Posterior Fossa Decompression with or without Duraplasty for Chiari type I Malformation with Syringomyelia

STATISTICAL ANALYSIS PLAN

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Study Title
Posterior Fossa Decompression with or without Duraplasty for Chiari type I Malformation with Syringomyelia: A prospective, cluster randomization trial of 148 subjects recruited from 36 centers

of the Park-Reeves Syringomyelia Research Consortium as well as an additional 7 research centers.

1. STUDY OBJECTIVES

1.1 Primary Objective

Specific Aim 1: Determine if PFD is associated with fewer surgical complications and less harm to patients than PFDD.
Hypothesis: PFD will be associated with fewer surgical complications and less potential harm to patients than PFDD.
Anticipated Outcome: Cerebrospinal fluid (CSF)-related complications ≤6 months (e.g. CSF leak, pseudomeningocele, aseptic meningitis, infection, hydrocephalus), and the requirement for additional surgery for wound revision or CSF diversion will be lower after PFD compared with PFDD.
Corresponding Variable Names for 'Complications':

- **CSF leak:** Form 16634 (10), ChiariPOCSFLeak
- **Pseudomeningocele:** Form 16402 (4), ChiariPOPseudomen
- **Aseptic meningitis:** Form 16420 (5), ChiariPOchemicalMeningitis
- **True meningitis:** Form 16416 (5), ChiariPOTrueMeningitis
- **Infection:** Form 16416 (5), ChiariPOWRInfection
- **Hydrocephalus:** Form 16427 (6), Hydrocephalus
- **Cervical Instability:** Form 16431 (6), CervicalInstability

Corresponding Variable Names for 'Additional Surgery for Wound Revision or CSF Diversion'

- **Required External drainage of CSF:** Form 16404 (4), ChiariPOExtDrainageCSF
- **Simple Over-Sewing of Wound for CSF Leak:** Form 16413 (5), SimpleOSWoundCSF
- **Surgical revision of wound in operating room:** Form 16414 (5), ChiariPOSurgRevision
- **Chemical Meningitis:** Form 16420 (5), ChiariPOchemicalMeningitis
- **CSF Leak:** Form 16415 (5), ChiariPOWRCSFLeak
- **Infection:** Form 16416 (5), ChiariPOWRInfection
- **Pseudomeningocele:** Form 16419 (5), ChiariPOWRPseudomen

Outcome –Count, Number of patients with a complication
Timeframe - ≤ 6 months

Time Period	Complication
Intra-Op	
	Vascular Injury
	Hemorrhage Requiring Evacuation
	Neurological Injury
	Death
	Other Complications
< 6 Months	
	Pseudomeningocele
	CSF Leak
	External Drainage Required
	Simple Over-Sewing of Wound for CSF Leak
	Surgical Revision of Wound in OR
	Chemical Meningitis
	True Meningitis
	Hydrocephalus
	Cervical Instability
	Other Complications, Procedure Specific
	Other Complications, Not Procedure Specific
> 6 Months	
	Cervical Instability
	Infection
	Hydrocephalus
	Other Complications, Procedure Specific

1.2 Secondary Objectives

Specific Aim 2: Determine if PFD provides non-inferior clinical improvement and syrinx regression compared to PFDD.
Hypothesis: Clinical improvement and syrinx regression provided by PFD will be non-inferior compared to those provided by PFDD.
Anticipated Outcome: Clinical symptoms, neurological function, and syrinx regression ≤12 months will be non-inferior following PFD when compared with PFDD.

- Rates of revision decompression surgery (PFD or PFDD) and progression of spinal deformity ≤12 months after PFD also will be non-inferior to PFDD. Please note that the time window is ≤12 months. When there are multiple visits within this window, the visit with the closest to 12 months after surgery will be used.
- For this aim, clinical symptoms and syrinx regression ≤12 months will be used as the primary outcome variable. Results based on the rates of revision decompression surgery and progression of spinal deformity will be exploratory.

Corresponding Variable Names for 'Clinical Improvement'

- Outcome – Scores, Limonadi/Binary -> compare for symptoms and neurological deficits

- Timeframe – compare preoperative to:
- <= 6 weeks
- 3-6 months
- 12 (+/- 2) months (primary)
- Binary Scoring is primary
- Limonadi Scoring specifics:
- Each subject was given a score for each symptom at each visit, 2=resolved, 1=improved, 0=stable, -1 = worse.
- Symptom scores within a patient were then averaged across visits (per Limonadi paper) to get patient-level symptom-specific scores.
- These patient-level symptom-specific scores were then averaged to get a single overall score per patient.
- These single overall scores per patient were then averaged within site randomization to get group comparisons between sites randomized to PFD and sites randomized to PFDD.
- Binary Scoring specifics:
- Each subject was given a binary score for each symptom at each visit, 1=positive outcome, 0=negative outcome.
- Symptom scores within a patient were then averaged across visits (per Limonadi paper) to get patient-level symptom-specific scores.
- These patient-level symptom-specific scores were then averaged to get a single overall score per patient.
- These single overall scores per patient were then averaged within site randomization to get group comparisons between sites randomized to PFD and sites randomized to PFDD.

Symptoms	
	Double Vision
	Sensory Symptoms
	Weakness Symptoms
	Dysphagia
	Hoarseness
	Choking
	Sleep Apnea
	Shortness of Breath
	Neck Pain
	Back Pain
	Trunk Pain
	Upper Extremity Pain
	Lower Extremity Pain
	Tremors
	Gait Ataxia
	Incontinence
	Sexual Dysfunction
	Headaches
Neurological Deficits	
	Papilledema*
	Nystagmus
	Disconjugate Gaze
	Extraocular Palsies
	Facial Weakness
	Disturbance in Facial Sensation*
	Hearing Loss*
	Hoarseness*
	Tongue Deviation*
	Weak Shrug*
	Weak Neck Rotation*
	Strength Assessment
	Strength Status – Left Upper
	Strength Status – Right Upper
	Strength Status – Left Lower
	Strength Status – Right Lower
	Light Touch Assessment*
	Light Touch – Entire Body*
	Light Touch – Torso*
	Light Touch – Saddle*
	Light Touch Extremities Assessment*
	LT Extremities – Left Upper*
	LT Extremities – Right Upper*
	LT Extremities – Left Lower*
	LT Extremities – Right Lower*

	Pinprick/Temp Assessment*
	Deficit Pin/Temp – Left Upper*
	Deficit Pin/Temp – Right Upper*
	Deficit Pin/Temp – Left Lower*
	Deficit Pin/Temp – Right Lower*
	Joint Pos. Sense Assessment*
	Deficit Joint Pos. Sense – Left Upper Extremity*
	Deficit Joint Pos. Sense – Right Upper Extremity*
	Deficit Joint Pos. Sense – Left Lower Extremity*
	Deficit Joint Pos. Sense – Right Lower Extremity*
	Deep Tendon Reflexes*
	Ankle Clonus*
	Babinski Reflex*
	Hoffman's Reflex*
	Gait Instability
	Romberg Response*
	Dysmetria*

