more advanced visual loss before recommending a surgical intervention. However, all studies evaluating interventions for IIH with more advanced visual loss are anecdotal, retrospective, and uncontrolled. Also, the various surgical procedures for IIH have not been compared with regards to efficacy, safety, complication rate, and long-term outcome. *Thus, as confirmed by a recent Cochrane review, there is an inadequate evidence base to guide clinicians in management of IIH patients with moderate to severe vision loss.*[24]

Based on Curry's results and extrapolating to 2014, estimating 2500 CSF shunt surgeries per year at a cost of about $38,500 per patient, and 250 ONSF surgeries at $23,000 per patient, surgical costs for IIH are estimated at $102 million per year.[25] Friesner and colleagues come to a similar conclusion regarding surgical costs. In addition, they estimated in 2007 dollars the total costs due to IIH to be $444 million per year,[26] so it is imperative that we obtain high quality data regarding the efficacy and safety of surgical treatments for IIH.

### 1.2.4 Pilot Data for Management of Moderate to Severe Visual Loss in IIH

In 2012, the IIH Study Group performed a retrospective chart review of consecutive newly diagnosed patients that met the modified Dandy criteria for IIH[27] from 30 of the 40 IIHTT sites. All patients were seen between January 2009 and September 2012, and had baseline PMD worse than -8.5 dB in at least one eye, as in the eligibility criteria for the SIGHT; this cutoff was chosen based on equipoise of the IIH Study Group – there was discomfort in randomizing subjects to surgery if they did not have at least -8.5 dB PMD in one eye with size III SITA Standard testing. Patients had undergone medical treatment, ONSF, or CSF shunting. Due to a small number of shunt patients, 3 additional sites were asked to abstract charts. Visual field outcomes (PMD) at 3-12 months after intervention were analyzed. Of 298 subjects meeting eligibility criteria stated above, 91 had pre- and post-intervention Humphrey Field Analyzer data available for analysis. (Table 1).

**Table 1. Mean and standard deviation (SD) of the PMD (in dB) of the best eligible eye from each treatment group.**

| | Initial | SD | Final | SD | Change | SD |
|---|---|---|---|---|---|---|
| **Medical** | -14.6 | 6.2 | -10.2 | 9.2 | 4.4 | 7.4 |
| **ONSF** | -15.3 | 7.1 | -12.4 | 9.0 | 2.9 | 8.3 |
| **Shunt** | -17.0 | 6.2 | -8.8 | 8.4 | 8.1 | 7.7 |

Although limited by their retrospective nature, these data suggest that both medical and surgical interventions may be effective for treating IIH patients with moderate to severe visual field loss, and that surgical procedures, especially CSF shunting, may be more effective (Figure 1).

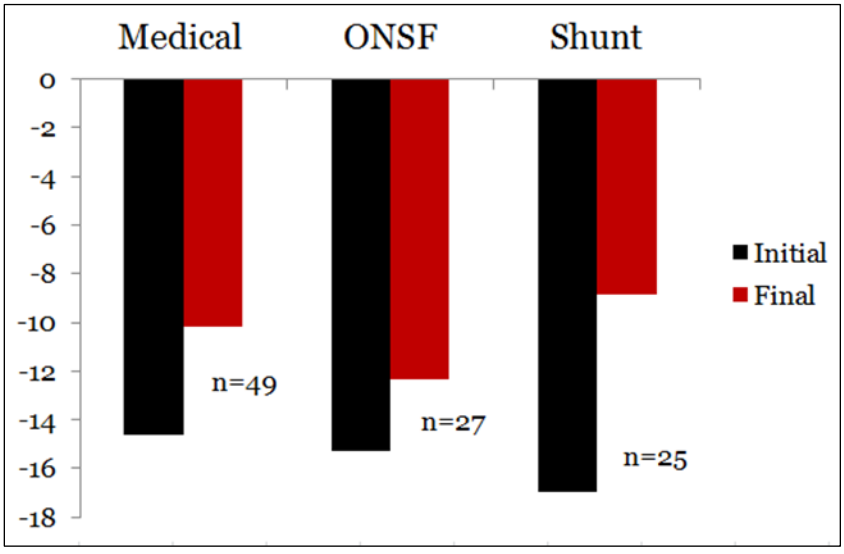



**Figure 1. Average PMD in the best eligible eye at initial presentation vs final visit 3-12 months later.**

#### 1.2.5 Use of OCT in Monitoring Papilledema in IIH

Papilledema is typically quantified from fundus photographs using the Frisén grading scale.[1] OCT can be used to objectively measure the degree of swelling and monitor treatment effects. Time-domain OCT provides cross sectional images of multiple retinal layers and the peripapillary retinal nerve fiber layer (RNFL) with a resolution of approximately 10 microns.[2-5] OCT has several advantages, based on optics, when compared to photographic imaging. OCT is also reasonably reproducible on repeat measurements in normal eyes and in eyes with glaucoma.[6-11] Limitations include no current algorithm specific for optic disc edema, particularly when it is severe. Fundus photography, the current gold standard and the technique that was used in the IIHTT, requires skilled interpretation of features that can be difficult to quantify.

Most prior OCT studies have investigated disorders that cause RNFL thinning; few report the effects of papilledema on RNFL or total retinal thickness. Time-domain OCT has been compared to fundus photographs in children with IIH.[12] Another study measured RNFL thickness, using scanning laser polarimetry (SLP) and not OCT, in IIH.[13] OCT has demonstrated subretinal macular fluid in patients with papilledema,[14] and we and others have shown RNFL thickening using OCT in patients with acute optic neuritis.[15-17] We have also found that OCT is superior to SLP in demonstrating and quantifying papilledema.[18] Other studies have compared RNFL thickness in papilledema and pseudopapilledema, but have not compared results with fundus photograph grades.[19,20] When using time-domain OCT in patients with severe papilledema, there can be inaccurate placement of the peripapillary ring to measure optic disc elevation and RNFL thickness, as well as failure of the algorithm used to measure RNFL thickness.

Newer three-dimensional spectral-domain OCT (SD-OCT) methods, such as the cube scan for data collection, give flexibility to find the exact measures of interest with increased resolution and scanning speed to acquire data over a wider area, thereby reducing sampling errors for higher density and faster scans (512 x 128 axial B-scans for a 6 mm2 area).[21] Coupling these advances with refined algorithms will improve the reproducibility and quantification of papilledema and RNFL alterations, even when swelling obscures the disc borders. Higher scan density should improve measurement of localized RNFL defects, which can be related to visual field loss.

## 1.3 Rationale

### 1.3.1 Discussion of Study Design

#### 1.3.1.1 Visual Field Monitoring

Patients who are newly diagnosed with IIH with moderate to severe visual field loss (with PMD between -6 dB and -27 dB with full threshold size V testing) may be treated with medical or surgical therapy. The current thinking, without class I or II evidence, suggests that aggressive intervention is required to prevent further visual deterioration and blindness. However, it is unclear if any of these treatments are effective for treating this subset of IIH patients. Patients with milder visual loss may benefit from medical therapy alone, as shown by the IIHTT.

Being an average, the PMD is a summary statistic that is less prone to perimetric variability than using individual or groups of test locations. It is assumed that visual loss by visual field examination best reflects neural damage due to increased intracranial pressure and in the IIHTT correlated well with QoL measures.

Standard automated perimetry uses size III stimuli. There is now considerable evidence that automated perimetry using size V stimuli has advantages in patients with moderate to severe visual loss.[29,30,32-36] These advantages include lower retest variability and about one additional log unit (10 dB) of useful dynamic range. Use of the larger size V stimuli also makes for an easier test for the patient due to an increase in visual field area in moderate to severely damaged visual fields. In addition, the size V stimulus was recently successfully used in another NEI sponsored clinical trial investigating retinitis pigmentosa.[31] Use in this trial will demonstrate its utility for optic neuropathies and we will relate size V results to the conventional size III results.

#### 1.3.1.2 OCT Monitoring

OCT analysis routines have been developed and optimized for glaucoma. Recent data suggest that OCT appears to be the best imaging modality to monitor papilledema and other optic neuropathies. In the IIHTT OCT sub-study, 89 subjects' (43 acetazolamide and 46 placebo) OCT measurements of swelling, average retinal nerve fiber layer thickness (RNFL), total retina thickness (TRT), and optic nerve head volume (ONHV) were similar in both treatment groups at baseline. At 6 months, the swelling in study eyes was reduced in both groups, but the acetazolamide group showed more reduction in RNFL (174 μm vs. 93 μm, p=0.001), TRT (218 μm vs. 121 μm, p=0.001), and ONHV (4.9 $\mu m^3$ vs. 2.4 $\mu m^3$, p=0.001) when compared with the placebo group.[37]

Furthermore, OCT showed greater improvements in the optic neural canal shape (inward deviation of the peripapillary RPE/Bruch's membrane borders) in the acetazolamide group than in the placebo group.[38] Sibony et al.[39] in another study showed reduction in the RNFL and less inward deviation of the peripapillary RPE/Bruch's membrane borders following interventions that lower intracranial pressure, such as lumbar puncture, VPS and acetazolamide treatment (see Figure 2).

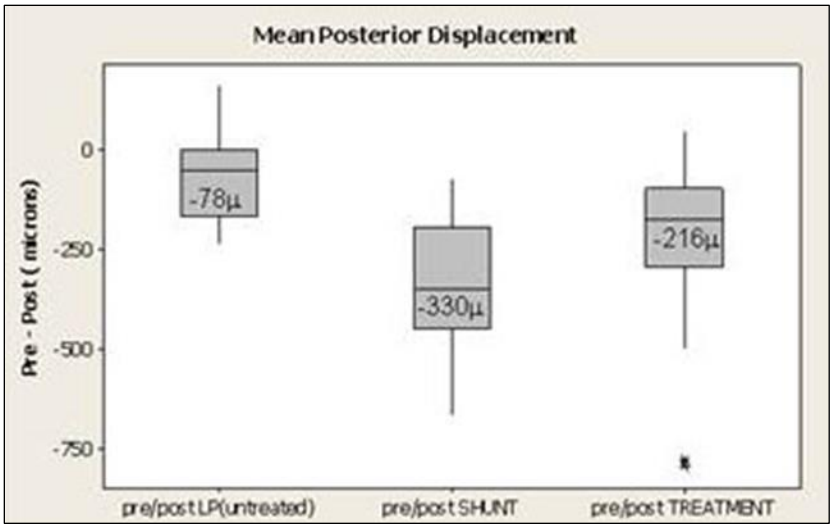



**Figure 2. Mean posterior displacement of the RPE-Bruch's membrane complex from pre- to post, following interventions (left to right: LP, VP shunt, ACZ) to lower intracranial pressure in IIH[39].**

We have also shown in a case series that the peripapillary RPE/Bruch's membrane positioning normalized within days of intracranial pressure-lowering procedures. These changes can also be seen in eyes with optic atrophy and no apparent papilledema. The deformation of the RPE/Bruch's membrane position appears to be an acute biomarker of changes in intracranial pressure, whereas the optic nerve morphology (edema) is a chronic biomarker that takes at least 1-2 weeks to respond. In some cases, the RNFL or ONH volume may be decreasing, but the RPE/Bruch's membrane does not change, suggesting that intracranial pressure may not be changing, yet axoplasmic flow may be improving or RNFL loss may be occurring. OCT will be done before lumbar puncture at screening/baseline and again at 6 months, to further characterize RPE/Bruch's membrane changes. The RPE/Bruch's membrane biomarker may represent a non-invasive objective method of monitoring intracranial pressure and, thus, may serve as a surrogate for identifying changes in intracranial pressure.

In another study evaluating 31 IIH patients with visual acuity of 20/25 or worse at presentation, macula ganglion cell layer thickness at presentation was mildly correlated ($r=0.44$, $p=0.005$), and at 2-3 weeks after presentation was strongly correlated ($r=0.76$, $p=0.0001$), with visual field outcome. Furthermore, a reduction of the ganglion cell layer thickness of > 10 µm within 2-3 weeks of presentation was also associated with a worse visual field outcome.[40]

We plan to further study changes in OCT parameters to determine their validity as biomarkers for changes in intracranial pressure and optic nerve damage. Preliminary studies suggest that OCT may facilitate early identification of optic nerve injury due to papilledema and have prognostic significance. We anticipate that OCT will provide information that helps guide treatment decisions.

#### 1.3.1.3 Discussion of Subject Characteristics

This study will enroll 180 individuals with IIH who are 18-63 years of age. This age range represents the population that is most likely to be affected by IIH. Children under 13 will not be included because IIH appears to be a different disease in this age group (no correlation with

obesity or gender; often arises from a secondary cause). Adolescents will not be eligible for the SIGHT since attrition in weight loss programs within this group of subjects is substantial, as high as 73% in some reports.[41] Only high intensity behavioral modification targeted towards children, combined with physical activity program and/or drug therapies have been shown to be effective in small studies. The SIGHT lacks the expertise and means to safely conduct this therapy of weight management in children. Further, the IIHTT provided data to measure the risk of high dose acetazolamide in adults. No such safety data is known in adolescents and the principal safety measures in the SIGHT will center on preservation of vision and surgical complications. We will exclude pregnant women and prisoners. We anticipate that the cohort will be primarily composed of women in their childbearing years that are overweight. Data available on the prevalence of IIH in the US population is limited. The best information on the demographic distribution of this condition comes from the IIHTT. Ninety-eight percent of trial subjects were women with a mean age of 29 ± 7.4 years. With regard to race, 65% of subjects were White, 25% were Black, and 10% reported another race. Thirteen percent of IIHTT subjects reported being Hispanic or Latino. As was the case for IIHTT, there will be substantial diversity in the types of enrollment centers used in SIGHT including private and university–based practices in both urban and rural settings. Every effort will be made to enroll a diverse population in the SIGHT.

### 1.3.2 Rationale for Medical and Surgical Treatment

#### 1.3.2.1 Medical Therapy

Medical therapy will consist of acetazolamide, furosemide when needed, and dietary intervention. The dosage of acetazolamide will be titrated from eight tablets daily (2,000 mg daily) to a maximum of 16 tablets daily (4 gm daily), as tolerated, taken in divided doses (bid) with meals. Four grams daily is the largest dosage used in clinical practice. In the IIHTT, the mean dosage used was 2.5 gm/day; 40% of subjects could tolerate 4 gm/day.

If the subject has side effects that substantially interfere with activities of daily living, we will use the highest dosage of study medication tolerated with a minimum of 1/2 tablet (125 mg acetazolamide) per day. Those failing to clinically improve by two weeks after achieving the maximally tolerated dosage of acetazolamide will be titrated up to 80-100 mg twice daily of furosemide (minimum dosage 20 mg per day) with potassium supplementation of 20 meq for each 40 mg of furosemide, as hypokalemia commonly occurs with this regimen.[42-44] A diet rich in potassium (fresh fruits and vegetables) will be encouraged for those taking furosemide and further supplementation will be given as needed.

All enrolled subjects will be advised to adopt a low sodium weight reduction diet with lifestyle modification developed by the Site Investigator. The treatment plan will be individualized and may include consultation with a dietician or referral to a formal weight loss program. Regression of papilledema and symptoms often occurs with a weight loss of 6% of initial body weight that may take months to achieve.[2,45,46] The IIHTT demonstrated that both the acetazolamide group and the placebo group achieved a reduction in weight.[2] The goal of the intervention in the SIGHT will also be 6% weight loss at six months.

