



Shriners Hospitals
for Children®

TITLE: Multi-Center: Non-Anesthetized Plexus Technique for Infant (BPBP) MRI
Evaluation (NAPTIME)

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Version	Description of Changes
March 8, 2017	Original Document
March 24, 2017	Added UC Davis as research site
May 31, 2017	Expanded enrollment criteria
June 21, 2017	Changes research coordinators (RC) to research staff (RS)
September 1, 2017	Added option for repeat MRI and data collection of MRI experience
March 6, 2018	Added information to email/handout provided to subject families prior to MRI

PROTOCOL SIGNATURE PAGE

Protocol Title: Multi-Center: Non-Anesthetized Plexus Technique for Infant (BPBP) MRI Evaluation (NAPTIME)

The signature below provides the necessary assurances that this trial will be conducted according to the stipulations of the protocol, including all statements regarding confidentiality. This is in compliance with the principles outlined in applicable US Federal regulations and Good Clinical Practice Guidelines (ICH E6 Section 4.5.1, 6.2.5, and 8.2.2)

Site Investigator's Name*: (please print)

Site Investigator Signature

Date Signed

** The protocol should be signed by the local investigator who is responsible for day to day study implementation at his/her specific site.*

List of Abbreviations

Adverse Event	AE
Unanticipated problems involving risks to subjects or others	UPIRTSO
Food and Drug Administration	FDA
Health Insurance Portability and Accountability Act	HIPAA
Institutional Review Board	IRB
Private Health Information	PHI
Medical Record Number	MRN
Shriners Hospitals for Children – Northern California	SHCNC
Principal Investigator	PI
Occupational Therapist	OT
Research Staff	RS
Magnetic resonance imaging	MRI
Somatosensory evoked potentials	SSEP

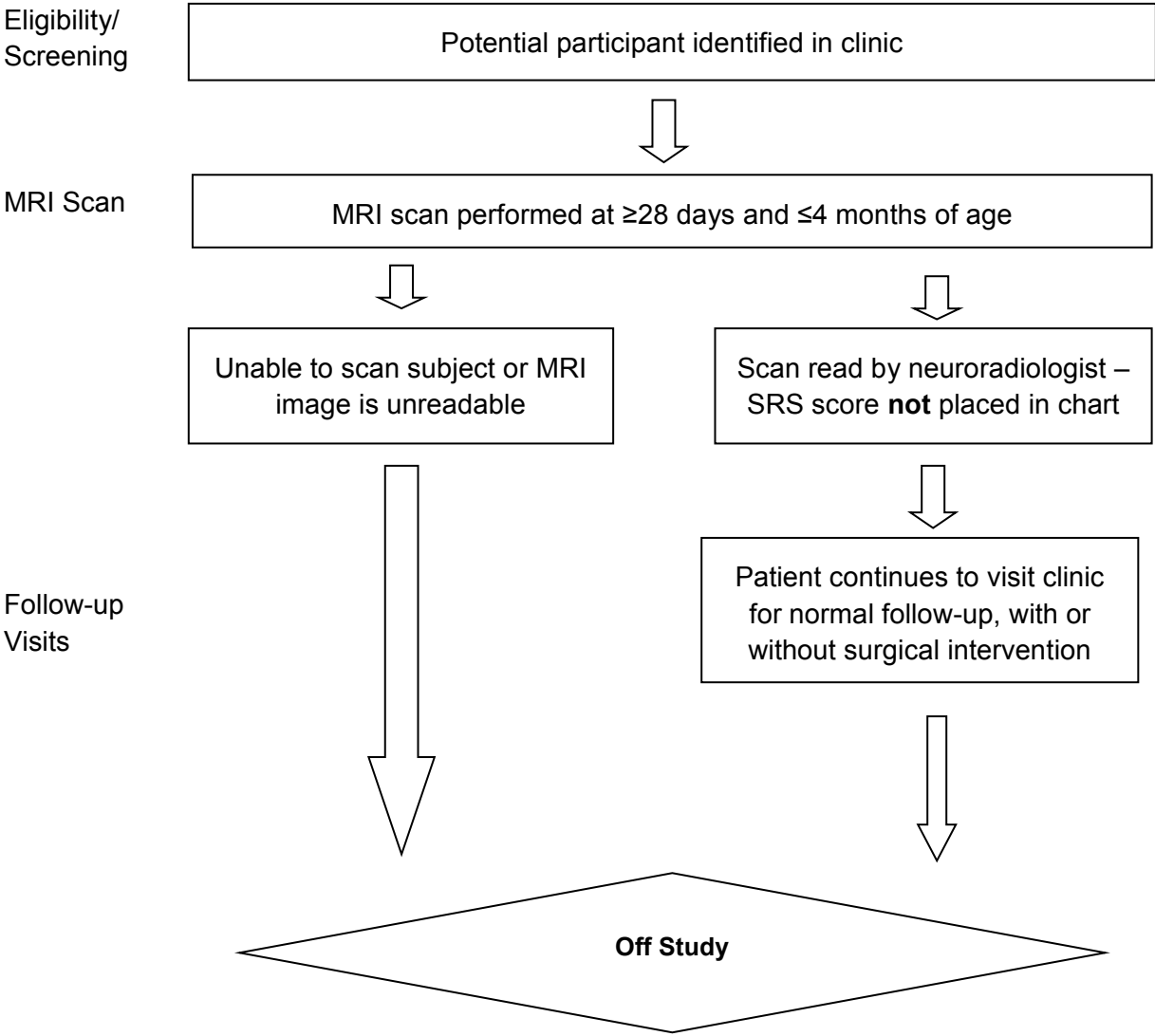
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Study Summary

