Title: A Placebo-Controlled Efficacy in iNPH Shunting (PENS) Trial

Short Title: PENS Trial

Protocol Number: IRB00305245

National Clinical Trial (NCT) Identified Number: NCT05081128

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
All	Updated version number and date	Keep document up to date
1.1-3, 3, 4.7-12, 8.1.2-8.2.3	End of study visit changed for closed shunt group from 12 to 15 months post-surgery (12 months of active shunting)	Allows all patients to be followed for 12 months of active shunting. Delays risk of unblinding assessors.
1.1, 4.1.1	Added orthostatic blood pressure collection at pre-screening visit	At the recommendation of the Data Safety Monitoring Board (DSMB)
1.3, 4.1.1, 4.1.3	Updated and new participant flow schemas	Increase clarity and reflect changes to the study schedule
1.3; 4.1	Changed drainage trial washout period from 2 to 4 weeks	Allow for sufficient washout from effects of drainage
1.3	Removed research MRI and extended neuropsychology exam for 9-month visit	Will be done for end of study visit for all patients
1.3	Updated footnotes to match new study schedule	Increase clarity and accuracy
3	Update CSF Biomarker Objectives	Align with Statistical Analysis Plan
2.3.3, 8.2.4	Changed Ruff 2&7 selective attention test to Animal Fluency and removed SF-12	Correct error
4.1.7-11	Corrected unblinded assessor to blinded assessor	Correct errors

4.1.10-11	**Move unblinding note to reflect new timepoint, including language about 12-month active shunting visit**	**Now unblinding at this visit**
4.1.11	**Corrected unblinded assessor to blinded assessor**	**Correct error**
4.1.11	**Added language regarding process for unblinding – participant should be asked which group they believe they are in**	**Increase clarity**
4.1.12	**New section summarizes the final visit for the closed shunt group**	**New study visit added**
8.2.4	**Added animal fluency and controlled oral word association to language skills. Removed SF-12.**	**Correct error**
8.3.3	**Added requirement to monitor for and report suspected elder abuse**	**At the recommendation of the Data Safety Monitoring Board (DSMB)**
8.2.6	**Clarified that contrast-enhanced MRI will only be performed at JHU**	**Correct error**
8.3.6	**Description of timeline and procedure for SAE reporting revised**	**Increase clarity**
8.3.6, 10.1.5	**Instances of "medical monitor" changed to "Medical Monitor"**	**Edited for consistency**
9.4.6	**Added table to document the trial's early stopping analysis for efficacy and futility**	**At the recommendation of the Data Safety Monitoring Board (DSMB)**
8.3.8	**Include a discussion of the criteria and process to hold enrollment for safety reasons**	**At the recommendation of the Data Safety Monitoring Board (DSMB)**
9.4.9	**Changed "with values over" to ≥**	**Increase clarity**
10.1.1.2	**Added guidance that the Teach-Back Consenting model should be used.**	**At the recommendation of the Data Safety Monitoring Board (DSMB)**
11	**Updated citations**	**Reflect changes**

I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Placebo-Controlled Efficacy in iNPH Shunting (PENS) Trial
Study Description:	This is a multicenter, randomized, blinded, placebo-controlled study of patients with suspected idiopathic normal pressure hydrocephalus (iNPH). Using FDA-approved technology, we propose a prospective randomized placebo-controlled clinical trial for the surgical shunting treatment of iNPH. These valve systems allow a well-maintained blinded placebo control because the surgical and adjustment procedures can be entirely identical in the active and placebo groups. Study patients will have demonstrated accepted neurosurgical guideline criteria for iNPH and are being considered for a cerebrospinal fluid (CSF) shunt placement. Two groups will be created based on a randomized shunt valve setting at implantation of either an “active” or a “placebo” group and compared at three months for change compared to baseline function. After this three-month comparison, all patients will be blindly adjusted to active shunting status and evaluated for efficacy at six and twelve months of active shunting. This delayed treatment design allows an appropriate group comparison period, followed by evaluation of both groups (all patients) for more extended shunt efficacy.

Objectives:

Primary Objective is the evaluation of CSF shunting in iNPH participants through a randomized comparison of improvement from baseline at three months between active (open shunt) and placebo-controlled (closed shunt) groups, using the **primary endpoint of gait velocity** to test the primary hypothesis: the treatment of idiopathic normal pressure hydrocephalus (iNPH) with an open shunt results in improved gait velocity.

Secondary Objectives:

1) Evaluate the effect of shunting on improving gait and balance between active and placebo-controlled groups at three months using the Tinetti assessment
2) Evaluate the effect of shunting on improving global cognition between active and placebo-controlled groups at three months using the total Montreal Cognitive Assessment (MoCA) score
3) Evaluate the effect of shunting on bladder control between active and placebo-controlled groups at three months using the OAB-q sf.

Exploratory/Tertiary Objectives

Efficacy:

- Evaluate the effect of shunting between active and placebo-controlled groups at three months using gait, modified Rankin Scale (mRS), and Core neuropsychology measures of cognition, mood.
- Evaluate the primary and secondary, and tertiary efficacy measures at three, six, and twelve months of active shunting in all participants.
- Evaluate the clinical improvement of all study participants at three, six and twelve months of active shunting

CSF Objectives

- To evaluate the role of Vascular Endothelial Growth Factor (VEGF) as a diagnostic or prognostic biomarker in differentiating iNPH from other neurodegenerative disorders that present with an iNPH phenotype.
- Identify cutoffs for established neurodegenerative CSF biomarkers that differentiate participants with iNPH from Alzheimer's disease (AD) participants and other dementias, adjusting the typical cut-offs of traditional AD related biomarkers for altered volume of distribution when CSF is available from clinical testing.
- Identify cutoffs for CSF biomarkers associated with improved 12-month response to active shunting, enabling improved selection of participants in future trials.

Imaging Objectives

- Measure the morphological features in and around the brain that are associated with gait improvement after shunt surgery.
- Determine physiological features measured by magnetic resonance imaging (MRI) that are associated with gait changes after shunting.

Neuropsychological Substudy Objectives

- For participants in the neuropsychology sub study, evaluate the effect of shunting on sustaining improvements in cognition, mood, behavior, and quality of life between active and placebo-controlled groups at three months and at twelve months of active shunting using core and extended measures of cognition and mood.
- For participants in the neuropsychology sub study, identify broad cognitive composites (using both Core and extended batteries).
- Assess treatment effect (and overall outcomes as appropriate) at three months and twelve months of active shunting for these composite measures.

Endpoints: iNPH functional improvement.

1) Primary clinical endpoint: gait (velocity) improvement from baseline with treatment.

2) Secondary clinical endpoints: balance, cognition, bladder control improvement from baseline

3) Imaging endpoint: volumetric, morphological, and flow, baseline and post treatment, associated with successful shunting

4) CSF biomarker endpoint: Differences in individual biomarkers levels and their ratios in patients selected for shunt surgery vs those not; similar differences in biomarkers in those with a sustained improvement in gait at 12 months after open shunt

Study Population: 100 adults ≥ 60 years with idiopathic normal pressure hydrocephalus (iNPH)

Phase: N/A

Description of Sites/Facilities Enrolling Participants: 20 participating academic hospitals in the United States, Canada, and Sweden

Description of Study Intervention: The primary intervention will be the initiation of the randomized initial shunt valve opening pressure setting to create a delayed treatment group in half of the study participants.

Surgical shunt implantation is the major procedure taking place in the study. However, since participant selection for surgery and the method of surgery are all part of the surgeon's standard care, it is not considered an intervention of the study. The specific adjustable implanted shunt will be an FDA-approved programmable CSF shunt (Certas Plus with SiphonguardTM, Codman, Integra). The implantation will follow the site's standard practice and preference of the neurosurgeon.

The neurosurgeon performing the implantation surgery will be aware of the assigned setting. The neurosurgeon performing the surgery will pre-set the adjustable valve to one of the two designated settings, while the shunt is in the sterile packaging, outside of the operating room, just before the operative case. The setting 4 (open shunt) or 8 (closed shunt) will be determined by the randomization that the neurosurgeon will access directly. The setting will be performed and verified by the neurosurgeon alone, without assistance.

At the 3-Month Visit, the neurosurgeon will adjust the shunt to open for the delayed group and mock adjust the shunt for the treatment group. A trained blinded assessor will perform the gait and cognitive tests during the follow-up visits and will remain blinded to the treatment assignment throughout the course of the study. The following assessments will be performed at baseline and 3, 6, and 9-months post-op, then at 12 months of active shunting (12 months post op for Active Shunt Group or 15 months post-op for Closed Shunt Group):

Cognition and Mood:

- Montreal Cognitive Assessment Test (MoCA)
- Symbol Digit Modalities Test (SDMT)
- NIH Toolbox: Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sort Test
- Beck Depression Inventory, 2nd edition (BDI-II)
- Lawton Activities of Daily Living/Independence in Activities of Daily Living (ADL/IADL)

Function: Modified Rankin Scale (mRS)

Bladder Control: Overactive Bladder Questionnaire, short form (OAB-q sf.)

Quality of Life (QOL): QOL Survey EQ-5D-5L

Adverse Events: Frequency of falls, surgical and non-surgical complications, related and unrelated

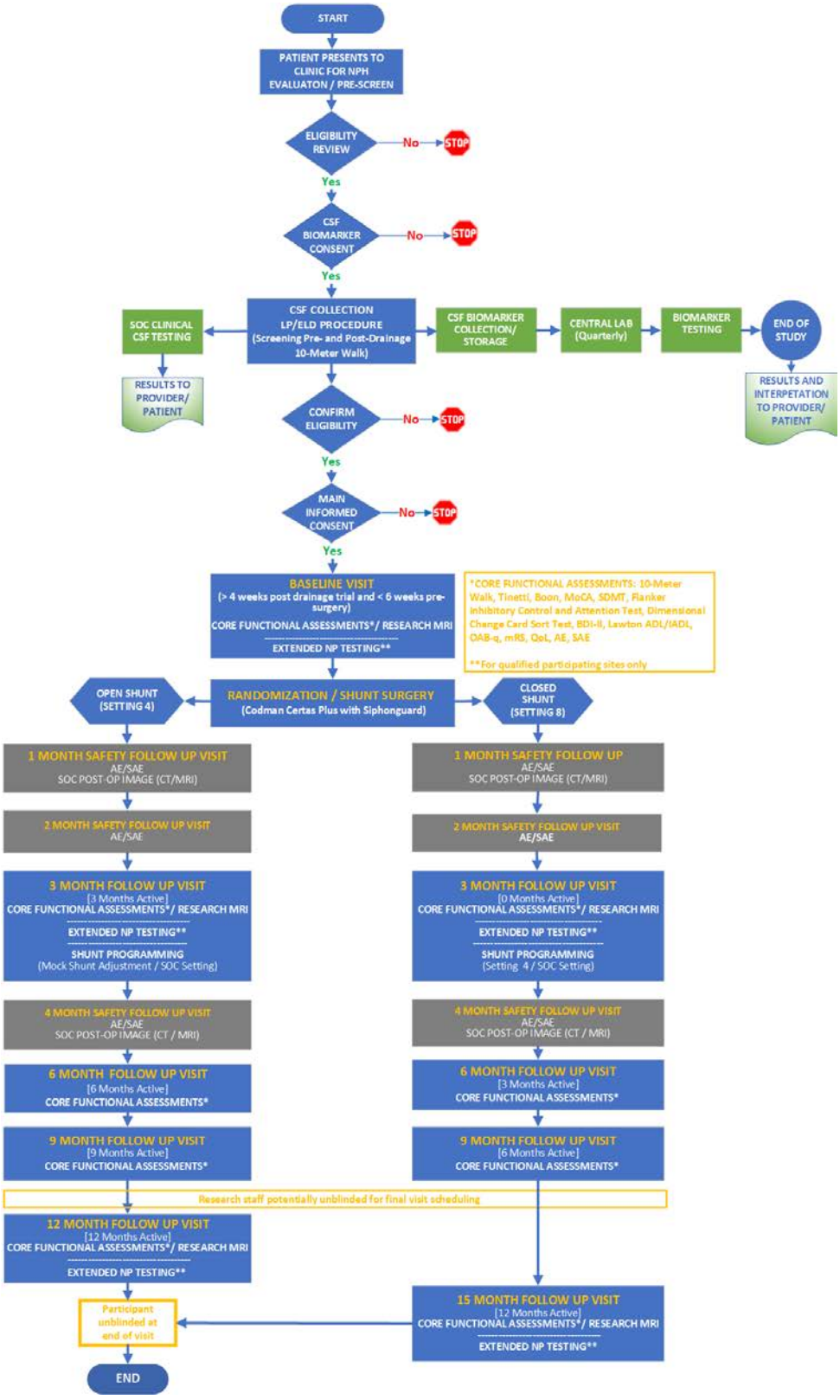
The following assessments will be performed at Baseline, 3-Month Visit, and 12 months of active shunting (12- or 15-Month Visit)

- Research MRI

- Extended Neuropsychology Battery (at participating sites only)

Study Duration:	4 years (48 months)
Participant Duration:	Up to 15 months (12 months for Active Shunt Group and 15 months for Closed Shunt Placebo Group)

1.2 SCHEMA


START
PATIENT PRESENTS TO CLINIC FOR NPH EVALUATON / PRE-SCREEN
ELIGIBILITY REVIEW
No
STOP
Yes
CSF BIOMARKER CONSENT
No
STOP
Yes
SOC CLINICAL CSF TESTING
CSF COLLECTION LP/ELD PROCEDURE (Screening Pre- and Post-Drainage 10-Meter Walk)
CSF BIOMARKER COLLECTION/ STORAGE
CENTRAL LAB (Quarterly)
BIOMARKER TESTING
END OF STUDY
RESULTS TO PROVIDER/ PATIENT
RESULTS AND INTERPETATION TO PROVIDER/ PATIENT
CONFIRM ELIGIBILITY
No
STOP
Yes
MAIN INFORMED CONSENT
No
STOP
Yes
BASELINE VISIT
(> 4 weeks post drainage trial and < 6 weeks pre-surgery)
CORE FUNCTIONAL ASSESSMENTS*/ RESEARCH MRI
EXTENDED NP TESTING**
*CORE FUNCTIONAL ASSESSMENTS: 10-Meter Walk, Tinetti, Boon, MoCA, SDMT, Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sort Test, BDI-II, Lawton ADL/IADL, OAB-q, mRS, QoL, AE, SAE
**For qualified participating sites only
OPEN SHUNT (SETTING 4)
RANDOMIZATION / SHUNT SURGERY (Codman Certas Plus with Siphonguard)
CLOSED SHUNT (SETTING 8)
1 MONTH SAFETY FOLLOW UP VISIT
AE/SAE
SOC POST-OP IMAGE (CT/MRI)
1 MONTH SAFETY FOLLOW UP
AE/SAE
SOC POST-OP IMAGE (CT/MRI)
2 MONTH SAFETY FOLLOW UP VISIT
AE/SAE
2 MONTH SAFETY FOLLOW UP VISIT
AE/SAE
3 MONTH FOLLOW UP VISIT
[3 Months Active]
CORE FUNCTIONAL ASSESSMENTS*/ RESEARCH MRI
EXTENDED NP TESTING**
SHUNT PROGRAMMING
(Mock Shunt Adjustment / SOC Setting)
3 MONTH FOLLOW UP VISIT
[0 Months Active]
CORE FUNCTIONAL ASSESSMENTS*/ RESEARCH MRI
EXTENDED NP TESTING**
SHUNT PROGRAMMING
(Setting 4 / SOC Setting)
4 MONTH SAFETY FOLLOW UP VISIT
AE/SAE
SOC POST-OP IMAGE (CT / MRI)
4 MONTH SAFETY FOLLOW UP VISIT
AE/SAE
SOC POST-OP IMAGE (CT / MRI)
6 MONTH FOLLOW UP VISIT
[6 Months Active]
CORE FUNCTIONAL ASSESSMENTS*
6 MONTH FOLLOW UP VISIT
[3 Months Active]
CORE FUNCTIONAL ASSESSMENTS*
9 MONTH FOLLOW UP VISIT
[9 Months Active]
CORE FUNCTIONAL ASSESSMENTS*
9 MONTH FOLLOW UP VISIT
[6 Months Active]
CORE FUNCTIONAL ASSESSMENTS*
Research staff potentially unblinded for final visit scheduling
12 MONTH FOLLOW UP VISIT
[12 Months Active]
CORE FUNCTIONAL ASSESSMENTS*/ RESEARCH MRI
EXTENDED NP TESTING**
15 MONTH FOLLOW UP VISIT
[12 Months Active]
CORE FUNCTIONAL ASSESSMENTS*/ RESEARCH MRI
EXTENDED NP TESTING**
Participant unblinded at end of visit
END