Corresponding Variable Names for 'Syrinx Regression'

- **Syringomelia Present** (yes/no): Follow-up Packet Section 25.0, Syringomelia
    - **Syrinx Maximum AP Diameter** (in mm): SyrinxMaxAPDiameter

Corresponding Variable Names for 'Progression of Spinal Deformity'

- Follow-Up Packet section 25.0 Follow-Up Radiographic Examinations, Scoliosis

Specific Aim 3: Determine if PFD is associated with superior QOL compared with PFDD.
Hypothesis: With fewer surgical complications, PFD will be associated with superior QOL compared with PFDD.
Anticipated Outcome: PFD will have superior QOL and will show improvements in overall QOL over time (≤12 months post-operatively) compared to PFDD. In particular, both physical metrics (evaluated by pain frequency, pain severity and non-pain symptoms) and psychosocial metrics will improve at a higher rate and in a shorter period of time after PFD compared to PFDD. QOL will be assessed at the same time points using the Chiari Health Index Pediatrics (CHIP), and the Health Utilities-3 (HUI-3). For this aim, CHIP QOL (≤12 months post-operatively) will be used as the primary outcome, and HUI-3 and the domain sub-scores presented below will be assessed as the secondary outcomes. Additional, sensitivity analyses will be performed for the CHIP QOL based on the last reported CHIP QOL scores including up to 24 months post-operatively.

Corresponding Metrics for QOL:
Assumptions on dates and times were based on the following:

- Assuming 1 Month = 30 days
- From protocol, we wish to report CHIP assessments are at baseline, within 6 weeks of surgery, within 3-6 months of surgery and within 12 +/- 2 months of surgery.
- CHIP QOL was calculated via the method described in: https://thejns.org/pediatrics/view/journals/j-neurosurg-pediatr/17/1/article-p76.xml
- Only patients with complete entries were considered in the report.
- Domain sub-scores (sums of indicators) for each of the following domains of CHIP:
    - Pain Frequency
    - Pain Severity
    - Non-Pain Symptoms
    - Psychosocial/Cognitive
- Overall QoL outcome (non-uniform weighted avg.) of the above 4 domains

2. STUDY DESIGN

This will be a cluster randomized control trial of 148 patients recruited from the 36 centers of the Park-Reeves Syringomyelia Research Consortium (PRSRC) as well as an additional 7 research centers. Randomization will occur at the center level with standardized surgical technique, and data will be recorded in the PRSRC prospective registry. In order to examine the main comparative effectiveness research (CER) question of surgical complications and potential harm to patients

(Aim 1), intra-operative complications and short (≤6 months) and long-term (6-12 months) postoperative complications will be recorded for both PFD and PFDD. For Aim 2, clinical symptoms, neurological function, and modified Chicago Chiari Outcome Scale (mCCOS) [22] scores will be measured pre-operatively and longitudinally at ≤6 weeks, 3-6 months, and 12±2 months after surgery. MRIs will be obtained (at a minimum) ≤ 6 months pre-operatively and 12±2 months post-operatively to compare the effect of surgery on syrinx size and spinal deformity. In order to test Aim 3 hypothesis, QOL will be assessed at the same time points using the Chiari Health Index Pediatrics (CHIP), and the Health Utilities-3 (HUI-3), holistically evaluating patients across psychosocial and physical dimensions.

3. SELECTION AND ENROLLMENT OF PARTICIPANTS.

3.1 Inclusion Criteria

1) Age ≤21 years old
2) Chiari malformation type I with ≥5 mm tonsillar ectopia
3) Syrinx diameter (recorded as the greatest antero-posterior or transverse diameter) 3-9 mm
4) MRI of the brain and cervical and thoracic spine are required prior to surgery and available to be shared with the DCC

3.2 Exclusion Criteria

1) Syrinx <3 mm and/or ≥10 mm
2) Neuro-imaging demonstrating basilar invagination (position of the superior tip of dens ≥5 mm above Chamberlain's line)
3) Neuro-imaging demonstrating clival canal angle <120°
4) Prior PFD, PFDD, or other surgery at the craniovertebral junction
5) CM+SM secondary to other pathology (e.g. a tumor)
6) Unable to share pre-decompression MRI of the brain and cervical and thoracic spine
7) Patients who do not wish to participate.

4.6 Randomization and Treatment Allocation

A cluster randomized controlled trial (C-RCT) will be conducted to compare the two major neurosurgical treatments for CM+SM, PFDD and PFD. The cluster size is expected to be on average 6 participants per center (~3 per center per year). In order to participate, PRSRC centers with multiple pediatric neurosurgeons were given the option of complying with the treatment allocation and following a standardized procedure or selecting a single study neurosurgeon for the group. If the latter scenario was chosen, the group had to agree that all CM+SM patients referred to that center must be treated by the study neurosurgeon. For cluster randomization, a computer-generated randomization sequence will be generated independently by the study statistician. All eligible participants within each cluster will then be approached for informed consent for the purposes of data collection for the trial.

4. STUDY INTERVENTIONS

4.1 Interventions, Administration, and Duration

The intervention performed will either be a PFD or PFDD. It will be predetermined, based on cluster randomization, which procedure each center performs on their respective participants. A computer-generated randomization sequence will be generated independently by the study statistician. The surgery will occur in each respective center's operating room. With the exception of uniformly receiving the designated center intervention, all research participants will receive usual clinical care in accordance with institutional practice and judgment. Clinical care will include at a minimum an initial clinical evaluation by a participating pediatric neurosurgeon, surgical treatment (PFDD or PFD) and associated perioperative care, and routine post-operative care with prescribed follow-up clinical assessments at ≤6 weeks, 3-6 months, and 12 months (+/- 2 months = 10-14 months) after surgery

4.2 Concomitant Interventions

4.2.1 Allowed Interventions

Medications or other treatments may be administered per usual institutional clinical practice. PFD or PFDD must follow the procedural guidelines outlined in this protocol.

4.2.2 Required Interventions

There are no required interventions outside of the PFD or PFDD procedure itself.

4.2.3 Prohibited Interventions

PFD or PFDD must be in accordance with the procedural guidelines outlined in this protocol. For the purposes of this study, PFD performed with dural opening but no dural closure is not permitted. Similarly, cases requiring concomitant cervical or occipito-cervical fusion or upfront direct syrinx surgery (syrinx fenestration or shunt) are not permitted.

4.3 Adherence Assessment

Periodic quality assurance checks will be performed primarily via remote monitoring by reviewing a random subset of operative notes at each participating site.