#### 1.3.2.2 Optic Nerve Sheath Fenestration

ONSF consists of either creating a window or making a series of slits in the optic nerve dural sheath just behind the globe. This treatment has been used for patients with progressive visual loss due to IIH. The demonstration of fistula formation[6,7] and some improvement of papilledema in the unoperated eye suggest that ONSF efficacy may be secondary to local decompression of the subarachnoid space with filtration of CSF into the orbit.[8] CSF pressure may be modestly lowered post-operatively, but the duration of this effect is unknown. In a meta-analysis of large case series of ONSF for IIH (Table 2), post-operative visual acuity or visual field results were equal to, or better than, pre-operative vision in 87% of patients reported. However, 13% of patients had worse vision in the post-operative period. Up to 50% of patients have post-operative headache relief with ONSF.[5] A report on 75 eyes of 54 patients undergoing ONSF suggested that patients undergoing ONSF may have substantial long-term failure rates.[12]

**Table 2. Case series of visual outcome after ONSF.**

| Study | Vision Worse | Vision Not Worse | Total |
|---|---|---|---|
| Hupp[47] | 6 | 11 | 17 |
| Sergott[48] | 0 | 23 | 23 |
| Brourman[49] | 0 | 10 | 10 |
| Goh[50] | 9 | 31 | 40 |
| Corbett[5] | 1 | 21 | 22 |
| Plotnik[51] | 4 | 27 | 31 |
| Acheson[52] | 3 | 17 | 20 |
| Kelman[53] | 3 | 26 | 29 |
| Banta[54] | 11 | 75 | 86 |
| Yazici[7] | 1 | 16 | 17 |
| Alsuhaibani[55] | 2 | 59 | 61 |
| Pineles[56] | 12 | 38 | 50 |
| Fonseca[57] | 3 | 11 | 14 |
| **Total:** | **13%** | **87%** | **420** |

#### 1.3.2.3 CSF Shunting

Various shunting procedures have been employed for the treatment of IIH. In general, the indication for a CSF shunting procedure has been failed medical therapy or intractable headache. The case series document efficacy in preserving vision in most cases (Table 3), but reveal a high rate of shunt failure and, thus, shunt revisions were often needed.[14-18] Compared to other shunting approaches (e.g., lumbo-peritoneal shunts), stereotactic ventriculo-peritoneal shunts (VPS) have lower failure and complication rates, and are easier to monitor and adjust.[19-22] While the shunting procedures preserved vision in many patients, long-term headache relief was achieved in only 50% after 36 months in one study.[19]

**Table 3. Case series of visual outcome after CSF shunting for IIH (NS = not studied).**

| Investigators | Year | Shunt Type | Failures | Vision Worse | Vision Not Worse | Total |
|---|---|---|---|---|---|---|
| Rosenberg[58] | 1987 | LP/VP/V+ | 20/37 | 9 | 28 | 37 |
| Johnston[14] | 1988 | LP/CA/VP/VA | 7/41 | 0 | 36 | 36 |
| Eggenberger[16] | 1988 | LP | 15/27 | 0 | 27 | 27 |
| Shapiro[59] | 1988 | LP | 0/4 | 1 | 3 | 4 |
| Burgett[15] | 1992 | LP | 19/30 | 1 | 29 | 30 |
| Bynke[20] | 1997 | VP | 7/17 | 0 | 17 | 17 |
| Tulipan[60] | 1998 | VP | 0/7 | NS | NS | 7 |
| Maher[61] | 2001 | VP | 3/13 | 0 | 13 | 13 |
| McGirt[19] | 2004 | LP/VP/VA | 23/42 | NS | NS | 42 |
| Abu-Serieh[62] | 2007 | VP | 6/9 | 0 | 9 | 9 |
| Nadkarni[63] | 2008 | LP | 10/40 | NS | NS | 40 |
| Abubaker[21] | 2011 | LP/VP | 12/25 | 0 | 25 | 25 |
| Kandasamy[64] | 2011 | VP | 5/17 | 0 | 17 | 17 |
| Sinclair[65] | 2011 | VP/LP | 27/53 | 5 | 48 | 53 |
| Tarnaris[22] | 2011 | LP/VP | 12/29 | 9 | 20 | 29 |
| El-Saadany[66] | 2012 | LP | 8/22 | NS | NS | 22 |
| Yadav[67] | 2012 | LP | 2/24 | 8 | 16 | 24 |
| Huang[68] | 2014 | VP | 7/19 | 1 | 18 | 19 |
| Rizzo[69] | 2014 | VP/LP | 4/15 | 0 | 15 | 15 |
| Fonseca[57] | 2014 | VP | 9/19 | 4 | 15 | 19 |
| **Total:** | | | **40%** | **8%** | **92%** | **374** |

## 1.4 Study Objectives

### 1.4.1 Primary Objective

The primary objective is to compare the efficacy of 1) medical therapy, 2) optic nerve sheath fenestration (ONSF) plus medical therapy, and 3) stereotactic ventriculo-peritoneal CSF shunting (VPS) plus medical therapy in newly diagnosed IIH patients with full threshold size V 24-2 PMD between -6 and -27 dB in at least one eye at study entry. Change in the PMD with stimulus size V from baseline to the first of Month 6 or time of treatment failure in the eye(s) qualifying for study entry will be the primary outcome variable.

### 1.4.2 Secondary Objectives

Secondary objectives are to compare changes in the following from baseline to 6 months among the three study groups:

- PMD with stimulus size V in the best eye qualifying for study entry
- Papilledema grade (Photographic Reading Center and site investigator ratings)
- OCT measures of:
  - Retinal nerve fiber layer thickness
  - Retinal ganglion cell layer thickness
  - Peripapillary retinal pigment epithelial (RPE)/Bruch's membrane deformation
- CSF pressure
- Visual acuity
- Quality of life (QoL) measures (NEI-VFQ-25 + 10-item neuro-ophthalmic supplement and the SF-36)
- Headache disability (HIT-6 Inventory)
- Headache severity

Other efficacy outcome variables, determined at Month 6, include treatment failure, surgical failure, presence of headache, presence of transient visual obscurations, and visual field examination ratings (improved, no change, worse) by the Visual Field Reading Center.

With the exception of CSF pressure, these outcome variables will also be examined at Months 12, 24 and 36.

Of special interest and a very important outcome is the time from randomization to treatment failure. Subjects will be followed for up to 3 years and the number of surgical failures and treatment failures will be analyzed. While a therapy may have a beneficial outcome at 6 months, it may not have a good outcome 1-3 years later; therefore, this is an important analysis.

Measures of safety include the following:

- Adverse events
- Serious adverse events
- Procedure complications and transient malfunctions of surgical procedures
- Blood pressure
- Laboratory test results (CBC with platelet count, electrolytes, potassium, bicarbonate, and liver function tests)

#### 1.4.3 Other Outcomes

- Anthropometric measures (weight, waist circumference)

## 1.5 Potential Risks and Benefits of the Study Interventions

### 1.5.1 Known Potential Risks

#### 1.5.1.1 Visual Loss

The primary risk of IIH is visual loss associated with papilledema. Subjects reaching treatment failure criteria will remain in the study but will be managed by the site investigators.

#### 1.5.1.2 Acetazolamide

Acetazolamide frequently causes paresthesias, altered taste sensation, asymptomatic metabolic acidosis (low serum bicarbonate), and fatigue. There is a small risk of kidney stones, and, very rarely, renal failure from acute tubular necrosis, liver enzyme changes, elevation of serum amylase, blood dyscrasias, Stevens-Johnson syndrome, and aplastic anemia. Based on the IIHTT, we anticipate that renal stones and allergic rashes will occur, though infrequently. Guidance on management of liver enzyme changes and renal stones is provided in the MOP. While there was minimal potassium loss in some IIHTT subjects treated with acetazolamide, there were no instances of hypokalemia requiring potassium supplementation.

Subjects will have laboratory studies throughout the study period to monitor their electrolytes. Aplastic anemia can occur in an individual by an idiosyncratic hypersensitivity reaction and cannot be predicted by routine monitoring of the blood count. Some patients may be allergic to acetazolamide, developing a rash (most common reaction), angioedema, stridor, or rarely, anaphylaxis. A history of sulfa allergy will not be an exclusion criterion due to the lack of evidence for cross reactivity with acetazolamide.[72] The study medication will be discontinued immediately if there is any evidence of an allergic reaction. At the conclusion of the subject's participation in the study, their treating physician will arrange a treatment plan independent of the study.

Hypokalemia: Epstein et al.[73] showed no evidence of clinically significant hypokalemia in 92 patients on acetazolamide unless they were also taking other diuretics. We confirmed this in the IIHTT.[2] Since acetazolamide-induced hypokalemia is so uncommon, serum electrolytes will be obtained at 1 month, 4 months, and 6 months (unless subjects develop symptoms of hypokalemia: weakness, fatigue, and muscle cramps). If a subject also requires treatment with furosemide, he/she will have close monitoring of serum electrolytes (including serum sodium and potassium) prior to each change in dosage, to be performed at a local laboratory. The dosage of furosemide will not be increased until it is documented that the potassium level is in the normal range. Once the final furosemide dosage has been reached, electrolytes will be checked at each visit.

Aplastic Anemia: Acetazolamide-induced aplastic anemia is dosage independent, usually delayed in onset, and usually fatal. According to prior studies[74,75], the incidence has been estimated as 1 per 15,000 patient years with a mean age of 71 years (range 56-86 years). The average onset is 3.5 months after initiation of treatment; it rarely occurs after six months of treatment. Monitoring of CBCs is not the standard of care. We will obtain a CBC at baseline and 4 months, and 6 months.

#### 1.5.1.3 Furosemide

Hypokalemia is the most common important side effect of furosemide. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Cases of tinnitus and reversible or irreversible hearing impairment and deafness have been reported in people taking furosemide. Reports usually indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, the use of higher than recommended doses, hypoproteinemia or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic drugs. Excessive diuresis from furosemide can occur that may require measures to prevent dehydration and hypotension. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated.

In summary, common side effects of furosemide are orthostatic hypotension and hypokalemia. Less frequent side effects are hyponatremia, hypocalcemia, hypochloremia, and hypomagnesemia. Also infrequent are cramps, diarrhea, drowsiness, dry mouth, loss of appetite, stomach cramps and photosensitivity.

### 1.5.2 Known Potential Benefits

Benefits from participation in the study include assignment to a treatment routinely used in clinical practice, easy access to care for IIH, closer and more careful follow-up assessments evaluating vision. Hopefully, in the future, other people might benefit from this study because of the knowledge that may be gained about IIH.

### 1.5.3 Risk Assessment

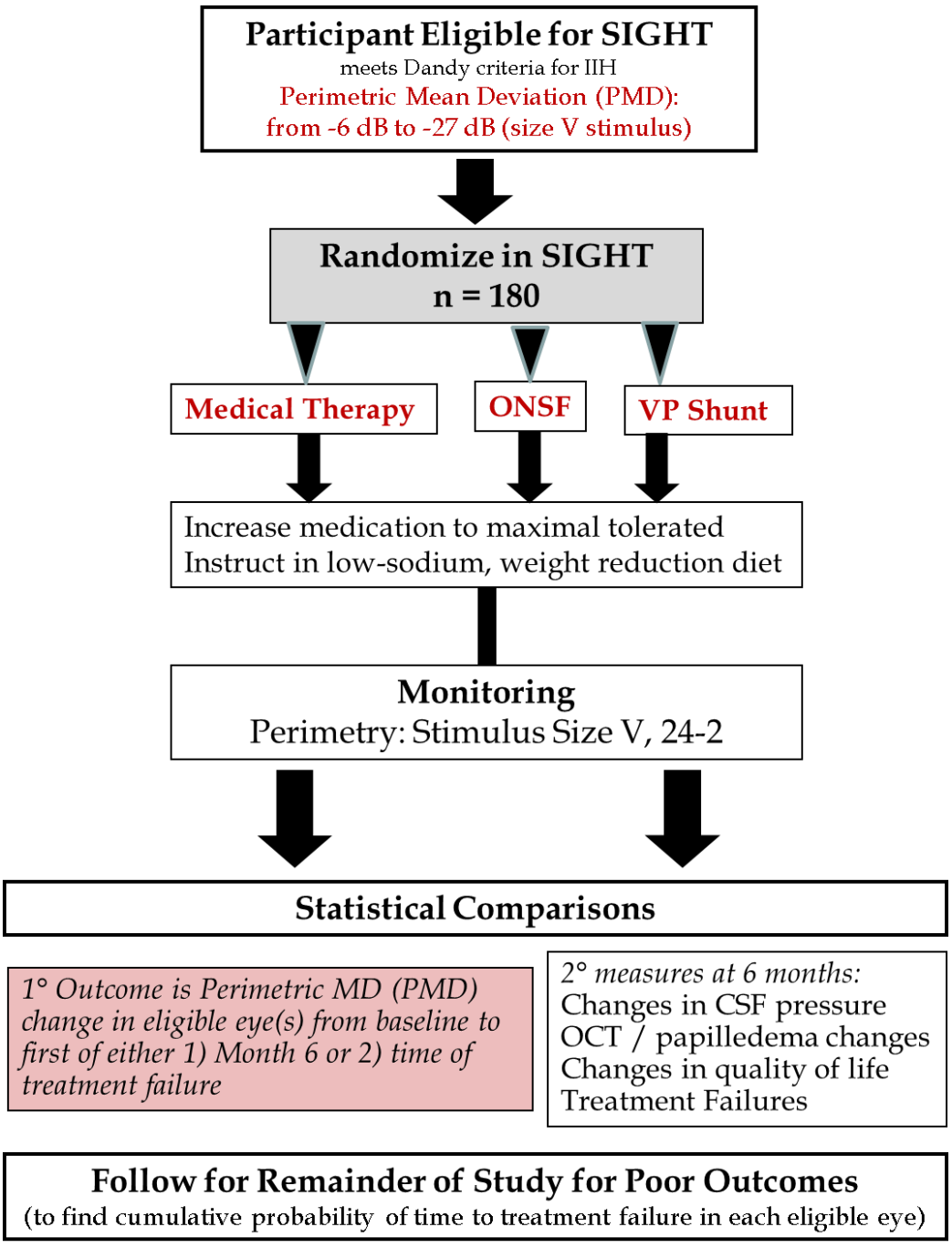
The risk level is considered to be research involving greater than minimal risk.

### 1.6 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Data will be directly collected in electronic case report forms, which will be considered the source data.