1.3 SCHEDULE OF ACTIVITIES (SOA)

Item	Pre-screening	Baseline[3]	Surgery[3]	One-Month Safety Follow-up[4]	Two-Month Safety Follow-up[4]	Three-Month Follow-up	Four-Month Safety Follow-up[4]	Six-Month Follow-up	Nine-Month Follow-up	Twelve OR Fifteen-Month[9] Follow-up
Window		+4 weeks	-6 weeks	-14/+30 days						
SOC Physical Exam[10]	•									
CSF Consent[1]	•									
History/Demographics	•									
Pre-Screening Drainage Trial/CSF collection	•									
Study Consent[1]		•								
Pre-Op Imaging		•								
Randomization/Surgery			•							
Shunt Programming			•			•				
Post-OP Imaging				•			•			
Research MRI		•				•				•
Creatinine measurement		•				•			•	
Gait Velocity Testing[2]	•	•				•		•	•	•
Tinetti Assessment and Boon Gait Scale[2]		•				•		•	•	•
Core Neuropsychology Battery[2, 7]		•				•		•	•	•
Modified Rankin Scale (mRS)		•				•		•	•	•
QOL Survey EQ-5D-5L		•				•		•	•	•
OAB-q Short Form Symptom Severity Subscale[2]		•				•		•	•	•
Extended Neuropsych Battery (Participating Sites Only)[8]		•				•				•
Concomitant Medications		•		•	•	•		•	•	•
SAEs/Neurological/ Urological AEs/Falls[5]	•	•	•	•	•	•	•	•	•	•
Non-serious AEs[6]				•			•			

1. Patients undergoing iNPH evaluation that have not yet completed a drainage trial will be asked to sign a prescreening consent for CSF collection during their standard lumbar puncture or extended lumbar drain. Participants that are eligible for randomization based on the results of the drainage trial will be approached, usually by the neurosurgeon, for consent for the randomized trial. Participants that are found ineligible may not repeat the assessments for rescreening but may be rescreened if a subsequent drainage trial is performed per standard of care (SOC).
2. Assessment must be performed by a PENS trained assessor. Multiple study assessors may be designated, e.g. one assessor for gait assessments and one for neurocognitive assessments.
3. Baseline assessments and surgery should be scheduled no less than 4 weeks after the baseline assessment/drainage trial to allow for washout. Baseline assessments may be performed the day of surgery prior to surgery. The neurosurgeon must complete randomization after the participant is cleared and prepped for surgery and before entering the OR.
4. Safety visits are meant to follow each site's standard safety follow ups post-surgery or post adjustment while ensuring the safety of participants. Participants may be contacted by phone, telemedicine, or seen in the clinic. Standard imaging will be collected, and it should be documented that the neurosurgical team reviewed the imaging for safety issues.

5. All neurological, urological and serious adverse events will be reported throughout the course of the trial starting with signing consent. Falls will be documented on a fall log through the course of the trials starting with signing consent.
6. Adverse Events: non-serious adverse events will only be recorded for 30 days after shunt insertion and then for 30 days after shunt adjustment. At all other timepoints, non-serious adverse events may be reported at the discretion of the clinician.
7. Core Neuropsychological Battery: MoCA (see Section 8.2 for version), SDMT, NIH Toolbox: Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sort Test, Beck Depression Inventory-Second Edition (BDI-II), Lawton ADL/IADL. The Core Neuropsychological Battery must be completed by a PENS-trained assessor.
8. Extended Neuropsychological Battery assessments are only to be performed by sites selected to participate in the neuropsychology substudy. All neuropsychological assessments should be performed by a certified neuropsychologist or a psychometrist or advanced trainee supervised by a neuropsychologist on the study.
9. The final research visit will take place after 12 months of active shunting. Participants randomized to the Active Shunt group, will have a final 12-month follow up visit. Participants randomized to the Placebo group will have a final 15-month visit instead of a 12-month visit to capture 12 months of active shunting. Prior to the final visit, the study coordinator or other center staff may need to be unblinded for ease of scheduling, but every effort should be made to ensure the blinded assessor and patient remain blinded.
10. An orthostatic blood pressure measurement must be performed at the initial visit. If abnormal, the patient will be evaluated according to institutional standards before proceeding with NPH evaluation.

2 INTRODUCTION

2.1 STUDY RATIONALE

Although idiopathic normal pressure hydrocephalus (iNPH) has been recognized for five decades, barriers still exist in recognition, referral, and accurate diagnosis. Hesitance in referring elderly patients for surgical treatment of iNPH results from an incomplete understanding of its pathophysiology, controversy over the appropriate diagnostic work up, and a significant concern about the effectiveness and complications of surgical treatment. The approach to screening, diagnosis and treatment of iNPH varies throughout the world, though success rates in experienced centers are similar in uncontrolled studies.

The lack of consensus regarding tests predicting outcome of surgery in iNPH, and the skepticism of iNPH in the neurology and neurosurgery communities reflect the limitations of iNPH clinical research to support current iNPH practices. iNPH clinical research paradigms have not changed for over 20 years. A survey described the uncertainty surrounding the treatment of iNPH and the need for a placebo-controlled study. iNPH is underdiagnosed because of widespread skepticism regarding diagnostic tests and treatment outcomes. Although thousands of shunts are implanted for iNPH each year, a significant proportion of neurologists and neurosurgeons do not believe that iNPH can be diagnosed accurately. Further, many physicians believe that shunt surgery does not improve patient outcome, or that the risk of complications is far greater than the odds of benefit. Convincing proof of shunting efficacy is likely to increase the number of iNPH patients receiving adequate treatment.[1] The Placebo-Controlled Efficacy in iNPH Shunting (PENS) trial is a multicenter, randomized, blinded, placebo-controlled design investigation of cerebrospinal fluid (CSF) shunt surgery.

Demonstration of the clinical efficacy of shunt surgery on iNPH in a placebo-controlled trial may change physicians' practice regarding the need to evaluate and treat properly selected patients for iNPH. As a result, the number of appropriately treated patients should increase significantly. Appropriate treatment will result in a reduction of unnecessary impairment and disability, a diminished need for health care services (including nursing home) among the elderly iNPH population, with associated reduction in long-term health care expenditures,[2] and a significant economic and psychosocial impact on patients and families. Additional advances in treatment will be facilitated by quantitation of true physiological effects, allowing comparison in subsequent studies. Attention may then focus on the identification of subpopulation that can benefit and demonstrate improvement in shunting materials and methods. The

results of this research, regardless of outcome, will significantly influence medical practice and population health. Demonstration of the clinical effectiveness of shunt surgery on iNPH in a blinded, placebo-controlled trial has the potential to end any doubts about the existence of the disorder, and can persuade many physicians of the need to evaluate and treat properly selected patients for iNPH. Assuming acceptance of the study results by practicing neurologists and neurosurgeons, as well as change in their clinical practice with respect to these patients, the result would be an increase in the number of appropriately treated patients, which should result in a reduction of unnecessary impairment and disability from untreated iNPH. Secondary benefits include a reduced need for health care services (including nursing home) by the elderly iNPH population, with associated reduction in health care expenditures and a significant economic and psychosocial impact on patients and families.

On the other hand, if no treatment effect of shunt surgery on iNPH is demonstrated, then the value of shunt surgery for suspected iNPH, as well as the associated risks and health care costs, will be called into question. The number of patients treated with shunt surgery for iNPH may be reconsidered and limited.

2.2 BACKGROUND

iNPH clinical research paradigms have not changed for over 20 years. The lack of consensus regarding iNPH diagnostic tests among iNPH experts, and the skepticism of iNPH in the neurology and neurosurgery communities reflect the limitations of iNPH clinical research to support current iNPH practices. While studies showing efficacy have been performed by Dutch, European, and Japanese centers,[3-5] these studies were not placebo controlled and were discrepant in diagnostic method and outcome measures that left questions about true effectiveness and patient selection.

The Johns Hopkins University (JHU) and the Adult Hydrocephalus Clinical Research Network (ACHRN) have recently completed a pilot randomized, blinded, placebo-controlled study in five centers, accruing 18 patients. This pilot has allowed development of the methods, measures and quality control proposed in this full study. Inclusion and exclusion criteria were refined and established. Pilot data, as well as data gathered from the AHCRN Registry, is used in the estimation of required patient volume, accrual time and number of sites needed for sufficient accrual. The Pilot also demonstrated the effort needed for accrual through more participating sites as proposed here. Our success in organizing and training these centers, and accruing patients supports, the feasibility of this larger effort. In summary, performing the Pilot study has established methods and site training, demonstrated patient accrual and produced preliminary data suggesting that that this study is feasible.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risk of shunt surgery: Patients are selected for shunt surgery because the clinical assessment of risks and benefits has been found to be favorable. Therefore, participation in the trial is expected to carry the same risk/benefit profile as shunt surgery.

Complications of shunting in this study are expected to be similar to shunt surgery in standard surgical practice. Based on the European Multicenter Study,[3] the expected complications and rates are:

1. Cerebral hemorrhage at the time of surgery <1%.
2. Shunt or wound infection <2%.

3. Wound dehiscence <1%.
4. Subdural hygroma 10%.
5. Subdural hematoma 6%.
6. Hematoma or hygroma requiring evacuation 1%.
7. Distal catheter failure 4%.
8. Proximal catheter failure 4%.
9. Valve failure 4%.
10. There is always a risk of death from any surgical procedure

For participants in the Closed Shunt Group, there is an increased risk of shunt occlusion.

Risk of Delayed Start: A recent study of the natural history of iNPH in which shunt surgery was inadvertently delayed for at least six months for 33 participants in Gothenberg, Sweden, found that without treatment, some participants improved while others worsened before surgery.[6] There is a potential risk of worsening gait and a tendency of falling among participants over the course of the first three months in the placebo group. If a fall is clinically significant, it may result in medical or surgical complications. However, in a recently published open-label randomization study that randomized 93 participants with idiopathic normal pressure hydrocephalus to an immediate vs. postponed treatment group over a similar time period (one year), the proportion of participants with serious adverse events did not differ significantly between the groups.[4] The same conclusion was found from the 18-participant pilot PENS study. In the pilot study, we did not see a decrease in the effectiveness of shunting over the course of one year.

Additionally, no published experience and little anecdotal experience exist with shunt function following four months in the virtual off setting of >400 mm H2O that will be used in the Closed Shunt Group. The potential for increased shunt occlusion after three months of no flow is possible, though less likely with CSF. The risk of CSF leak due to shunt closure is minimal especially in these participants with normal pressure. Other than identifying improvement in outcome measures at three months of active shunting, or identifying significant reduction in ventricular size or other imaging markers consistent with a functioning shunt at four months of active shunting, the only methods to confirm shunt function are radionuclide shunt patency study or, in Europe, CSF infusion testing. These will be performed only as clinically indicated after participants have experienced four months of active shunting.

MRI Risks:

- **Gadolinium (Gd) administration for MRI scans:** This contrast agent is FDA-approved and used routinely for MRI exams. The injection may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea or headache. These symptoms occur in less than 1% of people and resolve quickly. There is a small risk of an allergic reaction to gadolinium. However, a severe allergic reaction occurs in less than one in 300,000 people. People with moderate to advanced kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NSD). This causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. As a result, people develop skin thickening that may prevent bending and extending joints, resulting in decreased joint movement. In addition, people may experience fibrosis that spreads to other body parts, such as the diaphragm, muscles in the thigh and lower abdomen, and lining of the blood vessels in the lung. NSF/NSD is a progressive disease and can result in death. For subjects who have moderate to advanced kidney failure, the risk of

developing NFS/NSD is 1-5%. To rule out the presence of moderate to advanced kidney failure, a creatinine measurement < 1.4 mg/dl is required of all subjects in the 30 days prior to the MRI scan. We will perform point of care creatinine measurements (Nova Biomedical Stat Sensor, supported by Johns Hopkins Clinical Pathology Lab) on whole blood from a finger stick for participants who do not have an available creatinine measurement within this time frame. We will also ask the subject if they have any known kidney problems.

- **Risk of harm from MRI scans if undetected metal is present in their bodies:** All subjects will be asked to fill out an MRI screening sheet before the scan. Individuals with contraindications to MRI will be excluded. The effects of magnetic fields in an MR scanner have been extensively studied, and there are no significant risks known. However, the participant may be bothered by feelings of confinement and by the noise made by the magnet during the procedure. The magnet can cause electronic devices like pacemakers, beepers, and watches to malfunction, and some metal objects can be pulled into the magnet. If at any time subjects feel uncomfortable, they can discontinue the study.

Legal Risks: Loss of confidentiality of the subject is a potential risk of the study; however, safeguards are in place to protect against this.

Steps Taken to Minimize the Risks:

Delay. To minimize overall risks from delay, the delay for the placebo arm has been reduced to three months from a four-month delay on the pilot study. Sites will be trained at study initiation on best practices for limiting time from drainage trial to surgery to six weeks to avoid as much as possible additional delay beyond the placebo control delay. In addition, this study will collect data on fall frequency, injury and treatment. This data will be reviewed by the clinician and Data Safety Monitoring Board (DSMB).

Surgery. Rigorous surgical technique and antisepsis are standard clinical care in shunt implantation. Clinical monitoring for expected complications such as infection are performed so that early intervention may occur. Study participants will be contacted at one and two-months post-surgery to ensure their safety. Standard practice recommends the removal of a shunt when determined to be infected.

MRI. The risk of cryptic metal in the bodies of individuals getting an MRI scan will be minimized by administering a comprehensive set of questions, routine in the Kirby Center imaging facility. Pregnant individuals will be excluded from the study. We advise subjects to move slowly and, once they are positioned on the table, we move the person into the magnet slowly. Access to the scan room is strictly controlled to ensure that no ferromagnetic materials are introduced. The scanners to be used in these studies are FDA approved and operate under radiofrequency power monitoring software at all times. All scan procedures are FDA approved and are not classified as investigational devices. Some subjects may become claustrophobic, bored or restless in the scanner and will have the option for breaks or terminating the testing at any time without penalty if they so choose.

*Legal Risks***.** Every effort will be made to keep the information in the study confidential:

- Study participants will be assigned a code number and the code number only will be used to identify the clinical/cognitive/biomarker/scanning data;
- The computers on which the data will be stored are password protected;
- Written documents concerning the study will be kept in locked areas at the sites.

2.3.2 KNOWN POTENTIAL BENEFITS

Direct Benefits

There may or may not be direct benefit from being in this study.

Potential benefits include:

- More frequent and detailed monitoring of gait and cognition by multiple measures of each domain as long as subject is enrolled in the study
- More frequent imaging
- CSF biomarker results will be returned to patients and their physicians at the end of the study, which may help guide further clinical management of their potential neurologic comorbidity once participation in the study is complete.

