Post-operative Functional Changes in Children with Severe Neurological Impairment

Study Protocol

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BACKGROUND

Children with Severe Neurological Impairment (SNI) have significant neurological disorders, either genetic or acquired in origin[1], that result in developmental impairments influencing intellectual function, muscle tone, mobility and communication[2]. These children have ongoing health complexities that often require surgical procedures to manage their underlying condition, reduce pain burden, and improve functional limitations[3,4]. Examples of surgeries include spine stabilization, tendon releases, and gastrostomy.

Children undergoing major surgical interventions are at risk of developing acute onset and persistent postoperative functional decline (PoFD)[5], regardless of their pre-existing cognitive state. While evidence for PoFD exists, it has predominantly been reported in the frail elderly or focused on children without SNI[6–11]. To explore this phenomenon more systematically in children with SNI, we conducted qualitative interviews with 12 caregivers to investigate prolonged PoFD. Based on retrospective recall, 80% of caregivers reported unexpected, long-term PoFD in their children[13]. The changes occurred across a wide range of indicators; no two children were alike, making the use of broader categories of functional indicators of change challenging. Two previous studies examining the impact of hip and spinal surgery on health-related quality of life (including functional outcomes)[14,15] found a decrease in quality of life at six weeks post-surgery, followed by gradual improvement at 12 months and significant improvement five years after surgery[14,15]. However, these studies analyzed broader categories of function, without specific item-level quantification during the perioperative period. Furthermore, no prospective studies have systematically and specifically examined PoFD in a larger cohort of children with SNI.

While there are several factors hypothesized to contribute to PoFD, including prolonged anaesthesia exposure[16–19] and ongoing pain[20], emerging evidence suggests that inflammation due to surgery may be a more likely mediator. Surgery triggers a local inflammatory response with the potential to reach the brain[21–23]. Meta-analyses have found that certain inflammatory markers (eg. C-reactive peptide [CRP], interleukin-6) are significantly elevated in elderly patients with PoFD vs those without[1,2], and in adult mice, inhibiting inflammatory cytokines attenuates PoFD-related effects on cognition[3,4]. Children with SNI may be especially susceptible to inflammation-induced PoFD due to their neurological vulnerability and potentially dysregulated immune response[5]. Inflammation due to surgery may thus be a factor which interacts with neuronal processes to possibly contribute to PoFD. However, the perioperative inflammatory profile in children with SNI and its potential connection to PoFD has not yet been systematically studied.

Given the documented experiences with medical trauma in this group[6], we must identify family-informed methods before conducting large-scale work involving non-medically necessary data collection. Therefore, the purpose of this pilot study is to test the feasibility and acceptability of conducting an observational to explore PoFD in children with SNI. The ability to identify the best methods for evaluating potential functional decline (temporary or persistent) in children with SNI will assist in finalizing a study protocol for a planned larger study.

SIGNIFICANCE AND JUSTIFICATION

To our knowledge, this will be the first study to prospectively and quantitatively document item-level post-operative changes in function and quality of life for children with SNI and their caregivers. Expanding upon previous research[14,15] that has obtained a total score and sub-domain scores of function/health-related quality of life, this work aims to examine more specific, item-level details regarding function pre-

and post-operatively. Additionally, no prior research has investigated potential mechanisms of PoFD, including inflammation, in children SNI.

This pilot study will help refine methods for a planned larger study on this phenomenon. The implications of this future work may significantly improve peri-operative care for children with SNI. Pre-operatively, this could assist clinicians in guiding families through surgical decision-making[7] and the post-operative recovery trajectory. Post-operatively, our future findings could inform the development of targeted, clinically appropriate, postoperative rehabilitation goals as well as help identify needs for multidisciplinary health and community supports. This work will also set a foundation for research that investigates potential mechanisms for the changes in functional status, if present, which could inform interventions that ameliorate or prevent PoFD. Given the incurable nature of disorders that cause SNI, the impact of SNI and its functional implications on both the child and family is profound[26–28]. This line of work thus has implications to ultimately enhance the quality of life in children with SNI and their families.