5. STUDY PROCEDURES

5.1 Schedule of Evaluation

Assessment	Initial Visit	<6 Weeks Follow-Up Visit	3-6 Month Follow-up Visit	12 Month Follow-up Visit
Inclusion/Exclusion Criteria	X			
Cluster Randomization	X			
Informed Consent Form	X			
Demographics	X			
Presenting Symptoms	X			
Childhood History	X			
Developmental History	X			
Allergies	X			

Concomitant Medications	X			
Family History	X			
Social History	X			
General Exam	X			
Musculoskeletal Exam	X			
Initial Radiology	X			
Diagnosis	X			
Clinical Course of Treatment	X	X	X	X
Complications	X	X	X	X
Pt Status	X	X	X	X
CHIP	X	X	X	X
HUI-3 QOL	X	X	X	X
Follow-up Symptoms		X	X	X
Follow-up Medications		X	X	X
Follow-up General Exam		X	X	X
Follow-up Neurological Exam		X	X	X
Follow-up Musculoskeletal Exam		X	X	X
Follow-up Radiology		^	^	X
Additional Neurological/Orthopedic Exam		X	X	X

^ Any subsequent pre-operative images (Brain/spine MRI/CT/X-rays) will be shared, including in the following scenarios:

- Revision/redo decompression
- Syrinx shunt or fenestration
- Spinal Fusion

5.2 Adverse Events and Serious Adverse Events

SAFETY ASSESSMENTS

Complications will be recorded at the following time points:

- Intra-operatively
- ≤ 6 months after initial PFD or PFDD
- 6-12±2 months after initial PFD or PFDD

The following definitions are provided for clarification:

- Pseudomeningocele: an extradural and/or subcutaneous fluid collection resulting in discomfort or pain, limitation of movement, or CSF leak. Radiological evidence of fluid collection alone is not sufficient for diagnosis of pseudomeningocele.
- Hydrocephalus: requires external drainage, shunting, or endoscopic 3rd ventriculostomy.
- Infection: clinical diagnosis that may include fever, wound drainage, dehiscence, or elevated laboratory parameters in association with antibiotic treatment ± surgical debridement.
- Chemical (or aseptic) meningitis: clinical diagnosis prompting medical treatment (e.g. steroids); lumbar puncture and analysis of CSF cell profile not required but

will be tracked if available.
- True meningitis: lumbar puncture and positive cultures required.

Known potential complications include the following:
- Intra-operatively
  - Vascular injury
  - Hemorrhage requiring evacuation
  - Neurologic Injury
    - Cranial nerve injury or palsy
    - Weakness
    - Sensory Changes
    - Bowel Dysfunction
    - Bladder Dysfunction
  - Death

- Complications ≤ 6 months or 6-12±2 months after PFD or PFDD
  - Pseudomeningocele: Form 16402 (4), ChiariPOPseudomen
  - CSF leak: Form 16634 (10), ChiariPOCSFLeak
  - Hydrocephalus: Form 16427 (6), Hydrocephalus
  - Infection: Form 16416 (5), ChiariPOWRInfection
  - Aseptic meningitis: Form 16420 (5), ChiariPOchemicalMeningitis
  - True meningitis: Form 16416 (5), ChiariPOTrueMeningitis
  - Cervical Instability: Form 16431 (6), CervicalInstability

Possible interventions for known complications are as follows:
- Intra-operative complications
  - Evacuation of hemorrhage
  - Open or endovascular repair vascular injury
- ≤ 6 month or 6-12±2 month postoperative complications
  - Hydrocephalus
    - External ventricular or lumbar drain placement
    - Implantation of ventriculo-peritoneal or other permanent shunt
    - Endoscopic 3rd ventriculostomy for hydrocephalus
  - CSF leak:
    - Over-sewing of wound
    - External ventricular or lumbar drain placement
    - Surgical revision in the operating room
  - Pseudomeningocele
    - Percutaneous drainage
    - External ventricular or lumbar drain placement
    - Surgical revision in the operating room
  - Infection
    - Bedside debridement
    - Surgical revision in the operating room.
  - Shunt malfunction/infection
    - External ventricular or lumbar drain placement

        - Shunt externalization or removal with or without external ventricular or lumbar drain placement
        - Shunt revision in the operating room
    - Chemical meningitis
        - Lumbar puncture
        - Steroids
    - Bacterial meningitis
        - Lumbar puncture
        - IV antibiotics
    - Cervical instability
        - External orthosis (e.g. cervical collar, halo vest)
        - Surgical fusion
    - Cerebellar ptosis
        - Cerebellopexy

Separate from these complications, other unexpected complications that are related to the surgery and other adverse events that occur that are not related to the surgery will be recorded for the < 6 month and 6-12 (+/- 2 months) month time intervals. Such events will be reported by site investigators.

Specification of Safety Parameters

The presence of any of the following items will be considered as a harm to patients.

- **Intra-operative Complication**
    - Vascular injury resulting in dissection or stroke. Dissection will be diagnosed via angiographic imaging (CT angiogram, MR angiogram, catheter angiogram) and stroke via CT or MRI imaging.
    - Intracranial hemorrhage requiring return to surgery for evacuation
    - Neurological injury resulting in:
        - Cranial nerve deficit
        - New weakness
        - Sensory loss
        - Bowel or bladder dysfunction
    - Death
- **Complications ≤ 6 months after PFD or PFDD**
  See definitions above.
    - Pseudomeningocele
    - CSF Leak
    - Hydrocephalus
    - Infection
    - Chemical (or aseptic) meningitis
    - Bacterial meningitis
    - Cervical instability
    - Cerebellar ptosis with intractable headaches
- **Interventions for complication management <6 months after initial PFDD or PFD**

- Hydrocephalus
  - External ventricular or lumbar drain placement
  - Implantation of ventriculo-peritoneal or other permanent shunt
  - Endoscopic 3rd ventriculostomy for hydrocephalus
- CSF leak:
  - Over-sewing of wound
  - External ventricular or lumbar drain placement
  - Surgical revision in the operating room
- Pseudomeningocele
  - Percutaneous drainage
  - External ventricular or lumbar drain placement
  - Surgical revision in the operating room
- Infection
  - Bedside debridement
  - Surgical revision in the operating room.
- Shunt malfunction/infection
  - External ventricular or lumbar drain placement
  - Shunt externalization or removal with or without external ventricular or lumbar drain placement
  - Shunt revision in the operating room
- Chemical meningitis
  - Lumbar puncture
  - Steroids
- Bacterial meningitis
  - Lumbar puncture
  - IV antibiotics
- Cervical instability
  - External orthosis (e.g. cervical collar, halo vest)
  - Surgical fusion
- Cerebellar ptosis
  - Cerebellopexy

- **Complication 6-12 (+/- 2 months) months after initial PFDD or PFD**
  - Pseudomeningocele
  - CSF leak
  - Hydrocephalus
  - Infection
  - Chemical (or aseptic) meningitis
  - Bacterial meningitis
  - Cervical instability