Indirect Benefits

By being part of the first truly randomized study of shunt surgery in iNPH, the participants will help physicians understand the role of surgery in treatment. The findings from this trial would also help in the design of future studies that could determine the degree of improvement in various domains to help prognosticate accurately and the subpopulation that would derive the maximum benefit from shunt surgery.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Patients are selected for shunt surgery because the clinical assessment of risks and benefits has been found to be favorable. Therefore, participation in the trial is expected to carry the same risk/benefit profile as shunt surgery.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary study objective is the evaluation of CSF shunting in iNPH participants through comparison of improvement from baseline at three months between active and placebo-controlled groups, using the primary endpoint of gait velocity, to test the primary hypothesis: the treatment of idiopathic normal pressure hydrocephalus (iNPH) with an open shunt results in improved gait velocity.	The primary endpoint of gait velocity will be collected at baseline and at three months post-surgery to derive velocity change for the primary objective. **Gait:** • 10 Meter Walk	Unpublished data from the AHCRN cohort of patients with suspected iNPH (n=588) reveal that gait velocity is a significant marker of dysfunction. Additionally, uncontrolled studies have demonstrated that gait can significantly change following shunt surgery.[3,4,7]
Secondary		

1.Evaluate the effect of shunting on improving global cognition between active and placebo-controlled groups at three months using the Tinetti assessment	**Balance/Gait:** • Tinetti score	These three instruments assess balance, cognition, and bladder function, three dimensions of patient function affected by iNPH. The pilot study for this trial showed significant improvement in bladder function after active shunting compared to placebo.
2.Evaluate the effect of shunting on improving global cognition between active and placebo-controlled groups at three months using the total MoCA score	**Core Measure of Cognition:** Montreal Cognitive Assessment Test (MoCA)	
3.Evaluate the effect of shunting on bladder control between active and placebo-controlled groups at three months using the OAB-q sf.	**Bladder control:** • Overactive Bladder Questionnaire, short form (OAB-q sf.)	
Tertiary/Exploratory		
Tertiary Efficacy: Evaluate the effect of shunting between active and placebo-controlled groups at three months using gait, mRS, and Core neuropsychology measures of cognition, mood. Evaluate the primary and secondary, and tertiary efficacy measures at three, six, and nine months of active shunting in all participants. Evaluate the clinical improvement of all study participants at three, six and twelve months of active shunting	**Gait** • Boon Scale **Function:** • Modified Rankin Scale (mRS) **Core Measures of Cognition and Mood:** • Symbol Digit Modalities Test (SDMT) • NIH Toolbox: Flanker Inhibitory Control and Attention Test; Dimensional Change Card Sort Test • Beck Depression Inventory, 2nd edition (BDI-II) • Lawton Activities of Daily Living/Independence in Activities of Daily Living (ADL/IADL)	Boon Scale was used in the Dutch NPH Study[8]
CSF Objectives To evaluate the role of neurodegenerative (abeta42/40, ptau181, total tau, NFL) and neurovascular (CSF VEGF) as a diagnostic or prognostic biomarker in	**CSF Endpoints:** 1. CSF levels of abeta42, abeta40, NFL, ptau181, total-tau and VEGF 2. CSF abeta42/40 and ptau181/abeta42	**CSF Justification** Several cohort studies and case series have identified neurodegeneration biomarkers that can discriminate shunt responders vs non-responders. This will be examined in a prospective

differentiating iNPH from other neurodegenerative disorders that present with an iNPH phenotype. Identify cutoffs for established neurodegenerative CSF biomarkers that differentiate participants with iNPH from common neurodegenerative disorders of aging including Alzheimer's disease (AD), Lewy body dementia, Parkinson's disease, and vascular dementia, adjusting the typical cut-offs of common biomarkers for altered volume of distribution when CSF is available from clinical testing. Identify cutoffs for CSF biomarkers associated with improved 12-month response to active shunting, enabling improved selection of participants in future trials.		analyses in the current study. Specific markers like VEGF will be evaluated to identify the role of vascular pathology in iNPH and its potential role as a specific biomarker for iNPH rather than an exclusionary biomarker as demonstrated so far in other studies
Imaging Objectives Measure the morphological features in and around the brain that are associated with gait improvement after shunt surgery. Determine physiological features measured by MR imaging that are associated with gait changes after shunting.	**Imaging Biomarkers** • Ventricular volume • Evans Index, a ratio of ventricular width to brain width • Morphology: the degree and pattern of brain thinning and sulcal enlargement • CSF flow • Blood flow • Connectivity	**Imaging Justification** Anatomy and morphology of the brain has always been an essential part of the diagnosis of iNPH. Enlarged ventricles are the sine qua non of hydrocephalus. A second anatomical feature commonly considered in diagnosis is brain morphology, specifically the degree and pattern of brain thinning and sulcal enlargement. "Disproportionately enlarged subarachnoid space hydrocephalus" (DESH) has been proposed in the selection patients for shunting. This pattern describes increased CSF spaces laterally over the convexities but with small spaces at the brain apex.

		Physiological measures have also been considered in the diagnosis of iNPH. These have included dynamic changes in CSF flow through the cerebral aqueduct and changes in arterial and venous blood flow. In addition, changes in BOLD resting state functional MRI have been described.
Neuropsychology Substudy Objectives For participants in the neuropsychology sub study, evaluate the effect of shunting on sustaining improvements in cognition, mood, behavior, and quality of life between active and placebo-controlled groups at three, six, and nine months of active shunting using core measures of cognition and mood and at 3 months and at 12 months of active shunting using extended measures. For participants in the neuropsychology sub study, identify broad cognitive composites (using both Core and extended batteries). Assess treatment effect (and overall outcomes as appropriate) at three months and at 12 months of active shunting for these composite measures.	**Extended Neuropsychology Battery:** • Wide Range Achievement Test - Fifth Edition (WRAT-5) Reading • Controlled Oral Word Association Test (COWAT) • Hopkins Verbal Learning Test -Revised (HVLT-R) • Boston Naming Test (BNT)-short form • WAIS-III- Digit Span subtest • Trail Making Test • Animal Fluency • Stroop Color Word Test • Judgment of Line Orientation (JLO)-short form • Grooved Pegboard • Finger Tapping Test • Frontal Systems Behavior Scale (FrSBe) • Neuropsychiatric Inventory •	**Neuropsychology Justification** While improvements in gait and urinary incontinence have been clearly demonstrated following shunting, research on cognitive markers of treatment response has not been definitive.[1,9] General improvements in frontal-executive abilities have been observed several weeks-to-months following shunting, but findings are mixed and there has yet to be a systematic study to serially address the cognitive trajectory, the rate of change, and the broader pattern of expected changes.[10-15]
Safety Objectives Compare rates of overall falls and clinically significant falls (falls requiring intervention) in the active versus placebo-controlled group at three months, and also assess these event rates at three, six, and	**Safety Outcomes** • Frequency of overall falls, clinically significant falls, and surgical or drainage complications	

nine months of active shunting in the entire trial. Compare rates of subdural hematomas, hygromas, stroke and death in the active versus placebo-controlled group within 30 days of the study intervention (PENS shunt setting or 3-month shunt adjustment).		

4 STUDY DESIGN

4.1 OVERALL DESIGN

The proposed study is a multi-center, blinded, randomized, placebo-controlled investigation of CSF shunting for participants who are considered candidates for CSF shunt surgery for iNPH based on the 2005 NPH guidelines.[16]

The study will require 50 participants per arm (100 total), enrolled over 24 months at 20 investigative sites, with up to 15 months of follow-up. It is anticipated that participating sites will each recruit between five and eight participants over two years.

The primary intervention will be setting the FDA-approved Certas Plus with Siphonguard, programmable CSF shunt valve to active (Active Shunt Group) (setting 4) (110 mm H_2O) or placebo (Closed Shunt Group) (setting 8) (>400 mm H_2O) in a 1:1 ratio.

By the time of the primary objective evaluation at three months, the Closed Shunt Group will have had zero months of active treatment, and the Active Shunt Group will have had three months of active treatment. At three months, shunts for study participants in the Closed Shunt Group will be adjusted to setting 4 (recommended setting). To maintain blinding, all study participants will be adjusted/mock adjusted to the active setting in a similar fashion. Participants from both groups will not be adjusted before three months of active treatment, unless judged medically necessary by the treating team. Following the three-month study visit, all participants in each group may have shunt adjustments according to clinical standards at each center.

Procedures and data collection in the trial are displayed in the schedule of activities. Initial baseline assessments must be done by a PENS-trained blinded assessor at least four weeks post lumbar puncture (LP) or external lumbar drainage (ELD) and as close as possible to the date of surgery. Clinical data will be collected at the time of screening and throughout the intervention period. Follow-up information will be collected at three, six, and nine months for both groups, then at twelve months of active shunting (12 months for the Active Shunt Group and 15 months for the Closed Shunt Group). This section provides a summary of the data that will be collected.

4.1.1 PRE-SCREENING VISIT / CSF COLLECTION

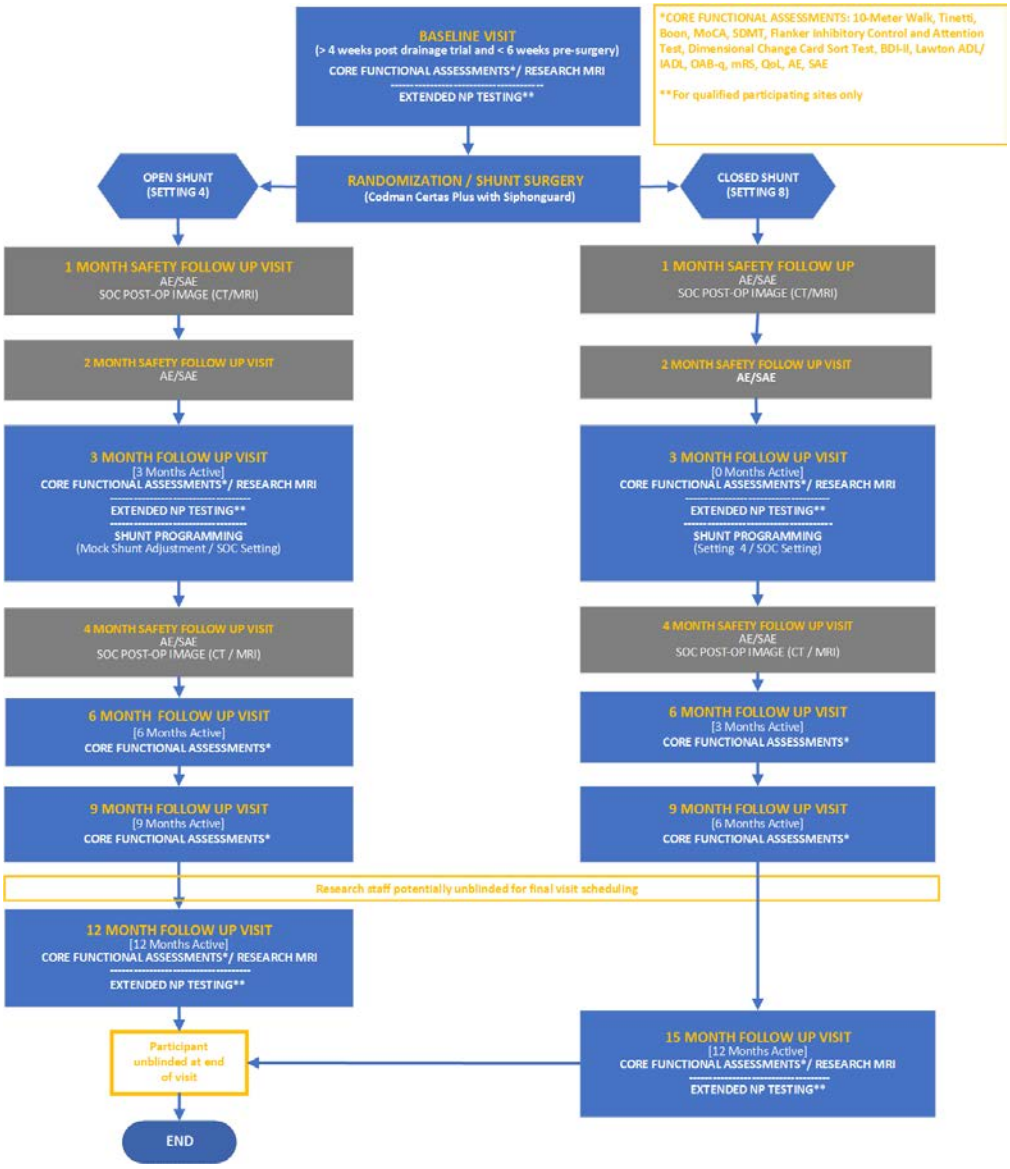
Patients that present to clinic for NPH assessment will be screened and evaluated for inclusion and exclusion criteria by the clinical investigator with assistance from research coordinator or co-investigator prior to their CSF drainage trial [Tap Test (large volume LP) or ELD (extended lumbar drainage)]. Patients that meet all prescreening criteria will be approached to sign the pre-consent for CSF collection. Participants who sign the pre-consent will have 10 mL CSF collected during their standard lumbar puncture or extended lumbar drainage to determine clinical benefit of CSF shunting for the participant as part of the screening process. It is important that staff perform the pre-and post-CSF drainage 10-meter walk assessment according to the Gait Manual or SOP. If symptoms are improved following CSF drainage according to inclusion criteria 2 and exclusion criteria 4, the participant will be referred to the neurosurgeon to discuss the trial. An orthostatic blood pressure measurement must be performed at the initial visit. If abnormal, the patient will be evaluated according to institutional standards before proceeding with NPH evaluation. A minimal set of screen failure information will also be collected on candidates that are not approached for consent in order to ensure there is no bias in the selection of study candidates. Information to be collected during this period includes demographics, medical and surgical history, physical examination, historical MRI or CT scan (within six months), and results of the CSF drainage trial pre- and post- testing.

4.1.2 ELIGIBILITY AND CONSENT

Participants that meet criteria for shunt surgery and are found eligible for the study will be approached, usually by the neurosurgeon, to discuss the main study consent. Once the participant has consented, the baseline assessments, research MRI, surgery, and randomization may be scheduled. The clinical investigator must sign off on participant eligibility before the baseline assessments are performed and participant is randomized. If the participant has a documented history of exclusionary co-morbidity (e.g. depression), the investigator will need to document that the diagnosis will not complicate the outcome evaluation based on the severity and nature of the diagnosis.

4.1.3 BASELINE VISIT

The figure below outlines patient flow for the Baseline Visit through End of Study.



Baseline assessments will be performed on all participants that sign the main study consent. The following assessments will be administered at baseline by trained study personnel at least 4 weeks after the drainage trial to allow sufficient washout for the effects of the drainage trial and as close as possible to the surgery date to get the most accurate baseline: 10 Meter Walk Test, Tinetti and Boon assessments, MoCA (see Section 8.2 for version), OABq, mRS, SDMT, NIH Toolbox: Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sort Test, Beck Depression Inventory-Second Edition (BDI-II), Lawton ADL/IADL., QOL Survey EQ-5D-5L, assessment of neurological, urological or serious adverse events or falls, and verification of concomitant medications since consent. Participants will have a baseline research MRI performed on a qualified scanner. A PENS-trained neuropsychologist or trained psychometrist will administer the extended neuropsychological battery (participating sites only). The baseline visit should be scheduled as close to the date of surgery as is feasible.

4.1.4 RANDOMIZATION AND SURGERY

Randomization to Active Shunt or Closed Shunt settings will occur at the time of the surgery. The neurosurgeon will perform randomization using an Internet-based randomization system with backup randomization envelopes; a block randomization design will be used, with the treatment assignment stratified by age (categorized as 60-69, 70-79, 80 or greater). Randomization must not be performed until the patient is cleared and prepped for surgery.

4.1.5 ONE-MONTH POST-SURGERY VISIT

At one-month post-surgery (-14/+30 days), participants will be contacted by phone or seen in the clinic and asked about any adverse events or falls that participants have experienced since surgery and their current list of concomitant medications. As part of the standard of care, a CT scan or MRI (per institutional standard) will be done at approximately one month after shunt implantation. Post-op imaging and medical records will be collected and reviewed for possible AEs.

4.1.6 TWO-MONTH POST-SURGERY VISIT

At two months post-surgery (-14/+30 days), participants will be contacted by phone or seen in the clinic and asked about any neurological, urological or serious adverse events, or falls that participants have experienced since their one-month follow up phone call and their current list of concomitant medications.

4.1.7 THREE-MONTH POST-SURGERY VISIT: PRIMARY OBJECTIVE MEASUREMENTS AND SHUNT SETTING CHANGE

At the three-month time point (-14/+30 days), the following assessments will be performed by the PENS-trained blinded assessor that performed the baseline assessments: 10 Meter Walk Test, Tinetti, Boon Scale, MoCA (see Section 8.2 for version), OAB-q, mRS, SDMT, NIH Toolbox: Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sort Test, Beck Depression Inventory-Second Edition (BDI-II), Lawton ADL/IADL, and QOL Survey EQ-5D-5L. A neuropsychologist or trained psychometrist will administer the extended neuropsychological battery (participating sites only). The investigator or designee that is not the blinded assessor will assess neurological, urological, serious adverse events or falls, verification of concomitant medications. The unblinded neurosurgeon will confirm shunt programming using the Certas Plus Indicator Tool in both groups. Participants will have a research MRI performed on the study qualified scanner.