### 1.7 Schematic of Study Design



## 1.8 Schedule of Study Visits and Procedures

### 1.8.1 Randomized Trial

| | | Safety Visit[1] | Safety Visit[1] | | | | | | Primary Outcome |
|---|---|---|---|---|---|---|---|---|---|
| **Overview of Study Procedures** | **SC/BL Visit (-3-0 days)** | **S Visit 1 wk ±4 days** | **S Visit 2 wks ±4 days** | **Visit 1 4 wks ±7 days** | **Visit 2 8 wks ±7 days** | **Phone call 12 wks ±7 days** | **Visit 3 16 wks ±7 days** | **Phone call 20 wks ±7 days** | **Visit 4 26 wks ±7 days** |
| Written Informed Consent | X | | | | | | | | |
| Eligibility Criteria | X | | | | | | | | |
| Med/IIH History/Update | X | | | X | X | | X | | X |
| Physical Exam | X | | | | | | | | |
| Lumbar Puncture | X | | | | | | | | X |
| Questionnaires | X | | | | | | | | X |
| Vital Signs with weight | X | X | X | X | X | | X | | X |
| Ocular Exam | X[2] | X | X | X | X | | X | | X |
| Refraction/Acuity | X | X | X | X | X | | X | | X |
| Perimetry | X[3] | X | X | X | X | | X | | X[3] |
| Fundus Photographs | X | | X | X | X | | X | | X |
| OCT | X[4] | X | X | X | X | | X | | X[4] |
| CBC with platelet count | X | | | | | | X | | X |
| Metabolic panel w LFTs, amylase and electrolytes | X | | | | | | X | | X |
| Electrolyte testing[5] | | | | X | X | | X | | X |
| Blood sample for storage | X | | | | | | | | |
| Pregnancy test | X | | | | | | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X |
| Concomitant Drug Therapy | X | X | X | X | X | X | X | X | X |
| Randomization | X | | | | | | | | |

| | | Safety Visit[1] | Safety Visit[1] | | | | | | Primary Outcome |
|---|---|---|---|---|---|---|---|---|---|
| **Overview of Study Procedures** | **SC/BL Visit (-3-0 days)** | **S Visit 1 wk ±4 days** | **S Visit 2 wks ±4 days** | **Visit 1 4 wks ±7 days** | **Visit 2 8 wks ±7 days** | **Phone call 12 wks ±7 days** | **Visit 3 16 wks ±7 days** | **Phone call 20 wks ±7 days** | **Visit 4 26 wks ±7 days** |
| Dispense/prescribe acetazolamide | X | | | X | X | | X | | X |
| Prescribe furosemide/potassium as needed | | | | X | X | | X | | X |
| Review Drug Compliance | | X | X | X | X | X | X | X | X |
| Dietary Counseling | X | | | X | X | | X | | X |

[1]Timing of 1 week and 2 week safety visits dependent on treatment group (timing for medical therapy group relative to randomization and timing for surgery groups relative to surgical procedure). The 2 week visit could be skipped if there is marked improvement (see section 5.1.2). One or both safety visits will be repeated after each surgical procedure.

[2] IOP must be measured at Screening to assess eligibility

[3]Two sets of FT size V at Screening; same requirement for week 26.

[4] If LP performed, OCT should be performed prior to LP. Another set of OCT testing after LP is optional at Screening.

[5] For subjects taking furosemide, will be done at local lab prior to each dose increase, once the final dose is reached, and then at each visit

### 1.8.2 Treatment Failure Identification Phase

| | | | | Final Study Visit | |
|---|---|---|---|---|---|
| **Overview of Study Procedures** | **Phone Call 39 wks ±7 days[1]** | **Visit 5 52 wks ±7 days** | **Visit 6 104 wks ±4 wks** | **Visit 7 156 wks ±4 wks** | **Unscheduled Visit[2]** |
| Written Informed Consent | | | | | |
| Eligibility Criteria | | | | | |
| Med/IIH History/Update | | X | X | X | X[3] |
| Physical Exam | | | | | X[3] |
| Lumbar Puncture | | | | | |
| Questionnaires | | X | X | X | |
| Vital Signs w weight | | X | X | X | X[3] |
| Ocular Exam | | X | X | X | X[3] |
| Refraction/Acuity | | X | X | X | X[3] |
| Perimetry | | X | X | X | X[3] |
| Fundus Photographs | | X | X | X | X[3] |
| OCT | | X | X | X | X[3] |
| CBC with platelet count | | | | | X[3] |
| Metabolic panel w LFTs, amylase and electrolytes | | | | | |
| Electrolyte testing[4] | | X | X | X | X |
| Blood sample for storage | | | | | |
| Pregnancy Test | | | | | |
| Adverse Events | X | X | X | X | X |
| Concomitant Drug Therapy | X | X | X | X | X |
| Randomization | | | | | |
| Dispense acetazolamide | | | | | |
| Prescribe furosemide/potassium as needed | | X | X | | X |
| Review Drug Compliance | X | X | X | X | X |
| Dietary Counseling | | X | X | | X |

[1] Telephone contacts will occur quarterly after the year 1 visit

[2] If early termination visit, testing will be the same as the primary outcome visit.

[3] If clinically indicated

[4] Only for subjects taking furosemide

# Chapter 2: Study Enrollment and Screening/Baseline Testing

## 2.1 Subject Recruitment and Enrollment

Study subjects will be recruited from ~40 clinical centers in the United States and Canada. Enrollment will proceed with the goal of 180 subjects entering the randomized trial. A maximum of 400 individuals may be enrolled in the study in order to achieve this goal. Subjects who have signed consent and started the screening process may be permitted to continue into the trial, if eligible, even if the randomization goal has been reached.

All eligible subjects will be included without regard to gender, race, or ethnicity. There is no restriction on the number of subjects to be enrolled by each site toward the overall recruitment goal. Non-identifying information about individuals who are deemed ineligible or decline to participate in the study will be recorded.

Some subjects will have been diagnosed with IIH prior to being referred to the study, whereas others may need to go through the diagnosis and screening process after consent is signed. Neuroimaging studies, diagnostic lumbar puncture, and blood tests are considered routine care regardless of the timing. The patient may have already had a lumbar puncture and blood testing, which may not need to be repeated if performed within 4-6 weeks of enrollment.

### 2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained.

For potential study subjects, the study protocol will be discussed with the potential study subject by study staff. The potential study subject will be given the Informed Consent Form to read. Potential study subjects will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

A copy of the consent form will be provided to the subject and another copy will be added to the subject's study record.

As part of the informed consent process, each subject will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed.

After speaking with the subject, questions will be answered about the details regarding authorization.

A subject is considered enrolled when the informed consent form has been signed.

## 2.2 Subject Eligibility Criteria

### 2.2.1 Subject Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1. Diagnosis of IIH by modified Dandy criteria (Table 4)
2. Age 18 to <64 years at time of consent
3. Age 18 to <61 years at time of diagnosis (time of diagnosis is the time at which the patient meets the modified Dandy criteria, usually after the lumbar puncture results are reviewed)
4. Presence of bilateral papilledema
5. Lumbar puncture within 6 weeks of screening visit or completed as part of screening: Opening CSF pressure >250 mmH2O **or** 200 to 250 mmH2O, with at least one of the following:
    a) Pulse synchronous tinnitus
    b) Cranial nerve VI palsy
    c) Echography for drusen negative and no other disc anomalies mimicking disc edema present
    d) MRV with lateral sinus collapse/stenosis, partially empty sella turcica on coronal or sagittal views of MRI, and optic nerve sheaths with filled out CSF spaces next to the globe on T2 weighted axial MRI scans

    *If the patient was treated with intracranial pressure lowering agents (e.g., acetazolamide) prior to obtaining a lumbar puncture, the agent(s) must be discontinued for at least 24 hours prior to performing the diagnostic lumbar puncture.*
6. At least one eye meeting all eligible eye inclusion criteria and no exclusion criteria
7. Able to provide informed consent
8. Investigator believes the participant is a good candidate for the study, including the probability of returning for follow-up.

**Table 4. Modified Dandy Criteria for IIH[27]**

| |
|---|
| 1. Signs and symptoms of increased intracranial pressure |
| 2. Absence of localizing findings on neurologic examination |
| 3. Absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, except for evidence of increased CSF pressure (>200 mm water). Abnormal neuroimaging except for empty sella turcica, optic nerve sheath with filled out CSF spaces, and smooth-walled non flow-related venous sinus stenosis or collapse,[70] should lead to another diagnosis |
| 4. Awake and alert |
| 5. No other cause of increased intracranial pressure present |

### 2.2.2 Subject Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation.

1. Treatment of IIH within the past 3 months with either (1) the maximally tolerated dosage of acetazolamide for at least one week or (2) more than one month of acetazolamide with a cumulative dosage of more than 45 grams

   *'Maximally-tolerated dose' is defined as dosage was reached where dosage could not be increased further either because of side effects or because a daily total dosage of 4 grams per day was reached.*

   *If individual discontinued acetazolamide in the past due to side effects, individual is only eligible if investigator believes that the individual is likely to tolerate acetazolamide, as it will be prescribed in the study.*

2. Treatment of IIH within the past 3 months with either (1) the maximally tolerated dosage of methazolamide for at least one week or (2) more than one month of methazolamide with a cumulative dosage of more than 4.5 grams

   *'Maximally-tolerated dose' is defined as dosage was reached where dosage could not be increased further either because of side effects or because a daily total dosage of 400 mg per day was reached.*

3. Treatment with topiramate within two months and average cumulative dosage for the preceding month of more than 700 mg per week

4. Previous surgery for IIH, including ONSF, CSF shunting, subtemporal decompression, or venous sinus stenting; *gastric surgery for obesity is allowed*.

5. Abnormalities on neurologic examination except for papilledema and its related visual loss or cranial nerve VI or VII paresis; *if other abnormalities are present, the patient will need to be discussed with the Study Director for study entry*.

6. Abnormal CT or MRI scan (intracranial mass, hydrocephalus, dural sinus thrombus, or arteriovenous malformation) other than findings known to occur with increased intracranial pressure. *Abnormalities on MRI that are not known to cause increased intracranial pressure are acceptable*.

7. Abnormal CSF contents: increased cells: > 8 cells; elevated protein: > 45 mg%; low glucose: < 30 mg% *(If the lumbar puncture produces a cell count compatible with a traumatic needle insertion, the patient does not need to be excluded if the CSF WBC after correction is 8 cells/$mm^3$ or less - see MOP for calculation. If >8 cells or >45mg% in CSF protein are documented in the CSF or calculated after conversion from a traumatic lumbar puncture, the patient can be discussed with the Study Director for possible inclusion.)*

8. Abnormal blood work-up indicating a medical or systemic condition associated with raised intracranial pressure

9. Diabetes mellitus with diabetic retinopathy

10. Ingestion of a drug or substance, or presence of a disorder, that has been associated with increased intracranial pressure within 2 months of diagnosis, such as lithium, vitamin A related products (e.g., Retin-A), or various cyclines *(see MOP for conditions and drugs)*
11. Laboratory test results showing severe anemia, leukopenia or thrombocytopenia, renal failure, or hepatic disease, based on the Site Investigator's judgment
12. Other condition requiring continued use of oral, I.V. or injectable steroids *(nasal, inhaled, or topical steroids are allowed since the systemic effects are small). Patients with a condition that resulted in recent or current use of steroids but may be safely tapered off will be handled on a case-by-case basis after discussion with Study Director/co-Director. See MOP for details.*
13. Presence of a medical condition that would contraindicate use of acetazolamide or furosemide or significantly increase surgical risk
14. Pregnancy or unwillingness for a subject of childbearing potential to use contraception during the first 6 months of the study

    *Women of childbearing potential must use an acceptable form of birth control during the first 6 months of the study. Acceptable forms include oral contraceptives, transdermal contraceptives, diaphragm, intrauterine devices, condoms with spermicide, documented surgical sterilization of either the subject or their partner, or abstinence.*
15. Presence of a physical, mental, or social condition likely to affect follow-up (drug addiction, terminal illness, no telephone, homeless)
16. Anticipation of a move from the site area within six months and unwillingness to return for follow-up at a SIGHT study site
17. Allergy to pupil dilating drops or narrow angles precluding safe dilation
18. Presence of a condition that contraindicates general anesthesia
19. Participation in an investigational trial within 30 days of enrollment that involved treatment with any systemic drug therapy or therapy that affects the eligible eye(s)

### 2.3 Eye-Level Eligibility Criteria

To be eligible, an individual must have at least one eye meeting the following inclusion criteria and none of the exclusion criteria.

If both eyes meet eligibility criteria, then both will be included in the primary outcome analysis.

#### 2.3.1 Eye-Level Inclusion Criteria

1. Visual field loss meeting the following criteria based on two full threshold 24-2 size V tests reviewed by the VFRC:
   - PMD from -6 dB to -27 dB
   - Reproducible visual loss present on automated perimetry including no more than 15% false positives
2. Visual acuity better than 20/200 (39 or more letters correct)

### 2.3.2 Eye-Level Exclusion Criteria

1. Intraocular pressure currently >28 mm Hg or >30 mm Hg at any time in the past
2. Refractive error of more than -6.00 or more than +6.00 sphere or more than 3.00 cylinder with the following exceptions:
   - Eyes with more than 6.00 D of myopia but less than 8.00 D of myopia are eligible if:
     1. there are no abnormalities on ophthalmoscopy or fundus photos related to myopia that are associated with visual loss (such as staphyloma, retinal thinning in the posterior pole, or more than mild optic disc tilt), and
     2. the individual will wear a contact lens for all perimetry examinations with the appropriate correction.
   - Eyes with more than 6.00 D of hyperopia but less than 8.00 D of hyperopia are eligible if:
     1. there is an unambiguous characteristic halo of peripapillary edema as opposed to features of a small crowded disc or other hyperopic change related to visual loss determined by the Site Investigator or the PRC Director (or his designate), and
     2. the individual will wear a contact lens for all perimetry examinations with the appropriate correction (which can be corrected for perimetry or the patient's own contact lens with over correction by lens at the perimeter).

   *Note: Refractive error exclusion and exceptions refer to sphere not spherical equivalent, with cylinder expressed in plus format.*
3. Other disorders causing visual loss except for refractive error and amblyopia, including cells in the vitreous or iritis
4. Large optic disc drusen on exam or in previous history (small drusen of the disc can occur with longstanding papilledema and are allowed if not so numerous that investigator determines they are contributing to vision loss)

## 2.4 Screening/Baseline Procedures

After informed consent has been signed, a potential subject will be evaluated for study eligibility through the elicitation of a medical history, performance of an ophthalmic exam including visual acuity testing and visual field testing, physical examination by study personnel and local laboratory testing if needed to screen for exclusionary medical conditions.

- Screening/baseline assessments must be completed within 3 days of signing the consent form.
- The only exceptions are 1) if there are perimetry performance issues requiring repeat examinations; 2) if there are unforeseen circumstances that delay the evaluation such as transportation issues, weather related delays or work-related issues. If an exception occurs, two additional days are allowed. During the screening/baseline visit, especially if there are unforeseen delays, the Site Investigator has the option to begin acetazolamide using the titration schedule in section 4.1.1.4.

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion.

Individuals who meet study eligibility requirements and agree to participate must discontinue any medications being used to treat IIH, except for acetazolamide. All diuretics other than acetazolamide must be discontinued immediately.

