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

FULL PROTOCOL TITLE

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

Study Chairman or Principal Investigator:

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Patient-Centered Outcomes Research Institute
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STUDY TEAM ROSTER

Research Team Member	Role in Study	Stakeholder Grouping	Responsibilities
David D. Limbrick, Jr., M.D., Ph.D.	P.I.	Clinician/ Physician	Oversees design, implementation, and conduct of entire study. Supervises the conduct of human subjects research, protects rights, safety and welfare of subjects. Reviews and submits interim and final reports on study. Leads meetings of the Investigators Committee. Responsible for research partners, stakeholders, and patient partners input during study meeting. Reviews and presents data to the DSMB. Oversees dissemination of study results with all members of the Investigators Committee.
Chevis Shannon, Ph.D.	Co-P.I.	Research Stakeholder	Serves as a liaison to patient advocacy groups. Oversees training and oversight of the quality of life instrument and study aim. Participates as a Site PI. Serves as a member of the Dissemination Committee. Participates in the development and writing of presentations and study manuscripts.
James Torner, Ph.D.	Co-P.I.	Research Stakeholder	Oversees Data Coordinating Center. Responsible for data analysis and interpretation. Participates in the writing of the development of presentations and study manuscripts. Assists with the preparations and presentation of reports for the DSMB.
Gerald Tuite, M.D.	Co-I	Clinician/ Physician	Serves as a liaison to patient advocacy groups. Oversees training and oversight of the quality of life instrument and study aim. Participates as a Site PI. Serves as a member of the Dissemination Committee. Participates in the writing of the development of presentations and study manuscripts.
Emine Bayman, Ph. D.	Co-I	Research Stakeholder	Performs data analysis and assists with interpretation. Participates in the writing of the development of presentations and study manuscripts. Assists with the preparations and presentation of reports for the DSMB.

T.S. Park, M.D.	Co-I	Clinician/ Physician	Oversees the network and its resources. Serves as administrative leader and study advisor. Facilitates the annual PRSRC meeting.
Michael Kelly, M.D.	Co-I	Clinician/ Physician	As a spinal deformity expert, is responsible for interpretation of all spinal deformity x-rays and the determination of progression/stability/improvement of deformity after surgery.
Hailey Vance, P.N.P.	Co-I	Clinician/ Nurse Practitioner	As a first point of contact for patients, provides important insight into concerns of patient/family members at all stages, from diagnosis through the post-operative period. Attends annual investigator meeting and participates on Investigator Committee calls. Assists in dissemination of study results.
Elaine Kennedy	Co-I	Clinician/ Nurse Practitioner	As a first point of contact for patients, provides important insight into concerns of patient/family members at all stages, from diagnosis through the post-operative period. Attends annual investigator meeting and participates on Investigator Committee calls. Assists in dissemination of study results.
Thanda Meehan R.N., B.S.N.	Co-I	Clinician/ Research Nurse	Ensures all study site surgeons and research coordinators are trained on the study protocol and procedures. Fields questions and assists with day-to-day issues for PRSRC (e.g. data entry, registry function). Organizes all study documents and coordinates efforts of multiple sites.
Samuel Reeves	Co-I	Patient Partner/ Family	Inspirational leader of PRSRC. Participates in study design, implementation, conduct, and dissemination of results. Provides input from a patient's or family's perspective about all study decisions. Ensures patient-centeredness of outcomes. Participates in all Investigator Committee meetings.
Lisa Reynolds	Co-I	Patient Partner / Family	Participates in study design, implementation, conduct, and dissemination of results. Provides input from a patient's or parent's perspective about all study decisions. Ensures patient-centeredness of outcomes. Participates in

			all Investigator Committee meetings. Facilitates approachable language for social media posts, press releases and website blogs.
Gina Tramelli	Co-I	Patient Partner / Family	Participates in study design, implementation, conduct, and dissemination of results. Provides input from a patient's or parent's perspective about all study decisions. Ensures patient-centeredness of outcomes. Participates in all Investigator Committee meetings. Facilitates approachable language for social media posts, press releases and website blogs.
Dorothy Poppe	Co-I	Patient Partner/ Patient Advocate	C.E.O. of Chiari and Syringomyelia Foundation. Participates in study design, implementation, conduct, and dissemination of results. Ensures patient-centeredness of outcomes. Participates in all Investigator Committee meetings. Assists with coordination of patient focus groups and dissemination of results.
Rick Labuda	Co-I	Patient Partner/ Patient Advocate	Executive Director, Conquer Chiari patient advocacy group. Participates in study design, implementation, conduct, and dissemination of results. Ensures patient-centeredness of outcomes. Participates in all Investigator Committee meetings. Responsible for social media posts, press releases and website blogs.
Jacob Greenberg, M.D., M.S.C.I.	Consultant	Clinician/ Researcher	Participates in study design, implementation, conduct, and dissemination of results. Participates in the interpretation and refinement of clinical outcomes metrics. Participates in the writing of the development of presentations and study manuscripts.
Angela Eschmann, R.N.	Consultant	Clinician/ O.R. Nurse	As the resource nurse and leader of the St. Louis Children's neurosurgical operating room staff, provides input regarding operative conditions potentially contributing to surgical complications.
Toni Goelz	Consultant	Clinician/ Physical Therapist	Provides unique perspective and insight into assessment and treatment of physical limitations related to CM+SM. Participates

			in study design, implementation, conduct, and dissemination of results.

PARTICIPATING STUDY SITES

Sites	Principal Investigators
All Children's Hospital	Tuite, Gerald, Jallo, George
Arkansas Children's Hospital/University of Arkansas School of Medicine	Albert, Greg
Arnold Palmer Hospital-Orlando Health	Olavarria, Greg
Boston Children's Hospital	Stone, Scellig
Children's Healthcare of Atlanta	Chern, Joshua
Children's Hospital at Dartmouth-Hitchcock/ Dartmouth Geisel School of Medicine	Bauer, David
Children's Hospital Colorado	O'Neill, Brent
Children's Hospital of Birmingham	Johnston, James
Children's Hospital of New York-Presbyterian/ Weill Cornell/Cornell University Medical College	Greenfield, Jeffrey
Children's Hospital of Phoenix	Adelson, David
Children's National Medical Center	Keating, Robert
Children's Hospital of Philadelphia	Heuer, Greg
Cincinnati Children's Hospital	Mangano, Francesco
Columbia University	Anderson, Richard
Dell (Seton) Children's Medical Center	George, Timothy, Tyler-Kabara, Elizabeth
Gillette Children's Hospital Minnesota	Graupman, Patrick
John Hopkins Children's Center/ Johns Hopkins School of Medicine	Jackson, Eric
Levine Children's Hospital/Carolinas Medical Center	Wait, Scott
Los Angeles Children's Hospital	McComb, J. Gordon
Lurie Children's Hospital of Chicago	Alden, Tord
Mayo Clinic Children's Hospital	Daniels, David
Miami Children's Hospital	Bhatia, Savjiv, Ragheb, John
MUSC Children's Hospital/Medical University of South Carolina School of Medicine	Eskandari, Ramin
Oregon Health & Science University	Selden, Nathan
Pennsylvania State University	Iantosca, Mark
Pittsburgh Children's Hospital	Tamber, Mandeep, Greene, Stephanie
Primary Children's Hospital	Brockmeyer,Doug
St. Louis Children's Hospital	Limbrick, David
Seattle Children's Hospital	Ellenbogen, Richard
Stanford University	Grant, Gerald
Texas Children's Hospital	Whitehead, Bill
The Children's Hospital at OU Medical	Mapstone, Timothy, Gross, Naina

Center/ Oklahoma University College of Medicine	
Nationwide Children's Hospital	Leonard, Jeffrey
University of Florida HSC-Jacksonville	Aldana, Philipp
University of Iowa	Menezes, Arnold
University of Michigan	Maher, Cormac
University of Texas – Houston	Shah, Manish
University of Minnesota	Guillaume, Dan
University of Vermont Children's Hospital/ University of Vermont College of Medicine	Durham, Susan
University of Wisconsin	Iskandar, Bermans
Vanderbilt University	Shannon, Chevis and Wellons, Jay
Wake Forest University	Couture, Daniel

Study Title
Posterior Fossa Decompression with or without Duraplasty for Chiari type I Malformation with Syringomyelia: A prospective, cluster randomization trial of up to 238 subjects recruited from 36 centers of the Park-Reeves Syringomyelia Research Consortium as well as an additional 8 research centers.

Objectives
Children with Chiari type I malformation (CM) and syringomyelia (SM), a 'rare disease', may suffer debilitating pain, spinal deformity, neurological deficits (myelopathy, weakness, sensory loss, and impaired gait), and a diminished quality of life (QOL) [1-3]. CM+SM is treated with neurosurgical decompression of the craniovertebral junction with either of two technical variations: 1) posterior fossa decompression with duraplasty (PFDD), the gold standard operation, which involves intradural microsurgical dissection and duraplasty; or 2) extradural posterior fossa decompression (PFD), in which the dura is not opened. **The Central Hypothesis of this proposal is that, compared with PFDD, PFD will be associated with fewer surgical complications and less harm to patients, yet will provide non-inferior clinical improvement and syrinx regression. With a more favorable risk profile and non-inferior clinical outcomes, patients undergoing PFD will experience superior QOL.** We will conduct a prospective, cluster randomized controlled trial of PFD versus PFDD in order to test this hypothesis and achieve the following Specific Aims:

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, and hydrocephalus) and requirement for additional surgery for wound revision or CSF diversion will be lower after PFD compared with PFDD.

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.

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.

Design and Outcomes
This will be a cluster randomized control trial of up to 238 patients (see section 9.5 data analysis, re-estimation in power calculations section below) recruited from the 36 centers of the Park-Reeves Syringomyelia Research Consortium (PRSRC) as well as an additional 8 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.