STUDY OBJECTIVES

In this pilot study, we will evaluate the feasibility and acceptability of our protocol to explore the functional post-operative trajectory in a developmentally and neurologically impaired pediatric population. We will evaluate consent rate, protocol delivery and outcome completion, and acceptability. We will also describe common elements of the experience of these children and their families, including information from a functional skills questionnaire, parental descriptions of pre-post abilities, and parental descriptions of their own quality of life. The objectives of our research are:

Primary outcomes

Objective 1: To evaluate the feasibility and acceptability of our study protocol for children and families living with SNI.

To evaluate feasibility we will use the following evaluation points:

1. Consent rate: The overall average consent rate of children/month.
2. Protocol delivery: The percent of on/off protocol children.
3. Outcome completion: The percent of children with complete outcome measures.

To evaluate acceptibilty, we will conduct end-of-study interviews with caregivers to assess outcomes related to the ease and utility of participating in the study, including our methods of data collection.

Secondary outcomes:

Our secondary aim is to explore patterns of recovery in children with SNI during the peri-operative period. We will assess:

Objective 1: Function in children with SNI, including exploring patterns in specific domains of gain/loss.

Objective 2: Quality of life in children with SNI and their families

Objective 3: Profile of inflammatory biomarkers to compare children's inflammation levels peri-operatively.

HYPOTHESIS

We expect to confirm feasibility and acceptability of conducting peri-operative research in this population, with at least 12 children consented in 1 year and >85% protocol delivery and outcome completion. We anticipate to be able to measure PoFD, quality of life for children and caregivers, and inflammatory biomarkers.

METHODOLOGY

Study Design

This study will use an observational, pre-post intervention design to evaluate our methods of documenting the post-operative functional trajectory and quality of life in children with SNI and their families during the peri-operative period. We will explore the functional abilities and quality of life of children with SNI and their parent/caregivers pre- and post- major orthopaedic surgery, and we will undertake measurements of inflammatory biomarkers

Study Population

Our study population will include 12 children with SNI and their parent/caregiver planning to undergo major orthopaedic surgery at the BC Children's Hospital Orthopaedic Clinics. One parent/caregiver may participate per child participant (the same parent/caregiver throughout the study).

Our study defines children with SNI as those with significant neurological disorders and evidence of developmental delay across all domains of daily function, who rely on assistive devices/technology for daily activities and well-being, such as mobility aids or feeding devices[8] To accurately assess the functional status of our participants for screening pre-operatively, we will use the Gross Motor Function Classification System (GMFCS)[30] and the Communication Function Classification System (CFCS)[31] during participant screening.

The GMFCS is a valid and reliable five-level standardized tool used to classify children and youth with SNI based on their level of movement ability[30,32–34]. For this study, we will include children classified at Levels II to V. Children in Level II may have difficulty balancing on uneven terrain, inclines, in crowded or confined areas and may require physical assistance or mobility device for walking over long distances. Children in Level III will walk with hand-held mobility devices and use wheeled mobility when traveling long distances. Children in Level IV have severe limitations in their walking ability, including with assistance, and rely on a wheelchair most of the time. Children in Level V have profound physical impairments that impact their head and trunk postural control; they are unable to sit, stand, or walk independently and voluntarily.

The CFCS is a valid and reliable five-level tool used to classify how individuals communicate with familiar and unfamiliar partners[31]. For our study, we will include children at Levels II to V. Children at level II alternates between being sender and receiver but may converse slower. Children at level III will typically communicate effectively with familiar communication partners, but not with unfamiliar partners. Children at Level IV are inconsistent in their ability to communicate with familiar communication partners. Children at Level V are rarely able to communicate effectively, including with familiar people, and often require alternative communication methods to interact.

"Major" orthopedic procedures are defined, for the purposes of this study, as operations that are equal to or greater than 90 minutes in "skin-to-skin" time (initial incision to skin closure). Orthopedic procedures (hip reconstruction and spine stabilization) are the most common major procedures that

children with SNI are exposed to, although they also experience many “minor” procedures, such as gastrostomy tube placement, tendon releases, and dental procedures. We are focusing on the longer procedures for this pilot study both because anecdotally, parents have not described the same degree of concern with shorter operations, and for methodological reasons, to improve the opportunity to identify this this phenomenon.