- **Interventions for complication management 6-12 (+/-2 months) months after initial PFDD or PFD**
  - Hydrocephalus
    - External ventricular or lumbar drain placement
    - Implantation of ventriculo-peritoneal or other permanent shunt

        - Endoscopic 3rd ventriculostomy for hydrocephalus
    - CSF leak:
        - Over-sewing of wound
        - External ventricular or lumbar drain placement
        - Surgical revision in the operating room
    - Pseudomeningocele
        - Percutaneous drainage
        - External ventricular or lumbar drain placement
        - Surgical revision in the operating room
    - Infection
        - Bedside debridement
        - Surgical revision in the operating room
    - Shunt malfunction/infection
        - External ventricular or lumbar drain placement
        - Shunt externalization or removal with or without external ventricular or lumbar drain placement
        - Shunt revision in the operating room
    - Chemical meningitis
        - Lumbar puncture
        - Steroids
    - Bacterial meningitis
        - Lumbar puncture
        - IV antibiotics
    - Cervical instability
        - External orthosis (e.g. cervical collar, halo vest)
        - Surgical fusion
    - Cerebellar ptosis
        - Cerebellopexy

Adverse Events and Serious Adverse Events

Adverse Event Reporting

All adverse events will be evaluated as to whether their occurrence was expected or unexpected. For this study, *expected* AEs include the following common surgical complications (*see above for definitions*):

- Pseudomeningocele
- CSF leak
- Infection
- Chemical meningitis
- Bacterial meningitis
- Hydrocephalus
- Need for surgical procedure for complication management
    - Oversewing of wound
    - Bedside debridement
    - Surgical revision in the operating room
    - External ventricular or lumbar drain placement
    - Implantation of ventriculo-peritoneal or other permanent shunt
    - Endoscopic third ventriculostomy for hydrocephalus

- Shunt revision in the operating room

Unexpected AEs will include uncommon surgical complications and AEs which may be unrelated to the study intervention:

- Clinically significant intracranial hemorrhage
- Skull fracture
- Positioning/pressure sores
- Cerebellar ptosis with intractable headaches
- Cervical instability
- Urinary tract infection
- Need for surgical procedure for complication management
    - Evacuation of hematoma
    - Cerebellopexy for cerebellar ptosis
    - Cervical or occipital-cervical fusion
- Deep venous thrombosis
- Unsolicited complications related to decompression surgery
- Unsolicited complications not related to decompression surgery

Data Collection Procedures for Adverse Events

After enrollment, AEs, whether expected or unexpected, will be recorded according to the date of first occurrence, severity, duration, and any treatment prescribed. Any medical condition present at the time of enrollment, which remains unchanged or improved, will not be recorded as an adverse event on the Adverse Events Log. All study subjects will be monitored for adverse events from the time of enrollment until the time of discharge from the hospital and at each follow-up evaluation. Adverse events for subjects who withdraw from the study will be monitored and reported until the point of study withdrawal.

Serious Adverse Events

Serious adverse events (SAEs) will be defined as untoward medical occurrences that result in a life-threatening change of condition, require further inpatient hospitalization, or result in persistent or significant disability/incapacity or death. In the current study, SAEs will include the following:

- Intra-operative vascular injury or stroke
- Neurological injury (cranial nerve deficit, new weakness, sensory loss, bowel or bladder dysfunction)
- Visceral injury
- Pulmonary embolism
- Pneumothorax
- Need for unexpected re-intubation
- Cardiopulmonary arrest
- Death
- Unsolicited SAEs related to decompression surgery

Unsolicited SAEs not related to decompression surgery

5.3 Safety Monitoring

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) comprised of two pediatric neurosurgeons with relevant expertise in CM+SM, a biostatistician, a clinical ethicist, and a patient partner will

assess and monitor the safety of the trial. The purpose of the DSMB is to advise the funding agency (PCORI), the study Principal Investigator (Dr. Limbrick), and the Investigators Committee 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 subjects, adherence to the study protocol, assessment of data quality, performance of individual clinical sites, review of serious adverse events and other subject safety issues, and review of formal interim statistical analyses of treatment efficacy. The DCC will send reports relating to these topics to DSMB members 10 days prior to each DSMB meeting. Based on prospectively defined guidelines to be outlined in the DSMB charter, the DSMB should recommend whether or not to terminate enrollment in the study because of potential safety concerns or high evidence of efficacy. The DSMB will also have the option to recommend stopping the study due to low likelihood of finding an effect if the trial continues (futility), or if the risks/benefit ratio is not favorable. Each DSMB meeting will result in a summary report that will be provided to the Investigator Committee, PCORI, and each local IRB.

6. INTERVENTION DISCONTINUATION

For the purposes of this trial, the intervention is either of two technical variants of surgical decompression for CM+SM, PFD or PFDD. While it is possible that intra-operative factors that could influence a surgeon's plan to carry out the intended procedure (PFD or PFDD), this would be highly unlikely. Nevertheless, if the surgical technique is aborted or changed during the procedure, participants will be followed per study protocol with all associated clinical care and data collection.

7. STATISTICAL CONSIDERATIONS

7.1 General Design Issues

The Central Hypothesis of this proposal is that, compared with PFDD, PFD will result in fewer surgical complications and thus less harm to patients within 12 months (±2 months) of surgery. With a more favorable risk profile and non-inferior effect on clinical outcome and syrinx size compared with PFDD, PFD will be associated with superior QOL.

This study is designed as a cluster randomized controlled trial (C-RCT) of the two major neurosurgical treatments for CM+SM: posterior fossa decompression with duraplasty (PFDD) and extradural posterior fossa decompression (PFD). This design was chosen with input from site investigators (neurosurgeons) in order to obtain participation from a large number of pediatric neurosurgeons and reduce crossovers and non-participation resulting from physician bias. While there is inherent individual surgeon bias, clinical equipoise exists across the field; this is underscored by the participation of >50% of the pediatric neurosurgeons in the United States in this RCT and support of this study by the AANS, the CNS, and the Joint AANS/CNS Pediatric Section.

7.2 Sample Size and Randomization

7.2.1 Treatment Assignment Procedures

This study is designed as a cluster randomized controlled trial (C-RCT) of the two major neurosurgical treatments for CM+SM: posterior fossa decompression with duraplasty (PFDD) and extradural posterior fossa decompression (PFD). This design was chosen with input from site investigators (neurosurgeons) in order to obtain participation from a large number of pediatric neurosurgeons and reduce crossovers and non-participation resulting from physician bias. During extensive discussions with PRSRC investigators and patient partners, there was significant concern for selection bias due to crossovers and selective enrollment if individual patients were randomized, a known problem in surgical trials [33]. Site investigators felt that having their entire practice randomized to one technique would increase surgeon comfort and experience with that approach, thereby decreasing tendencies for biased enrollment. Consequently, individual PRSRC centers will be randomized to perform either PFDD or PFD. In this design, PRSRC centers will be serve as the unit of inference for comparing PFDD and PFD, and the cluster size is expected to be 6 patients per center (3 per center per year). For cluster randomization, a computer-generated randomization sequence will be generated independently by the study statistician. Overall sample size of 148 participants will be enrolled. Approximately 74 participants per procedure over the two years of enrollment.