Interventions and Duration
This study will compare the outcomes of PFDD vs PFD. The study will occur over a five year period. The enrollment period will last for two years and 8 months. Data collection for each participant is for the primary analysis is to be one year and will be structured in the following manner:

- Pre-operative (the initial outpatient neurosurgery visit prior to decompression) including CHIP & HUI-3 QOL questionnaire
- Intra-operative
- Post-Operative
- ≤6 weeks post-operation including CHIP & HUI-3 QOL questionnaire
- 3-6 months post-operation including CHIP & HUI-3 QOL questionnaire
- 12±2months post-operation including CHIP & HUI-3 QOL questionnaire

- Data related to additional outpatient neurosurgery visits that occur during the one year collection period will also be collected.

MRI of the brain and cervical and thoracic spine are required prior to PFD or PFDD. Pre-operative lumbar spine MRI will be left to the discretion of the surgeon. MRI of the cervical and thoracic spine are required 12±2 months post-operatively.

- Imaging not required for study but included for review if available during the 1-year +/- 2 month study collection period:
    - Additional MRIs of the brain or cervical, thoracic, or lumbar spine obtained for the clinical care of the patient, including those performed due to:
        - Revision/redo decompression
        - Syrinx fenestration or syrinx shunt
        - Spinal Fusion
    - CT of the brain or cervical, thoracic, and lumbar spine
    - "Long cassette" or "scoliosis" X-rays and X-rays of the cervical, thoracic, and lumbar spine

Sample Size and Population

Overall sample size during the two years and 8 months enrollment period is 148 participants. Of this total, approximately 74 will have a PFD and approximately 74 will have PFDD. Participants will be between the ages of 0-21 years old and diagnosed with CM+SM without bias to gender, race, or ethnicity.

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.

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.

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.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Chiari type I malformation (CM) and syringomyelia (SM) are closely associated but incompletely understood disorders of the craniovertebral junction and spinal cord, respectively (Fig. 1). Syringomyelia (SM) is a potentially debilitating neurological condition characterized by the abnormal accumulation of fluid within the spinal cord and is observed most commonly in the setting of CM [1]. SM is classified as a 'rare disease' by the Office of Rare Diseases of the National Institutes of Health (NIH), with an estimated 7-9 new cases/year/100,000, and about 40,000 people currently affected in the United States [2-6]. Children with CM+SM frequently suffer chronic pain, including headaches and spinal cord dysesthesias, spinal deformity, and neurological deficits such as sensory loss or weakness [7-10]. Left untreated, these symptoms may progress to result in debilitating paralysis, progressive scoliosis requiring surgical correction, sexual dysfunction, or bladder and bowel incontinence. High cervical or brainstem SM may result cranial nerve dysfunction, respiratory failure, or apnea. Fortunately, progression of disease is gradual and may be halted—and in some cases reversed—with effective neurosurgical treatment [9-13].

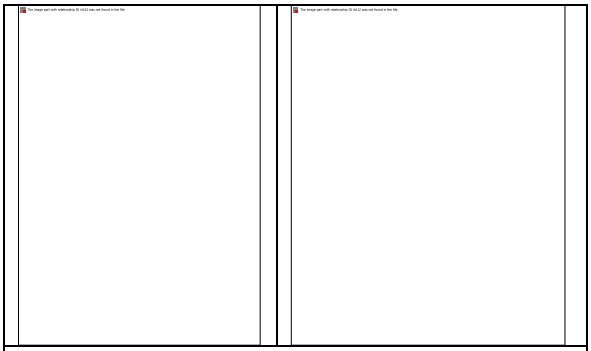

Figure 1. Schematic drawing (left) and T2-weighted sagittal MRI (right) demonstrating Chiari type 1 malformation (CM-1) and syringomyelia.

While it is widely recognized that surgical decompression of the craniovertebral junction provides symptomatic improvement and syrinx regression in up to 80-90% of patients with CM+SM [7, 9, 10, 12, 13], the optimal surgical technique remains highly controversial. The fundamental difference between the two major operative approaches for treating CM+SM is the surgical opening of the dura mater, the thickest and strongest of the three linings of the central nervous system. Opening the dura in this region provides access to the cerebrospinal fluid (CSF) cisterns, the surface of the cerebellar tonsils, the foramen of Magendie (the opening of the 4th ventricle), the brainstem, and the spinal cord. In cases when the dura is opened, a duraplasty is performed, which involves an expansile closure of the dura, typically with graft material. Many surgeons fervently believe that opening the dura, with or without intradural microsurgical dissection, followed by duraplasty is critical to restoring normal cerebrospinal fluid hydrodynamics at the craniovertebral junction (CVJ) and permitting reduction in the SM size.

2.2 Study Rationale

Syringomyelia is a rare disease associated with substantial, lifelong disability, ranging from chronic pain to debilitating paralysis, spinal deformity, and death from respiratory failure [14]. While some types of SM are not treatable, CM-associated SM is readily treated by neurosurgical decompression of the craniovertebral junction, which provides symptomatic improvement and syrinx regression in up to 90% of patients [15]. However, the optimal surgical technique—one that effectively eliminates symptoms and prevents disability while minimizing complications and harm to patients—remains unclear. The debate over which surgical technique, PFDD or PFD, to recommend to patients is among the most controversial topics in pediatric neurosurgery[16], and *currently these decisions are being made in the absence of evidence about the comparative effectiveness of PFDD or PFD*.

Termed posterior fossa decompression with duraplasty (PFDD), this combination of procedures is considered the 'gold standard' operation for CM+SM (Fig. 2). However, opening the dura carries a significant risk to patients (Table 1); a recent meta-analysis of numerous retrospective clinical series demonstrated surgical complications noted in 18.5% of patients who underwent PFDD (range 8.3-66.7%, Table 2). Due to this alarmingly high rate of complications, there has been increasing interest in recent years in extradural posterior fossa decompression *without dural opening or duraplasty* (PFD). PFD markedly reduces the surgical risks of PFDD, but its efficacy remains unclear, and patients who undergo PFD may experience inferior resolution of symptoms and may be more likely to require revision decompression surgery (Table 2). However, available data are derived primarily from single-center retrospective analyses [17-25], and at present, the choice of PFD or PFDD is largely based on surgeon preference or surgeon experience rather than medical evidence [26]; no evidence-based guidelines exist. **The current study proposes to address this critical gap in the management of CM+SM to compare the risk of harm to patients, the effectiveness, and the change in QOL associated with PFDD versus PFD**.

Table 1. Common surgical complications after PFDD or PFD.

Surgical Complication	**Surgical Procedures for Complication Management**
Pseudomeningocele	Oversewing of Wound
CSF Leak	Wound Revision
Chemical Meningitis	External CSF Drainage
Hydrocephalus	Req. for CSF Shunt

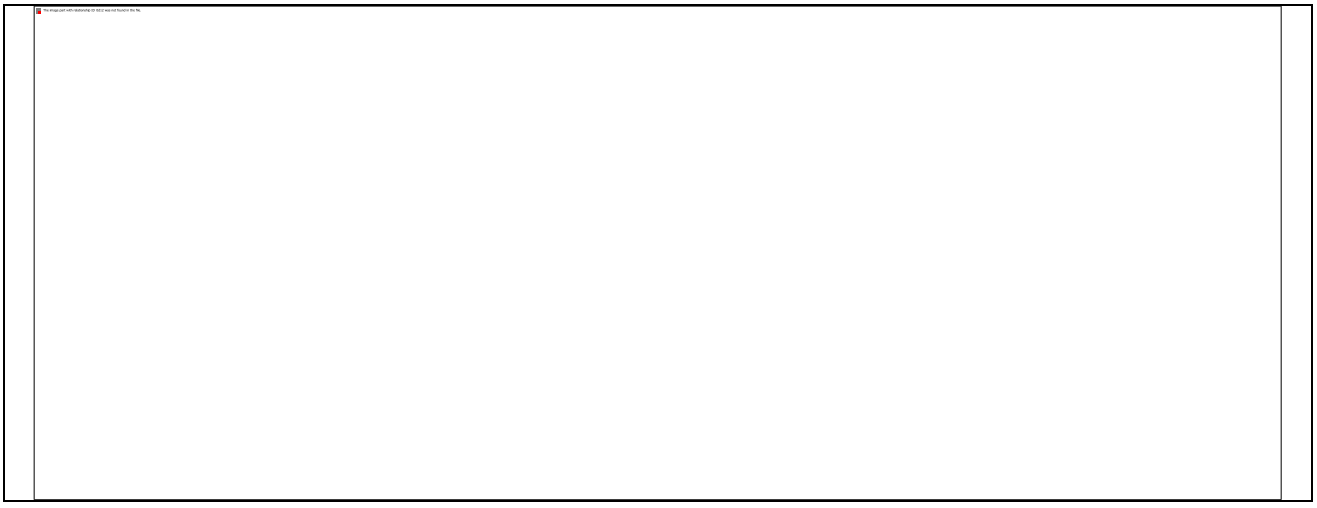

Figure 2. Surgical techniques for decompression for CM+SM. *A*, Planned areas of bone removal from the suboccipital region of the skull and C1 lamina. *B*, After bony decompression, the constricting epidural band at the level of the foramen magnum is resected. This is the end of the operation for the extradural posterior fossa decompression (PFD). If posterior fossa decompression with duraplasty (PFDD) is performed, the dura is opened sharply, exposing the cerebellar tonsils, brainstem, and upper spinal cord (*C*). After microsurgical dissection, the dura is sewn closed with a dural graft (*D*).

Table 2. Summary of existing literature comparing PFD and PFDD for CM+/-SM.