To maintain blinding, all study participants will be adjusted / mock adjusted to the active setting in a similar fashion at this visit. For study participants assigned to the Closed Shunt Group (setting 8) at randomization, the shunt will be set to recommended setting 4 or may be set at the discretion of the treating neurosurgeon. For participants assigned to the Active Shunt Group (setting 4) at randomization, the shunt will be set at the discretion of the treating physician according to each center's standards.

4.1.8 FOUR-MONTH POST-SURGERY VISIT

At four months post-surgery (-14/+30 days), participants will be contacted by phone or seen in the clinic and asked about any adverse events or falls that participants have experienced since their three-month visit and their current list of concomitant medications. A second CT scan or MRI (per institutional standard) will be done at approximately one month after shunt programming (four months post-surgery)

according to institutional standards. Imaging and medical records will be collected and reviewed for possible AEs.

4.1.9 SIX-MONTH POST-SURGERY VISIT

At the six-month time point (-14/+30 days), a PENS-trained blinded assessor that performed the baseline assessments will perform the following assessments: 10 Meter Walk Test, Tinetti and Boon Scale, MoCA (see Section 8.2 for version), OAB-q, mRS, SDMT, NIH Toolbox: Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sort Test, Beck Depression Inventory-Second Edition (BDI-II), Lawton ADL/IADL, and QOL Survey EQ-5D-5L. The investigator or designee that is not the blinded assessor will assess neurological, urological, serious adverse events or falls, verification of concomitant medications. The unblinded neurosurgeon will confirm shunt programming using the Certas Plus Indicator Tool in both groups.

4.1.10 NINE-MONTH POST-SURGERY VISIT

At the nine-month time point (-14/+30 days), a PENS-trained blinded assessor that performed the baseline assessments will perform the following assessments: 10 Meter Walk Test, Tinetti and Boon Scale, MoCA (see Section 8.2 for version), OAB-q, mRS, SDMT, NIH Toolbox: Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sort Test, Beck Depression Inventory-Second Edition (BDI-II), Lawton ADL/IADL, and QOL Survey EQ-5D-5. The investigator or designee that is not the blinded assessor will assess neurological, urological, serious adverse events or falls, verification of concomitant medications. The unblinded neurosurgeon will confirm shunt programming using the Certas Plus Indicator Tool in both groups.

4.1.11 TWELVE-MONTH POST-SURGERY VISIT (ACTIVE SHUNTING GROUP ONLY)

Unblinding Note: Prior to the twelve-month visit, the study coordinator or designee may be unblinded in order to schedule the final study visit. Participants in the Active Shunt Group will have the final study visit at twelve months to capture months of active shunting.

At the twelve-month time point (-14/+30 days), a PENS-trained blinded assessor that performed the baseline assessments will perform the following assessments: 10 Meter Walk Test, Tinetti and Boon Scale, MoCA (see Section 8.2 for version), OAB-q, mRS, SDMT, NIH Toolbox: Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sort Test, Beck Depression Inventory-Second Edition (BDI-II), Lawton ADL/IADL, and QOL Survey EQ-5D-5L. A neuropsychologist or trained psychometrist will administer the extended neuropsychological battery to participants randomized to the Active Shunt Group (participating sites only). Participants will have a research MRI performed on the study qualified scanner.

The investigator or designee that is not the blinded assessor will assess neurological, urological, serious adverse events or falls, verification of concomitant medications. The unblinded neurosurgeon will confirm shunt programming using the Certas Plus Indicator Tool in both groups. Once these assessments are complete, the neurosurgeon will ask the participant which arm they believe they were in then unblind the participant to their assigned arm.

4.1.12 FIFTEEN-MONTH POST-SURGERY VISIT (CLOSED SHUNTING GROUP ONLY)

Unblinding Note: Participants in the Closed Shunt Group will have a fifteen-month visit to capture 12 months of active shunting (since the shunt was opened at the 3 Month Visit).

At the fifteen-month time point (-14/+30 days), a PENS-trained blinded assessor that performed the baseline assessments will perform the following assessments: 10 Meter Walk Test, Tinetti and Boon Scale, MoCA (see Section 8.2 for version), OAB-q, mRS, SDMT, NIH Toolbox: Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sort Test, Beck Depression Inventory-Second Edition (BDI-II), Lawton ADL/IADL, and QOL Survey EQ-5D-5L. A neuropsychologist or trained psychometrist will administer the extended neuropsychological battery to participants randomized to the Active Shunt Group (participating sites only).

The investigator or designee that is not the blinded assessor will assess neurological, urological, serious adverse events or falls, verification of concomitant medications. The unblinded neurosurgeon will confirm shunt programming using the Certas Plus Indicator Tool in both groups. Once these assessments are complete, the neurosurgeon will ask the participant which arm they believe they were in then unblind the participant to their assigned arm.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Subjective factors in evaluation of iNPH treatment response, along with the strong potential of surgery and an implanted shunt to elicit a placebo response, have made a scientifically convincing demonstration of the true physiological treatment effect of shunting in iNPH difficult. Few studies have attempted to evaluate the extent of physiological versus placebo-induced shunt improvement in iNPH. These studies have been small and have often used invasive procedures such as ligature around the distal shunt catheter to produce the placebo condition. This has made true blinding difficult and re- quired a minor surgical procedure to remove the ligature and reverse the placebo condition.

Our study would be the first to take advantage of the virtual off setting of a programmable valve system to result in a blinded non-invasive placebo-controlled study, as we first proposed in 2012.[9]

There is a strong scientific and public health imperative to do such an evaluation. A placebo-controlled study is necessary to determine the clinical response to shunt surgery for iNPH. Either result of this study will have an important impact on care of the elderly: If shunting is proven effective, it may be offered to a proportion of the much larger group of iNPH candidates that have been estimated.[17,18] Further, a placebo-controlled study allows the evaluation of the placebo vs. physiological effect that will identify objective thresholds that distinguish shunt responders from non-responders. Alternately, if no difference in clinical or physiological response exists between the shunt and placebo groups, then the existence of shunt-responsive iNPH may be questioned and would significantly reduce the number of elderly patients undergoing unnecessary diagnostic procedures and surgery.

The most common reason for failure to improve on the diagnostic tests as well as shunt surgery is the prevalence of Alzheimer's Disease in the aging population. AD is known to cause ventriculomegaly; and gait abnormalities have been described even in prodromal AD, making the distinction from iNPH a clinical challenge. Therefore, CSF will be collected to potentially identify biomarkers that improve the clinician's ability to differentiate between these two conditions.

4.3 JUSTIFICATION FOR SHUNT

There are 5 major manufacturers of shunts. Until now the valves were either differential pressure valves or flow-regulated valves and none of them had the ability to be turned off even if clinically indicated. Thus, doing a placebo study of shunts often involved tying a ligature in the shunt catheter with variable results and adding complexity and additional intervention to untie the ligature. With the release of the new Codman Certas Plus 2.0, a virtual off setting is now available to stop flow of CSF through the shunt

system unless intracranial pressures exceed 400 mm which has not been documented in participants with iNPH. This shunt would also rapidly enable lowering settings if indicated in the judgement of the treating physician in the placebo arm without necessitating invasive intervention. No other commercially available shunt appropriate for treating NPH offers these features.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Participants will be eligible for enrollment if they meet all of the following inclusion criteria:

1. Age ≥ 60 years; and
2. Diagnosis of iNPH and recommendation for shunt surgery based on the Investigator's clinical judgement using criteria and testing as described in the iNPH Guidelines[19]; and
3. Evans Ratio ≥ 0.30; and
4. One positive supplementary test to include either large volume Lumbar Puncture or extended CSF drainage per institutional standards[16]; and
5. History or evidence of gait impairment (such as decreased step height or length, decreased speed, retropulsion as described in the iNPH Guidelines[19]) duration ≥ 6 months; and
6. Participant has the sensory motor skills, communication skills and understanding to comply with the testing and reporting required in the PENS trial; and
7. Participant is able to give written informed consent.

5.2 EXCLUSION CRITERIA

Participants will be ineligible for enrollment if any of the following exclusion criteria are met:

1. Unable to walk 10 meters with or without an assistive device; or
2. Screening fastest gait velocity > 1 m/sec prior to drainage trial **unless the patient's gait velocity improves** ≥ 30%; or
3. Unable to return to the study center for follow up evaluation and shunt programming; or

4. Participant is not medically cleared for shunt surgery per local standards; or
5. Secondary NPH. (Prior encephalitis, meningitis, subarachnoid hemorrhage, traumatic brain injury (including concussion) within two years or with brain injury or skull fracture on baseline imaging, brain abscess, brain tumor, obstructive hydrocephalus (including acquired aqueductal stenosis and carcinomatous meningitis); or
6. Prior or existing shunts, endoscopic third ventriculostomy, or any previous surgical intervention for hydrocephalus including lumbar CSF shunting; or
7. Previous intracranial neurosurgical procedure; or
8. Current treatment with anticoagulation medications or expected to be on anti- coagulation medications in future based on clinician evaluation; or
9. Symptomatic cerebral or cerebellar infarction occurring within 6 months from screening (asymptomatic lacunar infarctions are permitted); or
10. Diagnosis of Parkinsonian syndrome that, in the investigator's judgment, will impede the outcome evaluation; or
11. Diagnosis of schizophrenia or any psychiatric diagnosis (including depression) that, in the investigator's judgment, will impede the outcome evaluation (such as neuroleptic treatment for schizophrenia); or
12. Diagnosis of dementia disorder where the investigator considers cognition deficit limits participation in the study; or
13. Conditions impairing gait that are considered to be unrelated to hydrocephalus, such as hemiparesis, spasticity, cerebellar ataxia or musculoskeletal and joint disease, which will interfere with gait assessment or the potential for gait improvement.

Note on investigator judgement: Patients with comorbidities that would impede the evaluation of gait and neuropsychological evaluations must not be enrolled. However, due to the difficulty of diagnosing NPH, patients frequently present to clinic with prior diagnoses of comorbidities such as Parkinson's Disease, depression, and dementia. It is vital that the investigator carefully review the medical history against the clinical presentation of the patient and confirm that any comorbidities are not of a nature to impede the outcome evaluation. The investigator will document this review on the eligibility checklist.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. A minimal set of screen failure information will also be collected on candidates that are not approached for consent in order to ensure there is no bias in the selecting of study

candidates. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) trial may be rescreened only if a repeat lumbar drainage trial is clinically indicated. Rescreened participants should be assigned the same participant number as for the initial screening. Repeat CSF collection will not be performed.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Clinical investigators at each site will be neurosurgeons or neurologists. Site staff will screen each clinic patient for potential eligibility. Patients undergoing iNPH evaluation that have not yet completed a drainage trial will be asked to sign a prescreening consent for CSF collection during their standard lumbar puncture or extended lumbar drain. Participants that are eligible for randomization based on the results of the drainage trial will be approached, usually by the neurosurgeon, for consent for the randomized trial. Participants that are found ineligible may not repeat the assessments for rescreening but may be rescreened if a subsequent drainage trial is performed per standard of care (SOC). A screening log will be completed for all patients presenting to clinic for NPH evaluation, whether eligible or not eligible. If patients are determined to be eligible and are referred for a lumbar drainage trial, patients will be presented with a pre-screening consent form to have their CSF collected. If the patient has symptom improvement following CSF drainage, the PI or neurosurgeon will ask the patient if they would like to hear about the research study.

It is vital that the study-trained neurosurgeon or neurosurgical mid-level provider approach the patient to go over the risks of surgery and potential impact of delayed treatment. Those patients who indicate that they are not interested will receive standard treatment. Patients who express interest in participating will be provided with a copy of the informed consent document to review. The site staff will answer any questions or concerns relating to the study. The patient will be informed about the objectives of the study and the potential risks. Patients who choose to participate must sign an informed consent document prior to shunt insertion procedure. Patients who consent to the study will be scheduled for the shunt procedure. Prior to the procedure, site staff will review baseline assessments to make sure they are all completed.

Participants will receive compensation for participation in the amount of $100 for completing the 3-month visit, $50 for completing the 9-month visit, and $50 for completing the 12-month visit. Compensation may be in the form of cash, pre-paid card, check, or direct deposit, according to the standard workflow for compensating participants at each site. Compensation may be given after each study visit or at the end of the study according to the standard workflow for compensating participants at each site

As part of site startup, each site will develop a site-specific recruitment and retention plan. Assessment of the screening and randomization logs will facilitate assessment of the plan. Participant-facing materials will be developed for distribution in clinics. To increase referral and participant diversity, physician facing materials will be distributed to community physicians to educate the catchment area about NPH and establish a referral network.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The primary intervention will be the initiation of the randomized initial shunt valve opening pressure setting to create a delayed treatment group in half of the study participants.

Surgical shunt implantation is the major procedure taking place in the study; however, since participant selection for surgery and the method of surgery are all part of the surgeon's standard care, it is not considered an intervention of the study. The implanted shunt will be an FDA-approved programmable CSF shunt (Certas Plus with Siphonguard™, Codman, Johnson and Johnson, Raynham, MA USA). The device is commercially available and is being used in accordance with approved labeling. The catheter must be placed on the right-side frontal or parietal occipital. The valve is CertasPlus valve is positioned in the distal system on the posterior cranium, just below the burrhole for parietal occipital catheters and just below the tunneling inflection incision for frontal catheters.

6.1.2 SHUNT VALVE SETTING

The neurosurgeon performing the surgery will pre-set the adjustable valves to one of the two designated settings, while the shunt is in the sterile packaging, outside of the operating room, just before the operative case. The setting 4 (active shunt) or 8 (closed shunt) will be determined by the randomization that the neurosurgeon will access directly. The setting will be performed and verified by the neurosurgeon alone, without assistance.

At the time of the primary objective evaluation at three months, the Closed Shunt Group will have zero months of active treatment, and the Active Shunt Group will have three months of active treatment. At three months, shunts for study participants in the Closed Shunt Group will be adjusted to setting 4 (recommended setting) or at the discretion of the treating neurosurgeon. To maintain blinding, all study participants will be adjusted / mock adjusted to the active setting in a similar fashion. Participants from both groups will not be adjusted before three months of active treatment unless judged medically necessary by the treating team. Following the three-month study visit, all participants in each group may have shunt adjustments according to clinical standards at each center.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The Certas Plus with Siphonguard™ is commercially available and is being used in accordance with approved labeling. No product will be provided to the investigator.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not applicable.

6.2.3 PRODUCT STORAGE AND STABILITY

The device should be stored according to institutional policies.

6.2.4 PREPARATION

The device should be prepared for implantation according to the device label. The neurosurgeon performing the surgery will pre-set the adjustable valves to one of the two designated settings, while the shunt is in the sterile packaging, outside of the operating room, just before the operative case.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The neurosurgeon performing the implantation surgery will be aware of the assigned setting. A blinded PENS-trained assessor will perform the gait and cognitive tests at baseline and during the follow-up visits and will remain blinded to the treatment assignment throughout the course of the study. In order to avoid unblinding, the blinded assessor must not review the participant's medical record. Other support staff will review the medical record and enter data for the trial.

The neurosurgeon performing the surgery will randomize the participant then pre-set the adjustable valves to one of the two designated settings, while the shunt is in the sterile packaging, outside of the operating room, just before the operative case. The setting 4 or 8 will be determined by the randomization that the neurosurgeon will access directly. The setting will be performed and verified by the neurosurgeon alone, without assistance.

The setting will be recorded as "PENS study assigned setting" in the medical record. This variation from standard practice is necessary to preserve blinding of participants and other investigators. If it is necessary for clinical reasons outside the research protocol (and at any institution) to determine the shunt setting, the standard shunt indicator tool can be used to assess the valve setting at any time. Follow up per protocol schedule will continue for those participants whose shunt setting is modified.

As noted above, the neurosurgeon performing the surgery will be unblinded to the study participant treatment group and will not play a role in administering the study outcome assessments. The neurosurgeon or other medical personnel will assess the assigned/current valve setting using an indicator tool if this is deemed medically necessary to allow potential valve adjustment. Medical necessity is defined as clinician concern for participant risk for injury due to over- (subdural hematoma development) or under- (acute progressive hydrocephalus) drainage. The study participant will continue to receive standard appropriate medical treatment and remain in the study for data collection.