#### 2.4.1 Data Collection and Testing

The following procedures will be performed/data collected/eligibility criteria assessed:

- Inclusion and exclusion criteria assessed
- Demographics (date of birth, sex, race and ethnicity)
- Contact information
- Medical history
- Concomitant medications
- QoL questionnaires
- HIT-6 questionnaire
- Physical examination to include:
  - Weight, height, waist circumference, vital signs including measurement of blood pressure and pulse
  - Neurologic exam
- Refraction
- Visual Acuity tested following refraction using ETDRS charts
- Humphrey Visual Field testing (see section 2.4.1.1 below)
- Intraocular Pressure (Goldmann tonometry)
- Ophthalmoscopy with optic disc edema grading (Frisén scale)
- Biomicroscopy
- Fundus photographs
- Optical Coherence Tomography (OCT)* (optic nerve head and macula)
- Blood testing (CBC, electrolytes, liver function tests, renal function tests, amylase) if not done as part of routine care within 4 weeks (to be used in screening)
- Urine or serum pregnancy test for all women who have reached menarche and are premenopausal and are not surgically sterile
- Blood draw for storage (at screening only, with subject approval, discarded if patient not enrolled):

- With subject agreement, up to 20 ml of blood may be drawn and stored to use in future research of IIH.

- Lumbar puncture (if not completed within 6 weeks of screening visit)

*If lumbar puncture done as part of screening, OCT testing should be done *before* the lumbar puncture. Another set of OCT testing *after* the lumbar puncture is optional.

#### 2.4.1.1 Visual Field Examinations

At the screening visit, a Humphrey visual field result with 24-2 SITA-standard program using stimulus size III may be performed prior to two size V tests if a recent size III result is not available. The size III test can be used as a guide as to whether the subject is likely to have at least one eye meet eligibility criteria when size V testing is done.

- PMD using the size III stimulus should be approximately in range of -8.5 to -30 dB.

Two size V stimulus fields will be performed in each eye.

- The two size V stimulus visual field examinations will be transmitted to the Visual Field Reading Center which will evaluate the visual field results: In order for an eye to qualify for the trial, the average PMD with stimulus size V will have to be equal to or worse than -6 dB and better than -27 dB.

- If the Visual Field Reading Center confirms that the subject is eligible for randomization, it will document the average mean deviation of the two size V tests as well as which eyes qualify as eligible eyes.

- If the Visual Field Reading Center finds performance issues on the perimetry results, the examination will need to be repeated for the subject to be considered for the randomized trial.

*Depending on the subject's condition (e.g., suspected visual deterioration, fatigue), perimetry may be repeated later that day, or up to the 3-day deadline for randomization; the only exception being if a perimetry result is unreliable and requires a repeat examination, the site will have an additional two working days to complete the visual field examination. These additional sets of perimetry examinations will be submitted to the Visual Field Reading Center for confirmation/denial of eligibility.*

There will be times that perimetry results are not reliable and a repeat examination will be necessary. This may occur not only at the screening/baseline visit but also at any visit. Whenever two examinations are required (baseline, 6 months, treatment failure protocol) the following outcomes are possible:

1. Two examinations performed and: (1) performance criteria are met and (2) pathophysiologic appropriate visual field patterns match. The average of the mean deviations is used for the outcome. Acceptable performance criteria are: the false positive rate is less than 15%, the false negative rate is judged not to be excessive for the amount of visual loss, and gaze tracking data confirms acceptable fixation. All data from eyes in the study must meet these criteria; only results from eyes that do not meet these criteria

require a repeat examination. However, the criteria are eye specific so one eye may need to be retested.

2. If the conditions listed in 1 are not met, for a particular eye (or eyes), then for that eye (or eyes) the following should be done:
    a. a 3rd examination will be performed; if 2 of the examinations meet VFRC criteria, these 2 will be averaged for the outcome
    b. if 2 of the 3 examinations do not meet VFRC performance standards, the VFRC will discuss the subject's performance with the Site Perimetrist (masked) to determine the reason for poor results, assessing drowsiness, headache, effort and lens alignment
    c. if any of the above issues can be remedied, further visual field examinations will be performed under the new conditions until 2 acceptable tests are completed; the PMD average of these two twill be used for analysis
    d. if no reliable results are obtainable, the data will be treated as a missing value

# Chapter 3: Randomization Visit

## 3.1 Timing

Randomization should occur within 3 days of the start of screening/baseline testing, once the patient has met criteria for eligibility.

## 3.2 Randomization

Prior to randomization, the subject's understanding of the study protocol and willingness to participate and accept assignment to any of the three treatment groups should be confirmed.

Randomization will occur on the study website after eligibility is verified and the VFRC has approved randomization of the subject.

Once a study subject is randomized, that subject will be counted regardless of whether the assigned treatment is received. Thus, the investigator must not proceed to randomize an individual until he/she is convinced that the individual is eligible and will accept whichever treatment group is assigned through randomization.

Subjects will be randomly assigned with equal allocation to one of the three treatment groups.

- medical therapy
- medical therapy plus ONSF
- medical therapy plus VPS

Using a permuted block design, randomization will be stratified by PMD (average of 2 size V stimulus tests) in the eligible eye(s) (-6 dB to >-12 dB; -12 dB to >-20 dB; -20 dB to -27 dB). If a subject has two eligible eyes, the average PMD of the two eyes will be used for stratification.

## 3.3 Instructions to Subjects

Subjects in all groups will be dispensed acetazolamide (see section 4.1) and receive dietary counseling (see section 4.1.6). Acetazolamide should be started on the day of randomization unless the Site Investigator deems delays occurring during the screening/baseline examination may be harmful to the patient. In this case, the acetazolamide titration according to section 4.1.1.4 may be started prior to randomization.

For subjects in the two surgery groups, surgery should be performed as soon as possible, ideally within 3 days of randomization, but not more than 7 days.

# Chapter 4: Study Treatments

## 4.1 Medical Therapy including Diet

### 4.1.1 Acetazolamide

#### 4.1.1.1 Acquisition

Taro Pharmaceutical Industries will supply commercially available 250 mg acetazolamide tablets in bottles of 100. Supplies will be shipped to the study central pharmacy, which will package, label, and distribute the drug kits to the sites. Sites will dispense acetazolamide at visits during the 6-month randomized trial. At the 6-month visit, the subject will be given a prescription for acetazolamide and it will be the subject's responsibility to obtain the drug.

**Table 5. Composition of Acetazolamide**

| Component and Quality Standard (and Grade, if Applicable) | Function | Strength | |
|---|---|---|---|
| | | mg/tablet | % |
| Acetazolamide, USP | Active drug | 250.0 | 48.56 |
| Lactose NF Monohydrate 200 mesh | | 200.0 | 38.85 |
| Corn Starch NF/EP | | 48.0 | 9.32 |
| Gelatin NF | | 3.2 | 0.62 |
| Glycerine USP | | 1.6 | 0.31 |
| Purified Water USP/EP (1) | N/A | (80.00) | |
| Talc USP | | 9.0 | 1.75 |
| Sodium Starch Glycolate NF/EP | Binder | 1.5 | 0.29 |
| Magnesium Stearate NF/EP | Lubricant | 1.5 | 0.29 |
| **Total** | | **514.8** | **100** |

#### 4.1.1.2 Storage

All study-supplied medication must be kept in a secure, safe area under recommended storage conditions as stated on the labeling with access limited to persons directly involved in the study.

#### 4.1.1.3 Accountability of Acetazolamide Supplies

The site must maintain accurate records (including dates) of receipt, dispensing, return, and destruction of the study acetazolamide. Further details on the drug accountability process will be described in the manual of procedures.

#### 4.1.1.4 Dosing and Administration

All subjects in the three groups will be given acetazolamide with instructions for use.

- The study will use 250 mg tablets of acetazolamide.
- Tablets will be divided into two doses, taken with meals.

The initial dose will be 1,000 mg twice day and then increased.

Beginning on Day 3, the dose will be increased by 250 mg every 2 days until a dosage of 4 grams daily (16 tablets) is reached (day 17) or adverse events (including side effects that interfere with activities of daily living) prohibit increasing the dosage further.

During the titration period, subjects will be instructed to call the Site Coordinator to report any intolerable adverse events. The subject may need to be seen for an unscheduled visit for clinical assessment.

**Table 6. Acetazolamide titration schedule (number of 250 mg tablets)**

| Start Day | End Day | Breakfast | Dinner | Total Daily |
|---|---|---|---|---|
| 1 | 2 | 4 | 4 | 8 (2000 mg) |
| 3 | 4 | 4 | 5 | 9 (2250mg) |
| 5 | 6 | 5 | 5 | 10 (2500 mg) |
| 7 | 8 | 5 | 6 | 11 (2750 mg) |
| 9 | 10 | 6 | 6 | 12 (3000 mg) |
| 11 | 12 | 6 | 7 | 13 (3250 mg) |
| 13 | 14 | 7 | 7 | 14 (3500 mg) |
| 15 | 16 | 7 | 8 | 15 (3750 mg) |
| 17 | -- | 8 | 8 | 16 (4000 mg) |

If the subject is unable to tolerate the initial acetazolamide dosage, the dosage may be lowered to 3 tablets daily. The dosage may be subsequently decreased by one tablet every other day (or sooner if the subject is substantially symptomatic) if the subject is unable to tolerate it. If the subject is then able to tolerate the lower dosage, the daily dosage should be increased according to the table above, or more slowly at the Site Investigator's discretion. Additional attempts to increase the acetazolamide dosage beyond 17 days may be initiated at the Site Investigator's discretion, but not above a total of 4 grams per day. The dosing level achieved by Day 90 will be considered the subject's final dosage. This dosage will be maintained through the remainder of the treatment period unless the subject improves such that the dosage can be tapered or develops intolerable side effects.

If the acetazolamide is not tolerated at a dosage of 250 mg, then 125 mg (1/2 tablet) will be tried. If this is not tolerated, furosemide will be initiated as described in section 4.1.2.

#### 4.1.1.5 Stopping the Dosage Titration

The Site Investigator can stop or decrease the dosage titration if the subject has reached maximal benefit (in the SI's opinion) or there is a safety concern. He/she can consult the Study co-Director as necessary.

See section 4.1.4 below for tapering details regarding VPS group.

### 4.1.2 Addition of Furosemide

If a participant cannot tolerate any dose of acetazolamide or fails to improve clinically (for example, worsening on the basis of: 1) subject report of progressive visual loss, 2) papilledema is worsening, 3) OCT measures are worsening, 4) ETDRS acuity worsens more than 4 letters, or 5) PMD worsens more than 2 dB) after 2 weeks on the maximally tolerated dosage of acetazolamide, furosemide will be added, initiated at 20 mg bid. If the decision is unclear, the case should be discussed with the Study co-Director.

The furosemide dose will be increased up to a maximum of 80 mg bid unless adverse events prohibit further dosage increase, with electrolytes checked ~4 days after each dose increase. After ~4 days of furosemide treatment, electrolytes will be checked (including serum sodium and potassium). If sodium and potassium are normal, the dose will be increased to 40 mg bid. Again after ~4 days, electrolytes will be checked and if normal the dose will again be increased to 60 mg bid and then if after another ~4 days and normal sodium and potassium, the dose will be increased to 80 mg bid and electrolytes checked after ~4 days. Subsequently, electrolytes will be checked at every visit as long as furosemide is being taken. Standard of care electrolyte testing will be done at a local laboratory.

- An unscheduled visit may be needed to initiate furosemide.
- Subjects requiring furosemide will be given a prescription for the medication (the study will not provide the drug). 20 meq of potassium per day will be prescribed to take concomitant with furosemide and increased by 20 meq per day for each 40 mg of furosemide dosed.
- If the Site Investigator determines there has been improvement with a dose of 80 mg bid (160 mg/day) and expects that a higher dosage may be beneficial, the dose may be increased to 100 mg bid (200 mg/day) with close monitoring for hypokalemia and hyponatremia.

**Table 7. Furosemide titration schedule (20 or 40 mg tablets may be dispensed)**

| Start Day | End Day | Breakfast | Dinner | Total Daily (20 mg) |
|---|---|---|---|---|
| 1 | 2 | 1 | 1 | 2 (40 mg) |
| 4 | 5 | 2 | 2 | 4 (80 mg) |
| 8 | 9 | 3 | 3 | 6 (120 mg) |
| 12 | 13 | 4 | 4 | 8 (160 mg) |
| *16 | 17 | 5 | 5 | 10 (200 mg) |

*This optional dosage escalation is continued to 200 mg per day only if the Site Investigator determines there has been improvement up to this point and expects that a higher dosage may be beneficial, with close monitoring for hypokalemia and hyponatremia.

### 4.1.3 Assessment of Subject Compliance with Medical Therapy

Subjects will be asked to bring the used study drug bottles to each visit. At each study visit during the first 6 months, the subject's compliance with the acetazolamide dose will be assessed

by pill counts and chloride levels. If the chloride level is not below normal limits, whether the subject is taking the drug should be questioned unless he/she was prescribed a very low dosage.

#### 4.1.4 Tapering of Medical Therapy

All subjects will have their pharmacotherapy tapered when the Site Investigator believes that the dosage should be decreased if he/she believes the subject has achieved maximal benefit. For example if the papilledema grade becomes < 1 in both eyes, and the PMD has improved substantially and IIH symptoms are not interfering with activities of daily living, the taper could begin.

The Site Investigator can also taper pharmacotherapy when subject safety dictates a change.

For subjects in the VPS group, the acetazolamide dosage should be tapered starting on the day of the surgery. See the MOP for details.

Otherwise, it is suggested that dosages of each drug be tapered in increments of 25% of the maximum daily dose of one or both study drugs biweekly until either the patient is off medications or reaches a dosage where there is recurrence or worsening of IIH.

The Site Investigator may consult with the Study co-Director at any time regarding tapering if needed.

#### 4.1.5 Discontinuation of Medical Therapy

Subjects who permanently discontinue taking study medication should be encouraged to remain in the study off medication and continue to be seen according to their original study visit schedule, but will not have routine blood testing performed.

Discontinuation of therapy will be reported on either a visit or phone contact form.

#### 4.1.6 Dietary Consultation

All subjects will be advised to adopt a low sodium weight reduction diet with lifestyle modification by the Site Investigator. The treatment plan will be individualized and may include consultation with a dietician or referral to a formal weight loss program.

### 4.2 Optic Nerve Sheath Fenestration

ONSF will be performed by a qualified orbital surgeon, with timing indicated below. See MOP for orbital surgeon qualifications. Either a medial or supero-medial lid crease approach may be utilized (see MOP more details). The surgery will make a window in the dural sheath of at least 4 mm in length under the operating microscope. The procedure will be considered successful if CSF egress is noted at the time of fenestration. Post-operative visits will be performed according to the surgeon's usual routine.

- If both eyes meet study entry criteria, ONSF will be performed on the eye with the worst PMD first, ideally within three days of randomization. If the other eye still meets eye-level eligibility criteria at two weeks after surgery on the first eye, ONSF will be performed on the second eye. If the second eye improves at two weeks after surgery on the first eye and no longer meets eligibility criteria, ONSF will not be performed on that eye.
- If only one eye meets entry criteria as an eligible eye, ONSF will be performed on the eligible eye ideally within three days of randomization.
    - If the second eye is not eligible for the study because visual field MD is too good, but the eye worsens (i.e. PMD -6 dB or worse with size V perimetry at any time during study follow-up), ONSF will be performed on the non-eligible eye. Also, if the non-eligible eye meets criteria for temporary treatment failure (see section 5.6.3 below), it will be operated on even if the PMD is not worse than -6 dB.
    - If the second eye is not eligible for the study because visual loss is too severe, ONSF will be considered at two weeks after surgery on the eligible eye.