	N value		% Clinical Improvement		% Syrinx Improvement		% CSF-related Complications		% Req. Repeat Decompression	
Article	PFDD	PFD	PFDD	PFD	PFDD	PFD	PFDD	PFD	PFDD	PFD
Munshi (2000)	21	11	85.7	72.7	100	50.0	66.7	0	0	18.2
Ventureyra (2003)	8	8	100	62.5	100	0	NR	NR	---	---
Navarro (2004)	53	56	62.3	72.2	NR	NR	34.0	3.6	9.4	14.3
Limonadi (2004)	12	12	OR 1.5*	OR 1.7*	100	---	8.3	0	NR	NR
Yeh (2006)	85	40	97.6	90.0	85.0	66.7	10.0	0	5.9	0
Galarza (2007)	40	20	79.2	33.3	77.7	40.0	NR	NR	NR	NR
Mutchnick (2010)	64	56	NR	NR	NR	NR	NR	NR	3.1	12.5
Litvack (2013)	47	63	91.4	90.0	NR	NR	19.2	0	0	1.6
Lee (2014)	36	29	CCOS 14.6**	CCOS 14.7**	76.9	100	19.4	0	2.8	6.9
Meta-Analysis										
Durham (2008)	316	266	78.6	64.6	87.0	56.3	18.5	1.8	2.1	12.6
p-value	NA		p=0.12		p=0.56		p=0.0003		p=0.01	

*Odds Ratio (OR) reported; **Chicago Chiari Outcome Scale (CCOS) reported; NR=Not reported; NA=Not Applicable

The current study—which has been guided by patients and families, patient advocacy organizations, physician and non-physician stakeholders, and supported by the American Association of Neurologic Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the Joint AANS/CNS Pediatric Section —is designed to address this critical gap in the management of CM+SM by comparing the risk of harm, effectiveness, and impact on QOL between PFDD and PFD.

The information that will be obtained from this study is of paramount importance to patients and families who are faced with making critically important and consequential healthcare decisions at a time of extreme duress. Patients and families are often overwhelmed to learn that they have a complex and progressive neurological disorder with long-term implications for their health. This shock is often compounded by disappointment upon learning that there are significant unknowns in the treatment of their condition— *"Which surgery should we choose?" "Which has higher risks?" "Which is more likely to harm my child?" "Is one more likely to help my child?" "I don't want them to suffer through this more than once."* Right now, these questions are unanswerable; the current study will help patients and families to answer these questions and make informed healthcare decisions about how best to help their children while minimizing the risk of harm. In designing this study with patient partners and advocacy groups, this was a resounding priority for research in CM+SM.

This study will have tremendous impact by identifying the surgical approach (PFDD or PFD) that: 1) minimizes surgical complications and potential harm to patients; 2) maximizes symptomatic relief and syrinx resolution; and 3) provides the highest Quality of Life (QOL) for patients. The results of this study will *transform* management of this disorder in real and substantial ways that are critically important to patients and families, stakeholders, and clinicians by:

1. Addressing the knowledge gap in treating CM+SM: **No high quality evidence-based data exist for the treatment of CM+SM. The results of this study will enable us to establish best neurosurgical practices to improve healthcare delivery and outcomes for CM+SM by minimizing patient harm while maximizing symptomatic relief and QOL.**
2. Assist patients and families with difficult healthcare decisions: The information provided through this study will **create a paradigm shift away from the current reliance on individual surgeon preferences and experiences. In its place, these results will enable patients and families to appreciate the rationale, risks, and benefits of the various surgical strategies for CM+SM so that *they* can make informed, consequential decisions regarding their own healthcare**.
3. Understand the impact of CM+SM, both acutely and chronically, on QOL in children. To date, nearly all CM+SM studies have focused on physician assessment of clinical outcomes in CM+SM. **By employing disease-specific, patient-centered QOL instruments, this study will provide entirely novel, rigorously determined insights into the impact of CM+SM on QOL in children and how QOL changes in the short- and long-term after surgery.**

3. STUDY DESIGN

SPECIFIC AIMS

Children with Chiari type I malformation (CM) and syringomyelia (SM), a 'rare disease', may suffer debilitating pain, spinal deformity, neurological deficits (myelopathy, weakness, sensory loss, and impaired gait), and diminished quality of life (QOL) (2, 7, 8, 27). CM+SM is treated with neurosurgical decompression of the craniovertebral junction with either of two technical variations: 1) posterior fossa decompression with duraplasty (PFDD), the gold standard operation, which involves intradural microsurgical dissection and duraplasty; or 2) extradural posterior fossa decompression (PFD), in which the dura is not opened. **The Central Hypothesis of this proposal is that, compared with PFDD, PFD will be associated with fewer surgical complications and less harm to patients, yet will provide non-inferior clinical improvement and syrinx regression. With a more favorable risk profile and non-inferior clinical outcomes, patients undergoing PFD will experience superior QOL.** We will conduct a prospective, cluster randomized controlled trial of PFD versus PFDD in order to test this hypothesis and achieve the following Specific Aims:

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, and hydrocephalus) and requirement for additional surgery for wound revision or CSF diversion will be lower after PFD compared with PFDD.

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.

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.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS.

This study will leverage the unique resources of the Park-Reeves Syringomyelia Research Consortium (PRSRC), a U.S.-based network of major children's hospitals, each with a high-volume pediatric neurosurgery and orthopedic surgery center. For the current study, additional PRSRC sites have been recruited and agreed to participate, (please refer to Appendix I for a full listing of the structure of the PRSRC). Due to the highly specialized pediatric neurosurgical care required for the management of CM+SM, each site serves as a regional referral center for this rare condition, and the demographics of patients cared for at each site are thus representative of the demographic distribution of each region.

4.1 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

4.2 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

4.3 Study Enrollment Procedures

Potential participants will be identified, screened, and recruited through the clinical practices of 48 participating 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)

and should not be randomized, that patient will be excluded from the study. Effective randomization will occur through the random distribution of patients to centers employing each procedure (PFDD and PFD).

Barriers to enrollment will be addressed by monthly review of each site's screening log and REDCap screening/enrollment tool, which includes individuals who were eligible for enrollment, but were not enrolled in the study. These logs (see Appendix III) REDCap results will be supplied by St. Louis Children's Hospital/Washington University-St. Louis and will be reviewed to assure that each participating hospital is enrolling subjects actively and without significant bias. If study enrollment is slower than anticipated, more ancillary PRSRC sites will be added. PRSRC has been approached by numerous other pediatric neurosurgical centers, and adding more ancillary sites is readily feasible.

4.4 Subject Recruitment

When the clinical site coordinator and/or investigator becomes aware of a patient who is potentially eligible for enrollment into the study, patient eligibility will be confirmed, and the study investigator or coordinator will approach the child's parent/guardian and/or the patient (as applicable) to offer participation. Each center will maintain a screening log and complete a REDCap screening/enrollment tool for any participants who are eligible for enrollment, but are not enrolled into the study. These data will be reviewed to assure that each participating center is enrolling subjects without significant bias.

4.5 Parental Permission and Child Assent

After determining that a subject is eligible, the site investigator or designee will approach the parent/guardian to offer participation for their child in the study. The parent/guardian will be informed about the objectives of the study and the potential risks and benefits of trial participation. If the parent/guardian refuses permission for their child to participate, then all clinical care will be provided to the child in accordance usual institutional practice. Assent will be obtained for patients meeting age requirements for assent. Informed consent/assent will be obtained in the relatively focused atmosphere of a clinic or similar room rather than the more chaotic pre-operative holding area just before surgery.

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. 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.

5. STUDY INTERVENTIONS

5.1 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. Patients will be given the opportunity to re-consent into a study extension where any visits occurring within 5 years postoperatively will be documented, and the QOL questionnaires may be given annually. Research data will be collected at all stages by trained study research assistants/coordinators with strict oversight by site investigators using standard data collection forms. Neuro-imaging is a critical element of the trial, required both for enrollment and to monitor treatment efficacy. As such, MRI of the brain and cervical and thoracic spine are required prior to surgery. Pre-operative lumbar spine MRI will be left to the discretion of the surgeon. MRI of the cervical and thoracic spine are required 12 months (+/-2 months = 10-14 months) post-operatively. These are required for clinical care of CM+SM patients, regardless of participation in the study, and funding is not requested for these examinations. MRI of the lumbar spine, CT of the brain or cervical/thoracic/lumbar spine, "long cassette" or "scoliosis" X-rays, and/or X-rays of the cervical/thoracic/lumbar spine are not required but, will be reviewed if obtained. In the case where the patient returned outside the window for primary analyses, a secondary analysis will include those visits up to 24 months.

Each center will be informed which arm they have been randomized to before enrollment occurs. Therefore, every potential participant/family will be aware of which procedure would be performed if s/he agreed to participate. If the procedure is not an appropriate fit for a particular patient or, the patient/family is not comfortable with the predetermined procedure, the patient will not be enrolled and they will be offered standard of care treatment by the clinical team at that center

5.2 Handling of Study Interventions

All pediatric neurosurgeons involved in the study have completed both an accredited neurosurgery residency and a 1-year subspecialty fellowship in pediatric neurosurgery at a program accredited by the Accreditation Council for Pediatric Neurosurgery Fellowships (ACPNF) or by The American Osteopathic Association (AOA) and are either certified or eligible for certification by both the American Board of Neurological Surgeons (ABNS) and the American Board of Pediatric Neurological Surgery (ABPNS) or the American Osteopathic Board of Surgery (AOBS). Prior to participating in the study, each pediatric neurosurgeon must submit documentation verifying that s/he has performed ≥20 PFDD/PFD cases at the level of attending pediatric neurosurgeon *or* that that s/he performed ≥5 PFDD/PFD cases in the year preceding the participation in the study; and

3) review two videos showing the study-approved operative technique for PFDD and PFD in step-wise fashion. As detailed in the videos, PFDD and PFD both begin with a midline posterior suboccipital incision extending from the level of the inion inferiorly. Suboccipital craniectomy ± cervical laminectomies are performed based upon the level of tonsillar position on the pre-operative MRI. The posterior atlanto-occipital membrane and any additional constricting epidural bands are then dissected off the dura and bisected. For PFD, the operation is complete (dural scoring or splitting is permitted), and wound closure is initiated. For PFDD, the dura is then incised and retracted for microsurgical dissection. Intradural maneuvers are performed at the surgeon's discretion based on the intra-operative findings, but may include exploration/fenestration of an arachnoid veil, lysis of adhesions, or tonsillar reduction. Following the intradural dissection, the duraplasty is performed with autologous graft or dural substitute, and the wound is closed in standard fashion. Dural opening without subsequent dural closure is not permitted for PFDD or PFD.

5.3 Concomitant Interventions

5.3.1 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.

5.3.2 Required Interventions

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

5.3.3 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.