Randomization will be in a 1:1 ratio to active or placebo (closed) shunt settings. At the time of the standard three-month evaluation, all study participants will be similarly non-invasively adjusted to bring all participants in both groups to the active setting while maintaining blinding of the participants. All settings will be verified by the adjusting neurosurgeon.

6.4 STUDY INTERVENTION COMPLIANCE

The unblinded neurosurgeon will confirm the randomized shunt setting at the time of surgery and at the 3-month visit and sign an attestation form to confirm that the setting was at the randomized setting. At subsequent visits, the neurosurgeon will confirm and attest whether this setting remains programmed as per the prior visit. Adjustments will be documented on the Valve Adjustment Log.

6.5 CONCOMITANT THERAPY

Standard therapies and medications should be administered according to standard post-operative care at the local site. This includes use of psychoactive medications, occupational and physical therapy, etc. If a study participant must be treated with oral or intravenous anti-coagulation medications, the clinician will use clinical judgement about shunt adjustment following local SOC.

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements related to an adverse event, medications for Alzheimer's disease, medications for Parkinson's disease, mediations for depression or anxiety, Anticoagulants, Sedatives, Hypnotics, and medical marijuana. Other medications should not be documented on the Concomitant Medications Log. Concomitant medications will be recorded at each study visit.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

All participants withdrawn early from the study must have a reason for withdrawal recorded on the Early Termination Form, and the circumstances leading to withdrawal must be described.

- If the study intervention is discontinued by the clinical care team because of adverse event, i.e. the shunt is adjusted prior to the three-month visit, this does not constitute participant withdrawal from the study. Such participants will continue to be followed and evaluated in the trial. All participants randomized in this study will be analyzed as per the intention-to-treat principle.
- If the participant is determined ineligible after consent but before randomization, the participant will be considered a screen failure.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Early Termination Form. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, will not be replaced.

A participant may choose to withdraw from the study at any time and the clinician will determine the most appropriate treatment for such a participant. Since participants in the closed group undergo treatment delay, this delay may be terminated by shunt programming to an open state only if this change is considered medically necessary. The medical course of randomized participants will continue to be reviewed for neurological, urological or serious adverse events until 12-month post-surgery clinic visit. If the participant experienced such adverse event from the time of surgery to twelve months post operatively, the adverse event will be followed until resolution or 12-month study visit, whichever is earlier.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the 12-month visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant to reschedule the missed visit as close to the visit window as possible and counsel the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable until 12 months post-surgery, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 VIDEO RECORDING OF GAIT ASSESSMENTS

The Gait Assessments (10-Meter Walk, Tinetti Assessment, and Boon Scale) will be video recorded using dedicated iPhones, phone holder mounted on a tripod, and the Anonymous app on the iPhone. Recordings will be submitted to a central reviewer at Johns Hopkins University who will review for quality control across enrolling centers. The central reviewer will view all gait assessment recordings to ensure that study teams are conducting the assessments according to the Manual of Operations (MOO) and provide additional trainings if instructions are not followed.

8.1.2 GAIT VELOCITY: 10-METER WALK TEST

Gait velocity will be assessed with the 10-Meter Walk Test at baseline (prior to randomization) and post-operatively at three, six, and nine months, and then at twelve months of active shunting (12 OR 15-month visit) by a PENS-trained blinded assessor. While velocity measurement is a standard clinical measurement, we request the following method for uniformity and quality. Study participants will be assessed by a PENS-trained assessor who is blinded to randomization (for assessments that take place after surgery) under conditions that are standardized and similar at each measurement, e.g., similar footwear to what is usually worn.

Study participants are encouraged to walk in the same manner relative to their status at inclusion and relative to their assistive device, i.e., if a walker or a cane was used in the baseline gait velocity assessment, then the same assistive device (if needed) should be used in the post-operative gait assessment. The test surface should be consistent, i.e., always a hard surface, or always a carpeted surface. Hard surfaces are recommended. The 10-meter distance should be measured and marked on the floor so that the examiner can time properly. The participant is instructed to start walking at the start

line and continue to walk as quickly as they feel comfortable, yet safely until they are beyond the finish line.

The examiner starts the stopwatch when the participant's leading foot takes its first step and stops the clock when the participants leading foot crosses over the finish line. The time in minutes and seconds (to 1/10th second) are recorded. Three gait velocity tests are performed and recorded. The best (fastest) of all three gait velocity tests will be used to determine eligibility at screening, including percentage of improvement if over 1m/sec, and used for the primary analysis, although the mean will also be evaluated and auxiliary analyses will evaluate these endpoints. Training for uniform assessment of this primary outcome measure will be performed at each center.

8.1.3 TINETTI ASSESSMENT

The Tinetti Assessment will be assessed at baseline (prior to randomization) and post-operatively at three, six, and nine months, then at twelve months of active shunting (12 OR 15-month visit) by a PENS-trained blinded assessor. Tinetti is used to assess gait and balance. In addition, this test is used to evaluate the perception of balance and stability. The Tinetti Assessment is composed of two portions and patients may use any assistive devices that they would normally use. The patient is scored out of a total of 28 possible points and rates patients as high, moderate, or low risk for falls.

8.1.4 OVERACTIVE BLADDER-Q SHORT FORM (OAB-Q) SYMPTOM SEVERITY SUBSCALE

The OAB-q SF will be assessed at baseline (prior to randomization) and post-operatively at three, six, and nine months, then at twelve months of active shunting (12 OR 15-month visit) by a PENS-trained blinded assessor. OAB-q is a brief, self-administered, participant-reported outcomes tool with two scales assessing symptom bother and health-related quality of life (HR-QOL) in participants with OAB.

This questionnaire asks how much the participant has been bothered by selected bladder symptoms during the past four weeks. The participant is instructed to indicate which answer best describes the extent to which the participant was bothered by each symptom during the past four weeks. The test is scored according to the scoring instructions. Study participants will be asked to complete the form at baseline (prior to randomization) and post-operatively at three, six, and nine months, and then at twelve months of active shunting (12 OR 15-month visit).

8.2 OTHER ASSESSMENTS

8.2.1 CEREBROSPINAL FLUID (CSF) COLLECTION

Participants will sign a pre-screening consent to have CSF collected during their standard lumbar puncture or extended lumbar drainage. When patients undergo a lumbar puncture or extended CSF lumbar drainage trial as part of their standard of care assessment to select patients for shunt surgery, in addition to the procedure consent, research consent will be obtained to bank the CSF left over after clinically indicated CSF tests have been sent. CSF will be collected directly in special low-protein binding polypropylene 10 ml collection tubes provided by the Biomarker Core. CSF will need to be frozen in a -80°C freezer immediately after collection (goal within 2 hours) and shipped to the CSF Core Lab at Johns Hopkins University on dry ice as a batch shipment. Packing and shipping instructions will be provided in a separate Manual of Operations.

CSF will be analyzed for AD biomarkers in the CLIA-certified lab at Johns Hopkins. Because the results of the AD biomarker testing could bias patients and their care team, the results of this test will be withheld until the end of the study. We expect to collect CSF from about 300 participants in order to randomize 100 participants.

8.2.2 MODIFIED RANKIN SCALE (MRS)

The mRS is a six-point disability scale with possible scores ranging from zero to five and will be assessed at baseline (prior to randomization) and post-operatively at three, six, and nine months, then at twelve months of active shunting (12 OR 15-month visit) by a PENS-trained blinded assessor. The examiner completes the scale based on the history and examination of the participant. The test is scored according to the scoring instructions.

8.2.3 CORE NEUROPSYCHOLOGICAL BATTERY:

All centers will administer the core neuropsychology screening battery. Each measure will be administered at baseline (prior to randomization) and post- operatively at the three, six, and nine months, and then at twelve months of active shunting (12 OR 15-month visit) in all enrolled patients by a PENS-trained blinded assessor and will be administered and scored according to standard instructions in the respective test manuals. The following assessments are included in the core screening battery:

Montreal Cognitive Assessment (MoCA)[20] The MoCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal. See the manual of operations for information on which version to use at which visit.

Symbol Digit Modalities Test (SDMT)[21] The SDMT provides a measure of sustained attention and processing speed and requires approximately five minutes to perform. Only the standard form should be used in this study.

NIH Toolbox: Flanker Inhibitory Control and Attention Test and Dimensional Change Card Sort Test The NIH Toolbox Flanker Inhibitory Control and Attention Test measures both a participant's attention and inhibitory control. [22,23] The Dimensional Change Card Sort (DCCS) is a standard procedure for assessing executive functioning early in development.[24]

Beck Depression Inventory- Second Edition (BDI-II)[25] – The Beck Depression Inventory is a 21-item self-report questionnaire that measures cognitive, affective, somatic, and performance-related symptoms of depression requiring five to ten minutes to complete. Scores range from 0-63.

Lawton ADL/IADL Scale - The Lawton Scale is a 16-item questionnaire used to assess independent living skills requiring five to ten minutes to complete. The ADL/IADL Questionnaire[26,27] was modified for the Older Americans Resources and Services (OARS) Program developed at the Duke University Center for the Study of Aging and Human Development, and has been published by Psychological Assessment Resources as part of the Calibrated Neuropsychological Normative System.[28] Both self- and informant- ratings are available. For each form, the respondent is asked to rate the examinee's level of everyday functional independence for six physical activities of daily living (ADLs) and nine instrumental activities of daily living (IADLs). The respondent also rates examinee for incontinence.

8.2.4 EXTENDED NEUROPSYCHOLOGICAL BATTERY (SUBSTUDY):

Extended neuropsychology testing will be done only at those centers that have a neuropsychologist or trained psychometrists to administer and supervise the testing using standardized methods. We anticipate that 10-12 centers will meet the criteria to administer the extended neuropsychology battery and plan to enroll 60-80 patients who will undergo extended testing. Sites not selected to participate in the extended neuropsychological substudy will only perform the Core Neuropsychological Battery.

The extended neuropsychological battery will assess a broader range of cognitive functions and consists of tests that were chosen based on their clinical and empirical sensitivity to the spectrum of cognitive and behavioral functions known to be compromised in NPH. Because the study design requires repeated testing, whenever possible, tests with alternate forms were selected in order to control for practice effects. Administration and scoring of each instrument will be standardized as described in the respective test manuals. In addition to the cognitive testing, questionnaire measures of functional status, psychiatric symptoms and quality of life are also included. The extended neuropsychological test battery (projected administration time is 120-150 minutes, including questionnaires) will be administered at baseline, at the 3-month follow up visit and at 12 months of active shunting. A complete list of tests included in the extended neuropsychological test batteries are listed below and a full description of the tests with references is included in the supplemental materials.

- **Premorbid Intellectual Ability:** *Wide Range Achievement Test - Fifth Edition (WRAT-5) Reading*[29]
- **Language skills**
  - *Boston Naming Test*[30]
  - *Animal Fluency*[31]
  - *Controlled Oral Word Association*[32]
- **Attention and Executive functions**
  - *WAIS-III*[33] *Digit Span subtest*
  - *Trail Making Tests A and B*
  - *Stroop Color Word Test*[35]
- **Visuo-constructional skills** *Judgment of Line Orientation (JLO)-short form*
- **Memory functions** *Hopkins Verbal Learning Test-Revised (HVLT-R)*[36]
- **Motor skills**
  - *Grooved Pegboard Test*
  - *Finger Tapping Test*[37]
- **Psychological Functioning, Adaptive Functioning and Quality of Life**
  - *Frontal Systems Behavior Scale*[38]
  - *Neuropsychiatric Inventory*[39]

8.2.5 QOL SURVEY EQ-5D-5L

This is a 5-item (EQ-5D-5L), 2-item (EQ-VAS) and 2-item (HA/ABD Pain) questionnaire that is used to assess quality of life and additionally presence of headache and abdominal pain and will be assessed at baseline (prior to randomization) and post-operatively at three, six, and nine months, and then at twelve months of active shunting (12 OR 15-month visit) twelve months by a PENS-trained blinded assessor.

8.2.6 IMAGING BIOMARKERS

Pre-Trial Optimization Imaging Phase

In order to optimize the research imaging protocol healthy subjects and NPH patients will be recruited prior to enrollment to the treatment study. For these participants, the study will require one visit for each participant during which the MRI scan will be performed. The MRI scans will last approximately 60 minutes. MRI techniques will be analyzed for image quality (presence or absence of artifacts) and signal-to-noise ratios. Once the scan is optimized, a human phantom will be scanned at each site to ensure optimization on each site scanner. Participants in this phase will sign a separate consent form.

Treatment Phase

Brain MRI acquisition procedures will be performed on a 3T system using a quadrature or phased-array head coil. MRI scans obtained on 3T GE, Philips, or Siemens machines are preferred, but other vendors and magnet field strengths will be accepted if the preferred scanner vendor or strength are not available. If preferred vendor or magnetic field strength are not available, the study coordinator or designee will need to notify JHU PENS coordinators for approval. A site MRI technologist will be responsible for MRI quality control, including notifying JHU PENS coordinators if MRI software/hardware modifications or updates occur or are anticipated to occur. The goal is to collect data with high image contrast and minimal variations due to protocol changes, image artifacts, and noise. Standard research-quality MR images including T1-weighted, T2-weighted, Fluid-attenuated Inversion Recovery (FLAIR), resting state fMRI, Diffusion Tensor Imaging (DTI), and phase contrast will be acquired at each site for each imaging session with each patient.

Post-Gd anatomical images will also be acquired for participants enrolled at Johns Hopkins only (see below). Imaging requirements will be described in a separate manual. Note: Subjects who have moderate to advanced kidney failure may participate but will be excluded from the post-contrast sequences due to the risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NSD) when receiving gadolinium administration for MRI scans. A creatinine measurement < 1.4 mg/dl is required of all subjects in the 30 days prior to the MRI scan. JHU will follow their institutional guidelines for gadolinium administration.

Other Images

Most sites will also acquire additional images as a part of their standard clinical imaging protocols. If additional images are required or recommended and time permits, these may be useful for both clinical and research purposes and will be incorporated in the study whenever possible. These images will be different for each site and could include: T2*- or susceptibility-weighted images, arterial spin labeling (ASL) MRI, vascular-space-occupancy (VASO) MRI etc.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom. For purposes of this trial, adverse events will only be recorded for 30 days after shunt insertion and then for 30 days after shunt

adjustment. However, all neurological, urological and serious adverse events and falls will be reported throughout the course of the trial starting with signing consent.

The principal investigator (PI) or designee at each clinical site will evaluate all adverse events that occur within the specified timeframe. Adverse events not previously documented in the study will be recorded on the Adverse Event Record Log. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment should be established.

Falls, however, will be recorded on separate case report forms for the duration of the study and will not be collected on the AE record forms. Serious adverse events resulting from falls will be reported as described below.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Seriousness: The seriousness of clinical adverse events will be recorded by the site investigator and categorized. A serious adverse event (SAE) is an adverse event that:

- results in death; or
- is life-threatening (the participant was, in the view of the clinical site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect; or
- any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: While variations in MoCA score are expected, a decrease in MoCA score of ≥ 2 points must be reviewed by the investigator for seriousness as part of safety monitoring.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Mild	Awareness of sign or symptom that does not interfere with the participant's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes, but does not hinder, the Subject's usual activity and / or may require treatment.
Severe	Symptom(s) causing severe discomfort and significant impact on the participant's usual activity and requires treatment or intervention.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Relatedness: The suspected relationship between study interventions and any adverse event will be determined by the site investigator using the following criteria. *Relatedness may **not** be assessed by a research coordinator, and must be assessed by an investigator.*

- Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, and concomitant drugs or procedures administered to the subject.
- Possibly Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the study subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.
- Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and cannot reasonably be explained by other factors such as the study subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.
- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to study intervention and cannot be explained by concurrent disease or other drugs or chemicals.

8.3.3.3 EXPECTEDNESS

Expectedness of the Event: All adverse events reportable per protocol, including serious adverse events, will be evaluated as to whether their occurrence was expected (as described in the protocol or consent forms) or unexpected.