Title	Multi-Center: N on- A nesthetized P lexus T echnique for I nfant (BPBP) M RI E valuation (NAPTIME)
Short Title	NAPTIME
Population:	Infants with unilateral brachial plexus birth palsy
Number of Subjects	100
Study Duration	5 years
Study site(s)	Shriners Hospitals for Children - Northern California UC Davis Medical Center Boston Children's Hospital Gillette Children's Specialty Healthcare
Objectives	<p>Primary Objective: Verify whether non-sedated 3D volumetric structural magnetic resonance imaging (MRI) obtained in the first 4- 12 weeks of life can reliably discriminate between brachial plexus birth palsy (BPBP) injury patients who require surgical reconstruction versus those who will recover spontaneously.</p> <p>Secondary Objective 1: To assess whether MRI findings for pre-operative planning in infants with BPBP, specifically the level(s) and extent of injury of each nerve root and the location of root injury (pre- vs. post-ganglionic), correlate with intraoperative findings identified during brachial plexus reconstructive microsurgery.</p> <p>Secondary Objective 2: Two standard BPBP clinical measures – the Active Movement Scale (AMS) and Toronto scores will be used to confirm clinical outcomes of our decision-making both for and against surgery.</p>
Statistical Methodology	The primary analysis for this will be assessing the discriminant ability of the SRS system to distinguish patients who do versus do not go on to surgery, by estimating the area under the receiver operating characteristic (ROC) curve with a 95% confidence interval.

Study Schema



1.0 Introduction:

1.1 Background

Brachial plexus birth palsy (BPBP) affects approximately 1 in 1,000 children at birth, and though the majority of infants regain full function of the affected arm, many of these injuries result in lifelong disability. Varying degrees of BPBP, from mild (neuropraxia) to severe (post-ganglionic root rupture or pre-ganglionic root avulsion), are indistinguishable on the initial clinical exam. Serial clinical examination is the current gold standard for separating infants who will recover spontaneously from those who will need reconstructive surgery. Unfortunately, this “wait and see” period may last for up to 6 months, and the effectiveness of surgery can decrease during this time. The surgeon must balance the fact that 60-80% of infants with BPBP will recover spontaneously without surgery with the knowledge that earlier nerve repair improves outcomes for infants with more severe injuries. A non-invasive diagnostic test which differentiates these two groups of infants with BPBP within weeks of birth may help improve surgeons’ prognostic accuracy and therefore the treatment of this disorder. In addition, currently surgeons rely on operative exploration, visual inspection and somewhat non-specific somatosensory evoked potentials (SSEPs) to differentiate pre-ganglionic and post-ganglionic injuries, which have completely different surgical treatments. A pre-operative test that provided accurate and specific diagnosis of each root injury would improve pre-operative planning and accuracy of treatment.

We have developed a rapid (<10 minute imaging acquisition) volumetric magnetic resonance imaging (MRI) sequence with high spatial resolution and soft tissue contrast that does not require sedation or administration of a contrast agent and provides an accurate assessment of the level and severity of both pre- and post-ganglionic BPBP injuries [1]. The pilot data we acquired on 9 infants demonstrates the ability of this imaging protocol to distinguish those infants who went on to surgery at 6 months of age from those who made a spontaneous recovery. Additional study enrollment would validate the ability of imaging protocol to differentiate between operative and non-operative injuries, which would benefit both groups: first, those with injuries who do require surgery could potentially be reconstructed earlier and more accurately, and second, families of the majority of infants who will recover spontaneously could be spared months of worry. Our research goal is to recruit a total of 100 patients over a 5-year period yielding at least 70 evaluable patients at three institutions (Shriners Northern California, Boston Children’s Hospital, and Gillette Children’s Specialty Hospital) utilizing the same imaging, serial clinical exams, and surgical protocols as our pilot study.

1.2 Risks, Benefits and Alternatives

1.2.1 Risk Category

This study is no greater than minimal risk. Subjects will not encounter risks greater than those they would encounter in daily life.