5.4 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.

6. STUDY PROCEDURES

6.1 Schedule of Evaluation

Assessment	Initial Visit	<6 Weeks Follow-Up Visit	3-6 Month Follow-up Visit	12 Month Follow-up Visit	14 months to 5 years postoperative
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	Optional
Complications	X	X	X	X	Optional
Pt Status	X	X	X	X	Optional
CHIP	X	X	X	X	Required
HUI-3 QOL	X	X	X	X	Required
Follow-up Symptoms		X	X	X	Optional
Follow-up Medications		X	X	X	Optional
Follow-up General Exam		X	X	X	Optional
Follow-up Neurological Exam		X	X	X	Optional
Follow-up Musculoskeletal Exam		X	X	X	Optional
Follow-up Radiology		^	^	X	Optional
Additional Neurological/Orthopedic Exam		X	X	X	Optional

^ 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

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Screening evaluations and associated studies for determining eligibility must be completed within 6 months of study entry.

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

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

Consenting Procedure

Informed consent will be obtained in the relatively focused atmosphere of a clinic or similar room rather than the more chaotic pre-operative holding area just before surgery.

When a clinical site investigator and/or research coordinator identifies a candidate for the study, patient eligibility will be confirmed, and the study investigator or coordinator will approach the individual to offer participation. After a thorough discussion to inform the patient and family of the rationale and objectives of the study and the risks, benefits, and alternatives to participation, written informed consent will be obtained from a parent or legal guardian (patient <18 years of age) or the patient themselves (patient ≥18 years of age). Additionally, assent will be obtained for patients of appropriate age, according to individual institutional practices. If study participation is declined, then all clinical care will be provided to the child in accordance with institutional practice and judgment. Each center will maintain a log of any individuals who are eligible for enrollment, but are not enrolled in the study. These logs will be reviewed to assure that each participating hospital is enrolling subjects without significant bias. In uncertain cases, adjudication of patient eligibility will be performed by a committee blinded to intervention and outcome and considering only the information available at the time of enrollment. Patients will be offered the opportunity to re-consent to participate in continued data collection for five years post-operatively.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

In order to allow participants and their families the opportunity to make an informed decision about participating in the study, the consent and assent shall be reviewed and signed prior to surgery. Enrollment may occur in one of the follow manners: 1) the participant signs the consent (participant 18 years); 2) at least one parent/legal guardian signs the consent (participant less than 18 years old); or 3) participant less than 18 years old co-signs the consent with at least one parent/legal guardian (requires that the participant is able to read the consent and understands and agrees with it; this may vary by the institution's local IRB's guidelines). For those participants who are unable to read and understand the consent, but are able to read, understand, and agree with the assent, that document will be signed based on the IRB guidelines.

Baseline Assessments

Baseline assessment data to be collected at the initial visit includes the following:

- Demographics
- Symptoms
- Childhood History
- Developmental History
- Allergies
- Concomitant Medications
- Family History
- Social History
- General Exam
- Neurological Exam
- Musculoskeletal Exam
- Radiology
    - Brain and cervical and thoracic spine MRI
    - MRI of the lumbar spine, CT of the brain or cervical/thoracic/lumbar spine, "long cassette" or "scoliosis" X-rays, and/or X-rays of the cervical/thoracic/lumbar spine are not required but will be reviewed if obtained.
- Diagnosis
- Clinical Course of Treatment
    - PFD or PFDD
- Complications
- CHIP
- HUI-3 QOL
- Patient Status
- Additional Neurological/Orthopedic surgery (if applicable)

Randomization

Individual trial centers will be randomized to perform either PFDD or PFD. In order to participate, trial 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 before the respective participating site enrolls a participant. All eligible participants within each cluster will then be approached for informed consent for the purposes of data collection for the trial. Each participant/guardian will know the randomized treatment selection at the time of the informed consent process.

6.2.3 Follow-up Visits

Data to be collected at follow-up visits includes the following:

- ≤ 6 weeks postoperative visit:
    - Clinical Course of Treatment
        - Any orthotics
        - Decompression
        - Any fusion or syrinx surgery
    - Complications

- CHIP (if > 1 visit during this period only collect for 1st visit)
- HUI-3 QOL(if > 1 visit during this period only collect for 1st visit)
- Patient Status
- Follow-up Symptoms
- Follow-up Medications
- Follow-up General Exam
- Follow-up Neurological Exam
- Follow-up Musculoskeletal Exam
- Follow-up Radiology Exam (if applicable)
- Additional Neurological/Orthopedic Surgery

- 3-6 months postoperative visit:
  - Clinical Course of Treatment
    - Any orthotics
    - Decompression
    - Any fusion or syrinx surgery
  - Complications
  - CHIP (if > 1 visit during this period only collect for 1st visit)
  - HUI-3 QOL (if > 1 visit during this period only collect for 1st visit)
  - Patient Status
  - Follow-up Symptoms
  - Follow-up Medications
  - Follow-up General Exam
  - Follow-up Neurological Exam
  - Follow-up Musculoskeletal Exam
  - Follow-up Radiology Exam (if applicable)
  - Additional Neurological/Orthopedic Surgery

6.2.4 Completion/Final Evaluation

Data to be collected at the final visit (12 +/- 2 months postoperative) includes the following:

- 12 ±2 months postoperative visit:
  - Clinical Course of Treatment
    - Any orthotics
    - Decompression
    - Any fusion or syrinx surgery
  - Complications
  - CHIP (if > 1 visit during this period only collect for 1st visit)
  - HUI-3 QOL (if > 1 visit during this period only collect for 1st visit)
  - Patient Status
  - Follow-up Symptoms
  - Follow-up Medications
  - Follow-up General Exam
  - Follow-up Neurological Exam
  - Follow-up Musculoskeletal Exam
  - Follow-up Radiology Exam

        - MRI of the cervical (including craniovertebral junction) and thoracic spine MRI
        - MRI of the brain or lumbar spine, CT of the brain or cervical/thoracic/lumbar spine, "long cassette" or "scoliosis" X-rays, and X-rays of the cervical/thoracic/lumbar spine are not required but will be reviewed if obtained.
    - Additional Neurological/Orthopedic Surgery

7. SAFETY ASSESSMENTS

Complications will be recorded at the following time points:

- Intra-operatively
- ≤ 6 months after initial PFD or PFDD
- 6-12 (+/- 2 months) months after initial PFD or PFDD

***For definitions of complications for this trial, see Section 7.1.*

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 after PFD or PFDD
    - Pseudomeningocele
    - CSF Leak
    - Hydrocephalus
    - Infection
    - Chemical meningitis
    - True meningitis
    - Cervical instability
    - Cerebellar ptosis with intractable headaches

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 first 6 months.

- Complications > 6 months after PFD or PFDD
    - Cervical instability
    - Infection
    - Hydrocephalus

        - Cerebellar ptosis with intractable headaches

Other unexpected complications that are related to the surgery will be recorded at the time interval of >6 months postoperatively.

Possible interventions for known complications are as follows:

- Intra-operative complications
    - Evacuation of hemorrhage
    - Open or endovascular repair vascular injury
- ≤ 6 months postoperative complications
    - 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
    - Shunt placement for hydrocephalus
    - Cervical collar and/or fusion for cervical instability
    - Cerebellopexy for cerebellar ptosis

- > 6 months postoperative complications
    - Surgical revision in operating room for the following:
        - Infection
        - Pseudomeningocele
    - Lumbar puncture for true meningitis
    - Shunt placements for hydrocephalus
    - Cervical collar and/or fusion for cervical instability
    - Cerebellopexy for cerebellar ptosis

7.1 Specification of Safety Parameters

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
        - Cranial nerve deficit

        - New weakness
        - Sensory loss
        - Bowel or bladder dysfunction
    - Death
- **Complications ≤ 6 months after PFD or PFDD**
    - 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.
    - 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.
    - True meningitis: lumbar puncture and positive cultures required.
    - Cervical instability
    - Cerebellar ptosis with intractable headaches
- **Need for interventions for complication management <6 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
    - Cerebellopexy for cerebellar ptosis
- **Complication ≤12 (+/- 2 months) months after initial PFDD or PFD**
    - 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.

- 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.
- True meningitis: lumbar puncture and positive cultures required.
- Cerebellar ptosis with intractable headaches

- **Need for interventions for complication management ≤12 (+/- 2 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
    - Cerebellopexy for cerebellar ptosis

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Complications and adverse events will be captured starting with intra-operative period and will continue for one year postoperatively. Additional surgeries, such as a decompression redo/revision, fusion surgery, anterior/ventral decompression, syrinx shunt, and syrinx fenestration will also have surgical complications and adverse events monitored and recorded for the one year collection period.

7.2.1 Preliminary Data

The Park-Reeves Syringomyelia Research Consortium (PRSRC) is a U.S.-based network of 36 major pediatric neurosurgery centers focused on improving the care of children with CM+SM. The largest research effort for CM+SM to date, PRSRC began enrolling patients both retrospectively and prospectively in 2011. Through the PRSRC, comprehensive clinical and radiographic data have been obtained on >600 CM+SM patients. Table 3 summarizes the post-operative complications observed in 589 subjects with complete data who underwent PFDD or PFD since 2011, as support for PFD has grown. Within the PRSRC, rates of complications are remarkably consistent with those reported in the meta-analysis by Durham and Fjeld-Olenec in 2008 (Table 2)[27], with complications noted in 17.8% following PFDD versus 2.7% after PFD. In addition, a corrective neurosurgical procedure for complication management was needed more often after PFDD compared to PFD (10.1% versus 2.7%). However, repeat decompression surgery for persistent disease was required in only 5.0% of PFDD cases versus 12.3% after PFD.

Table 3. Complications and Need for Repeat Surgical Decompression for CM+CM in the Park-Reeves Syringomyelia Research Consortium.