See section 4.6, Management of the Non-Eligible Eye, for exceptions.

Administration of intravenous and topical corticosteroids is permitted intra-operatively, but systemic corticosteroids are not to be administered post-operatively (see MOP for details). Medical therapy will be continued until the Site Investigator believes that the dosage should be stopped or decreased because the subject has improved; he/she may contact the Study co-Director to decide on how to proceed. See section 4.1.4, Tapering of Medical Therapy.

### 4.3 CSF Shunting

CSF shunt surgery will occur ideally within 3 days of randomization by a certified neurosurgeon. See MOP for surgeon qualifications. Using a frameless image-guided stereotactic system, a ventricular shunt catheter will be positioned in the lateral ventricle of the cerebral hemisphere not associated with speech. The ventricular catheter will be connected to an adjustable valve and the distal shunt system will be placed in the peritoneal cavity. Post-operative computed tomography of the brain will be obtained to confirm shunt tip placement. Post-operative visits will be performed according to the surgeon's usual routine.

Since the purpose of this procedure is to normalize CSF pressure, the Site Investigator will taper medical therapy at the time of the surgery and then further if/when he/she is confident that the VPS is working (see section 4.1.4, Tapering of Medical Therapy).

## 4.4 Prohibited Medications, Treatments, and Procedures

Corticosteroids, topiramate, methazolamide, and additional diuretics (other than furosemide) may not be used during the study period (except intra-operative corticosteroids with ONSF). Should a subject begin an excluded treatment during the trial, this will be reported on a visit or phone contact form. The Study Director/co-Director will determine whether there is a potential safety risk and whether study treatment needs to be discontinued.

Other treatments for IIH, including bariatric surgery and transverse sinus stenting, will not be allowed during the first six months.

## 4.5 Concomitant Medications

### 4.5.1 Allowed Concomitant Medications

All concomitant medications must be used in accordance with approved labeling and as prescribed unless they are commonly used off-label for the prescribed purpose.

Headaches may persist as a major management problem in IIH patients after study treatments have been given.[82,83] The headache can be treated with standard prophylactic vascular headache remedies: non-steroidal anti-inflammatory drugs and tricyclic antidepressants may be effective. Low dosage amitriptyline is suggested; the initial dosage will be 10 mg at bedtime, gradually increasing to a maximum of 50 mg at bedtime, if needed. Weight gain is a well-known side effect of amitriptyline; by using a low dosage and monitoring the subject's weight, we anticipate minimizing this untoward effect. Acute headache may be treated with non-steroidal anti-inflammatory drugs (naproxen 500 mg bid), but their use will be limited to no more than three days per week to prevent analgesic rebound (medication overuse) headache. Table 8 below gives the Site Investigator a group of medications from which to choose. These medications should not be used more than 3 days per week.

**Table 8. Medications available for the symptomatic treatment of headache.**

| Medication* | Maximum Daily Dosage** |
|---|---|
| Naproxen sodium | 1 gram |
| Acetaminophen | 1500 mg |
| Aspirin | 1950 mg |
| Ibuprofen | 1600 mg |
| Acetaminophen with codeine 30 mg | 4 tablets |
| Butalbital/APAP or Butalbital/ASA | 4 tablets |

* Acetaminophen, aspirin, and non-steroidal anti-inflammatory drugs are preferred.

** Symptomatic treatment should be limited to 3 times weekly or less to prevent analgesic rebound (medication overuse) headache. Subjects requiring symptomatic headache treatment more than 3 times per week should be prescribed a preventive medication.

There is no single agent that will be effective and tolerated by all subjects needing prophylactic headache therapy. Table 9 below takes into consideration the undesirable side effects of many available agents for headache prevention. Gabapentin has few drug interactions, but may

increase the serum concentration of barbiturates and morphine. The selective serotonin reuptake inhibitors may produce a small amount of weight gain within the first year of usage. Protriptyline is the least sedating of the tricyclic antidepressants and is least likely to produce weight gain of medications in this class, but also may not be as effective at headache relief.

**Table 9. Preventive medications for headache.**

| 1st-Tier Medications | |
|---|---|
| **Medication** | **Suggested Starting and Final Dosages** |
| Amitriptyline | 10 mg qhs, up to 50 mg qhs if needed* |
| Vivactil™ (protriptyline) | 5 mg qhs, up to 10 mg bid if needed* |
| Naproxen | Up to 1 gram daily in divided doses |
| Nortriptyline | 25 mg qhs |
| * May be associated with weight gain; monitoring required | |
| **2nd-Tier Medications** | |
| **Medication** | **Suggested Starting and Final Dosages** |
| Gabapentin | 100 mg qhs, up to 400 mg TID if needed |
| Fluoxetine | 20 mg daily |

Subjects already taking preventive medication for headache at study entry may continue using their preventive medication *unless they are taking topiramate*. It is uncertain if the carbonic anhydrase inhibition associated with topiramate is sufficient to have potential therapeutic value in IIH; this could confound the results of the study.

### 4.6 Management of the Non-Eligible Eye

In general, non-eligible eyes are treated the same as eligible eyes. The non-eligible eye will have the same evaluations as the eligible eye. The only difference between eligible and non-eligible eyes is only the eyes that qualify at baseline (i.e., eligible eyes) will be included in the primary outcome analysis.

If a non-eligible eye worsens, the protocol for worsening of an eligible eye will be used. In the case of medical therapy, the dosage protocols for acetazolamide and if needed furosemide will be used. If there is worsening of a non-eligible eye in the optic nerve sheath fenestration group, the procedure will be performed on the 2nd eye if PMD worsens to -6 dB or worse with size V perimetry at any time during study follow-up or if the non-eligible eye meets criteria for temporary treatment failure (see section 5.6.3 below). If there is worsening of a non-eligible eye in the CSF shunting arm, medical therapy will be given and an evaluation for shunt failure will be done. Non-eligible eyes can be used to classify the subject as a treatment failure.

If only one eye meets study entry criteria and the other eye has worse vision by PMD than the eligible eye (e.g. PMD worse than -27 dB, refractive error too great, previous damage to the eye due to trauma, inflammation or infection) treatment of the eligible eye will take precedence; so in the case of optic nerve sheath fenestration, the eligible eye will be done first. However, there may be situations where the non-eligible eye requires the first operation. For example, if fixation is threatened only in the non-eligible eye. If the Site Investigator has concerns about the non-

eligible eye and believes it should be operated first, a decision will be made with the Study co-Director as to which eye is operated first.

### 4.7 Treatment during the Treatment Failure Identification Phase

After the 26 Week primary outcome visit, subjects will transition to the Treatment Failure Identification Phase. Ongoing treatment will continue following the guidelines for the first six months (26 weeks) as long as treatment failure criteria are not met at which time treatment will be at the discretion of the Site Investigator. Investigators are urged to employ treatments from another arm of the study before other treatments under these circumstances.

# Chapter 5: Study Visits and Procedures

## 5.1 Randomized Trial

### 5.1.1 Study Visits and Phone Contacts

During the randomized trial, follow-up visits for all three groups will occur at weeks 4, 8 16, and 26 (± 7 days) timed from the day of randomization.

Post-operative visits may also be performed by the surgeon according to the surgeon's usual routine.

Additional office visits may occur as needed.

Phone contacts will occur at 12 and 20 weeks (±7 days).

### 5.1.2 Safety Visits

Safety visits will occur in addition to study visits, with the timing dependent on the treatment group. The medical therapy only group generally will have visits 7 days and 14 days (± 4 days) following randomization whereas the surgery groups generally will have visits 7 days and 14 days (± 4 days) following each surgical procedure. Visit schedules can be modified at investigator discretion based on the participant's course and the 14-day visit could be skipped if there is substantial improvement in papilledema after 7 days. Additional visits can be scheduled as indicated. Reoperations at any time also will have a similar safety visit schedule.

### 5.1.3 Study Visit Procedures

The following procedures will be performed for all subjects at each study visit, unless otherwise specified:

- Medical/IIH history update
- Adverse Events
- Concomitant Medications
- Vital signs, including weight; (waist circumference at 26 Week only)
- Clinical Laboratories
- Refraction
- Visual Acuity
- Ocular Examination
- Metabolic Panel (16 and 26 Week only)
- CBC (16 and 26 Week only)
- Humphrey visual field testing with 24-2 full-threshold program using size V stimulus
  - at 26 Week, <u>two</u> visual field examinations

953 ➢ At other study visits, one visual field examination will be done, but the VFRC may
954 request the visual field examination be repeated

955 • Fundus Photographs
956 • OCT* (optic nerve head and macula)
957 • Dispense/prescribe acetazolamide and, if needed, furosemide
958 • Drug Compliance/Accountability
959 • Dietary counseling
960 • QoL questionnaires (26 Week only) – at study site or online
961 • HIT-6 questionnaire (26 Week only) – at study site or online
962 • Lumbar puncture for CSF opening pressure measurement (26 Week; voluntary)

963 *The 26 Week OCT must be done *before* the lumbar puncture.

964 **5.1.4 Phone Contact Procedures**

965 The Site Coordinator will contact the subject by telephone to review adverse events.

966 • Medical/IIH History update
967 • Adverse Events
968 • Review of Concomitant Medications
969 • Review of Drug Compliance

970 Additional phone contacts, texts, and emails may be performed as needed.

971 **5.1.5 Safety Visit Procedures**

972 The following procedures will be performed for all subjects at each safety visit:

973 • Adverse Events
974 • Concomitant Medications
975 • Vital signs, including weight
976 • Refraction
977 • Visual Acuity
978 • Ocular Examination
979 • Humphrey Visual Field testing with 24-2 full-threshold program using size V stimulus
980 • OCT (optic nerve head and macula)
981 • Fundus Photographs (only at week 2)
982 • Drug Compliance/Accountability

## 5.2 Treatment Failure Identification Phase

### 5.2.1 Follow-up Visits

Follow-up visits will occur at weeks 52 (12 months), 104 (2 years), and 156 (3 years) +4 weeks as long as the study is ongoing.

### 5.2.2 Study Visit Procedures

Procedures at these visits will include the following:

- Medical/IIH history update (includes all new treatments and adjustments of dosages)
- Adverse Events
- Concomitant Medications
- Vital signs, including weight
- Refraction
- Visual Acuity
- Ocular Examination
- Humphrey Visual Field testing with 24-2 full-threshold program using size V stimulus
- Fundus Photographs
- OCT (optic nerve head and macula)
- Drug Compliance
- QoL questionnaires – at study site or online
- HIT-6 questionnaire – at study site or online

If subject wants to discontinue birth control after the 6-month RCT, this should be discussed with the Site Investigator.

### 5.2.3 Phone Contact Procedures

A phone, text or email contact will occur at 39 weeks by site staff. Subsequent contacts (every 3 months, starting at month 15 through month 33) will be by Coordinating Center staff for a structured interview to determine if IIH symptoms have worsened. If the caller has concerns about the subject, the site investigator will be notified and will be responsible for contacting the subject.

## 5.3 Unscheduled Visits

An unscheduled visit can be performed at any time at investigator discretion, including the circumstance where the subject reports that IIH symptoms have worsened or if any unexpected adverse events develop. Testing performed and management decisions will be dependent on the circumstances of the visit and the findings.

## 5.4 Extra Assessments for Subjects Who Appear to be Worsening

If a subject appears to be worsening, the subject will receive a combination of frequent contact (phone, text, email) and unscheduled visits. The Site Investigator will determine at the end of each visit whether the subject appears to be worsening clinically [guidelines being: 1) subject report of progressive visual loss, 2) papilledema is worsening, 3) OCT measures are worsening, 4) ETDRS acuity worsens more than 4 letters, or 5) PMD worsens more than 2 dB]. If the Site Investigator is unsure how to proceed, he/she will review the case with the Study co-Director.

## 5.5 Early Termination

For subjects who are withdrawing or being withdrawn from the study, a final visit should be scheduled as soon as possible.

Procedures to be performed during the visit are the same as those listed in section 5.1.3.

## 5.6 Surgical Malfunction

VPS and ONSF malfunction will be evaluated at every visit if symptoms and findings suggest it. If the Site Investigator, based on all clinical findings, believes that there may be a surgical procedure malfunction/failure, he/she will request an SMRC review. Similarly, if the Photo Reading Center or Visual Field Reading Center identify lack of improvement or worsening, a SMRC review can be triggered.

### 5.6.1 Criteria for SMRC Review

Any of the below can trigger an SMRC review:

1. Either visual criteria for treatment failure are met (see section 5.7.1)
2. Papilledema: failure of papilledema to improve from baseline or worsening of papilledema following improvement
3. Site investigator believes there is substantial worsening of the subject's condition even if none of the other criteria are met

### 5.6.2 Surgical Malfunction Review by SMRC

When triggered, the SMRC will review all available clinically-related information and reading center results to determine whether there is a non-disease associated cause (mechanical cause) for the lack of improvement or worsening. The site surgeon and investigator will participate in the review process as needed. The SMRC may request that certain exams be repeated for further evaluation. The evaluation for VPS may include a radionuclide shunt study. The evaluation for ONSF may consider orbital MRI or echography. If the SMRC believes a surgical malfunction is likely, the subject's surgical procedure will be evaluated to check the viability of the procedure. If the SMRC decides there was a problem with the surgery or a surgical device malfunction, they will discuss the case with the site investigator, the surgeon, and the Study co-Director (or committee member) to determine whether re-operation is indicated.

The subject's safety is priority so if a site investigator or the SMRC Chair is confident a surgical malfunction occurred and emergent re-operation is needed, re-operation may be performed prior to full SMRC review.

#### 5.6.3 Temporary Treatment Failure

Temporary treatment failure is a situation that can occur in either of the surgical arms where the subject meets criteria for treatment failure (see section 5.7.1) and then has their surgical procedure revised or, in the case of ONSF, either revised or the other eye operated on. If the subject then recovers vision and no longer meets the criteria for treatment failure, they will continue the protocol treatment. If repeat surgery is not successful in improving vision out of the treatment failure criteria range, the case goes to the Adjudication Committee to determine if treatment failure has occurred.

### 5.7 Treatment Failure

Possible treatment failure will be evaluated at every visit if symptoms and findings suggest it. If the Site Investigator, based on all clinical findings, believes that there may be a treatment failure, the worsening will be confirmed with a repeat visual field examination (and ETDRS acuity testing if needed) on the same day or within four days of the original visual field. If the Visual Field Reading Center identifies lack of improvement or worsening, the site will be notified and repeat testing performed. If the worsening is confirmed (both visual field examinations having PMD that exceeds the cutoff value in 5.7.1 below), the case goes to the Adjudication Committee to determine if treatment failure has occurred.