Study participant eligibility criteria

Inclusion Criteria

1) Children with SNI, including the Gross Motor Function Classification System (GMFCS) levels II to V and Communication Function Classification System (CFCS) levels II to V, and;
2) undergoing major orthopaedic surgical management of musculoskeletal pathology (spine or hip; major defined as a greater than or equal to 90 minute procedure with skin-to-skin contact) at the BC Children's Hospital and;
3) between 5 and 18 years at the time of their surgical procedure

Exclusion Criteria

1) GMFCS level I and CFCS level I
2) Non-English-speaking Parents/Caregivers

Control group - justifications and eligibility criteria

We aim to recruit 5 control participants specifically for our biomarker analysis (ie. we will only collect demographics and blood samples). The inclusion of this control group allows for a direct comparison of the pre-, peri-, and post-operative inflammatory responses between children with SNI vs neurotypical patients undergoing similar procedures. This is essential for discerning whether any observed altered biomarkers levels specific to children with SNI (ie. and not seen in neurotypical patients), or if they reflect a generalized postoperative inflammatory response. This comparison strengthens the interpretation of our biomarker findings by providing a baseline, which will reduce the risk of misattributing inflammation-related findings solely to the presence of SNI rather than the general surgical response. Additionally, the inclusion of controls improves the clinical relevance of our study, as it will help determine whether children with SNI exhibit exaggerated, prolonged, or distinct inflammatory responses compared to their neurotypical counterparts. These insights will be critical for guiding future research and potential interventions aimed at mitigating PoFD in children with SNI.

Inclusion Criteria

1) Neurotypically developing children (GMFCS I and CFCS I)
2) Undergoing major orthopaedic surgical management of musculoskeletal pathology (spine or hip; major defined as a greater than or equal to 90 minute procedure with skin-to-skin contact) at the BC Children's Hospital
3) Between 5 and 18 years of age at the time of their surgical procedure

Exclusion Criteria

1) Non-English-speaking parents/caregivers

Participant Screening and Recruitment

Participants for this study will be recruited in-person through the BC Children’s Hospital Orthopaedic Clinics, including the Orthopedic Cerebral Palsy Clinic (CP Clinic) and the Spine Clinic. Study participants

will receive $100 remuneration for their participation in the study, and control participants will receive $50 remuneration for their participation.

Participant Screening

1) *Screening through standard-of-care clinical visits*

The BCCH Orthopedic Clinic (Hip and Spine) will serve as the main recruitment site, where children with SNI and neurotypical children with scoliosis attend regular orthopedic visits. Prospective participants will be identified from a list of patients who will be attending a regular clinic visit at both the Orthopedic Cerebral Palsy Clinic and Spine Program by respective clinic Research Assistants (RAs). Following identification, the RAs at each respective clinic will screen patients as standard for their own studies and flag patients that align with our study's inclusion criteria; for the Hip Clinic, this will be for the Hippy Lab's Outcomes of Hip Interventions for Children with Cerebral Palsy – An International Multi-Centre Prospective Comparative Cohort Study (Ethics ID # H14-01402) study using PowerChart prior to patients' clinical visits, and Spine Program RAs will screen patients independently. The Clinic RAs will then provide the Siden Lab RA with a list of their potential participants with information relevant to the Post-Op Changes Study. Using this list, the Siden Lab RA will then screen for Post-Op Changes Study inclusion criteria (age, GMFCS and CFCS status, on track for major hip/spine surgery), and will coordinate with Clinic RAs to visit these participants at their upcoming pre-operative appointment.

2) *Screening through surgical slate – Hip Clinic*

The Siden Lab RA will receive an operating room slate for the patients scheduled for surgery in the upcoming month from the Hip and Spine Clinics' Medical Office Assistant(s), along with the dates of surgery and pre-operative appointments. These participants may then be screened for our inclusion criteria by the Siden Lab Research Nurse using PowerChart; for eligible participants, arrangements will then be made for participants to be approached and recruited at their pre-operative appointment.