	PFDD		PFD	
	n	**%**	**n**	**%**
Surgical Complications				
Vascular Injury	1	0.20%	0	0%
Pseudomingocele	28	5.4%	1	1.4%
CSF Leak	20	3.9%	1	1.4%
Infection	2	0.4%	0	0%
Chemical Meningitis	24	4.7%	0	0%
Hydrocephalus	15	2.9%	0	0%
Cervical Instability	2	0.40%	0	0%
Total	92	17.8%	2	2.7%
Surgical Procedures for Complication Management				
Oversewing of Wound	6	1.2%	1	1.4%
Wound Revision	13	2.5%	1	1.4%
External CSF Drainage	22	4.3%	0	0
Shunt Required	10	1.9%	0	0%
Req. for Cervical Fusion	1	0.20%	0	0%
Total	52	10.1%	2	2.7%
	PFDD		**PFD**	
	n	**%**	**n**	**%**
Repeat Decompression Surgery (PFDD or PFD)	26**	5.0%	9	12.3%

*n=589 total. Imbalance in PFDD (n=516) vs PFD (n=73) results from the epoch of enrollment (2002-2014); PFD only offered routinely since 2010).
**One patient had 3 repeat decompressions.

In planning a clinical trial for CM+SM, it is important to select appropriate inclusion criteria for study patients in order to: 1) enhance homogeneity in disease severity among study participants; 2) permit appropriate comparisons across participants and groups; and 3) ensure clinical equipoise among treating physicians. With this goal in mind, our group recently created the Chiari Severity Index, or CSI, a pre-operative instrument that stratifies children with CM+/-SM based on their probability of postoperative improvement[12]. The CSI was developed in conjunction with patient and families and uses their input as a critical arbiter of outcome. Two advanced methodologies, sequential sequestration and conjunctive consolidation, were used to identify key clinical and radiographic predictors of clinical outcome and then to integrate them into one useful CSI (Fig. 3).

We also recently completed a systematic review of outcome methods used in studies of CM+SM and noted that studies of CM+SM were significantly impeded by inconsistent and limited methods of evaluating clinical outcomes[28]. The majority of papers used a clinician's "gestalt" impression of symptomatic improvement (Fig. 4). Only 3 papers used scales validated in patients with CM+/-SM, and only 7 articles incorporated patient-response instruments. Our review emphasized the need for CM+SM-specific patient-based instruments to improve research in this field [28].

Figure 3. The Chiari Severity Index, or CSI, was developed using sequential sequestration of pre-operative clinical and radiographic parameters, followed by conjunctive consolidation of independent clinical and radiographic indices via [12]. Syrinx size was the only radiographic measure associated with clinical outcome, with a critical threshold of 6 mm diameter.

The Chiari Health Index in Pediatrics (CHIP) was developed in response to the deficiencies noted in our systematic review and addresses the following criteria: 1) it focuses on the complaints most important to CM + SM patients; 2) it relies on patient involvement in answering the questions; 3) it is age-appropriate; and 4) and it helps inform clinical decision making regarding the treatment and management of these patients [29]. As with other Health-Related QOL (HRQOL) inventories, the CHIP was designed to be discriminative, evaluative, and predictive [30, 31]. A single 45-item form, the CHIP can be completed by a parent only, a child only, or a parent and child together.

Psychometric research methodologies, including item generation and development, evaluation of construct validity, test-retest reliability, and confirmatory factor analysis were used in the development and validation of the CHIP (Table 4). The number of items for each component is as follows: pain frequency 5, pain severity 5, non-pain symptoms 11, and psychosocial characteristics 24. In our initial studies, we have demonstrated that the CHIP is a feasible, reliable, and valid assessment of HRQOL in pediatric CM + SM patients. In particular, each domain and the overall HRQOL tool showed strong feasibility (i.e. the practical ability of participants to complete the survey) and internal consistency within their respective domain ($\alpha \geq 75\%$), a measure of reliability of the test [32]. In addition, the physical ($r = 0.73$) and psychosocial components ($r = 0.94$), as well as overall HQROL score ($r = 0.83$), had high test-retest reliability, even over a median test-retest interval of 70 days. Finally, we demonstrated the construct validity of the CHIP by showing the correlation between CHIP scores and concurrent HUI-3 scores within similar domains [32].

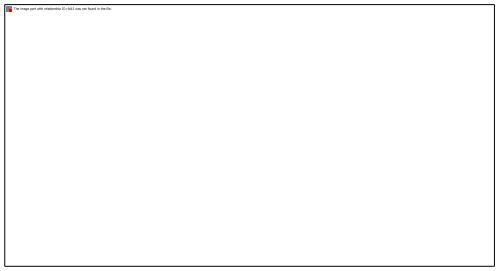

Figure 4. Systematic review of outcome methods used in 74 CM+/-SM studies revealed inconsistent and limited methods of evaluating clinical outcomes; a majority of papers relied on clinician 'gestalt' assessments rather than CM+SM-specific, patient-based instruments.[28]

Table 4. Chiari Health Index for Pediatrics (CHIP) Instrument Characteristics [29].

	Mean±SD	Range	Floor effect	Ceiling effect	Feasibility (% complete)	Consistency (Cronbach's α)	Test Re-test Reliability (Pearson's r)

Physical	0.66±0.20	0.27-1.00	0%	2%	84%	0.89	0.73
Pain Frequency	0.59±0.26	0.00-1.00	2%	7%	100%	0.84	0.62
Pain Severity	0.69±0.20	0.19-1.00	0%	7%	95%	0.75	0.83
Non-Pain	0.82±0.17	0.32-1.00	0%	22%	87%	0.85	0.83
Psychosocial	0.68±0.17	0.29-0.97	0%	0%	85%	0.92	0.94
Overall HRQOL	0.66±0.18	0.33-0.97	0%	0%	75%	0.92	0.83

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
- CSF Leak
- Hydrocephalus
- Infection
- Chemical meningitis
- True meningitis
- Cervical instability
- Cerebellar ptosis with intractable headaches

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. For inclusion of all followed patients in the case where the patient returned outside the planned study follow-up window, a secondary analysis will include those visits up to 24 months.

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
    - Cerebellar ptosis with intractable headaches
    -

- **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

7.3 Reporting Procedures

Reporting Procedures
The PI of the Study, Dr. Limbrick, will act as the medical monitor for the study. If Dr. Limbrick is unavailable, a qualified physician will be designated to fulfill this function. SAEs will be reported by the clinical site investigator to the Clinical and Data Coordinating Centers (CCC and DCC) within 24 hours. The DCC will report all events that are classified as serious, unexpected, and study-related to the study Steering Committee, and the DSMB, by fax or telephone, within 3 calendar days of receiving the report from the clinical site. A written report will be sent to the DSMB within 15 calendar days and these reports will be sent to clinical investigators for their submission to their respective IRBs. The DSMB will also review all AEs (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The DCC will provide written summary of the DSMB's periodic review of AEs to clinical site investigators for submission to their respective IRBs.

Institutional Review Board (IRB) Reporting

SAEs that are judged to be related to participation in the study will be reported to site investigators at all participating clinical centers. Each site investigator will need to report these to the site's local IRB. Each IRB will assess the impact of these reports on its judgement to allow the study to continue at the respective site. After each DSMB meeting, the DSMB report indicating approval to continue the study will be provided to each participating clinical center, and should be included in the annual IRB renewal materials. This DSMB recommendation will be based on DSMB examination of all SAEs that have been reported, review of interim reports, and ongoing validity and scientific merit of the study.

7.4 Follow-up for Adverse Events

Data Collection Procedures for Adverse Events
All study subjects will be monitored for adverse events. Adverse events, whether expected or unexpected, will be recorded according to the time frame of first occurrence. Time frames are distinguished as intra-operative, ≤6 months, and >6 months. Each time the participant returns for an outpatient neurosurgery visit, s/he will be queried by the study staff for adverse events. Details of an event should be investigated and study documentation supported with the related medical records. Interventions related to the adverse event will be noted in the study database per the Data Elements. Any medical condition present at the time of enrollment, which remains unchanged or improved, will not be recorded as an adverse event.

7.5 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.

8. 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.

9. STATISTICAL CONSIDERATIONS

9.1 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 (+/- 2 months) 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. In the case where the patient returned outside planned study follow-up window, a secondary analysis will include those visits up to 24 months.

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.

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, and hydrocephalus) and requirement for additional surgery for wound revision or CSF diversion will be lower after PFD compared with PFDD.

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.

Specific Aim 3: Determine if PFD is associated with superior QOL compared to 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.

9.2 Sample Size and Randomization

9.2.1 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 per center. For cluster randomization, a computer-generated randomization sequence will be generated independently by the study statistician. Overall sample size of up to 238 participants will be enrolled. Approximately 50% participants per procedure over the enrollment period.

Potential participants will be identified, screened, and recruited through the clinical practices of 36 participating PRSRC sties in addition to 8 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).

9.3 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.

9.4 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.

Because this is a surgical trial, an Adjudication Committee, consisting of two pediatric neurosurgeons and one pediatric neuroradiologist and 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).

9.5 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.

Final Comparative Analysis

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.

Comparison methods

The primary outcome is a binomial outcome measured as a surgical complication and/or requirement for reoperation for complication management ≤6 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].

Secondary outcomes include Treatment Efficacy variables and Quality of Life variables. Continuous variables measured at 3 time points over the 12 (+/- 2 months) 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 GEE methods accounting for cluster. In the case where the patient returned outside the planned study follow-up window, a secondary analysis will include those visits up to 24 months.

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. As the 5th subgroup, the effect of surgeon's experience on the occurrence of surgical complications and requirements for re-operations for complications for each procedure during the 1st vs 2nd year of the award period will be assessed. 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. If the test of interaction indicates a significant interaction for any subgroup, then, Gail and Simon's test of qualitative interaction will be performed [41]. 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 the syrinx diameter will be performed. Each of the three specific aims will be separately analyzed within the syrinx diameters of 3 to 6 mm and 7 to 9 mm for exploratory purposes. 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.

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 238 patients, approximately 119 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. The same power level can also be achieved by enrolling patients from 30 centers with an average cluster size of 5.

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 a minimum of 148 subjects total (74 per group) and up to 238, over the entire trial enrollment period, which is proposed to be extended to December 31, 2018.