Potential participants will be identified, screened, and recruited through the clinical practices of 36 participating PRSRC sties in addition to 7 other sites. In this trial, the randomization unit will be the PRSRC center; therefore, the same intervention will be used for all qualifying patients enrolled at each center. If a surgeon in a PRSRC center strongly believes that a patient should undergo a certain procedure (PFDD or PFD), the patient will not be randomized. Effective randomization will occur through the random distribution of patients to centers employing each procedure (PFDD and PFD).

Aim 1: Power Calculations

For the purpose of sample size estimation, data from in the Park-Reeves Syringomyelia Research Consortium (PRSRC) were analyzed (ambispective enrollment, n=589 subjects with complete data); specifically, surgical complications ≤12 months were used to calculate the sample size. In this dataset, surgical complications were noted in 17.8% of PFDD cases and 2.7% of PFD cases. This is consistent with reported values from a recent meta-analysis, where the rates for CSF-related complications for PFDD and PFD were 18.5% and 1.8%, respectively [27], as well data reported in case series [17, 25] and a systematic review [42]. We expect to observe a similar difference in PFDD versus PFD cases in the proposed study. Because of the clustered randomized nature of the trial, the intraclass correlation coefficient (ICC) should be taken into account. The ICC is defined as the proportion of the between cluster (PRSRC center) variation to the total variation. Since the cluster sizes are small (6 per PRSRC center), and we have a large number of centers available for enrollment (47 total), the effect of ICC on sample size will be small. Thus, using the PRSRC values of 17.8% for PFDD and 2.7% for PFD, and assuming equal number of subjects per group and two-sided type I error rate of 0.05, to reach 90% power, 36 centers averaging 6 subjects per center will be required for the trial assuming the ICC is 0.05. To account for 2% dropout rate, we originally planned to recruit 40 centers with a cluster size averaging 6 subjects with overall sample size of enrolled patients of 240 patients, approximately 120 patients per procedure over the two years of enrollment.

Aim 1: Sample Size Recalculation (November 29, 2017)
The original sample size calculation was performed based on surgical complication rates (≤12 months) from Park-Reeves Syringomyelia Research Consortium (PRSRC) estimates (17.8% in PFDD and 2.7% in PFD cases). We originally did not have an estimate for the ICC. Based on the literature, we assumed ICC of 0.05 in our calculations [43]. The overall sample size of enrolled patients would be 240 patients, approximately 120 patients per procedure over the two years of enrollment.

In preparation for our PFD trial annual meeting on November 29, 2017, we performed a sample size re-calculation, using the ICC observed from the 47 patients enrolled in the study and for which complete data was available as of November 28, 2017. It should be noted that the data was only used to calculate the ICC; no interim analyses were performed. The ICC based on the first enrolled 47 patients was 0.000059, much smaller than what was assumed (0.05) for the original sample size calculation. However, we expect this ICC estimate to change with more enrollments.

Enrollment in the trial has increased over time and continues to do so (for example, 10 patients were enrolled in both November and December, 2017 and the total trial enrollment is now 83). However, when calculated at the time of the annual meeting at the end of November 2017, the average accrual rate, calculated over the entire 19-month period of the study, was 6 patients per month. Thus, using the conservative projection of 6 patients per month over the course of an enrollment extension ending 12/1/2018, we expect the total number of subjects to be at least 145 (73 + 12 x 6). (73 was the total enrollment when these calculations were made at the end of November; however, as noted above, 10 patients were recruited in December.)

Based on the enrolled 47 patients in the database with complete data as of 11/28/17, the average cluster size is 2.9. If we assume each center enrolls 3 more patients over the enrollment extension, the average cluster size increases to 5.9. With the current ICC estimate of 0.01 and using the original estimates for the complication rates (17.8% in PFDD and 2.7% in PFD), with the projected sample size of 145, we can still reach 84% power by enrolling patients from 24 centers with an average cluster size of 6 (144 subjects total). The same power level can also be achieved by enrolling patients from 30 centers with an average cluster size of 5. To account for a potential 2% loss to follow up rate, we planned to recruit 148 subjects total (74 per group) over the entire trial enrollment period.

It should be noted that it is assumed that the average cluster size is 6 in all centers for these calculations. The design effect (DE) concept is used in cluster randomized trials to inflate the sample size of the study, compared to the traditional randomized trials [44]. When cluster size is fixed, DE = 1 + [(m - 1) x ICC]; where m is the average cluster size and ICC is the intraclass correlation coefficient. In other words, the sample size of the study can be calculated by traditional methods, and should be multiplied by the DE. Under the assumption that m = 6 and ICC = 0.01, DE becomes 1.05. To compare 17.8% vs 2.7% surgical complication rates for a (*not clustered*) randomized trial, with 84% power, and 0.05 type I error rate, we would need to enroll 136 patients total. This is also listed in the sample size calculator above under the "unadjusted box". For a DE value of 1.05, this sample size should be multiplied by 1.05 to find the sample size of a cluster randomized trial to reach same power. Therefore, the sample size of the clustered randomized trial would be 136 x 1.05 = 142.8 ~143.

The variable cluster size is common in cluster randomized trials. Eldridge et al considered the effect of variable cluster size on the sample size calculation for cluster randomized trials [45]. They showed that the DE value can be calculated for variable class sizes. DE' = 1 + {(cv^2 +1) m - 1} x ICC; where cv is the coefficient of variation of cluster sizes (standard deviation of cluster sizes divided by the mean cluster size). The cv is 1.08 for our study. If we use the current average cluster size of m = 2.9, DE' becomes 1.06. In other words, the sample size of the study should be inflated to 136 x 1.06 = 144.16~145 to reach 84% power. This assures us that our planned sample size of 145 patients will allow us to reach 84% power even if our cluster sizes will not be fixed at 6.

It should be noted that, as of March 6th 2018, only 1 of 100 enrolled patients was lost to follow-up. However, to account for a potential 2% loss to follow up on the 145 subjects needed (72 per group), we will recruit 148 subjects total (74 per group) over the entire trial enrollment period, which is proposed to be extended to December 31, 2018.