1.2.2 Potential Risks

1.2.2.1 There is a small risk of loss of confidentiality.

1.2.2.2 While there is no known direct effect of high static magnetic field strength, there are secondary safety considerations of the static magnet field to consider, namely the possibility that medical equipment (for example, pacemakers) will malfunction in the magnetic field, or that the magnetic force exerted by the static field will cause motion of ferromagnetic materials (either implanted or external to the body). These are standard issues involved in MR imaging, and we already have procedures in place to address them for imaging. MRI safety is documented by screening the patient prior to scan and by completing a questionnaire prior to scan. The risks are reasonable in that the anticipated benefits and/or knowledge gained from the results of this study could determine other medical treatments that provide a better clinical outcome.

1.2.3 Protection Against Risk

1.2.3.1 Data collected will be recorded in such a manner (coded) that subjects will not be identified. The key code and all study documents with coded data (such as case report forms) will be stored in a locked cabinet file and/or password-protected computer file in an access controlled office only accessible to research personnel. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

1.2.3.2 MRI safety is well documented in neonates. Additional risks are further reduced by preformatting the MRI with swaddling and MRI safety questionnaire and screening prior to the scan. To eliminate the risk of injury from external objects, there will be a “zero-tolerance” policy for ferromagnetic materials in the scan room during patient scans. Subject’s parent/guardian will remove all ferromagnetic items (jewelry, pocket contents, belt buckles, footwear with steel nails or toe covers, etc.) before entering the magnet room, and only non-magnetic equipment will be allowed within the scan room. All subjects are subjected to a metal detector screening (similar to that performed at airport security booths) before being permitted to enter the scanning suite.

1.2.4 Potential Benefits to the Subject

The results from this study could benefit future patients by providing an earlier stratification of injury severity and the opportunity for earlier surgery for those who may need it.

1.2.5 Alternatives to Participation

The patient can choose to not participate in the study and they will continue to receive standard care at the research site.

2.0 Objectives:

2.1 Objectives

2.1.1 Primary Objective

Verify whether non-sedated 3D volumetric structural magnetic resonance imaging (MRI) obtained ≥ 28 days and ≤ 4 months old can reliably discriminate between brachial plexus birth palsy (BPBP) injury patients who require surgical reconstruction versus those who will recover spontaneously.

2.1.1.1 Hypothesis:

The SRS will effectively be able to discriminate between infants who require surgical reconstruction versus those who will recover spontaneously.

2.1.2 Secondary Objective 1:

Assess whether MRI findings for pre-operative planning in infants with BPBP, specifically the level(s) and extent of injury of each nerve root and the location of root injury (pre- vs. post-ganglionic), correlate with intraoperative findings identified during brachial plexus reconstructive microsurgery.

2.1.2.1 Hypothesis:

MRI findings for pre-operative infants will exhibit characteristics similar to those found intraoperatively.

2.1.3 Secondary Objective 2:

Two standard BPBP clinical measures – the Active Movement Scale (AMS) and Toronto scores will be used to confirm clinical outcomes of our decision-making both for and against surgery.

2.1.3.1 Hypothesis:

AMS and Toronto scores will improve to functional levels at final follow-up for those subjects who were determined not to need surgery. AMS and Toronto scores will improve following surgical intervention for those subjects who undergo surgery.

3.0 Subject Selection:

3.1 Inclusion Criteria

3.1.1 Diagnosis of brachial plexus birth palsy.

3.1.2 Age at consent ≤ 4 months

3.2 Exclusion Criteria

3.2.1 Bilateral brachial plexus birth palsy.

3.2.2 Age at MRI < 28 days or > 4 months old (patients can be enrolled prior to 28 days of age, but the imaging must occur in the 28 days to 4 months' time period). The lead PI will need to approve the enrollment of a subject who will have the MRI after 90 days of age.

3.2.3 Concomitant medical conditions that would preclude performance of or confound interpretation of MRI or any clinical assessment.

- 3.3 Number of Subjects
Up to 100 subjects will be enrolled from the three research sites.
- 3.4 Inclusion of Gender, Minorities, and Vulnerable Populations
 - 3.4.1 Entry into this study is open to patients of both genders.
 - 3.4.2 Entry into this study is open to patients of all ethnic backgrounds.

4.0 Study Design/Procedures:

- 4.1 General Design
 - 4.1.1 This will be a multicenter prospective cohort study of patients with BPBP. The study will take place at Shriners Hospitals for Children – Northern California, Boston Children’s Hospital, and Gillette Children’s Specialty Healthcare. MRIs for subjects at SHCNC will be performed at UC Davis Medical Center.
 - 4.1.2 All infants with BPBP between 0 and 12 weeks of age who present for treatment to a participating site will be offered participation in this study. Those infants with concomitant birth injuries that would make positioning in the MRI scanner difficult or painful (such as a birth humerus or clavicle fracture) will have their enrollment deferred. If the injury heals and the MRI can be performed within the required age range, they may be included in the study. If not, they will be excluded. Those infants who attempt to complete or actually complete the MRI scan but end up with unusable images will continue to be followed clinically, but will be removed from participation in this study. Table 1 below shows the visit schedule for study participants and what forms/activities need to be completed at each visit.