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 center), and we have a large number of centers available for enrollment (48 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 will recruit 48 centers with a cluster size averaging 6 subjects. Therefore, overall sample size of enrolled patients will be 148 patients, approximately 74 patients per procedure over the enrollment period. These numbers are achievable, as our data suggest there is >500 potential study candidates across the 48-center network over two years.

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 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 concluded 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 rates. 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 0.17 units, for the clinical improvement outcome, is smaller than 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.

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.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

The DCC will create source documents and disseminate them to all of the participating centers. Ultimately, the data on the source documents will be transcribed to an electronic database created by the DCC. Similarly, imaging will be uploaded to a separate electronic platform, the Central Neuroimaging Database Archive (CNDA). This platform is maintained and managed at Washington University-St. Louis.

10.2 Data Management

The DCC will monitor each site's data and interpret the respective imaging. The University of Iowa will oversee the DCC and process data in the following manner:

- Data Management
  - Design and modify data dictionary (the information that is being collected)
  - Design and modify SQL Server database
  - Quality Control
- Retrieval and Reports

- Assist in preparation of data quality reports
- Assist in preparation of progress reports

- Design and Analysis
  - Consult with investigators in design and analysis of research questions

10.3 Quality Assurance

10.3.1 Training

All pediatric neurosurgeons involved in the study have completed both an accredited neurosurgery residency and a 1-year subspecialty fellowship in pediatric neurosurgery at a program accredited by the Accreditation Council for Pediatric Neurosurgery Fellowships (ACPNF)) or by The American Osteopathic Association (AOA) and are either certified or eligible for certification by both the American Board of Neurological Surgeons (ABNS) and the American Board of Pediatric Neurological Surgery (ABPNS) or the American Osteopathic Board of Surgery (AOBS). Prior to participating in the study, each pediatric neurosurgeon must submit documentation verifying that s/he has performed ≥20 PFDD/PFD cases at the level of attending pediatric neurosurgeon *or* that that s/he performed ≥5 PFDD/PFD cases in the year preceding the participation in the study; and 3) review two videos showing the study-approved operative technique for PFDD and PFD in step-wise fashion. As detailed in the videos, PFDD and PFD both begin with a midline posterior suboccipital incision extending from the level of the inion inferiorly. Suboccipital craniectomy ± cervical laminectomies are performed based upon the level of tonsillar position on the pre-operative MRI. The posterior atlanto-occipital membrane and any additional constricting epidural bands are then dissected off the dura and bisected. For PFD, the operation is complete (dural scoring or splitting is permitted), and wound closure is initiated. For PFDD, the dura is then incised and retracted for microsurgical dissection. Intradural maneuvers are performed at the surgeon's discretion based on the intra-operative findings, but may include exploration/fenestration of an arachnoid veil, lysis of adhesions, or tonsillar reduction. Following the intradural dissection, the duraplasty is performed with autologous graft or dural substitute, and the wound is closed in standard fashion. Dural opening without subsequent dural closure is not permitted for PFDD or PFD. Periodic quality assurance checks will be performed by reviewing a subset of operative notes from randomly selected participating surgeons.

The DCC will have a representative train each participating site's research personnel how to collect data on source documents; transcribe them to the electronic database; and instructions on how to upload imaging to the Central Neuroimaging Data Archive. Training will be documented and must be completed before access is granted to the respective portal.

10.3.2 Quality Control Committee

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.

Members of the DSMB will include a pediatric neurosurgeon with relevant expertise in CM+SM, a neuroradiologist, a biostatistician, a clinical ethicist, and a patient partner (Sandy Spears).

10.3.3 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
  - Cerebellar ptosis with intractable headaches
- **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
  - Cerebellopexy for cerebellar ptosis

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.

10.3.4 Protocol Deviations

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

10.3.5 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.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

Candidates for participants in the proposed study, "Posterior Foss Decompression with or without Duraplasty for Chiari type I Malformation with Syringomyelia" are between the ages of day-of-life 1 through 21 years. Children are a vulnerable population, and it is critical that their protection be given the utmost consideration. We will conduct our research under the most stringent guidelines, the Good Clinical Practice (GCP) guidelines. In a multi-institutional study setting, the protection of children becomes more complex and involves multiple research institutions with their respective institutional review boards (IRBs), the funding agency (PCORI), the data safety monitoring board (DSMB), Park-Reeves Syringomyelia Research Consortium (PRSRC) investigators, and the PRSRC Research Advisory Board, which will serve as the study steering committee It is paramount that the PI and the DCC ensure that these entities work in collaboration to

protect pediatric subjects and verify that the study is fully compliant with all regulatory and ethical requirements and policies.

Patient partner and mother of a CM+SM patient, Sandy Spears, will serve as a patient representative on the study's Data Safety and Monitoring Board. In doing so, she will help to ensure that the safety and rights of study participants is protected throughout the duration of the study.

The DCC will provide training for clinical site investigators and designees regarding study procedures and GCP. The following measures are designed to protect against risk.

Risk due to loss of confidential information
Risk due to loss of confidential information is mitigated by several factors. All evaluation forms and reports will be identified only by a coded number to maintain patient confidentiality. All records will be kept in a locked/password protected computer. Clinical information will not be released without the written permission of the parent or legal guardian, except as necessary for monitoring by the funding agency, the DCC, or other governmental regulatory bodies. Specifics pertaining to this study for risks due to loss of confidential information are detailed below.

PRSRC Registry Electronic Database (EDB)
Data for this study will be entered into the electronic database system maintained by the DCC. The server facility is locked and separately secured from the remainder of the DCC. Its entry and exit access to the building is monitored by cameras, additional key codes, and security personnel year round. The DCC coordinates its network infrastructure and security with the ITC (Information Technology Center) information systems at Washington University-St. Louis. This provides effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes multiple firewalls, routers, and high-speed switches. User authentication is centralized with four Windows 2012R2 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies. Both access methods providing at least 128 bit encryption. All DCC Web-based systems use the SSL protocol to transmit data securely over the internet. Direct access to DCC machines is only available while physically located in the DCC offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against the servers, and IT staff is automatically notified of intrusion alerts. Security is maintained with Windows 2012R2 user/group domain-level security. Users are required to change their password every 90 days, and workstations time out after 5 minutes of inactivity. All files are protected at group and user levels. Database security is handled in a similar manner with group-level access to databases, tables, and views in Microsoft SQL Server.

The investigators and staff of the DCC are fully committed to the security and confidentiality of data collected for the study. All personnel involved with the DCC

have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. All users are required to sign specific agreements concerning security, confidentiality, and use of our information systems before access is provided.

Centralized Neuroimaging Data Archive (CNDA)
The Centralized Neuroimaging Data Archive (CNDA) is an imaging informatics platform that provides secure data management services for Washington University – St. Louis and collaborating investigators. The CNDA's services include automated archiving of research imaging studies from all of the University's scanners, automated quality control and image processing routines, and secure web-based access to acquired and post-processed data. The CNDA currently stores over 60,000 individual sessions, representing data from a wide range of multi-site and in-house studies. It also manages thousands of non-imaging experiments, including neuropsychological, clinical, biomarker, and behavioral data. The CNDA is built on XNAT [51, 52], a widely used open source imaging informatics platform designed to facilitate common data management and productivity tasks for neuroimaging and associated data. Notable features include: 1) support for a range of image upload/download methods, including DICOM, web services, and web browsers; 2) an extensible data model that simplifies the incorporation of new data types by automatically generating the necessary database tables and relations, user interface components, and search engine plug-ins; 3) quality control modules and audit trails, including a virtual quarantine that houses uploaded data until authorized users have validated them and a complete history profile that tracks all changes made to the managed data; 4) a secure web-based user interface for data entry and access; 5) a sophisticated search engine that builds queries across data types; 6) an online image viewer that supports a number of common neuroimaging formats, including DICOM and Analyze; and 7) a pipeline engine for automating image processing routines.

The CNDA is widely used to support studies that include geographically dispersed data acquisition sites and analysis teams. Example studies include the Dominantly Inherited Alzheimer Network (DIAN), a 15-site study of inherited Alzheimer's disease that includes PET, MR, neuropsychological, clinical, and tissue data; the Park-Reeves Syringomyelia Research Consortium a 36-site study of Chiari malformation and syringomyelia in subjects under 21 years of age, including MR, CT and CR data; and INTRUST, a 10-site study of traumatic brain injury and post-traumatic stress disorder in combat veterans. Scans are uploaded using a user friendly web-based tool that removes identifiers from the image file metadata and transfers the files to the CNDA over an encrypted protocol.

The CNDA implements a number of features and procedures to ensure the security and integrity of the data it hosts and full HIPAA compliance. All data coming into and out of the CNDA are transmitted over secure channels using SSL. All data are stored on a level 5 RAID device with disaster recovery and offsite backup. Snapshots of the relational database are taken nightly, enabling reconstruction of the database from any

time point in the study. Access to study data is restricted to authorized users who are assigned specific access privileges (create, read, edit, delete) according to their role in the study. All logins and access to data are tracked in the internal audit system.

The CNDA offers a number of features to monitor and maintain the quality of acquired data. As data are uploaded to the system, sequence details (e.g. flip angle, repetition time) can be validated against a study specific protocol to ensure that the acquisition is compliant. Noncompliant scans are flagged in the system for immediate follow-up. Automated image analysis routines are then executed to determine overall image quality specific to the acquisition type. For fMRI, for example, signal to noise and subject movement histograms are generated. The CNDA also supports radiological evaluation and manual quality assessments that can be optionally used by studies. The output from these routines is available to users in web-based reports and is flagged when key values fall outside acceptable limits.

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

11.2 Informed Consent Forms

The consent form will include the following:

- Purpose statement
- Participant commitment
- Costs
- Risks
- Benefits
- Disclosure of alternative
- Statement of confidentiality
- Study contact information

When a clinical site investigator and/or research coordinator identifies a candidate for the study, patient eligibility will be confirmed, and the study investigator or coordinator will approach the individual to offer participation. After a thorough discussion to inform the patient and family of the rationale and objectives of the study and the risks, benefits, and alternatives to participation, written informed consent will be obtained from a parent or legal guardian (patient <18 years of age) or the patient themselves (patient ≥18 years of age). Additionally, assent will be obtained for patients of appropriate age, according to individual institutional practices. If study participation is declined, then all clinical care will be provided to the child in accordance with institutional practice and judgment.