Aim 2: Non-Inferiority Margins and Power

The non-inferiority margins for this trial were determined in conjunction with a panel of experts on CM+SM and related treatment (the Park-Reeves investigators), our non-physician stakeholder partners, and our patient partners, Gina Tramelli, Elizabeth O'Keefe, Lisa Reynolds, Sandy Spears, Sam Reeves, Dorothy Poppe, and Rich Labuda. Using a clinical, Delphi-type approach [46] for the complex measure of clinical improvement, the research team agreed upon a non-inferiority margin of no more than 20% lower response for PFD from the PFDD group. The clinical improvement rate (the improvement from baseline to 12 months) for the PFDD group was provided as 78.6% in the Durham study [27]. Thus, with the sample size of 72 subjects per group (after an assumed 2% dropout), we can conclude the non-inferiority of the PFD to PFDD with a margin of 0.17 units (α=0.05, 80% power). This corresponds to clinical improvement rate of 61.6% in the PFD group. It was shown in the Durham study that the clinical improvement following PFD was 64.6%.

Determine if PFD provides non-inferior clinical improvement compared to PFDD (Non-inferiority Design)							
Outcome	**PFDD**	**PFD**	**Data Source**	**Non-inferiority Margin**	**α-level**	**Subjects per group**	**Power**
Clinical Improvement	44/56 (78.6%)	51/79 (64.6%)	Durham [27]	0.17	0.05	72	80%

For these calculations, the drop-out rate is assumed to be 2%, and the one-sided type I error rate is 0.05.

After determination with the Delphi method, the non-inferiority margin was subsequently confirmed as appropriate using Rothman's 95-95 approach [47, 48] and the FDA guidelines for selecting the non-inferiority margin for non-inferiority clinical trials [49]. Using these methods, the non-inferiority margin was estimated using the effect of the standard treatment (PFDD) from Durham's meta-analysis [27], with the lower 1-sided 95% confidence interval for the random-effects meta-analysis calculated to be used as a non-inferiority margin. When the data from the PFDD group from the Durham study was used for the clinical improvement outcome, the 95% lower 1-sided confidence interval from the random effects model was calculated as 0.611. In our proposal, we defined the non-inferiority margin as the difference between the clinical improvement rates in the PFDD and PFD groups (π_{PFDD} - π_{PFD}). For the clinical improvement outcome, this corresponds to the non-inferiority margin of 0.786 – 0.611 = 0.175 units. Therefore, our

recommended non-inferiority margin of 0.175 units for the clinical improvement outcome is consistent with the FDA-recommended largest acceptable non-inferiority margin of 0.175 units.

In contrast to clinical improvement, syrinx regression is an objectively measurable and easily quantifiable outcome. It is measured by comparing syrinx size on MRI scans obtained before and after surgery. When the effective sample size is 68 subjects per group, and assuming 89.1% syrinx regression rate in the PFDD group [27], the non-inferiority margin is 0.135 units to reach 81% power. A non-inferiority margin of 0.135 units represents no more than 13.5% reduction from the PFDD group in terms of syrinx regression. Note that a one-sided type I error rate of 0.05 was assumed, and the 'Two group test of equivalence in proportions' option in nQuery Advisor was used for the sample size calculations.

Determine if PFD provides non-inferior syrinx regression compared to PFDD (Non-inferiority Design)							
Outcome	**PFDD**	**PFD**	**Data Source**	**Non-inferiority Margin**	**α-level**	**Subjects per group**	**Power**
Syrinx Regression	261/293 (89.1%)	31/38 (81.2%)	Durham [27] and PRSRC	0.135	0.05	72	81%

For these calculations, the drop-out rate is assumed to be 2%, intra-class correlation coefficient is 0.05, and the one-sided type I error rate is 0.05.

Aim 3: Power Calculations

Based on preliminary data using the Chiari Health Index in Pediatrics (CHIP)[50], we observed a 0.12±0.16 unit improvement in Quality of Life (QOL) scores following PFDD. Our sample size of 72/group (effective sample size of 68/group) will provide 82% power to detect a 0.20±0.16 unit improvement in CHIP QOL scores following PFD (α =0.05). Both from an analytical standpoint and from the view of PRSRC investigators and our patient partners, this value represents both a significant and meaningful increase in QOL

7.3 Interim analyses and Stopping Rules

The *Posterior Fossa Decompression with or without Duraplasty for Chiari type I Malformation with Syringomyelia* study will appoint an independent Data Safety Monitoring Board (DSMB) of members. The DSMB will meet once prior to the start of the study, and will approve the final protocol prior to its implementation. Additionally, the DSMB will establish a charter to guide its function. The charter would include rules of procedure, definitions of a meeting quorum, and information about meeting logistics.

The purpose of the DSMB is to advise PCORI, the Principal Investigator (Dr. Limbrick), and the Investigators Committee 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 subjects, adherence to the study protocol, assessment of data quality, performance of individual clinical sites, review of serious adverse events and other subject safety issues, and review of formal interim statistical analyses of treatment efficacy. The DCC will send reports relating to these topics to DSMB members 10 days prior to each DSMB meeting. Based on prospectively defined guidelines to be outlined in the DSMB charter, the DSMB should recommend whether or not to terminate enrollment in the *Posterior Fossa Decompression with or without Duraplasty for Chiari type I Malformation with Syringomyelia* study because of potential safety concerns or high evidence of efficacy. The DSMB will also

have the option to recommend stopping the study due to low likelihood of finding an effect if the trial continues (futility), or if the risks/benefit ratio is not favorable. Each DSMB meeting will result in a summary report that will be provided to the Investigator Committee, PCORI, and each local IRB.

7.4 Outcomes

The goal of this study is to supply patients and families with the information about the risks and benefits of PFDD and PFD that *they feel* are most important in making informed clinical decisions. As such, the primary outcome of interest is reduction in harm to patients, measured as surgical complications and/or requirement for reoperation for complication management ≤12 (+/- 2 months) months after initial PFDD or PFD. Complications and reoperation are associated with additional pain as well as emotional and psychological stress, longer hospital stays, and lost time from school/work. Secondary outcomes focus on efficacy outcomes and will include: 1) comparison of pre-operative symptoms and neurological deficits at ≤6 weeks, 3-6 months, and 12 (+/- 2 months) months after surgery and syrinx size and spinal alignment (coronal and sagittal Cobb angles) at 12 (+/- 2 months) months after surgery; and 2) assessment of QOL (including psychosocial and physical dimensions) at baseline, ≤6 weeks, 3- 6 months, and 12 (+/- 2 months) months after surgery. This outcome will be evaluated using the CHIP and the HUI-3 QOL instruments where analyses based on CHIP will be used as the primary results for aim 3 in case CHIP and HUI-3 results do not agree.

Because this is a surgical trial, an Adjudication Committee, consisting of two pediatric neurosurgeons and one pediatric neuroradiologist independent of the design and conduct of the trial, will adjudicate the primary outcome measure. The committee will review the primary endpoint based on a blinded review of clinical notes, data forms and imaging studies. Decisions by the adjudication committee will determine final outcomes. Consensus definitions of CSF-related complications following neurosurgery have been developed [34]. These definitions have been reviewed and approved by the neurosurgeons participating in the study and will be used in this trial. Likewise, the extent of syrinx resolution following surgery will be determined by centralized review of blinded imaging studies. By contrast, treatment failure (i.e. need for revision PFDD or PFD) will be determined individually by the treating surgeon in consultation with the patient/family, since such decisions are inherently subjective and based both on the surgeon's level of concern and the patient's discomfort and relative acceptance to the inherent risks of surgery (either PFD or PFDD).