Table 1. Schedule of visits.

Forms/ Activity	Enroll- ment	Follow-up					
	Baseline	Study visits until surgery decision	Surgery (if needed)	Study visits until Month 12	Month 12	Month 18 (±3 mo)	Month 30 (±3 mo)
Enrollment	X						
Patient Assessment	X	X		X	X	X	X
Procedures			X				
MRI Assessment	X						
Study Closeout	X*	X*	X*	X*	X*	X*	X

* If MRI cannot be completed, if patient withdraws, or is lost to follow-up.

4.2 Avoiding Bias

4.2.1 Patient enrollment

All infants with BPBP between 0 and 12 weeks of age who present for treatment to a participating site will be offered participation in this study.

4.2.2 Surgeon blinded to SRS score

Surgeons will be blinded to neuroradiologist-derived SRS score. SRS score will not be put into the medical record so that the surgeons are blinded to the SRS score.

4.2.3 Standardization of indications for surgery

Surgeons will adhere to standard indications for microsurgery in infants with BPBP. These are: 1) flail arm and Horner's syndrome 2) Toronto score less than 3.5, 3) failure to recover antigravity elbow flexion and/or antigravity shoulder abduction (AMS score for elbow flexion and/or abduction less than 5), 4) failure to bring the hand to the mouth (cookie test), or other clinical indication of lack of appropriate nerve recovery.

4.3 Study Procedures

4.3.1 Study Visits

At the baseline visit, we will collect patient demographics, prenatal and perinatal history, as well as information on any concomitant birth injuries. A standardized physical examination will be conducted at the enrollment visit and all subsequent study visits, consisting of the Toronto Score and AMS score. The Narakas score and the MRI will take place at or around the time of enrollment into the study. At the time of the MRI scan, the neuroradiologist will document the status of each nerve root as normal, post-ganglionic rupture, or pre-ganglionic avulsion, in addition to calculating the numerical SRS. For those infants who undergo microsurgery, we will document the indications for surgery, operative findings at each nerve root, and procedure performed at each nerve root.

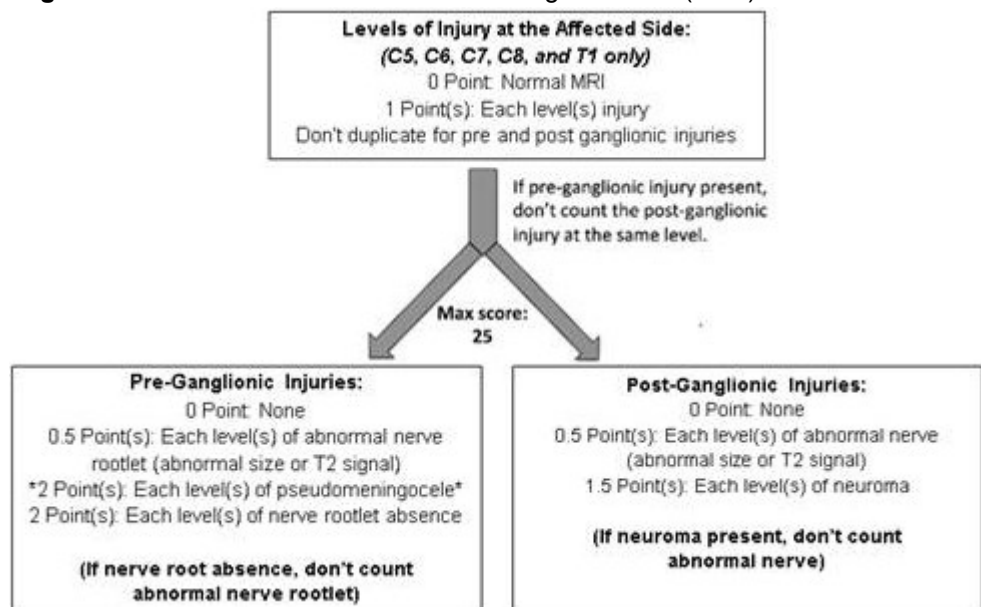
4.3.2 MRI Scan and Shriners Radiological Score