#### 5.7.1 Treatment Failure Criteria

If either of the below criteria for worsening are met, the subject will be considered for treatment failure by the Adjudication Committee:

1. Worsening of Full Threshold Size V 24-2 Perimetry.
    a. Average baseline MD is equal to or better than -4 dB and visual function worsens more than 2 dB MD from the baseline average.
    b. Average baseline MD is worse than -4 dB and equal to or better than -6 dB and visual function worsens more than 3 dB MD from baseline average.
    c. Average baseline MD is worse than -6 dB and visual function worsens more than 4 dB MD from baseline average.
2. Worsening of 2 or more lines of ETDRS visual acuity

#### 5.7.2 Treatment Failure Review by Adjudication Committee

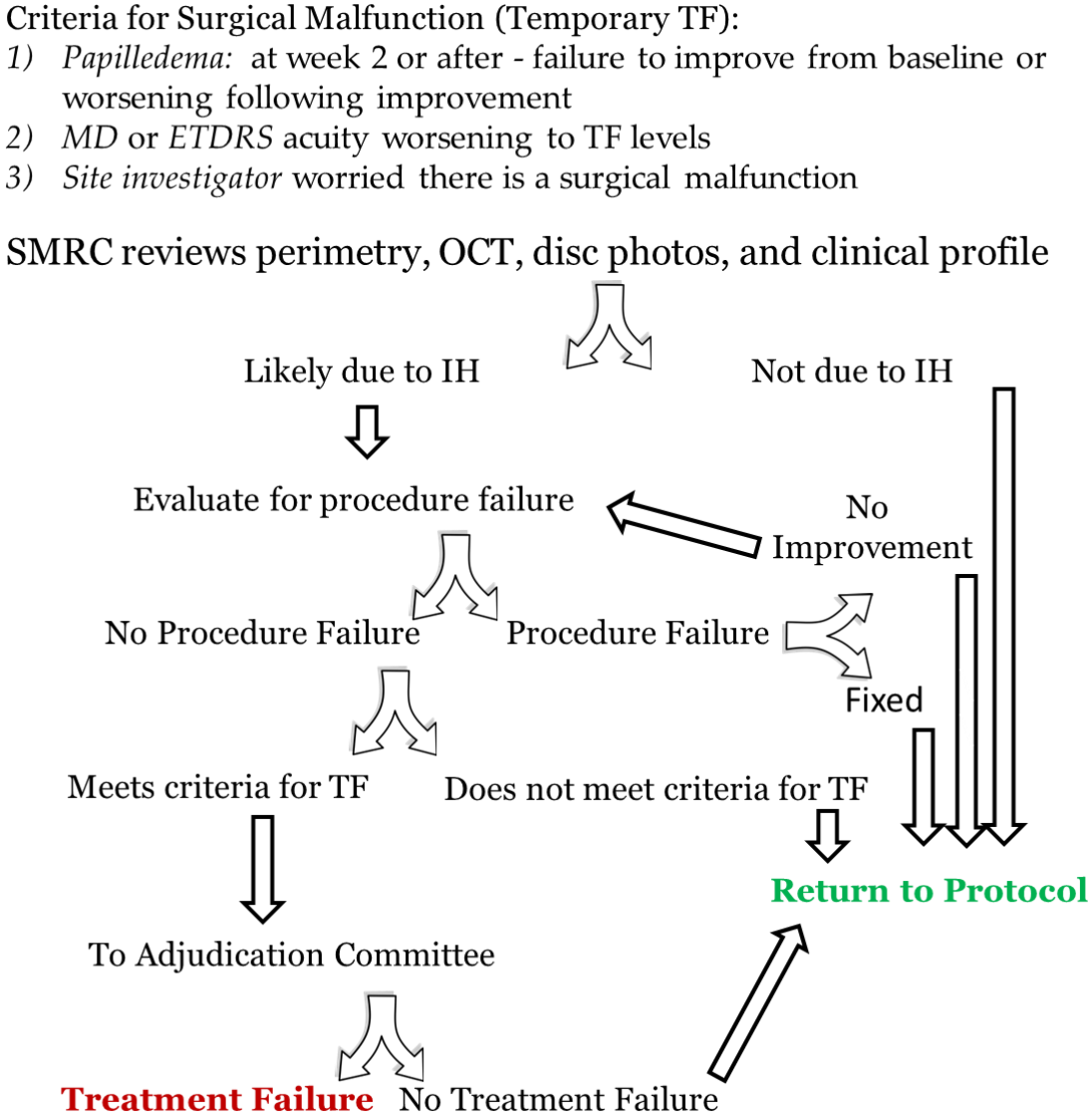
The Adjudication Committee will review possible treatment failures and determine if a treatment failure has occurred. The committee will be masked to treatment assignment and using all available clinically-related information, including fundus photo results, will decide whether the failure is most likely due to increased intracranial pressure or from another cause, such as perimetric artifact, poor subject effort, or the presence of another unrelated cause of visual loss.

If the Adjudication Committee determines that a possible treatment failure is most likely due to IIH, the subject will be classified as having experienced a treatment failure. All cases that are sent to the Adjudication Committee will be reviewed first by the Study Director. If it is obvious that the patient meets criteria for treatment failure, they will be so designated. The case will subsequently be reviewed by the Adjudication Committee.

When a subject meets the criteria for treatment failure, it is preferred that subsequent therapy come from one of the other two treatment arms but this decision will be deferred to the judgment of the Site Investigator. These subjects will continue to be followed at their set times for the full follow-up period (up to 3 years). The date of a confirmed treatment failure will be the date of the first visual field that triggered the Adjudication Committee review.

If treatment failure is not confirmed, the subject will continue to follow his/her treatment group's protocol.

**Figure 3. Algorithm for Review by Surgical Malfunction Review Committee**




### 5.7.3 Visit Schedule Once Treatment Failure is Reached

When a subject reaches treatment failure prior to the 6 Month visit window, the subject should be brought back as soon as possible for an unscheduled visit and all 6 Month visit procedures should be performed. The subject should be directed to remain on medical therapy (if on medical therapy) until seen for this visit, unless instructed otherwise by the Site Investigator. The subject should then return for the scheduled 6 Month visit and then the 12 Month visit. After the 12 Month visit, subjects will then continue in the Treatment Failure Identification Phase of the study with annual visits.

# Chapter 6: Testing Procedures, Questionnaires, Clinical Assessments, and Laboratory Testing

## 6.1 Testing Procedures

The testing procedures are noted below and details are provided in the Site Procedures Manual.

## 6.2 Intraocular Pressure

Intraocular pressure will be measured using Goldmann tonometry.

## 6.3 Refraction and Visual Acuity

At each protocol visit, a standardized refraction will be performed in both eyes. This will be followed by testing of visual acuity using ETDRS charts. Both will be administered by a certified technician masked to treatment group as best as possible.

Although it is not possible to fully mask the technician to whether or not a subject had ONSF, all subjects will wear hairnets during the testing after randomization through the Week 8 visit in order to provide masking to VPS.

## 6.4 Papilledema Grading

Site investigators will be trained to grade papilledema using the Frisén scale.[77]

Fundus photography: Digital fundus photographs centered on the optic disc will be taken at each visit. The severity of papilledema will be graded by the Photography Reading Center (PRC) using the Frisén scale.[77,78]

## 6.5 Perimetry

Automated perimetry will be performed using the Humphrey Field Analyzer (HFA) 24-2 full-threshold program using a size V stimulus in both eyes by a certified technician masked as best as possible to treatment group. The MOP provides a detailed description of this procedure.

Although it is not possible to fully mask the visual field technician to whether or not a subject had ONSF, all subjects will wear hairnets during the visual field examination after randomization through the Week 8 visit in order to provide masking to VPS. The use of a standardized visual field protocol should limit the influence of the visual field technician on the results of the examination.

## 6.6 OCT

Spectral-domain OCT evaluations of the optic nerves, peripapillary RNFL, and macula will be obtained using a Cirrus™ (Carl Zeiss-Meditec, Inc, Dublin, CA) or Spectralis® (Heidelberg Engineering, Inc, Carlsbad, CA) spectral-domain OCT. The subject must have the same brand of OCT machine used for data collection at each visit.

### 6.7 Lumbar Puncture

Lumbar puncture is performed as part of usual care at baseline. Although repeat lumbar puncture is not considered standard of care, subjects will undergo a second voluntary lumbar puncture for CSF opening pressure measurement at the 6-month visit, following the procedure detailed in the MOP.

### 6.8 Quality of Life Assessment

The NEI VFQ-25 and the 10-item Neuro-ophthalmic Supplement to the VFQ-25 will be used, as well as the SF-36v2.[79] Testing time is approximately 20 minutes.

### 6.9 Headache Disability Rating

Headache disability will be rated using the HIT-6 (Headache Impact Test),[80] a 6-item scale that is commonly used to rate migraine disability and has been validated for IIH. Testing time is 1-2 minutes.

### 6.10 Neurologic and Physical Examination

A standard neurological evaluation will be performed at screening. When indicated, a general medical examination will be performed.

### 6.11 Clinical Laboratory Tests

CBC with platelet count will be obtained at Baseline and at Weeks 16 and 26 for all subjects.

A comprehensive metabolic profile, including liver function tests, electrolytes, and amylase, will be obtained at Baseline and at Weeks 16 and 26 for all subjects.

For subjects taking furosemide, serum potassium and sodium levels will be checked prior to each dosage change, after reaching the maximum tolerated dosage, and then at each subsequent visit. This testing will be performed at a local laboratory.

Routine clinical laboratory tests will be performed locally by the site or the subject's local laboratory if travel to the site is not convenient. The Site Investigator will review the laboratory values. The Site Investigator will prescribe appropriate supplementation for hypokalemia, hyponatremia and symptomatic bicarbonate deficiency, and may enlist the help of the subject's primary physician to help manage abnormal laboratory results, if necessary.

# Chapter 7: Adverse Event Reporting

## 7.1 Adverse Events

### 7.1.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study subject, irrespective of the relationship between the adverse event and the study drug or surgery (see 7.1.2 for what adverse events require reporting in this protocol).

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

### 7.1.2 Reporting Adverse Events

Symptoms and signs, including visual symptoms and headaches, that are considered to be due to IIH will be captured on a visit/phone case report form and are not considered to be adverse events unless SAE criteria are met.

Certain adverse events that are known side effects of acetazolamide and furosemide will be captured on a visit/phone case report form (including paresthesia, dizziness, nausea, vomiting, diarrhea, loss of appetite, acid reflux, skin rash, dyspnea, hypercapnia, depression, anxiety, tinnitus, fatigue) for all subjects, regardless of whether taking study medication. A separate Adverse Event Form is only completed for these specific events if SAE criteria are met or the event was severe enough that it resulted in discontinuation of study drug.

Expected symptoms post-surgery will be captured on a visit/phone case report form. A separate Adverse Event Form is only completed for these specific events if SAE criteria are met or if the onset date is outside the expected duration of occurrence post-surgery, regardless of intensity.

Laboratory results of interest will be recorded on a laboratory data case report form. A separate Adverse Event Form is only completed for laboratory abnormalities that are considered clinically significant by the investigator.

During the first 6 months, all other events (not described above) meeting the definition of adverse event will be reported on an Adverse Event Form. After the first 6 months, only those events meeting SAE criteria will be reported on an Adverse Event Form.

#### 7.1.3 Relationship of Adverse Event to Study

The study investigator will assess the relationship of any adverse event reported on an Adverse Event Form to be related or unrelated to a study intervention or procedure by determining if there is a reasonable possibility that the adverse event may have been caused by the intervention or procedure.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Yes

There is a plausible temporal relationship between the onset of the adverse event and the study intervention/procedure, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention/procedure; and/or the adverse event abates or resolves upon discontinuation of the study intervention/procedure or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the adverse event has an etiology other than the study intervention/procedure (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention/procedure.

#### 7.1.4 Intensity of Adverse Events

The intensity of an adverse event will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity; thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

- MILD: Usually transient, requires no special treatment, and does not interfere with the subject's daily activities.
- MODERATE: Usually causes a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- SEVERE: Interrupts a subject's usual daily activities and generally requires systemic drug therapy or other treatment.

#### 7.1.5 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary.

### 7.1.6 Outcome of Adverse Event

The outcome of each reportable adverse event will be classified by the investigator as follows:

- RECOVERED/RESOLVED: The subject recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE: The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- NOT RECOVERED/NOT RESOLVED: An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
  - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
  - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- FATAL: A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- UNKNOWN: An unknown outcome is defined as an inability to access the subject or the subject's records to determine the outcome (for example, a subject that was lost to follow-up).

All clinically significant abnormalities of clinical laboratory measurements or adverse events occurring during the study and continuing at study termination should be followed by the subject's physician and evaluated with additional tests (if necessary) until diagnosis of the underlying cause, or resolution. Follow-up information should be recorded on source documents.

If any reported adverse events are present when a subject completes the study, or if a subject is withdrawn from the study due to an adverse event, the subject will be contacted for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the subject until the adverse event has resolved or stabilized.

## 7.2 Pregnancy Reporting

If pregnancy occurs during the 6-month RCT, study drug will be discontinued. The occurrence of pregnancy will be reported on an AE Form.

## 7.3 Timing of Event Reporting

Serious, unexpected treatment-related adverse events must be reported to the Coordinating Center within 24 hours via completion of the online serious adverse event form.

Other reportable adverse events as defined in section 7.1.2 will be reported within 3 days of the investigator becoming aware of the event by completion of an electronic case report form.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 10 working days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

The sponsor will report any serious, unexpected treatment-related adverse events to the FDA.

## 7.4 Stopping Criteria

### 7.4.1 Subject Discontinuation of Study Drug

Rules for discontinuing study drug use are described below.

- The investigator believes it is unsafe for the subject to continue to receive the drug. This could be due to the development of a potential side effect of the drug, a new medical condition or worsening of an existing condition; or subject behavior contrary to the indications for use of the drug that imposes on the subject's safety
- The subject requests that the treatment be stopped
- Subject pregnancy during 6-month RCT (discontinuation at investigator discretion during Treatment Failure Identification Phase)

Even if the study drug is discontinued, the subject will be encouraged to remain in the study through the final study visit.

## 7.5 Medical Monitor

A Medical Monitor will review all reported adverse events reported on an Adverse Event Form, solicited events captured on a visit/phone case report form, and laboratory abnormalities.

The Medical Monitor will assess each event for appropriate coding of intensity, criteria for SAE, relationship to study drug/procedure, and MedDRA classification. The Medical Monitor's coding will be considered final.

## 7.6 Independent Safety Oversight

A Data and Safety Monitoring Committee (DSMC), selected by the National Eye Institute, will provide study oversight. The Committee will be sent serious, unexpected, treatment-related adverse events for expedited review and all adverse events in a cumulative report approximately every 6 months.

## 7.7 Criteria for Suspending or Terminating Overall Study

There are no pre-specified criteria for suspending or terminating the study. Such decisions will be made by the DSMC based on their review of accumulated safety data.

# Chapter 8: Miscellaneous Considerations

## 8.1 Subject Compensation

Subject compensation will be specified in the informed consent form.

## 8.2 Subject Withdrawal

Participation in the study is voluntary, and a subject may withdraw at any time. For subjects who withdraw, their data will be used up until the time of withdrawal. If possible, a final visit will be completed for all subjects who are terminating the study early (see section 5.5).