7.5 Data Analyses

A Priori Plans for Data Analysis

Descriptive Statistics

Using CONSORT guidelines for cluster-randomized trials,[53] We will present descriptive statistics, for continuous variables the mean (+/-standard deviation) or median (minimum, maximum) values and for categorical variables the frequencies and proportion for each cluster. These presentations will be carried out at baseline and at 12-month follow-up. We will provide reasons for dropouts.

Planned sensitivity analyses to determine the impact of key assumptions. Due to the fact that each patient in a given center will be assigned to the same procedure, it is possible to observe unequal overall sample sizes for each procedure. The initial analysis plan is to give equal weights to all clusters. If there is imbalance in the prognostic factors, we will use weighted analyses where the cluster-level summary score is weighted inversely proportional to the reciprocal of its estimated variance.

Initial analysis will be conducted using per Treatment group assignment prior to adjudication, as it aligns more to in-practice clinical procedures. Sensitivity analyses will be conducted based upon Intent-to-Treat (ITT) (as randomized), and per Protocol (actual treatment) grouping definitions, both pre and post adjudication. Patients with a second Chiari surgery will be analyzed in two different ways in sensitivity analysis, one including vs one excluding second surgeries. and will be.

Comparison methods
Specific Aim 1: Hypothesis: PFD will be associated with fewer surgical complications and less potential harm to patients than PFDD.

Anticipated Outcome: Cerebrospinal fluid (CSF)-related complications ≤6 months (e.g. CSF leak, pseudomeningocele, aseptic meningitis, infection, hydrocephalus), and the requirement for additional surgery for wound revision or CSF diversion will be lower after PFD compared with PFDD.

The primary outcome is a binomial outcome measured as a surgical complication and/or requirement for reoperation for complication management ≤12 (+/- 2 months) months after initial PFDD or PFD. To account for within cluster correlation, possibly variable cluster size and the relatively small number of clusters in this cluster randomized trial, generalized estimating equations (GEE) with small-sample correction or random effect logistic regression will be used for the primary analysis of this cluster randomized trial [35, 36].

Specifically, a GEE model with a logit link function and adjustment for baseline covariates can be expressed as follows:

$$logit(\pi_{ij}) = \mu + \delta T_i + x_{ij}\beta$$

where $T_i = 1$ if group i is assigned PFD and 0 otherwise. Accordingly, δ is the intervention effect. Let x_{ij} is the p-dimensional vector of group-level of individual level covariates from individual j ($j = 1, \ldots, n_i$) nested in center i ($i = 1, \ldots,$ # of active centers here); and β is the vector of covariate effects. Also let the outcomes (CSF-related complication ≤6 months, yes/no) are independently distributed as $y_{ij} \sim$ Bernoulli(π_{ij}). Further let, μ be the log-odds of positive outcome ($y_{ij} = 1$) for PFDD subjects with reference values for covariates ($x_{ij} = 0$) and average random effect ($\gamma_i = 0$). The exchangeable correlation structure will be used for the within-group homogeneity for the correlation structure of the outcomes. Note that, this correlation parameter corresponds to the intraclass correlation coefficient (ICC).

Specific Aim 2:
Hypothesis: Clinical improvement and syrinx regression provided by PFD will be non-inferior compared to those provided by PFDD.
Anticipated Outcome: Clinical symptoms, neurological function, and syrinx regression ≤12 months (± 2 months) provided by PFD will be non-inferior compared to those provided by PFDD. The non-inferiority margin is defined as the difference between the outcome rates by treatment. For the clinical improvement outcome, a non-inferiority margin of 0.17 units will be used. A non-inferiority margin of 0.135 units will be used for the syrinx regression outcome.

Clinical symptoms, neurological function, and syrinx regression are defined as rates of change from baseline to 12 months. The 1-sided confidence interval for the difference in rates between the PFD and PFDD groups will be calculated and compared to the corresponding non-inferiority margins.

Second Chiari surgeries will be analyzed as 1) the proportion requiring a surgical revision and 2) the type of second surgery performed (same or cross-over). The 1-sided confidence interval for the difference in rates between the PFD and PFDD groups will be calculated and compared to the corresponding non-inferiority margins.

Specific Aim 3:
Hypothesis: With fewer surgical complications, PFD will be associated with superior QOL compared with PFDD.
Anticipated Outcome: PFD will have superior QOL and will show improvements in overall QOL over time (≤12 months post-operatively (± 2 months)) compared to PFDD. In particular, both physical metrics (evaluated by pain frequency, pain severity and non-pain symptoms) and psychosocial metrics will improve at a higher rate and in a shorter period of time after PFD compared to PFDD.

Secondary outcomes include Treatment Efficacy variables and Quality of Life variables. Continuous variables measured at 3 time points over the 12-month follow-up will be analyzed using longitudinal analysis with linear mixed models including the random cluster effect. Binomial and ordinal data will be analyzed using Mixed Model methods accounting for cluster. In addition, sensitivity analyses will be conducted where the missing data points will be imputed based on the last observation carried forward.

It should be noted that for Aim 3, primary analyses will be based on the QoL exam performed at 10 to 14-month window. A sensitivity analyses will also be performed based on the last QoL exam available at any time ≥ 3 months after surgery. Analyses based on the mixed effect model will also be performed where both cluster effect and error terms will be random.

Missing data: Based on PRSRC data and early data from this trial, loss to follow-up rate is expected to be low (<2%). To prevent missing data, we will meet with patients at 1 month, 3-6 months and at 12+/-2 months after the procedure. Every effort, including phone call reminders to patients, will be made to decrease loss to follow-up. Loss to follow-up, missing data, and the reasons leading to loss of follow-up or data will be recorded. In case of missing data, we will impute missing data using different methods. Because of the repeated measures nature of the data, the 'last observation

carried forward' method will be utilized [37]. In addition, Buck's method, which is the extended version of regression imputation, will be used [38]. The Buck's imputation will be based on the observed values of patient's age, CM (≥ 5mm tonsillar ectopia), syrinx diameter, and pre-operative comorbidities. In addition to the overall rates of missing data for each procedure, because of the cluster randomized trial, we will also monitor the missing data within each cluster and center and report the discrepancy between the loss to follow-up rates for each procedure. Special attention will be given and separately reported if the entire cluster is loss to follow-up. As a sensitivity analysis for the missing data, study results will be compared for the following three conditions: 1) patients with missing primary outcome variable are excluded from analyses; 2) results with last observation carried forward, and 3) results with Buck's method. Robustness of the results under each scenario will be assessed.