11.3 Participant Confidentiality

Each center will be responsible for coding data prior to entry in the PRSRC database. Each center will be required to demonstrate IRB approval from their own university or

institution. The electronic database and CNDA is password-protected. For subjects enrolled at Washington University-St. Louis, we will maintain a key with the de-identification and coding information in a locked office.

All records related to a participant's research will be stored in locked filing cabinets or on computers protected with passwords. The participant's identity on these records will be indicated by a case number rather than by name, and the information linking these case numbers with the participant's identity will be kept separate from the research records. The participant will not be identified by name in any publication of the research results.

All data collected will be entered into the PRSRC Registry Electronic Database (EDB). This EDB was created in 2011 and has been used for collection of prospective, multicenter clinical and radiographic patient data since 2012. PRSRC privacy and confidentiality principles have been maintained in accordance with the PCORI Standards for Data Registries, HIPAA regulations, Good Clinical Practice guidelines, and the Washington University-St. Louis Human Research Protection Office. Each PRSRC site and PRSRC ancillary site shares a detailed data use agreement with Washington University-St. Louis. Prior to accessing the PRSRC Registry EDB, PRSRC investigators and coordinators from each site must demonstrate IRB approval by their own institution and undergo an online training and privacy/confidentiality module. A coded, limited data set may then be entered, with the key to the code maintained at each collaborating site. This information will only be kept onsite at each institution and will only be available to key personnel of this study, data monitors and IRB officials as needed. At the conclusion of the study, the de-identified data will be retained indefinitely by the P.I. The data with PHI will be destroyed at the conclusion of the study. The PRSRC, PCORI, this institution, the Principal Investigator, and his/her staff will comply with any and all laws regarding the privacy of such information.

11.4 Study Discontinuation

The study may be discontinued at any time by the Principal Investigator, David Limbrick, MD, PhD; the IRB, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

Below are the list of committees involved with the research study. See *appendix II*.

- Dissemination Committee
- PRSRC Research Advisory Board
- PRSRC Research Team
- Study Steering Committee
- Data Safety and Monitoring Board
- Adjudication Committee

13. PUBLICATION OF RESEARCH FINDINGS

A *Dissemination Committee* has been created to monitor the efficacy of efforts aimed at disseminating study progress and research results. This committee will include Drs. Limbrick (study PI) and

Shannon (Co-PI), Dr. Tuite (Site PI and key personnel), as well as Haley Vance (Co-I, certified pediatric nurse practitioner-acute care, non-physician stakeholder) and Elaine Kennedy (Co-I, certified pediatric nurse practitioner, non-physician stakeholder) and the leaders of our patient advocacy group partners, Mr. Labuta and Ms. Poppe (both Co-Is). The Dissemination Committee will also include patient partners and Co-Is, Ms. Reynolds and Ms. Tramelli. Finally, as study results become available, the PRSRC will convene a consensus conference to discuss the results and their implications for clinical practice and patient education, and to draft evidenced-based guidelines for the surgical treatment of CM+SM.

A data sharing procedure has been developed by the research team in accordance with PCORI guidelines to facilitate the use of these data by other researchers. All code books, statistical programming code, and a cleaned, de-identified copy of the final data set will be made available to other researchers if requested within 9 months of the final analysis. Likewise, datasets will be provided to any peer-reviewed journal requesting this information in support of manuscripts that resulted from the project. Researchers requesting access to the data will be directed to the Washington University Chiari website (https://chiari.wustl.edu) where a description of the available data and the data release policy will be posted. The researchers will then submit a short proposal (no more than 5 pages) to Dr. Limbrick, principal investigator. This proposal would then be reviewed by the PI, the research team and patient partners. If there are concerns about confidentiality arising from the project, data will not be released. Assuming that confidentiality can be maintained, the committee will make every effort to share data and will only deny requests under the following conditions:

1. The central purpose of the study is not research or evaluation.
2. The research goals are not feasible using the current study data.
3. The proposed research involves data that may compromise the privacy or confidentiality of individuals, providers or institutions.
4. The data processing necessary to produce the requested files places an unusually heavy burden on the data processing staff.
5. The requestors have not demonstrated the necessary experience and expertise required to carry out the proposed research.

If there are specific concerns raised during the review process, the reviewer's comments will be sent to the requestor and the requestor will be given the opportunity to respond to these comments and resubmit his/her proposal. Any manuscripts or publications that result from the use of PRSRC data by other research teams will be reviewed by the PRSRC investigators to insure patient and provider confidentiality. This last review is not intended for scientific purposes, only to protect confidentiality.

REFERENCES References Cited

1. (NINDS), N.I.o.N.D.a.S. *NINDS Syringomyelia Information Page*. 2015.
2. Research, O.o.R.D. *Syringomyelia*. 2009.
3. Di Lorenzo, N. and F. Cacciola, *Adult syringomyelia. Classification, pathogenesis, and therapeutic approaches.* J Neurosurg Sci, 2005. **49**(3): p. 65-72.
4. Heiss, J.D., et al., *Elucidating the pathophysiology of syringomyelia.* J Neurosurg, 1999. **91**(4): p. 553-62.
5. Small, J.A. and P.H. Sheridan, *Research priorities for syringomyelia: a National Institute of Neurological Disorders and Stroke workshop summary.* Neurology, 1996. **46**(2): p. 577-82.
6. Brickell, K.L., et al., *Ethnic differences in syringomyelia in New Zealand.* J Neurol Neurosurg Psychiatry, 2006. **77**(8): p. 989-91.
7. Arnautovic, A., et al., *Pediatric and adult Chiari malformation Type I surgical series 1965-2013: a review of demographics, operative treatment, and outcomes.* J Neurosurg Pediatr, 2015. **15**(2): p. 161-77.
8. Fernandez, A.A., et al., *Malformations of the craniocervical junction (Chiari type I and syringomyelia: classification, diagnosis and treatment).* BMC Musculoskelet Disord, 2009. **10 Suppl 1**: p. S1.
9. Hida, K., et al., *Pediatric syringomyelia with chiari malformation: its clinical characteristics and surgical outcomes.* Surg Neurol, 1999. **51**(4): p. 383-90; discussion 390-1.
10. Mueller, D. and J.J. Oro, *Prospective analysis of self-perceived quality of life before and after posterior fossa decompression in 112 patients with Chiari malformation with or without syringomyelia.* Neurosurg Focus, 2005. **18**(2): p. ECP2.
11. Tisell, M., J. Wallskog, and M. Linde, *Long-term outcome after surgery for Chiari I malformation.* Acta Neurol Scand, 2009. **120**(5): p. 295-9.
12. Greenberg, J.K., et al., *The Chiari severity index: a preoperative grading system for Chiari malformation type 1.* Neurosurgery, 2015. **76**(3): p. 279-85.
13. Vakharia, V.N., M.R. Guilfoyle, and R.J. Laing, *Prospective study of outcome of foramen magnum decompressions in patients with syrinx and non-syrinx associated Chiari malformations.* Br J Neurosurg, 2012. **26**(1): p. 7-11.
14. Batzdorf, U., *Primary spinal syringomyelia. Invited submission from the joint section meeting on disorders of the spine and peripheral nerves, March 2005.* J Neurosurg Spine, 2005. **3**(6): p. 429-35.
15. Tubbs, R.S., et al., *The pediatric Chiari I malformation: a review.* Childs Nerv Syst, 2007. **23**(11): p. 1239-50.

16. Wellons, J.C. and M.D. Smyth. *Neurosurgical Face Off: Durotomy and Duraplasty Versus No Durotomy and Duraplasty*. in *Annual Scientific Meeting of the American Association of Neurological Surgeons*. 2013. New Orleans.
17. Munshi, I., et al., *Effects of posterior fossa decompression with and without duraplasty on Chiari malformation-associated hydromyelia.* Neurosurgery, 2000. **46**(6): p. 1384-9; discussion 1389-90.
18. Ventureyra, E.C., H.A. Aziz, and M. Vassilyadi, *The role of cine flow MRI in children with Chiari I malformation.* Childs Nerv Syst, 2003. **19**(2): p. 109-13.
19. Navarro, R., et al., *Surgical results of posterior fossa decompression for patients with Chiari I malformation.* Childs Nerv Syst, 2004. **20**(5): p. 349-56.
20. Limonadi, F.M. and N.R. Selden, *Dura-splitting decompression of the craniocervical junction: reduced operative time, hospital stay, and cost with equivalent early outcome.* J Neurosurg, 2004. **101**(2 Suppl): p. 184-8.
21. Yeh, D.D., B. Koch, and K.R. Crone, *Intraoperative ultrasonography used to determine the extent of surgery necessary during posterior fossa decompression in children with Chiari malformation type I.* J Neurosurg, 2006. **105**(1 Suppl): p. 26-32.
22. Galarza, M., S. Sood, and S. Ham, *Relevance of surgical strategies for the management of pediatric Chiari type I malformation.* Childs Nerv Syst, 2007. **23**(6): p. 691-6.
23. Mutchnick, I.S., et al., *Decompression of Chiari malformation with and without duraplasty: morbidity versus recurrence.* J Neurosurg Pediatr, 2010. **5**(5): p. 474-8.
24. Litvack, Z.N., R.A. Lindsay, and N.R. Selden, *Dura splitting decompression for Chiari I malformation in pediatric patients: clinical outcomes, healthcare costs, and resource utilization.* Neurosurgery, 2013. **72**(6): p. 922-8; discussion 928-9.
25. Lee, A., et al., *Comparison of posterior fossa decompression with or without duraplasty in children with Type I Chiari malformation.* Childs Nerv Syst, 2014. **30**(8): p. 1419-24.
26. Rocque, B.G., et al., *Treatment practices for Chiari malformation type I with syringomyelia: results of a survey of the American Society of Pediatric Neurosurgeons.* J Neurosurg Pediatr, 2011. **8**(5): p. 430-7.
27. Durham, S.R. and K. Fjeld-Olenec, *Comparison of posterior fossa decompression with and without duraplasty for the surgical treatment of Chiari malformation Type I in pediatric patients: a meta-analysis.* J Neurosurg Pediatr, 2008. **2**(1): p. 42-9.
28. Greenberg, J.K., et al., *Outcome methods used in clinical studies of Chiari malformation Type I: a systematic review.* J Neurosurg, 2015. **122**(2): p. 262-72.
29. Shannon, C.N., et al., *The Chiari Health Index for Pediatrics.* J Neurosurg Pediatr, 2015. **In Press**.
30. Guyatt, G.H., B. Kirshner, and R. Jaeschke, *Measuring health status: what are the necessary measurement properties?* J Clin Epidemiol, 1992. **45**(12): p. 1341-5.
31. Kirshner, B. and G. Guyatt, *A methodological framework for assessing health indices.* J Chronic Dis, 1985. **38**(1): p. 27-36.
32. Carmines, E.G. and R.A. Zeller, *Reliability and Validity Assessment. Quatitative Applications in the Social Sciences.* Vol. 17. 1979, Newbury Park, CA: Sage Publications.
33. Weinstein, J.N., et al., *Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort.* JAMA, 2006. **296**(20): p. 2451-9.