An MRI will be performed according to the protocol specified in Appendix A. Families will be given instructions prior to their MRI appointment to keep their child awake prior to the exam and to feed them within 30 minutes of the exam to increase the chance of the baby being sleepy during the exam time. Tips for a successful MRI and website links to the MRI sounds and a MRI cartoon may also be provided. Each infant will be positioned in an MRI scanner either using a swaddle blanket or using a vacuum suction controlled infant positioner, the MedVac Immobilizer (CFI Medical, Fenton, MI) [26]. The MRI scanning protocol is composed of a localizer sequence followed by traditional sagittal T2 sequence and 3D proton density CUBE (General Electric trade name, Milwaukee, WI) or SPACE (Siemens Medical USA, Malvern, PA) coronal sequence oriented in the plane of the cervical spine and extended anteriorly to include the involved brachial plexus. The total scanning will be approximately 8 minutes excluding initial positioning time, of which the localizer, traditional sagittal T2 and coronal 3D proton density CUBE/SPACE sequences are 1 minute, 3.4 minutes and 3.5 minutes respectively. Subjects' experience with the MRI scanning process will be

recorded, e.g. the number of times the subject wakes up during the scan or the total time needed to obtain the scan.

Each subject's MRI scan will be reviewed independently by neuroradiologist investigators. The neuroradiologists will interpret the MRI scan and report their findings in the medical record as per standard clinical protocols. Surgeons and families will be aware of these findings and will be able to view the images. However, the SRS calculation will be performed outside the medical record and will not be available to surgeons until after data collection is completed in order to minimize bias. Our pilot data demonstrated inter-rater reliability (Krippendorff's alpha) of 0.78 for calculation of the SRS. The neuroradiologist investigators at the other study centers will read and calculate SRS scores for the pilot study subjects with the goal of exceeding an inter-rater reliability of 0.75 with the other neuroradiologists prior to testing study subjects. In addition, during the study period, a subset of MRI scans will be de-identified and shared between institutions for the purposes of inter-observer and intra-observer analysis. Figure 1 illustrates the calculation of the SRS score from the MRI findings. Each injured level is first assigned 1 point, with additional points assigned for pre-ganglionic injuries: 2 points for each absent nerve rootlet, 2 points for each pseudomeningocele, 0.5 points for each abnormal nerve rootlet; and for post-ganglionic injuries: 1.5 points for each neuroma and 0.5 points for each abnormal nerve. If the zone of injury includes both the pre- and post-ganglionic regions, only the pre-ganglionic injury is scored. The total radiologic score ranges from 0 points (no evidence of nerve root injury on MRI) to 25 points (all 5 levels with pre-ganglionic pseudomeningoceles and absent nerve rootlets). In addition, the neuroradiologist will score each nerve root level as intact, post-ganglionic rupture, or pre-ganglionic avulsion. This information will then be compared with the findings at surgery as described above for those infants who undergo surgery.

Figure 1. Calculation of the Shriners Radiological Score (SRS)



4.3.2.1 Subjects who do not complete the scan or end up with unusable images can repeat the MRI up to two additional times as long as they are within the eligibility window.

4.3.3 Surgery

The decision to proceed to surgery will be made by the operating surgeon using the accepted standard clinical indications. These are: 1) flail arm and Horner's syndrome 2) Toronto score less than 3.5, 3) failure to recover antigravity elbow flexion and/or antigravity shoulder abduction (AMS score for elbow flexion and/or abduction less than 5), 4) failure to bring the hand to the mouth (cookie test), or other clinical indication of lack of appropriate nerve recovery. For those infants in the study who undergo microsurgical plexus exploration, the status of each nerve root will be recorded by the operating surgeon as intact, postganglionic rupture, or pre-ganglionic avulsion. This status will be determined based on the intraoperative appearance of the nerve root as well as intraoperative SSEP testing as follows: avulsed (no repeatable response with maximal stimulation), ruptured (repeatable response to SSEPs but without distal motor function), or intact (repeatable response to SSEPs with distal motor function).

4.3.4 Follow-up

AMS and Toronto score data will be collected prospectively at subsequent routine clinic visits. Infants will be examined until 6 months of age or until a decision for surgery is made, then until 1 year of age depending on the infant's recovery. After 1 year of age the progression of clinic visits varies based on the severity of the child's injury, with planned study visits at 18 and 30 months of age (2.5 years of age/ \pm 3 mo), regardless of surgery decision (i.e., both cohorts will be followed).

4.3.5 Removal from study

Subjects will be dropped from the study if a readable MRI is not produced, even after multiple attempts.

4.3.6 Description of study treatments or exposures/predictors

The primary predictor is the MRI-based Shriners Radiological Score (SRS.) Each patient's MRI will be read by the local study neuroradiologist and given a score between 0 and 25. The secondary predictors are the specific neuroradiologist interpretations of the MRI at each level (for later comparison with intraoperative findings).

4.4 Subject Recruitment Plans and Consent Process

4.4.1 Waiver of HIPAA Authorization for Recruitment of Prospective Subjects

4.4.1.1 HIPAA authorization will be obtained at the time of informed consent. We are requesting a waiver of HIPAA authorization for recruitment of prospective subjects. The use of health information for screening purposes does not represent more than a minimal risk to privacy.