Heterogeneity of Treatment Effect (HTE): As an exploratory analyses, to assess if the procedure is most beneficial for a specific subgroup, the heterogeneity of the effect of performing PFDD vs PFD will be assessed within the following pre-determined subgroups based on: 1) patient age at the time of surgery (<5 years, 5-12 years, 13-18 years); 2) CM status (5-12 mm tonsillar ectopia, >12 mm tonsillar ectopia) [39]; 3) syrinx diameter (3-6 mm, 7-9 mm); and 4) preoperative hydrocephalus or neuromuscular disease, two comorbidities associated with increased morbidity following pediatric CM +/- SM surgery [40]. Demographic and comorbidity data will be collected by trained study research assistants/coordinators with strict oversight by site investigators using standard data collection forms. For HTE analysis, the test of procedure (PFD vs PFDD) by subgroup effect (such as age) interaction will be performed to assess the homogeneity of the procedure effect within each subgroup. All pre-specified subgroup analyses (patient's age, CM status, syrinx diameter, comorbidity, and surgeons' experience) will be reported regardless of observing a statistically significant or not-significant effect.

Sub-analysis by Syrinx size (3-6 mm, 7-9 mm): A planned subgroup analysis for each of the 3 to 6 mm and 7 to 9 mm syrinx diameters will be performed for each of the 3 aims. The test of interaction will be used to assess if the treatment effect is homogeneous within each of the syrinx size subgroups (3- 6 mm vs 7-9 mm). If the test of interaction indicates heterogeneity, using the whole 3 to 9 mm syrinx diameter range, analyses will be performed, to identify, if any, a cut-off point to propose using one surgical method over the other. For example, whether the PFD is associated with greatly fewer surgical complications when the syrinx diameter is less than 5mm, but surgical complication rates are similar for PFD and PFDD when the syrinx diameter is ≥6 mm will be examined.

Secondary Analysis

The aims will be evaluated using the overall population who were followed from 6 months to 24 months after enrollment. Analysis will be performed to compare the per Treatment groups for time to last follow-up in order to determine if there is differential follow-up times between groups. Analysis of Aims 2 and 3 will be similar to the primary analysis with adjustment for time to last follow-up as a covariate.

Aim 3 includes some questions that may not be applicable for younger children. For example, keeping up with schoolwork or difficulty with math. Therefore, for this ,a subgroup analysis for

those children age >5 years will also be performed. Additional analysis will include subdomain comparisons of:

Pain symptoms
- Headache
- Back pain

Non-pain symptoms
- Difficulty raising arms
- Difficulty walking
- Frequently lose balance

Psychosocial
- Tired
- Easily frustrated
- Trouble sleeping
- Difficulty concentrating
- Difficulty paying attention in class
- Forgetful
- Difficulty with reading
- Difficulty with math
- Difficulty learning new things
- Difficulty keeping up with schoolwork.

Covariates in this analysis will include medical history (Autism, ADHD, Known Psych Disease), pathology (known Craniofacial Anomalies, Known Skull Malformation, Known Hydrocephalus, Known Spine Column Disorder) and Syrinx (Syrinx Level Known, Syrinx AP Diameter).

Exploratory Analysis

Additional exploratory subgroup analyses will be performed for Aims 2 and 3. These analyses will include age (<5,5-12,13-18), CM status (5-12,>12 mm), and preoperative hydrocephalus or neuromuscular disease. These analyses will examine if there is differential response between the groups.

A model of response will also be performed with the additional covariates: parents education, gender, race, insurance, treatment complications, pain, headache, childhood history, hydrocephalus, skull formation, spinal column disorder, syrinx level, syrinx AP diameter, and improved syrinx size.

7.5.1 Metrics

Primary Outcome: measured as a binary (yes/no) variable. The presence of any of the following items will be considered as a poor outcome (harm to patients):

- **Intra-operative Complication**
  - Vascular injury resulting in dissection or stroke
  - Intracranial hemorrhage requiring return to surgery for evacuation
  - Neurological injury (new cranial nerve deficit, weakness, sensory loss, bowel or bladder dysfunction)
  - Death

- **Complication ≤12 (+/- 2 months) months after initial PFDD or PFD**
  - Pseudomeningocele: extradural and/or subcutaneous fluid collection resulting in discomfort or pain, limitation of movement, or CSF leak. Radiological evidence of fluid collection alone is not sufficient for diagnosis of pseudomeningocele.
  - CSF leak
  - Hydrocephalus: requires external drainage, shunting, or endoscopic 3rd ventriculostomy
  - Infection: clinical diagnosis that may include fever, wound drainage, dehiscence, or elevated laboratory parameters in association with antibiotic treatment ± surgical debridement.
  - Chemical (or aseptic) meningitis: clinical diagnosis prompting medical treatment (e.g. steroids); lumbar puncture and analysis of CSF cell profile not required but will be tracked if available.
  - Cervical instability

- **Need for surgical procedures for complication management ≤12 (+/- 2 months) months after initial PFDD or PFD**
  - External drainage for the following:
    - Hydrocephalus
    - CSF leak
    - Pseudomeningocele
    - Infection
    - Shunt malfunction/infection
  - Simple over-sewing of wound for CSF leak
  - Surgical revision in operating room for the following:
    - CSF leak
    - Infection
    - Pseudomeningocele
  - Lumbar puncture and steroids for the following:
    - Chemical meningitis
    - True meningitis
  - Implantation of ventriculo-peritoneal or other permanent shunt or endoscopic 3rd ventriculostomy for hydrocephalus.
  - Cervical collar and/or fusion for cervical instability

Secondary Outcomes:

- **Treatment Efficacy, measured ≤6 weeks, 3-6 months, and 12 (+/- 2 months) months after surgery:**
  - Status of clinical symptoms
  - Status of neurological findings
  - Syrinx diameter (in mm)
  - Spinal alignment (coronal and sagittal Cobb angles)
  - Need for revision of PFDD or PFD
- **Quality of life, measured ≤6 weeks, 3-6 months, and 12 (+/- 2 months) months after surgery**:

- Chiari Health Index in Pediatrics (CHIP)
- HUI-3.

7.5.2 Protocol Deviations

Protocol deviations will be reported to the local IRB per the respective institution's guidelines.

7.5.3 Monitoring

The DCC will monitor data quality primarily through the use of remote monitoring activities. Remote monitoring involves detailed review of the data entered by the Clinical Center and consultations with the Clinical Center investigator and/or research assistant/coordinator to review safety and data quality. This may require uploading de-identified copies of specific parts of the medical record, patient study file, regulatory documentation, or other source documents to the DCC staff who will review those materials against the data recorded in the electronic data capture system. This helps assure protocol compliance and accurate data collection. The DCC may conduct more remote monitoring activities early in the trial to assure protocol compliance and identify any training issues that may exist. Safety of subjects will be monitored and ensured in accordance with the DSMB plan. The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the DCC, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives of the IRB for each study site.