A subject may be withdrawn from the study at the discretion of the Site Investigator or the Study co-Director for the following reasons:

- Adverse event, but only if follow-up presents a risk to the subject's safety
- Noncompliance with study medications, but only if follow-up presents a risk to the subject's safety
- Development of a condition, but only if follow-up presents a risk to the subject's safety

Prior to withdrawing subject from the study, the Site Investigator must contact the Study co-Director to discuss the case.

## 8.3 Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL and the enrollment center, Mount Sinai in New York, NY. De-identified subject information may also be provided to research sites involved in the study.

# Chapter 9: Statistical Consideration

## 9.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to viewing any outcome data. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

## 9.2 Intention-to-Treat Principle

The primary statistical analyses for this trial will be performed according to the intention-to-treat principle and will include all randomized subjects and eligible eyes. Every effort will be made to retain subjects in this study, to promote adherence to the study protocol, and to collect all data at every visit. If a subject cannot tolerate study medication or refuses to receive the study intervention, we will continue to follow and evaluate that subject if he/she is willing. If a subject drops out, attempts will be made to bring the subject back for a final evaluation. Compliance with trial procedures, drop-outs/drop-ins, and reasons for subject withdrawal will be carefully tracked throughout the study.

## 9.3 Analysis of the Primary Outcome Variable

### 9.3.1 Primary Statistical Model

The primary outcome variable will be the change from baseline to the first of Month 6 or time of treatment failure in PMD in an eligible eye, with data from all eligible eyes included in the primary analysis. The primary statistical analysis will involve fitting an analysis of covariance model using generalized estimating equations (GEE) with treatment group as the factor of interest and baseline PMD as a covariate. These analyses will accommodate correlation among the within-subject responses between the two eyes; an exchangeable working correlation structure will be used. Standard errors for the model parameters will be estimated using the robust "sandwich" estimators. The model also does not rely on the assumption of normality.

This model will be used to determine Bonferroni-adjusted confidence intervals for the three pair-wise differences among the adjusted treatment group mean responses (treatment effects); likewise, tests will be performed to compare the adjusted treatment group means using a Bonferroni-adjusted two-tailed significance level. An overall confidence coefficient of 98.3% and corresponding significance level of 1.7% for each comparison will be maintained, but as discussed in section 9.8.2 below, the confidence coefficient for interval estimation and significance level for hypothesis testing will be adjusted for the interim analysis for efficacy.

Treatment of subjects who have reached criteria for treatment failure will be at the discretion of the Site Investigator, and this treatment may yield a different outcome than randomized treatment (investigators are urged to employ treatments from another arm of the study before other treatments under these circumstances). For this reason, the primary outcome variable for subjects who reach criteria for treatment failure prior to Month 6 will be the PMD measured at the time of treatment failure for purposes of the primary analysis. It is anticipated that no more than 15% of subjects will reach criteria for treatment failure prior to Month 6. As the most important of the secondary outcome variable analyses, A secondary outcome analysis will be performed that will

include the PMD for these subjects that was obtained at Month 6, regardless of treatment received after treatment failure.

#### 9.3.2 Adjustment for Baseline Characteristics

If clinically important differences are found between the groups at baseline, particularly with regard to important variables such as age, gender, race/ethnicity, or visual acuity, the primary outcome analyses will be repeated after statistically adjusting for these differences. These analyses will be considered secondary, however.

#### 9.3.3 Investigation of Treatment by Covariate Interactions

We will investigate the interaction between treatment group and selected baseline covariates (age, race/ethnicity, PMD, papilledema grade, RNFL thickness, total retinal thickness, optic nerve head volume, visual acuity, presence of transient visual obscurations, and the symptom of constant visual loss) separately by adding the appropriate main effect and interaction terms to the primary statistical model and testing for significance of the interaction. Since the power to detect potentially meaningful interactions will be limited, the magnitudes of mean responses to treatment in the relevant subgroups will be examined. The observation of clinically important subgroup differences in mean treatment response will serve as hypothesis generation for possible future studies designed to address specifically the issue of differential therapeutic response. Although these analyses are purely exploratory, those involving papilledema grade, PMD, visual acuity, and race/ethnicity will be given higher priority.

#### 9.3.4 Verification of Model Assumptions

The underlying assumptions of the statistical model to be used in the primary analysis will be thoroughly checked (e.g., linearity), and remedial measures (e.g., transformations) may be taken if serious violations of these assumptions are detected.

#### 9.3.5 Treatment of Missing Data

Multiple imputation will be used to deal with missing data. This will be applied using a regression-based imputation model. For subjects with complete data up to a particular visit, a multiple regression model will be fit that includes the outcome at that visit as the dependent variable and outcomes at previous visits and treatment group as independent variables. Separate models will be similarly constructed for each visit (Weeks 1, 4, 8, 16, and 26). Using these regression models, a missing value for a subject at a particular visit will be imputed as a draw from the predictive distribution given the outcomes at previous visits (some possibly imputed) and treatment group. This will be done sequentially starting with the Week 1 visit and ending with the Week 26 (Month 6) visit. This process will be repeated 100 times, resulting in 100 complete analysis data sets. The analyses will be performed separately for each of the 100 complete analysis data sets, and the results will be combined into one multiple imputation inference (estimated treatment effect and associated confidence interval and p-value) using Rubin's rules.[93,94] This approach is appropriate for data sets that have a monotone missing data pattern. If the data set does not precisely have this pattern, the monotone data augmentation method using Markov-Chain Monte-Carlo [95,96] will be used to impute the small amount of missing data that is required to make the missing data pattern monotone before applying the multiple imputation algorithm described above. This approach should accommodate missing data in an appropriate way under the missing at random (MAR) assumption.[88,89]

Separate secondary analyses may also be performed that, for example, may group subjects according to treatment actually received (whether or not this was the randomly assigned treatment) and/or exclude subjects who had incomplete follow-up, took less than a certain threshold of their medication, or had another major protocol violation. The identification of subjects to be excluded from these analyses will be determined before the masking is broken (i.e., before data analysis). Of course, such analyses may lead to biased estimates of the actual treatment effects, but they may provide an indication of the sensitivity of the analyses to drop-ins/drop-outs and noncompliance. Methods such as those based on propensity score stratification[90] or inverse probability weighting[91] can be employed in this setting in which non-randomized groups are to be compared.

### 9.4 Analysis of the Secondary Outcome Variables for Efficacy

The most important secondary outcome variable for efficacy will be change from baseline to Month 6 in PMD in an eligible eye, with data from all eligible eyes included in this analysis. This is in contrast to the primary outcome variable for efficacy that is change in PMD from baseline to the first of Month 6 or time of treatment failure in an eligible eye, with data from all eligible eyes included in this analysis.

The following additional secondary outcome variables will be evaluated at six months: change in CSF opening pressure measurement by lumbar puncture; change in papilledema grade (PRC and Site Investigator); changes in OCT measures (RNFL thickness, total retinal thickness, optic nerve head volume, ganglion cell layer thickness, optic nerve canal shape); changes in ETDRS visual acuity scores; changes in QoL assessments (SF-36, VFQ-25 and its 10-item supplement), changes in headache assessments (HIT-6 Inventory and headache severity); Visual Field Reading Center (VFRC) determination by three visual field experts of whether the visual field examination has improved, remained the same, or worsened; treatment failure; and surgical failure (transient or otherwise depending on attempts to repair malfunctions).

With the exception of CSF opening pressure, these outcome variables will also be examined at Months 12, 24, and 36. Of special interest is the outcome of time from randomization to treatment failure. Time from randomization to failure due to surgical malfunction (even if temporary) is also of interest in the long-term follow-up phase.

Treatment effects on secondary outcome variables for efficacy that are continuous will be analyzed using the same methods described above for the primary outcome variable, except that a working correlation structure will not be needed for variables that are not eye-specific. Variables to be analyzed in this manner include CSF opening pressure, OCT measures, quality of life as measured by the NEI-VFQ-25 + 10-item neuro-ophthalmic supplement and the SF-36, headache disability (HIT-6 Inventory), and headache severity.

The model will be used to determine Bonferroni-adjusted 98.3% confidence intervals for the three pair-wise differences among the adjusted treatment group mean responses (treatment effects) at Month 6; likewise, tests will be performed to compare the adjusted treatment group means at Month 6 using a Bonferroni-adjusted two-tailed significance level of 1.7%.

For categorical outcome variables that are dichotomous (e.g., presence of headache, surgical failure) or ordinal (visual field examination ratings by the VFRC, graded as improved, no

change, or worse), logistic regression models (or proportional odds models for ordinal outcomes) will be used to assess treatment effects. These models will include treatment group as the factor of interest and the baseline value of the outcome variable (for presence of headache) or baseline PMD (for surgical failure) as covariates. Likelihood-ratio tests will be performed for significance of the adjusted treatment group odds ratios representing pair-wise treatment group comparisons, and 98.3% confidence intervals will be constructed for these odds ratios. Other aspects of the analysis of the primary outcome variable (e.g., further adjustment for baseline factors, examination of interactions, verification of model assumptions) will also be considered.

For dichotomous outcomes that are measured repeatedly over time (e.g., presence of headache), if a subject is missing a response at a particular visit, missing data will be imputed using logistic regression-based multiple imputation.[93] For subjects with complete data up to a particular visit, a logistic regression model will be fit that includes the outcome at that visit as the dependent variable and outcomes at previous visits and treatment group as independent variables. Separate models will be similarly constructed for each visit. Using these logistic regression models, a missing value for a subject at a particular visit will be imputed as a draw from the predictive distribution given the outcomes at previous visits (some possibly imputed) and treatment group of the subject. This will be done sequentially starting with the Week 1 visit and ending with the Month 6 visit. This process will be repeated 100 times, resulting in 100 complete analysis data sets. The analyses will be performed separately for each of the 100 complete analysis data sets, and the results will be combined into one multiple imputation inference (estimated odds ratios [treatment effects] and associated confidence intervals and p-values) using Rubin's rules.[93,94]

## 9.5 Compliance Outcomes

Data concerning compliance with acetazolamide (pill counts, serum bicarbonate levels) and surgical therapy will be summarized by treatment group and visit. Subjects with two eligible eyes will have this information summarized by eye as well as by treatment group and visit. Change in weight will be used as a summary of compliance with diet.

## 9.6 Analysis of Safety and Tolerability Outcomes

### 9.6.1 Adverse Events

All reportable adverse events will be tabulated by treatment group in a listing of each reported Medical Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ Class. Details will be provided in a listing of each event.

In addition, the following will be tabulated by treatment group. When applicable, events will be tabulated by eye within person:

- Number of adverse events
- Number of subjects with at least one event
- Number of serious adverse events
- Number of subjects with at least one serious adverse event
- Number of hospitalizations and reasons for the hospitalization

- Number of adverse events thought by investigator to be related to study drug
- Number of subjects who stopped the intervention in response to an adverse event

For binary variables, Fisher exact tests will be used to compare treatment groups. For counts, groups will be compared using Poisson regression.

For each adverse event, the treatment groups will be compared in a pair-wise fashion regarding the occurrence of at least one event using Fisher's exact tests; numbers of individual events will also be described. The comparisons will be repeated excluding all mild symptoms. Similar analyses will be performed after grouping adverse events by body system using Medical Dictionary for Regulatory Activities (MedDRA) coding. All subjects will be included in these analyses.

#### 9.6.2 Tolerability Outcomes

Tolerability will be primarily measured by ability to complete 6 months of follow-up on the originally assigned treatment. A complete accounting of subject disposition will be summarized by treatment group, including a tabulation of subject withdrawals, dosage reductions/ discontinuations of study medication due to adverse events (with reasons for each), receipt of surgery other than that randomly assigned, and surgical failures.

#### 9.6.3 Laboratory Test Results and Vital Signs

Continuous measures of safety such as laboratory test results (e.g., CBC with platelet count, electrolytes, potassium, bicarbonate, and liver function tests) and vital signs and anthropometric measures (e.g., blood pressure, weight, and waist circumference) will be analyzed descriptively.

Proportions of subjects with particular laboratory test abnormalities will be compared between the treatment groups in a pair-wise fashion using Fisher’s exact tests.

### 9.7 Analysis of Long-Term Follow-Up Data

An important set of analyses will consider the outcome of time from randomization to treatment failure. The statistical analysis of this outcome variable will involve fitting a Cox proportional hazards regression model with treatment group as the factor of interest and baseline PMD in the best eligible eye as a covariate. This model will be used to determine Bonferroni-adjusted 98.3% confidence intervals for the adjusted hazard ratios for the three pair-wise treatment group comparisons; likewise, likelihood ratio tests will be performed for significance of these hazard ratios using a Bonferroni-adjusted two-tailed significance level of 1.7%. Kaplan-Meier curves will be used to describe the cumulative probability of treatment failure over time in each treatment group. For subjects who do not experience treatment failure, event times will be censored at the last subject contact at which the subject was determined to not have experienced treatment failure (e.g., at the time of premature withdrawal from the trial or at the final trial visit).

As described above for the primary outcome variable for efficacy, secondary analyses of time to treatment failure that adjust for additional baseline covariates may be considered depending on the comparability of the treatment groups at baseline, and examination of interactions between

treatment group and selected baseline covariates will be performed using the Cox proportional hazards model.

The underlying assumptions of the Cox proportional hazards models will be checked and a thorough analysis of the martingale residuals and other diagnostics will be performed[102]. Remedial measures (e.g., covariate transformation) will be taken if serious violations of these assumptions are detected. The proportional hazards assumption will be assessed graphically by plotting log(–log($\hat{S}$(t)) vs. log(time) for each of the treatment groups, and by plots of smoothed Schoenfeld residuals[101]. This assumption will also be examined by dividing the time scale into 6-month periods and estimating the treatment group hazard ratios separately in each of these periods through the use of time-dependent covariates[103]. The period length of 6 months may be adjusted prior to unmasking, based on the observed distribution of event times, if relatively few events occur during 6-month periods. Treatment group comparisons will be described in this manner if the proportional hazards assumption appears to be seriously violated.

An additional important assumption of the methods to be used to analyze time to treatment failure is the independence between the censoring time and the (unobserved) event time. Sensitivity analyses will be performed that treat subjects with event times that are censored prior to their scheduled end of follow-up as having experienced the event a short time (one week) after censoring.

Analyses of the primary and secondary outcome variables for efficacy using data collected after the 6-month visit will be analyzed according to the initial treatment strategy using the same methods described above. This will include surgical procedure complications or transient malfunctions. More complex analyses may be performed that take into account the introduction of other treatments (e.g., surgery in those assigned to medical therapy) depending on how often this occurs. It will necessarily be difficult to make inferences about the effectiveness of subsequent treatments; however, analyses using marginal structural models[100,104] may prove useful for this purpose. Outcomes such as surgical failure and IIH recurrence (in those whose vision is initially restored) will be summarized descriptively over time.