- 4.4.1.2 It would not be possible to conduct this study without access to PHI, because the research staff will need to identify appropriate candidates prior to contacting their respective families.
- 4.4.1.3 Data will be coded and stored in a secured locked office. PHI will not be reused or disclosed to any other person or entity, except as required by law or for authorized oversight of the research project. Any disseminated data will be aggregated and coded. PHI will be destroyed at the earliest opportunity but no sooner than 2 years from the completion of this study.
- 4.4.1.4 Only IRB approved research staff for this study and those authorized for oversight of the research project will have access to PHI.
- 4.4.1.5 We will screen the electronic medical record for appropriate candidates for this study. PHI that will be accessed are name, MRN, DOB, dates of clinic visits, and medical notes.

4.4.2 Recruitment

- 4.4.2.1 Patient recruitment will take place during regular clinic appointments at each center. Research staff (RS) at each site will screen clinic schedules for appropriate candidates and alert the surgeon prior to a candidate's visit. On the day of the clinic visit, the surgeon will introduce the study to the parents/legal guardian, including risks and benefits of study participation, and answer any questions. If the parents/legal guardians express interest in participating, the RS will provide additional information, answer any questions, and then go through the formal consent process and obtain signature(s). Child assent will not be required due to the age of the subjects. The family will be given a copy of the signed consent form for their records.
- 4.4.2.2 If patients will be seen for this first time between 28 days and 4 months of age, the RS will secure a time slot for the MRI scanner ahead of time so that the MRI can be performed on the same day as the clinic visit. In this way, the MRI scan will occur as soon as possible after enrollment into the study. Patients whose first visit occurs prior to the age of 28 days will complete the research MRI at their next regularly scheduled clinic visit or at another time of their choosing. A handout or email given to families will contain information and tips about the MRI so that families can plan for the extra time needed to complete the MRI.
- 4.4.2.3 To minimize patient/family burden, ensure a high rate of retention, and maximize the likelihood that complete data are collected for each patient, the study visit schedule will mimic a regular clinic visit schedule. The only deviation necessary would be to complete the research MRI.

4.4.3 Informed consent process

- 4.4.3.1 Informed Consent will be obtained from their legally authorized representative or guardian by study staff authorized to consent for this study.
- 4.4.3.2 The consent process will include a thorough discussion of all the elements outlined in the informed consent document, including but not limited to what is expected to happen during the study, risks and benefits of the planned assessments, and any possible alternatives.
- 4.4.3.3 Subjects and their guardians will be presented with a verbal introduction to the study. They will then review the consent document section by section with the research personnel. The research staff will state that participation in the study is voluntary and that their care will not be affected should they choose to not participate. They will also be told that they can withdraw from the study at any time.
- 4.4.3.4 Consent will be obtained in a private location.
- 4.4.3.5 The subject/parent or guardian will be provided with an ample amount of time to ask questions before making their decision through extensive discussion between the parent or guardian and the research staff. This discussion includes the subject or guardian summarizing study procedures in their own words to ensure their comprehension level is adequate.
- 4.4.3.6 Potential subjects may take as much time as they would like to consider their participation in the study.
- 4.4.3.7 Consent of subjects enrolled at SHCNC will be documented in OnCore. The original consent form at all sites will be stored in locked filing cabinets at each site that only the research staff has access to.
- 4.4.3.8 The subject/family will be given a copy of the signed consent form.

5.0 Subject Safety

5.1 Safety Assessment

This study does not include experimental procedures.

- 5.1.1 No toxicities, injuries, complications or significant risks are expected with activities other than nerve exploration. These activities, performed as part of standard clinical care, will not require reporting as a study AE. At SHCNC, all standard SHC policies will be followed to insure subject safety while participating in all study-related procedures.

5.2 Serious Adverse Event Reporting

- 5.2.1 Any Serious and Unexpected adverse event, and Grade III or above with a reported causality of “possible,” “probably,” or “likely” must be reported to the Study PI in an expedited method.

- 5.2.2 The PI will ensure that SHC Headquarters and all applicable regulatory organizations are notified per regulatory guidelines.
 - 5.2.2.1 Shriners Hospitals for Children must be notified of any Serious **and** Unexpected adverse event, via the OnCore reporting mechanism, within 10 days of occurrence.
- 5.2.3 Notifying participating investigators
 - 5.2.3.1 The study PI will notify all participating investigators of any reported SAE adverse event associated with the study.