Expected: An event is considered expected if it is known to be associated with the underlying condition (i.e. hydrocephalus) or is related to the study intervention (i.e. CSF drainage/delay) or non-study intervention (i.e. surgical procedure); and is mentioned in the protocol, informed consent or other study documents. An event may be expected despite the study participant's clinical state immediately prior to the event. For this protocol, expected adverse events include:[3]

1. Subdural hygroma.
2. Subdural hematoma.
3. Hematoma or hygroma requiring evacuation.
4. Epidural hemorrhage.
5. Subarachnoid hemorrhage.
6. Intraventricular hemorrhage.
7. Intraparenchymal hemorrhage.
8. Seizure, acute or chronic.
9. Vascular injury, pseudoaneurysm, dural sinus injury.
10. CSF leak.
11. Bacterial meningitis.
12. Shunt or wound infection.
13. Wound dehiscence.
14. Decline in MoCA score.
15. Proximal or distal shunt mis- or displacement.

16. Distal or distal catheter failure.
17. Valve failure.
18. Iatrogenic injury due to shunt passer.
19. Falls
20. Death

Unexpected: An event is considered unexpected if there are no prior data linking this event with either the condition or intervention under study or an event that occurred unexpectedly in the course of surgical treatment.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

For purposes of this trial, adverse events will be recorded for 30 days after shunt insertion and shunt adjustment while serious, neurological and urological adverse events will be collected throughout the trial from time of consent to the 12 OR 15-month follow-up. Events that occur following participant consent to participate in the trial, but prior to randomization, will not be reported as adverse events. These should be recorded as baseline conditions. If the event has not resolved by the final study visit, the status of the event at this time point should be reported.

After randomization, adverse events, whether expected or unexpected, will be recorded according to the date of first occurrence, severity, and their duration, as well as any treatment prescribed. Any medical condition that presents prior to randomization will be recorded in the participant's baseline history at study entry but will not be recorded as an adverse event at subsequent evaluations if it remains unchanged. However, worsening of a medical condition that was present at the time prior to randomization will be considered a new adverse event and will be recorded.

Abnormal laboratory values that are clinically significant will be recorded as adverse events and the clinical site investigator will assess the severity and relationship to the study. Laboratory values that are abnormal prior to randomization and that do not worsen will not be recorded as adverse events.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding vocabulary. Coding will be done centrally at the Data Coordinating Center (DCC) because this requires specific training.

All serious, unexpected and related adverse events, that are unresolved at the time of the participant's termination from the study or discharge from the hospital, will be followed by the site investigators until the events are resolved, participant is lost to follow-up, the adverse event is otherwise explained or has stabilized, or 12 months have passed from the time of randomization. Adverse experiences that begin after termination from the study will not be recorded as study adverse events.

8.3.5 ADVERSE EVENT REPORTING

Assuring participant safety is an essential component of this protocol. Each participating clinical center investigator has primary responsibility for the safety of the individual participants under his or her care. Clinical visits will occur at months 3, 6, 9 and 12 OR 15 months. Site staff will also call study participants or see them in the clinic at 1, 2, and 4 months. Clinical investigators may schedule additional clinic visits according to their standard of care or as needed for clinical reasons. The clinical sites will record all new or worsening symptoms or events as reported by the study participant or documented in the clinical sites' medical records for 30 days after shunt insertion and for 30 days after shunt adjustment. Participating sites

will report all neurological, urological and serious adverse events throughout the course of the trial. Other pertinent adverse events can be reported at the discretion of the clinician. All adverse events meeting these definitions occurring after study randomization through final follow up visit will be entered into the electronic data entry system provided by the DCC. In accordance with designated Institutional Review Board (IRB)/Research Ethics Board (REB) requirements, investigators may be required to report such events to the IRB/REB in addition to notifying the DCC.

Treatment or Action Taken: For each adverse event, the clinical site will record whether an intervention was required:

- Intervention: Surgery or interventional procedure
- Other Treatment: e.g. medications, therapy, etc.
- Change in shunt setting
- None: No action taken

Outcome of Event: Finally, the clinical site will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the participant returned to baseline status
- Recovered with permanent sequelae
- Symptoms continue

8.3.6 SERIOUS ADVERSE EVENT REPORTING

An independent Medical Monitor will be designated for this study. If the Medical Monitor is unavailable, a qualified physician will be designated to fulfill this function. Site investigators and/or research coordinators will report all serious adverse events to the DCC within 24 hours of the event or from the time the investigator became aware of the event. Site investigators and/or research coordinators will report all serious adverse events to the DCC within 24 hours of the event or from the time the investigator became aware of the event. The DCC will report all serious adverse events to the Medical Monitor within 3 business days. The Medical Monitor will notify the PI/CCC if it is determined evaluate whether that the event requires prompt reporting to the JHM sIRB. Upon notification of events that require prompt reporting, the PI (or designee) and will report events that require prompt reporting to the JHM sIRB as soon as possible after the event is discovered, but in all cases within 10 working days after discovery of the event. Reportable deaths must be reported to the JHM sIRB within 72 hours after discovery. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report any serious, unexpected, and study-related adverse events to the DSMB and study PI in an expedited manner (within 24 hours). In accordance with designated local IRB/REB requirements, the clinical site investigator may be required to report such events to their local IRB/REB in addition to notifying the DCC. The Medical Monitor will assess these serious adverse events reported from clinical sites in the trial. For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made. The DCC will provide to the PI and CCC a monthly summary report of the trial safety profile to include all AEs (aggregated by MedDRA body system classification), all SAEs, all protocol deviations aggregated by site, and all unanticipated problems.

Reportable deaths must be reported to the JHM IRB within 72 hours after discovery. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the

complete report, the DCC will report any serious, unexpected, and study-related adverse events to the DSMB in an expedited manner (within 24 hours). In accordance with designated IRB/REB requirements, the clinical site investigator may be required to report such events to their local IRB/REB in addition to notifying the DCC. The Medical Monitor will assess these serious adverse events reported from clinical sites in the trial. For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made. All SAE reports will be retained at the DCC.

In the unlikely event that the Medical Monitor believes an unexpected and study- related SAE warrants emergent cessation of enrollment in the trial, the DSMB will be immediately consulted. If the DSMB concurs with the judgment of the Medical Monitor, or if the DSMB cannot be reached expeditiously, the DCC will notify all site investigators to cease enrollment in the trial and will instruct them to report this to their designated IRB/REB. Resumption of enrollment will not occur without approval of the DSMB. Sites are expected to report serious, unexpected, and study-related SAEs per their designated IRB/REB's expedited reporting requirements. The DSMB will review all adverse events during scheduled DSMB meetings.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Falls: Falls will be recorded on a separate case report forms (CRFs). Therefore, they will not be recorded as adverse events.

Clinically significant falls, defined as falls requiring a clinic or ER visit for injury, will be reported to the Medical Monitor to review significance and relatedness to the trial.

If, at any time during the trial, the observed rate of significant, related falls in the placebo arm is at least double that in the active arm, and the number of falls in the placebo arm exceeds that in the active shunting arm by at least two, the medical monitor will be notified of the trend and the trend will be investigated. For example, if 2/4 patients in the active arm and 0/4 in the placebo arm have clinically significant falls, recruitment would be suspended, while recruitment would continue if the within-arm numbers were 2/4 and 1/4 or 1/4 or 0/4. As an example of invoking this algorithm later in the trial, if 3/20 patients in the active arm have clinically significant falls, recruitment would be suspended if 6/20 in the placebo arm report significant falls. The DSMB will be notified of the trend and the results of the investigation. The DSMB will be consulted for guidance on whether enrollment should be suspended.

Surgical Complications: While surgical complications exist in NPH shunting, the shunting performed in both arms of this study are standard practice. In the unlikely event that surgical complications are seen in greater than 30% of participants, the trend will be investigated to ensure it is not related to the study. The DSMB will be notified of the trend and the results of the investigation.

Elder Abuse: For the safety of vulnerable patients included in this trial, study team members should be alert to signs of elder abuse. Suspected elder abuse must be reported to the proper authorities according to institutional policies.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related to participation in the study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The site investigator will report unanticipated problems to the DCC within 24 hours. The DCC will report unanticipated problem events to CCC within 72 hours. The CCC will evaluate whether it meets the definition of JHM IRB for events requiring prompt reporting and report as soon as possible after the event is discovered, but in all cases within 10 working days after discovery of the event. Reportable deaths must be reported to the JHM IRB within 72 hours after discovery of the event. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report these unanticipated problems to the DSMB in an expedited manner (within 24 hours). In accordance with designated IRB/REB requirements, the site investigator may be required to report such unanticipated problems to their local IRB/REB in addition to notifying the DCC. In the event that the Medical Monitor believes that such an event warrants emergent suspension of enrollment in the trial, and the DSMB cannot be reached expeditiously, the DCC will notify all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the DSMB.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary hypothesis of the PENS trial is that treatment of idiopathic normal pressure hydrocephalus (iNPH) with an open shunt results in improvement in gait velocity at three months compared to initial surgical treatment with an open shunt. From an analytic point of view, a conservative approach cannot a priori rule out a highly unexpected harmful effect of open shunting, and thus the hypothesis will be evaluated in a two-sided fashion. A statistically significant finding from the primary analysis, detailed below, would rule out the null hypothesis of no difference in three-month change in gait velocity three months after surgical implantation of an open shunt compared to implantation of a closed shunt. The alternative hypothesis would be that there is a difference at three months between the two approaches, with the magnitude (including direction) of the treatment difference determined by analyses described below.

The secondary efficacy hypotheses of the trial are analogous to the primary hypothesis above, but evaluated for each of the three secondary efficacy outcomes.

9.2 SAMPLE SIZE DETERMINATION

The target sample size for the PENS trial was determined based on available preliminary data for the primary efficacy outcome of change in gait velocity. An NPH database from three centers that will participate in the trial (n=97) showed mean gait velocity improvement of 0.25 ± 0.29 m/s post-shunting among iNPH patients with baseline velocities <1 m/s. The AHCRN Registry (n=50) found similar mean post-shunting improvement of 0.32 ± 0.26 m/s. Our network's pilot randomized trial found a strong trend for active shunting benefit on 3-month gait velocity (active arm change: 0.28 ± 0.28, placebo arm:

0.06 ± 0.15, improvement vs. placebo of 0.21 m/sec, 95% CI=[-0.03,0.45]) Conservatively assuming a standard deviation of 0.29 m/s for 3-month change in gait velocity and estimating power based on a two-sided t-test with Type I error of 0.05, 46 evaluable participants in each arm yield 90% power to detect a significant treatment effect, if the true between-arm difference in change velocities is at least 0.2 m/s. We propose recruitment of 100 subjects to maintain power assuming conservative interim efficacy monitoring, as well as in case of slight loss to follow-up at 3 months or if variability in velocity change scores is larger than expected.

9.3 POPULATIONS FOR ANALYSES

All analyses will be undertaken by the intention-to-treat (ITT) principle, wherein all participants randomly assigned to a treatment arm will be counted in that arm regardless of adherence to protocol or possible crossover to the other treatment arm except for adverse events, which will use the as-treated principle (compare the participants based on the treatment regimen that they initially received).

Adherence to the assigned treatment is expected to be high, in the range of 85-90%, based on experience in previous interventional studies. Patients dropping out of the trial (including any who die during follow-up) will be included in safety and efficacy analyses to the extent that is possible and appropriate. Handling of such patients will be prespecified in the Statistical Analysis Plan (SAP) for this trial.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Continuous data, including values at each evaluation timepoint and relevant change scores, will be examined for marked departures from normality. In the absence of such departures, data will be summarized as means and standard deviations. Based on data from the PENS pilot study, it is expected that the prespecified primary and secondary efficacy outcomes will have distributions sufficiently close to normality to facilitate analysis of significance, and treatment effect estimation, using parametric approaches. For any outcomes with strong departures from normality, data will be reported using median and interquartile range, and the approach to evaluating treatment effect will rely on nonparametric approaches (e.g. use of van Elteren's test for age-stratified rank-based comparison of change scores). Detailed approaches to such analyses will be prespecified in the Statistical Analysis plan for the trial.

As is discussed for specific analyses below, all significance testing will be done using two-sided tests, with Type I error of 0.05 for the primary analysis of efficacy, and total Type I error limited to 0.05 for the three secondary efficacy analyses considered together. Covariates to be adjusted for in the formal efficacy analyses are prespecified below.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy outcome (difference between treatment arms in change in gait velocity between baseline and three-month evaluations) will be evaluated using an analysis of covariance (ANCOVA) model with 3-month velocity as the outcome, adjusting for baseline gait velocity along with assigned treatment arm and age stratum. A two-sided test with alpha level of 0.05 will evaluate the null hypothesis that change in gait velocity is not different between the assigned treatment arms; corresponding 95% confidence limits for treatment effect from this model will also be reported.

The primary efficacy analysis, per the intention-to-treat principle, will use assigned treatment arm. (Strictly speaking, the analyses may be viewed as modified intention to treat, in that any patients who are randomized but do not undergo shunt surgery will be excluded from all efficacy analyses). If any patients have unscheduled shunt setting changes before the 3-month evaluation, a corresponding per-protocol analysis will evaluate treatment effect on the subset of patients maintaining the initially assigned setting until the 3-month visit, but this analysis will be viewed and reported as supportive only. In the unexpected event that a patient is randomized within the incorrect age stratum, the correct age stratum will be used in the primary analysis of treatment effect in all analyses.

Based on gait velocity data in previous studies, we expect the primary efficacy outcome to have a sufficiently stable distribution that the parametric analysis will be appropriate for treatment effect estimation. As data is expected to be nearly complete for the 3-month timepoint, the primary analyses will be reported using patients with available data. Robustness assessments will be carried out using imputed data on any participants with missing 3-month data; specific approaches to imputation will be detailed in the Statistical Analysis Plan for this trial.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary efficacy analyses will assess treatment effect for three-month changes in the three prespecified formal efficacy outcomes: total Tinetti score, MoCA total score, and OAB-q score. Significance analysis for these outcomes will not be dependent on significance of the primary efficacy outcome of gait velocity. Two-sided tests will incorporate a Bonferroni-Holm stepdown procedure[41] to limit overall Type I error to 0.05 for these three comparisons. In this approach, the probability values for the three comparisons are ranked. If (and only if) the smallest p-value is below 0.05/3=0.0167, significance is declared for this outcome, and the next smallest p-value is evaluated. If (and only if) this next smallest p-value is below 0.05/2=0.025, the treatment comparison for the corresponding outcome is also declared significant, and in this case the third, least significant p-value is compared to the 0.05 level for a determination of significance for the corresponding outcome.

The analysis strategy for these three outcomes will be the same as for the primary efficacy outcome above, except that for the MoCA score analyses, age will be included as a continuous covariate, and years of education will be added as a second continuous covariate. The intention to treat principle will again be adhered to in the reporting of these efficacy analyses.

9.4.4 SAFETY ANALYSES

All AEs beginning after randomization through 30 days after initial shunting and after later shunt adjustments will be collected, as well as all serious and all neurological AEs reported at any time during the trial. All reported adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of incidence rates (frequencies and percentages), intensity, and relationship to study participation of reported AEs, will be presented overall for all randomized patients who were shunted as well as by treatment received (in most cases, initial shunt setting). Overall and arm-specific adverse event rates by MedDRA System Organ Class and Preferred Term will also be reported. Surgical events will also be presented separately. Presentations of event rates will use appropriate comparison approaches for “small sample” binary outcomes including exact confidence intervals and mid-p-values. Serious adverse events (SAEs) will be reported separately in a similar fashion to the more general AE reports. In addition, narratives will be available for each event.

In addition to adverse events, complications of shunting will also be presented, overall and by treatment received, with analyses/comparisons done in the same fashion as AEs. Occurrence of falls during follow-

up, will also be reported as a safety outcome and analyzed in a time-based fashion, with rates, confidence intervals, and between-arm comparisons carried out using Poisson-type models; technical details of these analyses will be prespecified in a Statistical Analysis Plan.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be summarized by treatment groups and overall, using appropriate statistics such as percentages for categorical factors and means/medians for continuous factors. Barring the highly unexpected setting of corrupted randomization, probability values will not be calculated for differences between treatment groups, as under proper randomization, distributions of all factors will be asymptotically equivalent between treatment groups.