34. Drake, J.M., et al., *Consensus definitions of complications for accurate recording and comparisons of surgical outcomes in pediatric neurosurgery.* J Neurosurg Pediatr, 2012. **10**(2): p. 89-95.
35. Huang, S., M.H. Fiero, and M.L. Bell, *Generalized estimating equations in cluster randomized trials with a small number of clusters: Review of practice and simulation study.* Clin Trials, 2016. **13**(4): p. 445-9.
36. Peters, T.J., et al., *Comparison of methods for analysing cluster randomized trials: an example involving a factorial design.* Int J Epidemiol, 2003. **32**(5): p. 840-6.
37. Little, R.J.A. and D.B. Rubin, *Statistical Analysis With Missing Data*. Second Edition ed. 2002, Hoboken, N.J.: Wiley.
38. Buck, S.F., *A method of estimation of missing values in multivariate data suitable for use with an electronic computer.* J Roy Statist Soc, 1960. **22**: p. 302-6.
39. Godzik, J., et al., *Relationship of syrinx size and tonsillar descent to spinal deformity in Chiari malformation Type I with associated syringomyelia.* J Neurosurg Pediatr, 2014. **13**(4): p. 368-74.
40. Greenberg, J.K., et al. *Population-Based Analysis of Complications Associated with Chiari Malformation Type 1 Surgery in Children.* in *AANS/CNS Joint Section on Pediatric Neurosurgery*. 2014. Amelia Island, Florida.
41. Gail, M. and R. Simon, *Testing for Qualitative Interactions between Treatment Effects and Patient Subsets.* Biometrics, 1985. **41**(2): p. 361-372.
42. Hankinson, T., R.S. Tubbs, and J.C. Wellons, *Duraplasty or not? An evidence-based review of the pediatric Chiari I malformation.* Childs Nerv Syst, 2011. **27**(1): p. 35-40.
43. Campbell, M.K., P.M. Fayers, and J.M. Grimshaw, *Determinants of the intracluster correlation coefficient in cluster randomized trials: the case of implementation research.* Clin Trials, 2005. **2**(2): p. 99-107.
44. Campbell, M.K., et al., *Sample size calculator for cluster randomized trials.* Computers in Biology and Medicine, 2004. **34**(2): p. 113-25.
45. Eldridge, S.M., D. Ashby, and S. Kerry, *Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method.* Int J Epidemiol, 2006. **35**(5): p. 1292-300.
46. Schumi, J. and J.T. Wittes, *Through the looking glass: understanding non-inferiority.* Trials, 2011. **12**: p. 106.
47. Rothmann, M., et al., *Design and analysis of non-inferiority mortality trials in oncology.* Stat Med, 2003. **22**(2): p. 239-64.
48. Rothmann, M.D. and H.H. Tsou, *On non-inferiority analysis based on delta-method confidence intervals.* J Biopharm Stat, 2003. **13**(3): p. 565-83.
49. Administration, U.S.D.o.H.a.H.S.F.a.D., *Guidance for Industry Non-Inferiority Clinical Trials*, U.S.D.o.H.a.H.S.F.a.D. Administration, Editor. 2010: Rockville, MD.
50. Ladner, T.R., et al., *Health-related quality of life in pediatric Chiari I malformation: the Chiari Health Index for Pediatrics (CHIP).* J Neurosurg Pediatr, In Press.
51. Marcus, D.S., et al., *The open-source neuroimaging research enterprise.* J Digit Imaging, 2007. **20 Suppl 1**: p. 130-8.
52. Marcus, D.S., et al., *The Extensible Neuroimaging Archive Toolkit: an informatics platform for managing, exploring, and sharing neuroimaging data.* Neuroinformatics, 2007. **5**(1): p. 11-34.
53. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster

randomised trials. BMJ 2004;328:702-708.

14. SUPPLEMENTS/APPENDICES

Appendix I

Participating Sites

Sites	Principal Investigators
All Children's Hospital	Tuite, Gerald, and Jallo, George
Arkansas Children's Hospital/University of Arkansas School of Medicine	Albert, Greg
Arnold Palmer Hospital-Orlando Health	Olavarria, Greg
Boston Children's Hospital	Scellig, Stone
Children's Healthcare of Atlanta	Chern, Joshua
Children's Hospital at Dartmouth-Hitchcock/ Dartmouth Geisel School of Medicine	Bauer, David
Children's Hospital Colorado	O'Neill, Brent
Children's Hospital of Birmingham	Johnston, James
Children's Hospital of New York-Presbyterian/ Weill Cornell/Cornell University Medical College	Greenfield, Jeffrey
Children's Hospital of Phoenix	Adelson, David
Children's National Medical Center	Keating, Robert
Children's Hospital of Philadelphia	Heuer, Greg
Cincinnati Children's Hospital	Mangano, Francesco
Columbia University	Anderson, Richard
Dell (Seton) Children's Medical Center	George, Timothy, and Tyler-Kabara, Elizabeth
Gillette Children's Hospital Minnesota	Graupman, Patrick
John Hopkins Children's Center/ Johns Hopkins School of Medicine	Jackson, Eric
Levine Children's Hospital/Carolinas Medical Center	Wait, Scott
Los Angeles Children's Hospital	McComb, J. Gordon
Lurie Children's Hospital of Chicago	Alden, Tord
Mayo Clinic Children's Hospital	Daniels, David
Miami Children's Hospital	Bhatia, Savjiv, Ragheb, John
MUSC Children's Hospital/Medical University of South Carolina School of Medicine	Eskandari, Ramin
Oregon Health & Science University	Selden, Nathan
Pennsylvania State University	Iantosca, Mark
Pittsburgh Children's Hospital	Tamber, Mandeep, and Greene, Stephanie
Primary Children's Hospital	Brockemeyer,Doug
St. Louis Children's Hospital	Limbrick, David
Seattle Children's Hospital	Ellenbogen, Richard
Stanford University	Grant, Gerald
Texas Children's Hospital	Whitehead, Bill

The Children's Hospital at OU Medical Center/ Oklahoma University College of Medicine	Mapstone, Timothy, Gross, Naina
Nationwide Children's Hospital	Leonard, Jeffrey
University of Florida HSC-Jacksonville	Aldana, Philipp
University of Iowa	Menezes, Arnold
University of Michigan	Maher, Cormac
University of Texas – Houston	Shah, Manish
University of Minnesota	Guillaume, Dan
University of Vermont Children's Hospital/ University of Vermont College of Medicine	Durham, Susan
University of Wisconsin	Iskandar, Bermans
Vanderbilt University	Shannon, Chevis and Wellons, Jay
Wake Forest University	Couture, Daniel

Appendix II

PRSRC Dissemination Committee

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Ms. Haley Vance	Nurse Practitioner
Ms. Elaine Kennedy	Nurse Practitioner
Mr. Rick Labuda	Patient Partner
Ms. Dorothy Poppe	Patient Partner
Ms. Lisa Reynolds	Patient Partner
Mrs. Gina Tramelli	Patient Partner

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Ms. Lisa Reynolds	Patient Partner
Mrs. Gina Tramelli	Patient Partner
Mr. Rick Labuda	Patient Partner
Ms. Dorothy Poppe	Patient Partner
Dr. Jacob Greenberg	Clinician/Research Consultant
Ms. Angela Eschmann	Clinician/OR Nurse Consultant
Ms. Toni Goelz	Clinician/Physical Therapist Consultant

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Manish Shah, MD	Children's Memorial Hermann Hospital/ Univ. of Texas School of Medicine

Robert Keating, MD	Children's National Medical Center/ George Washington U. School of Medicine
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Doug Brockmeyer, MD	Primary Children's Hospital/ Univ. of Utah School of Medicine
Jeffrey Ojemann, MD Richard Ellenbogan, MD	Seattle Children's Hospital/ Univ. of Washington School of Medicine
Prithvi Naryan, MD	St. Christopher Children's Hospital
David Limbrick, MD, PhD	St. Louis Children's Hospital/ Washington Univ. School of Medicine
William Whitehead, MD Robert Dauser, MD	Texas Children's Hospital/ Baylor Univ. School of Medicine
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Jeffrey Greenfield, MD	Children's Hospital of New York-Presbyterian/Weill Cornell/ Cornell University Medical College
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John Collins	Pediatric Neurosurgeon	New Jersey Pediatric Neuroscience Institute	Alternate
Alex Weil	Pediatric Neurosurgeon	CHU Sainte-Justine and Center hospitalier de l'Université de Montréal	Alternate

Appendix III

Screening Log

Institution:_____
PI:_____
Site Number:_____

Instructions:
Column 1: Enter subject number (start with 001, 002, 003, etc.).
Column 2: Document reason not consented even though eligible.
Column 3: The researcher entering this information acknowledges with his/her initials.