3) Screening through CST Cerner

The Medical Student Research Assistant with Level 2 Cerner access will filter their search on CST Cerner specifically for the 3 surgeons whose patients we have obtained permission to recruit from: Drs. Andrea Simmonds, Firoz Miyanji, and Kishore Mulpuri. This will result in a list of the operating schedule and pre-operative appointments for each surgeon. The RA will then access the patients' charts for those who have a confirmed surgery date or pre-operative visit to screen for our inclusion criteria to determine if they are eligible to be a study participant or a control. Screened eligible patients will be confirmed with the Orthopaedic team RAs prior to approaching the patient. With this, we will track all patients who would be eligible, as well as patients that we approached, in a password protected Excel Spreadsheet housed under our lab's V Drive. We have attached the spreadsheet under Recruitment documents which includes all data we will be collecting as part of this screening.

Participant Recruitment

1) *Recruitment at regular clinic visit:*

During the standard-of-care clinical visit of patients who will likely undergo surgery within ~6 months (as identified by the RAs/team of each clinic conducting screening), the patient's clinician will ask the

patient's parent/caregiver if they are interested in participating in research and will briefly introduce them to the study. If the patient's parent/caregiver is interested, the RA will approach the patient and their parent/caregiver regarding the details of the study. If the parent/caregiver is interested in participating, the RA will then obtain consent from the participants (the parent/caregiver may provide consent on behalf of their child) either electronically on a tablet as an E-Consent through REDCap or on paper. If this recruitment visit falls within three months of the study participant's scheduled surgery, the RA may then proceed to take baseline/outcome measurements. If the recruitment visit falls outside three months before the patient's surgery date, the RA may obtain demographic information, and baseline outcome measurements will be obtained at another clinical or pre-operative visit within three months of surgery (for study participants). The patient's parent/caregiver may alternatively request additional time to consider participating; in this case, they will be provided with a paper copy of the study details and consent form, and may be approached at their next clinical visit to re-determine interest. If they are controls and data collection can occur at the same time of recruitment and consent, then only demographic information will be collected.

2) Recruitment at pre-operative clinic visit:

After confirming patient's eligibility, the RA may approach the patient and their parent/caregiver regarding study participation during their pre-operative visit. During their pre-operative clinical visit, the patient's clinician will ask the patient's parent/caregiver if they are interested in participating in research and will briefly introduce them to the study. If the patient's parent/caregiver is interested, the RA will approach the patient and their parent/caregiver regarding the details of the study. If the parent/caregiver is interested in participating, the RA will then obtain consent from the participants (the parent/caregiver may provide consent on behalf of their child) either electronically on a tablet as an E-Consent through REDCap or on paper. The RA may then proceed to take baseline and outcome measurements for study participants, and only demographic information for control participants. The patient's parent/caregiver may alternatively request additional time to consider participating; in this case, they will be emailed a REDCap link to the consent form that they can fill out from home electronically. Once they have been consented, they can then receive a link to our relevant questionnaires (to be filled before surgery). The RA will then coordinate with the patient's MOA to ensure that the study visit timeline are timed congruently with clinical post-operative follow-up visits.

3) Recruitment on day of surgery

After confirming the patient's eligibility, if it is not possible to recruit at the pre-operative appointment the RA may approach the patient and their parent/caregiver regarding study participation on the day of their surgery prior to when the surgery begins. If the parent/caregiver and child agrees to participate, the RAs may obtain consent/assent and complete the baseline/outcome measurements at this time. The RA will then monitor CST Cerner to ensure that the clinical post-operative follow-up visits are timed congruently with the study visit timeline.

Recruitment video
At all three recruitment types, we will show our recruitment video to the study participants (children with SNI) to provide them with more information about the study prior to their review/signing of the consent form.

Sample Size Justification

We aim to recruit 12 study participants and 5 control participants for this pilot study, which will be useful to 1) test the feasibility and acceptibility of our methods and tools for later use on a larger scale, and 2) allow us to describe patterns in preliminary data to identify early associations that may guide the methodology of a larger study. A sample size of 12 study participants and 5 control participants is likely feasible, as the Orthopedic Clinic sees an average of 50 children for hip/spine surgery each year.

STUDY PROCEDURES

The study will include a total of six timed assessments (**Figure 1**). This includes three primary study assessments to collect functional survey and biomarker data: 1) at baseline (within three months of surgery), 2) 6 weeks post-operatively, and 3) 6 months post-operatively. Additionally, we will conduct three biomarker-specific collections during the time of surgery immediately prior to the initiation of the procedure, 12-24 hours post-operatively, and 1-2 weeks post-operatively, based on the physiology of the sequence of the innate and adaptive immune response systems. Most study assessments will be timed at standard of care visits at the BC Children's Hospital. Each primary study visit will take approximately 25-30 minutes. Total time of participation will be 1.5 – 2 hours. Measures will be taken congruently with standard clinical care data collection where possible to reduce participation burden. Some participants may be recruited exclusively for functional/quality of life data collection while the team awaits approvals for blood collection and storage, to allow for an increased sample size.