9.4.6 PLANNED INTERIM ANALYSES

The study will have a DSMB appointed by NIH. The DSMB will have a charter, will review and approve the protocol prior to implementation, and will review interim analyses as applicable. The purpose of the DSMB is to advise NIH and the Principal Investigators regarding the continuing safety of study participants and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study participants, adherence to the study protocol, assessments of data quality, performance of individual clinical center and review of serious adverse events and other safety issues.

The DCC for this trial will generate all analyses, and send analysis reports to the DSMB no more than two weeks prior to the scheduled data of a meeting. Results comparing outcomes by treatment arms will be initially be presented to the DSMB with treatment arm identity blinded. The DSMB will have the option to unblind to treatment arm identities at any time.

Based on the modest sample size and multi-year enrollment period, the DSMB will perform interim trial safety reviews at 6-month intervals. There will also be two formal efficacy monitoring looks, after approximately one-third and again after approximately two-thirds of the target population of 100 participants have been enrolled and have three-month efficacy data available. As early stopping for efficacy should be based on very strong evidence, these looks will incorporate prespecified conservative O'Brien-Fleming-type efficacy boundaries, implemented using the approach of Lan and DeMets to allow for flexibility in the actual number of outcomes available for review at each meeting. This conservative monitoring strategy will preserve Type I error at 5%, while having nearly-negligible effect on study sample size requirements. Early stopping for futility will also be considered during these interim efficacy looks; this assessment will employ the conditional power approach, where the trial is terminated for futility if estimated conditional power to detect a significant effect calculated by appropriate criteria (e.g. assuming the true treatment effect is as initially estimated, assuming effect is at its current point estimate, and calculated using predictive power) is below a prespecified threshold of 20% under all realistic scenarios.

Results comparing outcomes by treatment arms will be initially be presented to the DSMB with treatment arm identity blinded. The DSMB will have the option to unblind to treatment arm identities at any time.

Table 1 below shows the probability of stopping for a finding of superiority by each of the three looks (two interim looks and the final look) under various assumed magnitudes of treatment effect for the primary efficacy outcome of change in gait velocity from baseline to three months, assuming a standard deviation of 0.29 for three-month change velocity in each arm and 100 evaluable patients.

Table 1: Probability of Stopping for Superiority according to Treatment Effect Magnitude

Assumed True Treatment Effect Magnitude	Probability of Stopping with Superiority Finding at First Look	Probability of Stopping with Superiority Finding by Second Look	Probability of Stopping with Superiority Finding by Third Look (Study Type I error or Power)
0.0 m/s (null hypothesis)	<0.1%	1.4%	5.0 %
1.0 m/s	<0.1%	14.8%	40.0%
1.5 m/s	2.4%	36.7%	72.7%
2.0 m/s (assumed alternative)	6.9%	64.2%	92.8%
2.1 m/s (observed effect magnitude in PENS pilot study)	8.4%	69.3%	94.9%
2.5 m/s	16.3%	85.7%	99.0%
3.0 m/s	31.4%	96.2%	99.9%

Futility stopping will also be recommended if the estimated conditional power of the study, if continued, is <20% under realistic scenarios given the observed data at the time of interim analysis. Under the study design assumptions of a treatment effect of 0.2 m/s and within-arm standard deviation of 0.29 m/s, at the first interim look conditional power will be <20% if the interim *Z*-statistic is < -1.73 (indicating a strong trend of a benefit in favor of the placebo arm). Under the null hypothesis of no treatment effect, with n=33 observations the probability of observing such a trend (and thus the estimated chance of stopping for futility) is 4.2%. At the second interim look with n=67, conditional power is <20% if the *Z*-statistic is < 0.46; if there is truly no effect of active shunting, this corresponds to an estimated chance of stopping for futility by the second look of 67.7%.

9.4.7 SUB-GROUP ANALYSES

Primary, secondary, and tertiary outcomes will be examined within the following subgroups to assess possible heterogeneity in treatment effect:

- Age (categorized as 60-69, 70-79, 80 or greater)
- Sex
- Race
- Ethnicity

More specifically, the outcomes will be re-analyzed using the same outcome-specific linear model applied to the overall trial population, with the addition of a main effect of the subgroup and an interaction between the subgroup and treatment arm. If the interaction p-value is significant at the 0.05 level, this indicates some level of evidence that the effect of arm differs by subgroup level when predicting the outcome.

Multiplicity will not be adjusted for in the presented subgroup analyses, and this will be clearly noted in any results published from this trial. The key motivation for eschewing formal multiplicity adjustment is that we do not *a priori* expect extremely strong modifications of treatment effect by any of the above factors (although we certainly cannot rule out that such interactions exist). The PENS trial has therefore been designed and "powered" to detect a treatment effect in the overall population, rather than allowing definitive specification of differential strategies for subgroups of enrolled patients. Any

significant subgroup effects will be strictly reported as exploratory for potential confirmation in future studies. Reports of any such effects will also note the number of subgroups being examined, and discuss the strength of evidence for such an effect using clinical criteria as well as within-trial assessment of the criteria developed in the Predictive Approaches to Treatment Effect (PATH) statement.[42]

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

It is expected that individual patient data will not be presented in key publications; this is due in part to the modestly large number of participants and the amount of data collected. Individual de-identified patient data will be made available to researches in Public Use datasets after trial completion.

9.4.9 EXPLORATORY ANALYSES.

The PENS trial will report a substantial number of exploratory/tertiary analyses, from information collected in the main trial as well as the substudies. Formal adjustment for multiplicity will not be performed for exploratory analyses in the PENS trial. Reporting of these outcomes will clearly designate that these outcomes are to be viewed as tertiary/exploratory, and when appropriate report the total number of such outcomes that were examined in the setting of a particular report.

Tertiary efficacy outcomes with relevant distributions sufficiently close to normality will have 3-month treatment effect analyzed using the same ANCOVA approach as described above for the primary and secondary efficacy outcomes. Age and education level will be included as continuous covariates in the ANCOVA model for neuropsychological outcomes. Analogous nonparametric approaches will be used for analysis when necessitated by outcome distributions.

A key facet of long-term analysis of the cohort, whose technical details will be specified in the Statistical Analysis plan, will be the most appropriate reporting of outcomes over time. Linear mixed models (again with age stratum and, when appropriate, education level as covariates) will be fit to estimate benefit of open shunting over time for the various efficacy outcomes among patients combined across treatment arms. In these models, the follow-up timepoints (3, 6, and 12 months) will be considered to be the time since the shunt was set to the "open" position for each patient. An interaction between assigned treatment arm and time will also be fit and quantified in these models to evaluate and quantify any effect of "delayed shunting." If there is a delay effect (e.g., the patients initially treated with an open shunt show significantly more 3-month improvement for an outcome than what is seen 3 months after those initially receiving a closed shunt have setting changed to open), the most appropriate presentation for that outcome will be by treatment received, with estimation of treatment effect at each follow-up timepoint. If, as initially expected for most outcomes, there is no evidence for a delay effect, all randomized patients will be combined for presentation and estimation of shunt benefit on the various outcomes considered.

Each substudy will have its own Statistical Analysis plan prespecifying details of analyses to be performed. The additional neuropsychological outcomes collected among the approximately 60-80 participants at centers participating in the **neuropsychological substudy** will be analyzed and reported in the same fashion as Core Battery outcomes. While treatment effect will be assessed using analysis of covariance controlling for age and education as continuous covariates, due to the small sample size and low power to detect an assigned treatment effect, presentation will focus on trends observed over time in the entire substudy. Relationships of outcomes to one another, and to the various outcomes observed among all trial participants, will be examined. A key exploratory analysis making use of these relationships will generate principal components (among substudy participants, using Core Battery as well as substudy outcomes) to create a set of cognitive composites. The subset of composites associated

with eigenvalues > 1 will be compared between treatment arms, and assessed over time using the linear modeling approaches as for efficacy outcomes in the overall trial.

For the **CSF biomarker study**, we expect to screen around 300 subjects across all sites of whom 100 will be selected for PENS. We will use baseline CSF biomarker levels from all 300 samples, alone and combined with patient baseline status/comorbidities, to distinguish randomized ("suspected true iNPH") patients from the 200 phenotypically similar non-responders. Biomarker levels will be reported and compared between the two populations using appropriate criteria including rank-based tests for biomarkers with highly skewed distributions. We note that this component of the PENS trial is viewed as hypothesis-generating, and thus formal adjustment for multiplicity in these univariable comparisons will not be performed.

As these biomarkers are typically used diagnostically using cutpoints and biomarker ratios, and between-marker interrelationships between markers are likely, Classification and Regression Trees (CART) will be used as a primary analytic approach for this modeling, although logistic regression will be implemented as well. Key candidate CSF biomarkers in these models will include the neurogenerative markers abeta40, abeta42, total tau, ptau181, ratio of abeta42/abeta40 and abeta42/ptau181, and NFL . Random forests and other machine learning approaches will also be implemented to gain further insight regarding relative importance of various markers in segregating iNPH from other conditions.

Among the randomized population, similar modeling approaches will be used to assess relationships of CSF biomarkers with 3-month and longer-term outcomes post shunting. Magnitude of relationships (e.g., with change in gait velocity and MOCA) will be quantified using correlations and other appropriate measures.

For the **Imaging Study**, MRI assessments of cerebral ventricular and brain volumetrics, brain morphology, CSF flow, white matter connectivity, and resting-state functional network alteration will be used in similar fashion as potential predictors of favorable outcome post-shunting. Similar approaches will be used to assess biomarker predictors of 3-month and longer-term improvement in gait and other outcomes after shunting. We note that past studies have found that "black box" machine learning approaches such as random forests have markedly superior diagnostic performance, albeit without the explicit identification of specific biomarker cutpoints and interactions that can be obtained from CART and regression models.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The pre-screening and main consent materials are submitted with this protocol.

10.1.1.2 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. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The Teach-Back Consenting method should be used to ensure to confirm potential participants fully understand the consent.

The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants 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.

Those members of the research team who consent patients have been trained in informed consent procedures, are familiar with the protocol, and are listed as a consenter on the delegation log. Patients are generally given a copy of the consent and encouraged to review it in private prior to the appointment to sign consent. Patients are given adequate time and privacy to consider the research study. Before the patient signs the consent, the consenter must be satisfied that the participant understands the information provided, has had an opportunity to discuss the information and ask questions, and is aware that he/she may withdraw from the study at any time. Non-English-speaking participants will be consented according to Office of Human Research Protection (OHRP) and JHM IRB policies.

In the event teleconsent is utilized, participants will be provided with a copy of the Informed Consent prior to the teleconsent meeting either via email, fax, mail or previously provided during an in person visit. In events where a Physician/Mid-level provider consent signature is not required, the consent designee may proceed with teleconsent without an expectation for a follow-up in person consenting process.

Participants will be given adequate time to consider the research study and ask questions prior to signing the consent form. The consent designee must verify the participant physically signed the consent document either by viewing via video conference, obtaining a photo of the signed consent document, or obtaining verbal confirmation from the participant that he/she signed the consent form or agreed to participate electronically. The participant sign and date/time the informed consent document. The document is then mailed, emailed or faxed to the consent designee. The participant will be asked to return the original signed document on their first in person visit. If the Informed Consent form is mailed to the consent designee by the participant the IRB-approved consent designee will sign the copy, which they possess after the participant has acknowledged signature on their copy. Once the original is received by the consent designee the copies will be attached to make a single document. In all other

instances, once received, the IRB-approved consent designee signs, dates/times the informed consent document.

At the time of the first clinical encounter post teleconsent, where physician/mid-level provider consent is required, the physician/mid-level provider will review any additional study participant questions and discuss the risks, benefits and alternatives of the study in full detail, completing the physician/mid-level component of the consent process. If physician/Mid-level provider consent occurs remotely in a separate encounter from the main consent process, the previously stated process must be followed for the entire consent conversation. The Documentation of Physician Consent Form is then signed, dated/timed and all components of the consent are combined to one document. After the Informed Consent process is completed, the IRB approved study team member files the consent document in the Electronic Medical Record (EMR) system, including a note confirming the consent process. The entire consent document is also then filed in the research record.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to site investigators. If the study is prematurely terminated or suspended, the site Principal Investigator will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and/or IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. 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 the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies 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 participants in this study. The clinical study site will permit access to such records.

The study participant'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 the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Utah Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Utah DCC

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality (CoC) will be issued by the National Institutes of Health (NIH). 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 participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

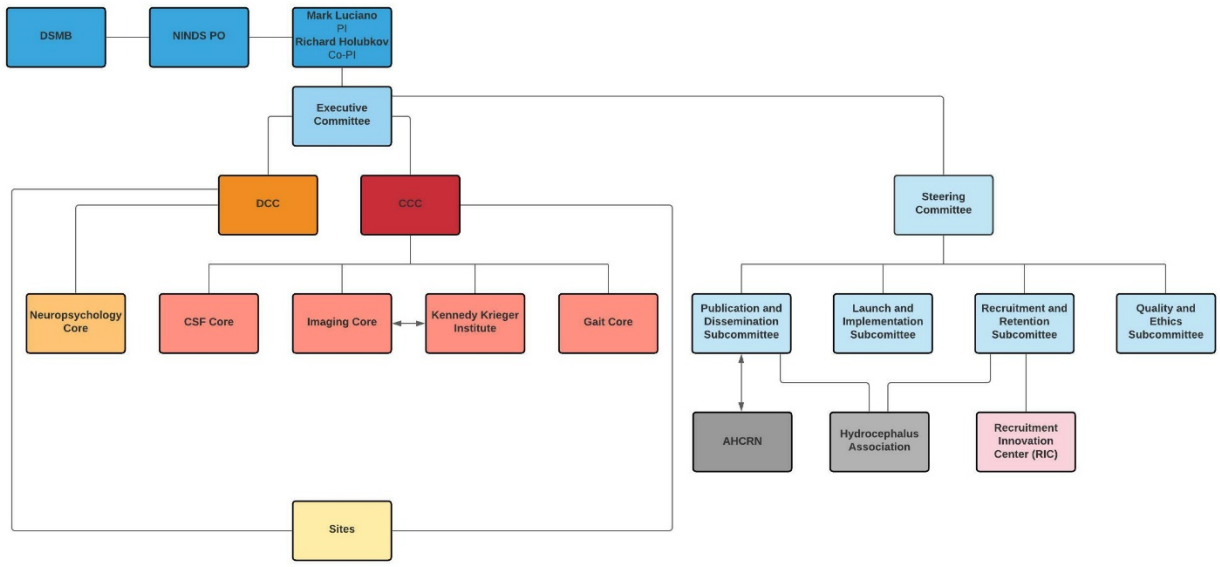
Language is included in the consent form to allow for future studies of patient data and biospecimens. Data will be kept in the DCC or JHU and CSF will be maintained in the JHU CSF Core Lab for future studies.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Mark Luciano, MD, PhD, FACS	*Ahmed Toma*
Johns Hopkins University	*National Hospital for Neurology and Neurosurgery (NHNN), Queen Square, UCLH NHS Foundation Trust*
600 N. Wolfe St, Phipps 126 Baltimore, MD 21287	*Queen Square, London WC1N 3BG, United Kingdom*
(410) 955-2259	*020 3448 3176*
markluciano@jhu.edu	*ahmedtoma@nhs.net*

Organizational Chart

The structure of leadership committees is represented in the organizational chart below.



Clinical Coordinating Center (CCC)

Johns Hopkins BIOS (Brain Injury OutcomeS), Department of Neurology, will serve as the Coordinating Center for this study and have IRB approval for their role of Clinical Coordinating. They will facilitate the single IRB review of the PENS protocol, and be responsible for project/site management, training, quality assurance, and regulatory compliance activities.

Data Coordinating Center (DCC)

The DCC is located in Salt Lake City, Utah, and is based at the University of Utah School of Medicine. The DCC personnel include data analysts, programmers, biostatisticians, project managers and other staff that assist in the overall planning, design, and implementation of the study projects. Services provided include data management, data storage, quality assurance, and monitoring.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including neurosurgeons, neurologists, gait experts, movement disorder specialists, ethicists, trialists, and operation specialists. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to The National Institute of Neurological Disorders and Stroke (NINDS).