6.0 Data Handling and Record Keeping

- 6.1 Data

Data collected will include demographic information, physical examinations, Toronto scores and AMS, MRI readings, and surgery information.
- 6.2 Data Storage
 - 6.2.1 The data collected for this study will stored (during and after the study) in OnCORE® Enterprise Research System, SHC's clinical research data management system housed on SHC servers. Members of the research team will enter data into the SHC system with unique user IDs and passwords. During the analysis phase, all secure web-based information transmissions will be encrypted.
 - 6.2.2 Source documents will be stored in locked filing cabinets that only authorized personnel will be able to access.
- 6.3 Confidentiality and Security
 - 6.3.1 All study data will be stored on SHC authorized servers outlined in this protocol. All computer systems will require a password to gain access. Data will be coded which will not allow for identification of any individuals from the code. The code sheet will be stored separately from the data.
 - 6.3.2 Investigators, approved study staff, and appropriate organizations such the sponsor, collaborators, government agencies, and IRB may review records for research, quality assurance, and data analysis.
 - 6.3.2.1 A limited data set from each site will be sent to Boston Children's Hospital for statistical analysis.
 - 6.3.3 In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital statistics (i.e. that the subject is alive) at the end of their scheduled study period.
- 6.4 Source Documentation
 - 6.4.1 Data from each measure will be recorded onto paper data collection sheets before electronic entry. During the study, these source documents will be

stored in locked filing cabinets that only the study team has access to and on encrypted, password protected computers. After the study, source document and study files will be archived in a locked secure environment.

6.5 Record Retention

6.5.1 Clinical research records at SHCNC will be retained per SHC Standard Operating procedure on *Clinical Research Records Retention*. Record retention at participating sites will follow their respective institutional guidelines.

6.5.2 Any finding that materially affect the safety and medical care of past subjects from this study will be reported to the IRB for 2 years after closure.

7.0 Quality Control and Quality Assurance

7.1 Subject Safety

Because there are no study initiated interventions, the risk to subjects' safety is minimal. No additional measures will be taken in regards to patient safety.

7.2 Quality Control

7.2.1 MRI

All participating neuroradiologists will evaluate and score the MRI for the patients who participated in the pilot study, to establish inter- and intra-rater reliability prior to reading MRIs for the study. The first two MRIs completed at each site will be de-identified to patient and site and will be distributed to and read by all 3 neuroradiologists.

7.2.2 Physical Exam Assessments

In order to standardize the AMS scoring, the lead occupational therapist will meet with the therapists at the other sites to ensure consistency of scoring. This meeting/training will ensure that all sites will be scoring in the same manner going forward.

7.3 Monitoring Plan

7.3.1 The individuals responsible for data safety and monitoring will be the PIs and Co-Investigators. There are no conflicts of interest to declare, as the investigators have no personal or financial interest in this study.

7.3.2 The PIs will assure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.

7.3.3 The PIs will complete yearly reports detailing the study progress and subject status, any adverse events and any protocol deviations. These items will be discussed at the investigator meetings. Data will be presented in a blinded manner for confidentiality. Protocol adherence will be monitored by the PIs and the Co-Investigators. Protocol deviations are reported to the IRB at the time of continuing review.

8.0 Statistical Considerations

8.1 Primary Study Endpoints

The primary endpoint is the surgeon's decision for or against surgery, typically made by 6 months of age. Surgeons will make their decision based on all available clinical data, including the MRI, but will be blinded to the neuroradiologist's scoring of the SRS and its components.

8.2 Secondary Study Endpoints

The secondary outcome will be the surgeon's intraoperative findings during brachial plexus reconstructive microsurgery. Specifically, agreement between MRI and intraoperative findings, with respect to the level(s) and extent of injury of each nerve root and the location of root injury (pre- vs. post-ganglionic) will be determined.

AMS and Toronto scores will be evaluated at 12, 18 and 30 months of age, which will correlate roughly with 6, 12, and 24 months post-operatively for those infants who undergo surgery.

8.3 Sample Size Determination and Power/Accrual Rate

The sample size was calculated based on the primary aim which is to determine the discriminant ability of the SRS system to discern infants requiring surgical intervention and those who will recover spontaneously, based on the area under the receiver operating characteristic (ROC) curve. To prove that the SRS has the discriminant ability to effectively identify surgical patients, we would like to demonstrate an area under the curve (AUC) of at least 0.90. Assuming an expected surgical rate of 30% and a null AUC of 0.75, 70 subjects would be required to achieve 80% power with a type I error of 5%. Table 2 indicates the variations in sample size calculation if the true surgical rate is higher or lower than 30%. This demonstrates that there is little variation in the number of necessary surgical subjects given various surgical rate scenarios. Obtaining at least 21 surgical subjects would provide greater than 80% power to test for an AUC of at least 0.90. Thus, the assumption of a 30% rate with an enrollment of 70 evaluable patients should be sufficient to meet the goals of the study.