Baseline Data Collection

Study participants who have consented will undergo a total of 3 primary study visits and 6 biomarker collections (**Figure 1)**. At Study assessment #1, demographic information for the child (including variables such as age, sex, race/ethnicity, primary diagnosis, GMFCS/CFCS/MACS score) and demographic information of the parent/caregiver (age, sex, relationship to child, employment status, household income, race/ethnicity, distance from home to primary medical facility) will be collected. Outcome measures (see below) will also be collected. Baseline data collection aims to capture the initial status of participants before any surgical intervention, providing a reference point for post-operative comparisons.

Outcome Measures

The follow study procedures correspond to our primary aims:

To assess feasibility, we will evaluate three primary feasibility outcomes at the time of data analysis. We will calculate consent rate, which is the overall average consent rate of children/month; protocol delivery, which is the percent of on/off protocol children; and outcome completion, the percent of children with complete outcome measures.

To assess acceptability, anytime after the 6-week timepoint , we will conduct semi-structured interviews with families to assess their experience in participating in this study. We will also ask families if there were any domains that were not included in our standardized functional/quality of life questionnaire and questions. Parents may select from pre-identified domains as prompts (including pain, energy, and sleep), and may also provide additional insight through open-ended conversation. Interviews will be recorded, transcribed, and analyzed using thematic analysis.

The follow study procedures correspond to our secondary aims:

Our primary tool for this study to measure our outcomes of function and quality of life will be the Caregivers Priorities and Child Health Index of Life with Disabilities (CPCHILD) Questionnaire[35], which has

been proved to be both valid and reliable[35,36]. The CPCHILD Questionnaire is used to assess the effectiveness of interventions aimed at improving and preserving outcomes for children aged 5-18 years old with severe disabilities, based on caregivers' perspectives. This questionnaire includes 37 items collected from the parent/caregiver measured across six domains: Personal Care/Activities of Daily Living; Positioning, Transferring, and Mobility; Comfort and Emotions; Communication and Social Interaction; Health; Child's Overall Quality of Life; with additional sections for Importance of Items to Child's Quality of Life, Facts about the Child, and Facts about the Caregiver. From responses, standardized scores can be retrieved on a scale of 0 to 100 for each domain, as well as a total score, and we will be examining comparisons at the item-level pre/post-operatively.

Parents/caregivers will also be asked to answer two supplemental questions to provide further insight into 1) other areas of function that were not described by CPCHILD and 2) the quality of life of caregivers.

Blood collection of study participants

To collect information regarding the peri-operative inflammatory profile, we will collect blood samples from study participants at all study time points:

- **Timepoint #1** (pre-operative appointment): during routine care through venipuncture by C&W Lab Technicians. An additional finger prick will be taken by technicians (non-routine).
- **Timepoint #2** (surgery): prior to incision through peripheral venous line by OR staff
- **Timepoint #3** (12-24 hours post-op): by bedside nurses in T6 or PICU
- **Timepoint #4** (1-2 weeks post-op)
    - Hip patients: non-routine collection by C&W Lab
    - Spine patients: by bedside nurses in T6
- **Timepoint #5** (6 weeks post-op): non-routine by C&W Lab
- **Timepoint #6** (6 months post-op): non-routine by C&W Lab

Participants may choose not to provide their blood samples and remain a participant for our functional questionnaire and quality of life-related data collection. Analysis of blood will be done in collaboration with the Core Facility for Neurology Biomarker Innovation/Wellington Laboratory.

A 3 mL aliquot of the child's blood will be set aside for our study. This blood will be transferred to the appropriate collection tubes (heparin coated) to prevent clotting and will be transported to the BC Children's Hospital BioBank for storage.