10.1.7 CLINICAL MONITORING

The investigators recognize the importance of ensuring data of excellent quality. Study clinical monitoring is critical to this process. Clinical monitoring has been a very effective tool for maintaining data quality in previous Adult Hydrocephalus Clinical Research Network studies, and this process will be utilized to ensure excellent quality data in this study. The DCC utilizes risk-based methodology to identify

and correct problems that may arise at sites. The risk-based approach to monitoring focuses on oversight activities and preventing or mitigating key risks to data quality, as well as to processes critical to human subject protection and integrity of the trial or study.

Site monitoring visits, when necessary, will be performed by a trained site monitor during the study period to ensure regulatory compliance, participant safety, and to monitor the quality of data collected. Source documents, regulatory documents and data collection forms may be reviewed. Interim visits will take place depending on grant budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. The site initiation may take place in person or remotely as group training made up of site investigators and research coordinators.

Study monitors must be provided with appropriate access to study materials and the medical records for study subjects. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the study monitor's review of data in the electronic medical record.

Remote monitoring is essential for this study. Remote monitoring involves detailed review of the data entered by the site and consultations with the site investigator and/or research coordinator to review safety and data quality. This may require uploading de-identified copies of specific parts of the medical record, regulatory documentation, or other source documents. Those materials will be compared against the data recorded in the electronic data capture system. This helps assure protocol compliance and accurate data collection. More remote monitoring activities may be conducted early in the trial to assure protocol compliance and identify any training issues that may exist. Documentation will be retained in accordance with Federal requirements. Safety of participants will be monitored and ensured in accordance with the DSMB plan.

A supplemental study-specific, risk-based monitoring plan, separate from the protocol will be completed which outlines specific criteria for monitoring. This plan may include the number of planned site visits, criteria for focused visits, additional visits or remote monitoring, a plan for chart review and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g., sample of all subjects within a site; key data or all data), the schedule of visits, how they are reported and a time frame to resolve any issues found.

10.1.8 QUALITY ASSURANCE (QA) AND QUALITY CONTROL (QC)

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

The investigators recognize the importance of ensuring data of excellent quality. Site monitoring is critical to this process. Site monitoring has been a very effective tool for maintaining data quality in previous studies, and we will utilize this process to ensure excellent quality data in the proposed study. Out\r site monitoring plan is designed to identify problems with sites and methods for handling problems that arise. Site monitors must be provided will full access to study materials and the medical records for study participants. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the site monitor's review of data in the electronic medical record.

A supplemental study-specific monitoring plan, separate from the protocol will be completed which outlines specific criteria for monitoring. This plan will include the number of planned remote monitoring visits, criteria for focused visits, or additional visits, a plan for chart review and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g. sample of all study participants within a site; key data or all data), the schedule of visits, how they are reported and a time frame to resolve any issues found. Remote site monitoring schedules will be determined by the CCC or DCC in coordination with the study principal investigator.

A screening log will list all identified patients who met the clinical criteria for the study and were referred for further evaluation whether eligible or not eligible. This screening log, together with the randomization log and the utilization of ICD10 and CPT codes, will allow assessment of numbers of eligible patients, percentage of eligible patients who are approached for consent, and the proportions of eligible/consented participants who are successfully randomized. These results will be regularly reviewed by the DCC or CCC and by the DSMB during scheduled meetings (as described below).

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Study data may be recorded on paper forms or directly entered into the electronic data capture (EDC) system. Paper forms will be retained at the clinical center and data will be entered by clinical site staff into the EDC system provided by the DCC at the University of Utah School of Medicine. Paper forms should also be scanned into the patient's electronic medical record. The investigator at each participating site is responsible for all aspects of study implementation, including participants follow-up, collection of accurate study data, and correct entry of the data into the data collection system. These tasks may be specifically delegated to other individuals at the site, but the site investigator is responsible to supervise all aspects of the study, and is responsible to assure that all staff involved in this study are adequately trained to perform the delegated tasks.

After subject enrollment and follow up have been completed, the DCC will prepare a final study database for analysis. A releasable database will be produced and completely de-identified in accordance with the definitions provided in the Health insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be recoded in a manner that will make it impossible to deduce or impute the specific identity of any participant. The database will not contain any institutional identifiers.

The DCC will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. In accordance with policies determined by the investigators and funding sponsors, the releasable database will be provided to users in electronic form.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 5 years from the date of publication per the Johns Hopkins Medicine IRB. 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.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to NINDS Program Official, Data Coordinating Center, Clinical Coordinating Center, and Office of the Study Chair. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a

way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NINDS has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

For this trial, a single IRB model will be adopted. Johns Hopkins IRB will serve as the central IRB (CIRB) for the national participating sites. In addition to the CIRB approval, each clinical center must inform their local IRB to fulfill any additional local regulatory requirements. International sites, however, must obtain approval from their respective IRB/REB prior to participating in the study. The designated regulatory staff at Johns Hopkins will track IRB/REB approval status at the international participating centers and will not permit participant enrollment without documentation of initial IRB/REB approval and maintenance of that approval throughout subsequent years of the project.

10.3 ABBREVIATIONS

ABD	Abdominal
AD	Alzheimer's Disease
ADL	Lawton Activities of Daily Living
AE	Adverse Event
AHCRN	Adult Hydrocephalus Clinical Research Network
ANCOVA	Analysis of Covariance
ASL	Arterial Spin Labeling
BDI-II	Beck Depression Inventory, 2nd Edition
CART	Classification and Regression Trees
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CI	Confidence Interval
CIRB	Central IRB
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COWAT	Controlled Oral Word Association Test
CPT	Current Procedural Terminology
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DCC	Data Coordinating Center
DCCS	Dimensional Change Card Sort Task
DESH	Disproportionate Enlarged Subarachnoid Space Hydrocephalus
DSMB	Data Safety Monitoring Board
DTI	Diffusion Tensor Imaging
EDC	Electronic Data Capture
ELD	Extended Lumbar Drainage
EMR	Electronic Medical Record
EQ-5D-5L	EuroQol 5 Dimension, 5 Level survey
EQ-VAS	EuroQol Vertical Visual Analog Scale
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional Magnetic Resonance Imaging
FrSBe	Frontal Systems Behavior Scale
GCP	Good Clinical Practice
Gd	Gadolinium

GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HA	Headache
HIPAA	Health Insurance Portability and Accountability Act
HR-QOL	Health-Related Quality of Life
HVLT-R	Hopkins Verbal Learning Test - Revised
IADL	Independence in Activities of Daily Living
ICH	International Conference on Harmonisation
iNPH	Idiopathic Normal Pressure Hydrocephalus
IRB	Institutional Review Board
ITT	Intention-To-Treat
JHM	Johns Hopkins Medicine
JHU	Johns Hopkins University
JLO	Judgement of Line Orientation
LP	Lumbar Puncture
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	The Montreal Cognitive Assessment
MOO	Manual of Operations
MOP	Manual of Procedures
MR(I)	Magnetic Resonance (Imaging)
mRS	Modified Rankin Scale
NCT	National Clinical Trial
NFL	Neurofilament Light
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NPH	Normal Pressure Hydrocephalus
NSD	Nephrogenic Fibrosing Dermopathy
NSF	Nephrogenic Systemic Fibrosis
OAB-q	Overactive Bladder questionnaire
OARS	Older Americans Resources and Services
OHRP	Office for Human Research Protections
OP	Operation
PATH	Predictive Approaches to Treatment Effect
PENS	Placebo-Controlled Efficacy in iNPH Shunting Trial
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
REB	Research Ethics Board

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDMT	Symbol Digit Modalities Test
SF	Short Form
SNP	Single Nucleotide Polymorphisms
SOA	Schedule of Activities
SOC	Standard of Care
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
VASO	Vascular-Space-Occupancy
VEGF	Vascular Endothelial Growth Factor
WAIS-III	Wechsler Adult Intelligence Scale – 3rd edition
WRAT-5	Wide Range Achievement Test – 5th edition

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.00	31Oct2021	N/A	Original IRB Submission
2.20	31Jan2022	DSMB approved protocol	Follow all patients for 12 months of active shunting, incorporate DSMB recommendations

11 REFERENCES

1. Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G, Gloss D. Practice guideline: Idiopathic normal pressure hydrocephalus: Response to shunting and predictors of response: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. Dec 8 2015;85(23):2063-71. doi:10.1212/wnl.0000000000002193

2. Williams MA, Sharkey P, van Doren D, Thomas G, Rigamonti D. Influence of shunt surgery on healthcare expenditures of elderly fee-for-service Medicare beneficiaries with hydrocephalus. *J Neurosurg*. Jul 2007;107(1):21-8. doi:10.3171/jns-07/07/0021

3. Klinge P, Hellstrom P, Tans J, Wikkelso C, European i NPHMSG. One-year outcome in the European multicentre study on iNPH. *Acta Neurol Scand*. Sep 2012;126(3):145-53. doi:10.1111/j.1600-0404.2012.01676.x

4. Kazui H, Miyajima M, Mori E, Ishikawa M. Lumboperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (SINPHONI-2): an open-label randomised trial. *Lancet Neurol*. Jun 2015;14(6):585-94. doi:10.1016/s1474-4422(15)00046-0

5. Boon AJ, Tans JT, Delwel EJ, et al. Dutch Normal-Pressure Hydrocephalus Study: randomized comparison of low- and medium-pressure shunts. *J Neurosurg*. Mar 1998;88(3):490-5. doi:10.3171/jns.1998.88.3.0490

6. Andren K, Wikkelso C, Tisell M, Hellstrom P. Natural course of idiopathic normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry*. Jul 2014;85(7):806-10. doi:10.1136/jnnp-2013-306117

7. Mori E, Ishikawa M, Hashimoto M, grp S. Study of idiopathic normal pressure hydrocephalus on neurological improvement (SINPHONI). *Journal of the Neurological Sciences*. Nov 15 2005;238(Supplement 1):S295-S295. NOT IN FILE.

8. Boon AJ, Tans JT, Delwel EJ, et al. Dutch normal pressure hydrocephalus study: baseline characteristics with emphasis on clinical findings. *Eur J Neurol*. Jan 1997;4(1):39-47. doi:10.1111/j.1468-1331.1997.tb00297.x

9. Eklund A, Koskinen LO, Williams MA, Luciano MG, Dombrowski SM, Malm J. Hydrodynamics of the Certas™ programmable valve for the treatment of hydrocephalus. *Fluids Barriers CNS*. Jun 29 2012;9(1):12. doi:10.1186/2045-8118-9-12

10. Tarnaris A, Toma AK, Pullen E, et al. Cognitive, biochemical, and imaging profile of patients suffering from idiopathic normal pressure hydrocephalus. *Alzheimers Dement*. Sep 2011;7(5):501-8. doi:10.1016/j.jalz.2011.01.003

11. Duinkerke A, Williams MA, Rigamonti D, Hillis AE. Cognitive recovery in idiopathic normal pressure hydrocephalus after shunt. *Cogn Behav Neurol*. Sep 2004;17(3):179-84. doi:10.1097/01.wnn.0000124916.16017.6a

12. Hellström P, Edsbagge M, Blomsterwall E, et al. Neuropsychological Effects of Shunt Treatment in Idiopathic Normal Pressure Hydrocephalus. *Neurosurgery*. September 2008;63(3):527-536. doi:*https://doi.org/10.1227/01.NEU.0000325258.16934.BB*

13. Thomsen AM, Børgesen SE, Bruhn P, Gjerris F. Prognosis of dementia in normal-pressure hydrocephalus after a shunt operation. *Ann Neurol*. Sep 1986;20(3):304-10. doi:10.1002/ana.410200306

14. Gustafson L, Hagberg B. Recovery in hydrocephalic dementia after shunt operation. *J Neurol Neurosurg Psychiatry*. Oct 1978;41(10):940-7. doi:10.1136/jnnp.41.10.940

15. Graff-Radford NR, Godersky JC. Normal-pressure hydrocephalus. Onset of gait abnormality before dementia predicts good surgical outcome. *Arch Neurol*. Sep 1986;43(9):940-2. doi:10.1001/archneur.1986.00520090068020

16. Marmarou A, Bergsneider M, Relkin N, Klinge P, Black PM. Development of guidelines for idiopathic normal-pressure hydrocephalus: introduction. *Neurosurgery*. Sep 2005;57(3 Suppl):S1-3; discussion ii-v. doi:10.1227/01.neu.0000168188.25559.0e

17. Israelsson H, Birgander R, Ambarki K, Eklund A, Malm J. Ventriculomegaly and balance disturbances in patients with TIA. *Acta Neurol Scand*. Mar 2012;125(3):163-70. doi:10.1111/j.1600-0404.2011.01520.x

18. Jaraj D, Rabiei K, Marlow T, Jensen C, Skoog I, Wikkelsø C. Prevalence of idiopathic normal-pressure hydrocephalus. *Neurology*. Apr 22 2014;82(16):1449-54. doi:10.1212/wnl.0000000000000342

19. Group IGS. INPH Guidelines Study Group. *Neurosurgery*. September 2005 2005;57(3):S2vi.

20. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. Apr 2005;53(4):695-9. doi:10.1111/j.1532-5415.2005.53221.x

21. Smith A. *Symbol digit modalities test*. Los Angeles: Western Psychological Services; 1973.

22. Weintraub S, Dikmen SS, Heaton RK, et al. Cognition assessment using the NIH Toolbox. *Neurology*. Mar 12 2013;80(11 Suppl 3):S54-64. doi:10.1212/WNL.0b013e3182872ded

23. Zelazo PD, Anderson JE, Richler J, et al. NIH Toolbox Cognition Battery (CB): Validation of Executive Function Measures in Adults. *Journal of the International Neuropsychological Society*. 2014;20(6):620-629. doi:DOI: 10.1017/S1355617714000472

24. Zelazo PD. The Dimensional Change Card Sort (DCCS): a method of assessing executive function in children. *Nat Protoc*. 2006;1(1):297-301. doi:10.1038/nprot.2006.46

25. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory (BDI-II)*. vol 10. Pearson; 1996.

26. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. STUDIES OF ILLNESS IN THE AGED. THE INDEX OF ADL: A STANDARDIZED MEASURE OF BIOLOGICAL AND PSYCHOSOCIAL FUNCTION. *Jama*. Sep 21 1963;185:914-9. doi:10.1001/jama.1963.03060120024016

27. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. Autumn 1969;9(3):179-86.

28. Schretlen DJ, Testa SM, Pearlson GD. *Calibrated Neuropsychological Normative System professional manual*. Psychological Assessment Resources; 2010.

29. Wilkinson GS, J. RG. Wide Range Achievement Test, Fifth Edition (WRAT5). Bloomington, MN: Pearson; 2017.

30. Kaplan E, Goodglass H, Weintraub S. The Boston Naming Test. Philadelphia: Lea & Febiger.; 1983.

31. Rosen WG. Verbal fluency in aging and dementia. . *Journal of clinical and experimental neuropsychology*. 1980;2(2):135-146.

32. Spreen O, Benton AL. Neurosensory Center Comprehensive Examination for Aphasia (NCCEA): Manual of instructions. Victoria, BC: University of Victoria; 1969.

33. Wechsler D. Wechsler Adult Intelligence Scale-III. 3 ed. San Antonio, TX: T he Psychological Corporation; 1997.

34. Ruff RM, Allen CC. Ruff 2 and 7 Selective Attention Test professional manual. Odessa, FL: Psychological Assessment Resources, Inc; 1996.

35. Golden CJ. Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Wood Dale, Illinois: Stoelting Company; 1978.

36. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. *The Clinical Neuropsychologist*. 1998;12(1):43-55. doi:10.1076/clin.12.1.43.1726

37. Reitan RM, & Wolfson, D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Interpretattion. . Tucson, AZ: Neuropsychology Press. ; 1985.

38. Stout J, Ready R, Grace J, Malloy P, Paulsen J. Factor Analysis of the Frontal Systems Behavior Scale (FrSBe). *Assessment*. 2003;10:79-85. doi:10.1177/1073191113492845

39. Cummings J, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44:2308-2314.

40. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. Mar 1996;34(3):220-33. doi:10.1097/00005650-199603000-00003

41. Holm J. A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*. 1979;6(2):65-70.

42. Kent DM, Paulus JK, van Klaveren D, et al. The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement. *Ann Intern Med*. Jan 7 2020;172(1):35-45. doi:10.7326/m18-3667