During the 1-year time frame of our pilot study, we identified 16 subjects that met eligibility criteria. Of these, 3 families declined participation, and 4 infants were not able to complete the MRI scan. As our technique of positioning the infant improved over the pilot study, we believe a higher percentage of infants will be able to complete the MRI scan successfully going forward. There is a similar volume of BPBP patients at our two institutions, such that we expect approximately 15 subjects per year will be eligible to participate at each site, with 10 per year at each site likely to consent and complete the MRI scan successfully. Thus, we will plan to enroll patients for the first 3.5 years of the study and expect to yield 105 eligible participants. Assuming that 85% of eligible infant's consent and at least 75% have adequate MRI scans, it will be possible to obtain the required sample size. A third site has been included to help guard against poorer than expected accrual and to provide for more generalizable results.

Table 2. Sample size required to detect an AUC of 0.90 with 80% power.

Surgical rate	Number of surgical subjects	Number of non-surgical subjects	Total number of subjects
25%	21	66	82
30%	21	51	70
35%	22	41	63
40%	23	34	57

8.4 Statistical Methods

The primary analysis for this will be assessing the discriminant ability of the SRS system to distinguish patients who do versus do not go on to surgery, by estimating the area under the receiver operating characteristic (ROC) curve with a 95% confidence interval. In addition, an optimal cutoff value for the SRS will be identified using Youden's Index which maximizes the sum of sensitivity and specificity. Sensitivity and specificity will be estimated to help quantify the utility of the SRS system to discern between surgical patient groups. The area under the ROC curve (AUC) for the SRS system may be compared to the AUC for the AMS, currently part of clinical surgical decision making, to assess whether the MRI score offers a comparable, earlier detection method for the need for surgical intervention. Secondary analysis will include comparing MRI nerve root findings at each nerve root level (C5, C6, C7, C8, and T1) with intraoperative root findings in surgical patients. Weighted kappa coefficients along with 95% confidence intervals will be estimated to assess the concordance in detecting intact, ruptured, or avulsed roots between MRI and intraoperative inspection. In addition, inter- and intra-rater reliability of the SRS will be assessed by estimating Krippendorff's alpha along with a 95% confidence interval. The AMS and Toronto evaluations at 18 and 30 months of age in the non-operative group will be used to confirm that these patients do achieve spontaneous recovery, and will be compared with the scores for the surgery group at the same time points.

9.0 Finance

9.1 Funding

This study is being funded by a grant from Shriners Hospitals for Children. Budgeted funds will be administered by the SHCNC RC and payments to BCH and Gillette Children's Hospital will be approved by Dr. James.

9.2 Costs to Subject

The subject is not anticipated to incur any additional costs at the study center for participation in the study. Costs for the MRI will be covered by grant funds.

10.0 Study Organization

10.1 Multiple PI Plan

The multiple PI plan was chosen because this study includes 3 institutions (Shriners Hospital – Northern California, Boston Children's Hospital, and Gillette Children's Specialty Healthcare), and at each institution, 2 different disciplines (pediatric hand surgeons and pediatric neuroradiologists). The leadership team has worked closely together on the pilot for this study, and 2 of the PIs (James & Bauer) have successfully collaborated on several research projects. Oversight of the study, along with scientific responsibility, will be provided by Dr. James and Dr. Bauer. The neuroradiologists at each institution will be responsible for the MRI studies. Dr. James, Dr. Bauer, and Dr. Van Heest will be responsible for examining the patients and collecting the outcomes data.

10.2 Phone meetings

The PIs will hold conference calls at least quarterly, and the RC at SHCNC will maintain an agenda and minutes for each call. Decisions on scientific direction will be made by the team, after receiving input from all members (representing both specialties and all institutions as appropriate); Dr. James will make the final decision if any conflicts arise.

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MRI scanning protocols for brachial plexus consists of the following pulse sequences:

- Each infant will be positioned in an MRI scanner either using a swaddle blanket or vacuum suction controlled infant positioner, the MedVac Immobilizer
- Required sequences:
 - Localizer sequence
 - Sagittal T2 sequence through cervical spine
 - Coronal 3D proton density CUBE (General Electric trade name, Milwaukee, WI) or SPACE (Siemens Medical USA, Malvern, PA) sequence oriented in the plane of the cervical spine and extended anteriorly to include the involved brachial plexus.
 - The total scanning time will be approximately 10-15 minutes excluding initial preparation time. Total study time will be 30 minutes.
- Optional sequences only when time allows and required sequences are diagnostic quality:
 - Coronal T2 fast spine echo
 - Coronal T2 fat saturation CUBE (General Electric trade name, Milwaukee, WI) or SPACE (Siemens Medical USA, Malvern, PA) sequence oriented in the plane of the cervical spine and extended anteriorly to include the involved brachial plexus.
 - Coronal STIR (Short TI Inversion Recovery) CUBE (General Electric trade name, Milwaukee, WI) or SPACE (Siemens Medical USA, Malvern, PA) sequence oriented in the plane of the cervical spine and extended anteriorly to include the involved brachial plexus.