A lancing device will be used for finger capillary sampling to collect 50uL of blood from the child. The blood sample will be immediately collected following puncture using capillary tubes and transferred into pre-labeled collection tubes (heparin coated to prevent clotting) and mixed to ensure the sample remains homogeneous. After collection, the sample will be stored at –80 C at the BC Children's Hospital BioBank.

Blood collection of control participants

Control participants will only have their blood drawn at three timpoints. Relative to study participants, blood samples will be collected from controls at:

- **Timepoint #2** (surgery): prior to incision through peripheral venous line by OR staff
- **Timepoint #3** (12-24 hours post-op): through routine venipuncture in T6
- **Timepoint #6** (6 months post-op): non routine bloodwork by C&W lab

At the conclusion of data collection, all blood samples will be transported to the UBC Wellington Laboratory (coordinated by the BC Children's Hospital BioBank).

Further, our Research Nurse will extract medication, surgery, and anesthetic-specific data (e.g. pain management drugs [anti-inflammatory, steroids, and immune-suppresants], surgery duration, anaesthesia-specific exposure) pre- and post-operatively from participants' electronic medical records for our team to better contextualize PoFD and inflammatory response.

Timeline
Measures will be taken at baseline (within three months of surgery), at the time of operation, 12-24 hours following operation, 1-2 weeks following operation, 6 weeks post-operatively and 6 months post-operatively as per the schedule below. Study visits will be timed congruently with standard clinical care visits or pre-operative/post-operative clinic visits.

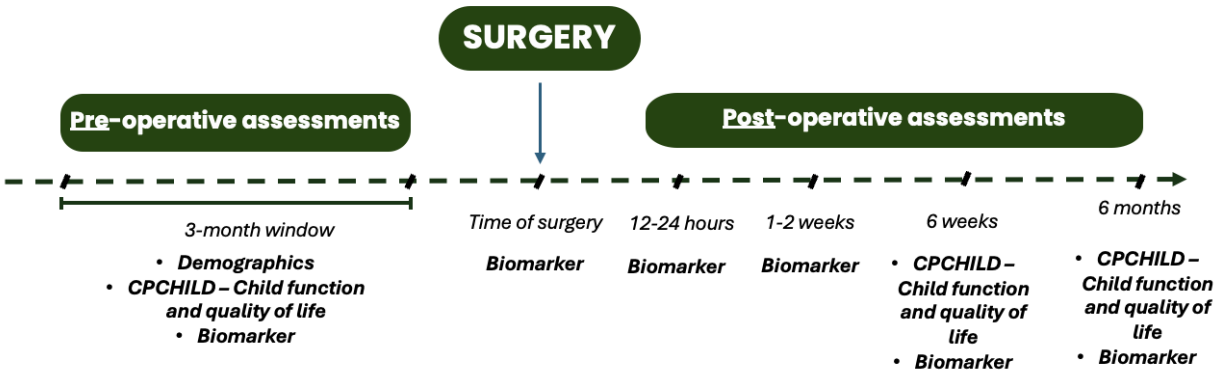

Figure 1. Study timeline for study participants

DATA ANALYSIS

Data analysis will focus primarily on evaluating the feasibility and acceptability of the study protocol. Baseline descriptive data will be presented as median and interquartile ranges, and categorical data by percentages. Primary feasibility outcomes (consent rate, protocol delivery, and outcome completion rates) will be described as percentages. Acceptability data will be analyzed from semi-structured interviews. Qualitative data from interviews with families will be analyzed using thematic analysis to identify common themes and insights regarding their experiences with the study protocol.

For secondary outcomes related to improvement and/or decline, we will describe patterns in 1) child's function, 2) quality of life of child and caregiver, and 3) inflammatory profile pre- and post-operatively. Given our small sample size, we cannot statistically confirm correlations of PoFD and inflammatory biomarkers, though we may detect patterns in specific markers.

In our analysis (all outcome measures), we hope to stratify our results by sub-category of GMFCS 5, as has been done previously. The sub-categories are presence of a gastrostomy tube, a tracheostomy,

history of seizures, and nonverbal status. Patients with 0 impairments will be classified as GMFCS level 5.0, patients with 1 impairment as level 5.1, patient with 2 impairments as level 5.2, and patients with 3 or more impairments as level 5.3. This stratification will allow us to examine participants' response to surgery based on an indicator of severity of their neurological impairment.