## 9.8 Interim Analyses

### 9.8.1 Interim Analyses for Safety

Interim analyses of safety data will be performed periodically throughout the trial. While the safety of subjects will be the primary concern of the DSMC, it is difficult to formulate precise stopping guidelines that would cover all of the possible situations that might arise. Adverse events, particularly serious adverse events and surgical complications, will have to be considered carefully by the DSMC in terms of treatment group imbalances and severity. Events of particular concern include the following: death, absence of light perception, hypokalemia (from Lasix use), surgery-associated visual loss (from either VPS or ONSF), fenestration failure and orbital infection (from ONSF), and shunt failure, infection, seizures, and subdural hematoma (from VPS). If potential safety concerns are identified, the DSMC may require review of visual field data in order to evaluate the risk-benefit of continuing the trial as planned or modifying (or halting) the trial.

### 9.8.2 Interim Analyses for Efficacy

We propose to perform a single interim analysis for efficacy based on the primary outcome efficacy variable. This will be performed after 50% of the subjects have completed (or were scheduled to have completed, based on their randomization date) their Month 6 visit and will only include data from these 50% of subjects. Given that recruitment of the 180 subjects will take place over 3 years, assuming that recruitment is uniform over time, it is anticipated that slightly fewer than 70% of the subjects will be enrolled at the time of the interim analysis.

The analysis will involve pair-wise comparisons among the treatment groups with respect to the primary outcome efficacy variable; the significance level used for each comparison will be that determined by an O'Brien-Fleming α-spending function for a two-group comparison divided by 3 (Bonferroni correction).[99] In this case, the boundaries will be $Z = 3.394$ for the interim analysis and $Z = 2.400$ for the final analysis. Assuming that there are 30 subjects per group and that the standard deviation is 6.5 dB at the interim analysis, the boundary will be crossed if a group difference exceeds approximately 5.7 dB. This monitoring procedure will have a negligible impact on the overall Type I error probability: the significance level at the final analysis corresponding to $Z = 2.400$ is $\alpha = 0.0164$. Point and interval estimates of treatment effects, as well as reported p-values, will be adjusted for the interim analysis. The bias-adjusted mean will be used for point estimation and confidence intervals and p-values based on the MLE (sample mean) ordering of the sample space defined by the group sequential design [97,98] will be reported in this case.

The efficacy boundary will be considered to be non-binding. We believe that it may be prudent to halt or modify the trial only if (1) two of the treatment groups are each shown to be superior to the third (in which case the third group may be dropped) or (2) one of the treatment groups is shown to be superior to each of the other two (in which case the trial may be halted). Of course, the relative safety profiles of the treatments would have to factor into these considerations as well.

## 9.9 Baseline Characteristics

Baseline characteristics of subjects will be summarized overall and by treatment group; formal statistical comparisons between treatment groups will not be performed. Continuous variables will be described using means, standard deviations, medians, quartiles, and ranges, and categorical variables will be described using percentages.

## 9.10 Sample Size Determination

In this clinical trial, 180 subjects with newly diagnosed IIH and moderate to severe visual loss (-27 dB ≤ PMD ≤ -6 dB) will be randomly assigned to receive either medical therapy, ONSF + medical therapy, or VPS + medical therapy (60 per group). This sample size should provide high power to detect group differences when the true differences are of clinical significance, allowing for an anticipated 10% drop-out. The rationale for the choice of a clinically significant treatment group difference of 4.5 dB is explained in the last paragraph below.

The primary outcome variable in this trial will be the change from baseline to the first of Month 6 or time of treatment failure in PMD in an eligible eye. An eye is defined as eligible if it satisfied the requirement of -27 dB ≤ PMD ≤ -6 dB at baseline. The sample size considerations

initially focus on data from the best eligible eye, since most subjects are expected to contribute only one eye to the primary analysis, but addition of the other eligible eye is also considered below. In 2012, the IIH Study Group performed a retrospective chart review of consecutive newly diagnosed patients that met the modified Dandy criteria for IIH[27] at 30 of the 41 participating sites. Data on PMD were available from 91 patients at two time points, before and after intervention, with the median follow-up time being 6.0 months (interquartile range 4.1 to 7.0 months). Patients received either medical treatment (n = 43), ONSF (n = 24), or VPS (n = 24). The mean (± standard deviation) changes in PMD (in dB) in the best eligible eye over the follow-up period were 5.5 ± 6.9 in the medical group, 2.0 ± 8.9 in the ONSF group, and 8.2 ± 8.0 in the VPS group; overall these values were 5.3 ± 8.0. The distribution of these changes was slightly more peaked than would be expected for a normal distribution, as illustrated in Figure 4a and 4b.

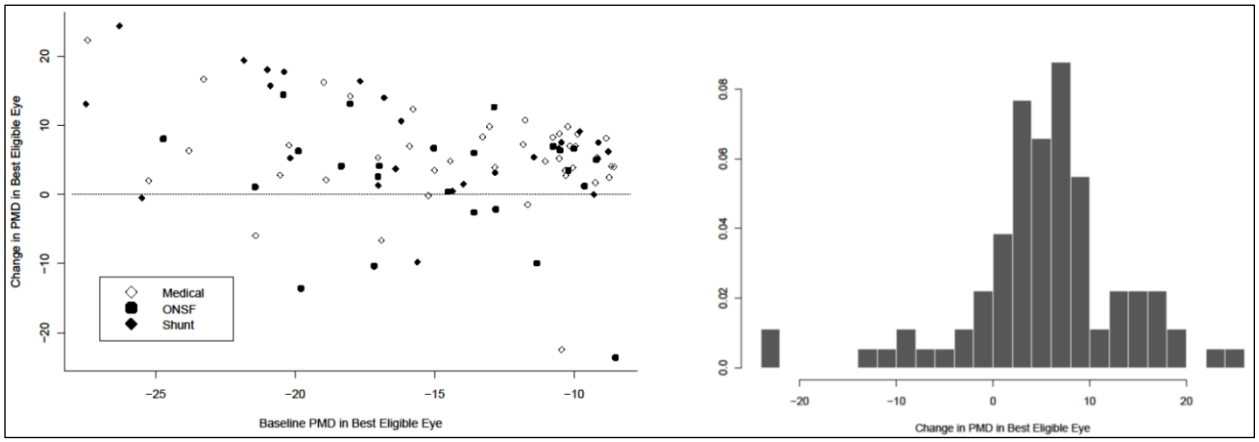



**Figure 4a and 4b. Distribution of Changes in PMD in the Best Eligible Eye**

**The figure on the left (a) shows the distribution of changes in PMD in the best eligible eye according to baseline PMD and intervention. Most of the patients demonstrated improvement in PMD. The figure on the right (b) shows a histogram of the changes in PMD in the best eligible eye regardless of intervention. The distribution appears to be characterized by a high concentration of changes between 0 and 10 PMD and is more peaked than normal.**

Given the cross-sectional nature of the preliminary data, sample size determination based on the use of GEE for the primary analysis is very similar to that based on the use of an analysis of covariance model. If an analysis of covariance model is fit to the preliminary data, with change in PMD as the outcome variable and treatment group and baseline PMD as the independent variables, the standard deviation of the residuals is 6.3 dB. The differences between treatment groups in adjusted mean response are quite small in this analysis: -0.09 dB difference between the ONSF and medical groups, and 1.13 dB difference between the VPS and medical groups. Also, a GEE analysis produces identical adjusted group means and slightly different estimated standard errors than those from the analysis of covariance model.

It may be noted that the standard deviation of the residuals in the above analysis of covariance model is substantially less than the standard deviations in the individual treatment groups, reflecting adjustment for the baseline value of PMD in the analysis of covariance model and the fairly strong correlation between the baseline and final PMD values (r = 0.52). When considering

only subjects who were followed for at least 5.5 months (n = 56), the correlation between the baseline and final PMD values was actually somewhat higher (r = 0.62) and the residual standard deviation in the analysis of covariance model was smaller (6.0 dB).

Assuming a standard deviation of 6.5 dB, consistent with the preliminary data, and a Bonferroni-adjusted two-tailed significance level of 1.7%, in order to detect a group difference assuming a true difference of 4.5 dB with 88% power, a sample size of 54 subjects per group is required. The sample size will be inflated to 60 subjects per group (180 total) to accommodate an anticipated 10% rate of subject withdrawal/dropout. The power remains above 80% even if the assumed standard deviation is as large as 7.1 dB.

The inclusion of the worst eligible eye is expected to increase power, but the increase is expected to be small (approximately 3%) because the preliminary data from the chart review indicate that only ~40% of subjects will contribute a second eligible eye to the analysis and the correlation between the outcomes in the two eyes is quite high (0.82 in our sample). This assumes that the group difference will be comparable in the best and worst eligible eyes, as we anticipate.

The chosen effect size of 4.5 dB is based on the following rationale. Visual field defects are similar in IIH and glaucoma[1,85] and data on the relationship between vision-specific quality of life (as measured by the NEI-VFQ-25) and PMD from the better seeing eye are available from 213 subjects with glaucoma in the Los Angeles Latino Eye Study[86]. A regression analysis yielded the finding that a change of 1 dB in PMD corresponded to an approximately one-unit score change on the NEI-VFQ-25 composite score.[86,87] In another study, Suner et al. used data from two clinical trials in neovascular age-related macular degeneration and anchor-based methods to estimate the change in NEI-VFQ-25 composite score that corresponds to a change of ≥ 15 letters (~ 3 lines) in visual acuity, a value generally accepted as clinically significant.[87] They concluded that a change of 4-6 points on the NEI-VFQ-25 composite score should be considered clinically significant. Taken together, the results of these two investigations suggest that a change in PMD of 4.5 dB corresponds to a change in NEI-VFQ-25 score that would be considered to be of minimal clinical significance.

# Chapter 10: Data Collection and Monitoring

## 10.1 Case Report Forms

The main study data are collected through electronic case report forms (CRFs).These electronic CRFs from the study website are considered the primary source documentation.

When data are directly collected in electronic case report forms, this will be considered the source data. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of subjects.

## 10.2 Study Records Retention

Study documents should be retained for a minimum of 3 years in accordance with NIH and FDA requirements. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## 10.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 312.

The data of most importance for monitoring at the site are subject eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Agent/Device accountability
- Communications with site staff

- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

## 10.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

## 10.5 Committees and Reading Centers

### 10.5.1 Resource Center (RC)

The Resource Center at Mount Sinai will oversee all three reading centers described below. The Resource Center will review quarterly quality control reports. Calls and on-site monitoring visits will be conducted as necessary to address substandard performance. The RC will also assist the reading centers in analyses of visual fields, fundus photos, and OCT images as needed.

### 10.5.2 Visual Field Reading Center (VFRC)

The Iowa VFRC will provide training and certification of all technicians (at least 2 per clinic site) so that valid perimetry results are transmitted, read, stored and archived. They will also provide ongoing analysis of the primary outcome variable, perimetric mean deviation (PMD) to the sites, Jaeb Center, RC, Adjudication Committee, Surgical Malfunction Review Committee and SSC.

Sites will upload Humphrey Field Analyzer size V Full Threshold native data files using the secure VFRC upload facility. The VFRC will then generate a size V “Statpac”-like pdf printout with the necessary statistical indices and transfer the pdf back to the site for all valid submitted visual field examinations.

Data will be stored on a secure server. Daily, weekly and monthly backups of the data will be made with offsite storage as well.

Each examination will have quality control checks for internal validity. Monthly and quarterly quality control reports will be generated for the RC and SSC.

#### 10.5.3 Photographic Reading Center (PRC)

The Rochester PRC will provide training and certification of all technicians (at least 1 per clinic site) so that valid photographic images are transmitted, read, stored and archived. They will also provide ongoing grading of the photos to the sites, Jaeb Center, RC, Adjudication Committee, Surgical Malfunction Review Committee and SSC.

Fundus photos will be transferred to the PRC from the site via a secure file transfer upload client. Each site will be given an internal address and password that allows the site to upload subject images.

Data will be stored on a secure server. Daily, weekly and monthly backups of the data will be made with offsite storage as well. Quality Control reports will be prepared on a quarterly basis.

#### 10.5.4 Optical Coherence Tomography Reading Center (OCTRC)

The OCTRC will provide training and certification of all technicians (at least 1 per clinic site) so that valid OCT images are transmitted, read, stored and archived. They will also provide ongoing assessment of thickness measurements and evaluation of the optic nerve head neural canal shape deformations to the sites, Jaeb Center, RC, Adjudication Committee, Surgical Malfunction Review Committee and SSC.

Raw data will be transferred to the OCTRC from the site via UC Davis OCTRC's secure File Transfer Protocol (FTP) site. These raw data will be uploaded into the Cirrus Research Browser for assessment and quality control by the OCTRC.

Data will be stored on a secure server. Daily, weekly and monthly backups of the data will be made with offsite storage as well. Quality control reports will be produced by the OCTRC on a quarterly basis.

#### 10.5.5 Surgical Quality Assurance Committee (SQAC)

There will be a SQAC composed of two orbital surgeons and two neurosurgeons. They will certify study surgeons and provide quality control, as detailed in the MOP.

#### 10.5.6 Surgical Malfunction Review Committee (SMRC)

The SMRC will review patients in the trial that are worsening and determine if possible surgical malfunction exists. The review is triggered if the criteria described in section 5.6.1 above are met.

### 10.5.7 Adjudication Committee (AC)

A three member committee appointed by the Study Steering Committee (SSC), plus the Study Director, will review subjects that meet the criteria for possible treatment failure. All treatment failure cases will be reviewed first by the Study Director or committee chair for safety reasons. This committee will be charged with deciding whether the worsening of the subject is most likely due to increased intracranial pressure and is a failure of therapy, or the worsening of PMD is more likely due to another reason. A report of all decisions will be sent to the Data and Safety Monitoring Committee (DSMC). Records of visual fields, fundus photos, and OCTs will be provided to the coordinating center to organize with the clinical information for use by the Study Director and AC.

# Chapter 11: Ethics/Protection of Human Subjects

## 11.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

## 11.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented subjects need to be re-consented.

## 11.3 Informed Consent Process

### 11.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the subjects and their families. Consent forms will be IRB-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. All subjects will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### 11.3.2 Subject and Data Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, the coordinating center, reading centers, and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of NORDIC.

The study monitor, other authorized representatives of the coordinating center and NORDIC, and representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by IRB, NIH, other regulatory bodies, and institutional regulations.

Visual field data will be transmitted to the VFRC at the University of Iowa, OCT image data will be transmitted to the University of California at Davis Reading Center, and optic disc photographs will be transmitted to the Photographic Reading Center at the University of Rochester. These data will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. All study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research. The study data entry and study management systems used by clinical sites and by the Jaeb Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and placed in the public domain by the Jaeb Center.

The Certificate of Confidentiality provided by NIH further protects the privacy of study subjects. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to subjects.

### 11.3.3 Future Use of Stored Specimens

Permission to collect and store blood samples for future use will be included in the informed consent. With the subject's approval, blood specimens will be labeled by study ID and stored in a central lab for use by researchers, including those outside of the study.

These samples could be used for research such as metabolomics studies on lipid and proteins, which include gender and obesity hormones, and microRNA for specific proteins or autoimmune factors.

All studies will be performed after a written protocol for testing and analysis are approved by the study steering committee and local IRB(s). Specimens will be transferred to research labs at research institutions as needed to perform the approved investigations.

The central lab will also be provided with a code-link for each subject that will allow linking the biological specimens with the clinical information collected during the trial, maintaining the masking of the identity of the subject.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

# Chapter 12: References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