Blood collection

In collaboration with facilities and technologies of the UBC Wellington Lab, biospecimens will be analyzed on the Alamar Biosciences ARGO HT platform, a fully automated immunoassay platform designed for NUcleic acid Linked Immuno-Sandwich Assay (NULISA) technology. The NULISA technology is a ligation-based assay which suppresses assay background using a dual capture and release mechanism with oligonucleotide-conjugated antibodies. It is designed to detect proteins across a high dynamic range with high sensitivity through next-generation sequencing of barcoded reporter DNA produced by the assay which also allows high multiplex capability. Analysis will include relative quantitation of a panel of 120 analytes designed to profile major hallmarks of central nervous system diseases (CNS) using the NULISAseq CNS Panel 120 assay. This assay is commercially available from Alamar Biosciences, and has been validated for sensitivity, precision, cross-lot, and cross-machine performance. Validation testing includes dynamic range, specificity, spike recovery, dilution linearity, sensitivity, intra-run, inter-plate, and inter-lot precision and accuracy. Each NULISA assay run contains 4 negative controls (NCs), 3 sample controls, 3 inter-plate controls (IPCs), and up to 86 samples. Each sample is spiked with the same concentration of an internal control (IC) used in the normalization procedure and as a method for assessing the uniformity of the assay run. IPC samples are pooled plasma controls used to normalize samples between experiments and to assess performance of the assay. NC wells are reactions where no sample input is provided and is used to assess limit of detection (LOD) for each target assay and to assess run quality. SC samples are pooled plasma controls from an independent source different from IPCs. SCs are used for calculating intra- and inter-plate coefficient of variation (CV). Specimens are assayed in singlicate in randomized order with no dilution required. Quality control measures, including but not limited to, CV of spiked IC signal across all samples, CV of the total assay signal across all IPCs, Median CV of all IPC targets, and percentage of targets that are detectable, defined as detectable if > 50% samples have signal > limit of detection, are recorded every run. Raw sequencing reads are processed to generate target- and sample-specific counts called NULISA Protein Quantification (NPQ) values. The raw sequencing reads are first normalized to the IC to control for well-to-well variation and then normalized to the median IC-noramlized counts for the IPC samples for plate-to-plate variation.

With respect to statistical analysis of our control group, our primary analysis will involve a group comparison at each timepoint to assess whether, and to what extent, any biomarkers are altered (increased or decreased) in children with SNI compared to our controls. Given the large biomarker panel (approximately 120 biomarkers), data visualization using volcano plots will be employed. Multiple comparison adjustments will be applied using the false discovery rate (FDR) correction method (Benjamini-Hochberg). Biomarker significance will be determined based on effect size thresholds, specifically log2(fold change), with a significance level set at 5% (Type I error). Additionally, associations between biomarkers and study variables (e.g., age, sex) will be explored using Wilcoxon rank-sum tests.

Outcomes

The following outcomes will be utilized to deem our study feasible and acceptable:

Feasibility:

1. Consent rate: An average consent rate of 2-3 children/month
2. Protocol delivery: The protocol can be implemented with >85% protocol delivery.
3. Outcome completion: >85% of outcomes will be complete and measured as scheduled.

Acceptability:

4. General positive report on participation based on semi-structured interview

Secondary outcomes; we will explore pre- and post-operative data to describe patterns in:

1. Function of the child, as scored on the CPCHILD;
2. Quality of life of caregiver, as described by supplemental question;
3. Inflammatory profile of child

DATA STORAGE

All participants will receive unique study ID numbers to be used on all written forms and samples to maintain confidentiality. A master list linking identifiers to study codes will be kept separately in a password protected electronic location with the Siden Lab Research Coordinator. All de-identified data will be transcribed and stored in a secure, password-protected REDCap database with access limited to the authorized study team. Any hard copy data will be stored in locked filing cabinets with the Siden Lab at BC Children's Hospital. Hard copy documents and data will be kept for five years following study completion and then destroyed. Biospecimen will be securely stored until they are destroyed at the UBC Wellington Lab. Informed consent documents will describe the measures taken to protect participant data, and participants will be assured that their information will be used solely for the purposes of this study. All electronic communications involving participant data will use encrypted channels to prevent unauthorized access.

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