Optimizing the Management of Pain and Irritability
in Children with Severe Neurological Impairments

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SUMMARY

The purpose of this project is to develop, test, and disseminate a new approach to reducing and resolving pain in children with developmental brain disorders, specifically those with severe neurological impairments (SNI). It focuses on the problem of ongoing, unexplained, and difficult-to-treat pain and irritability that many children with SNI, and their families, experience. Our goal is to improve the assessment and treatment of pain and irritability in children with complex health conditions and multiple disabilities who have limited communication and cognition. These children are amongst the most vulnerable seen in any hospital or clinic.

Our plan is to evaluate the effectiveness of an integrated clinical pathway (i.e. a sequential order of standardized evaluation steps) for managing unexplained pain and irritability in children with complex conditions and limited communication.

BACKGROUND

Children with SNI are typically non-verbal, non-mobile and have limited cognitive abilities. SNI is an overarching descriptive term for children with significant challenges due to disorders affecting the neurological system, both acquired and congenital. In SNI, cognition and communication are affected and often motor skills, vision, hearing, and autonomic function (temperature, digestion, etc.) are also impaired. SNI is a result of diverse conditions, such as hypoxic-ischemic encephalopathies (severe cerebral palsy), traumatic brain injuries, childhood neurodegenerative diseases, and many other genetic conditions.

Defining Pain in a Complex Pediatric Population

In a study of the prevalence of pain in the general pediatric population, 12% of children report some pain each week. In several studies of children with SNI, however, pain is far more prevalent, and is seen in up to 42% of children on a daily basis. In one study, pain was a problem for 73% of children with SNI at least one day of every fourteen, and for 67% of these children the pain was rated moderate to severe by parents. As shown in our work and that of others, of all of the symptoms causing suffering, pain is the most common one reported by parents of children with SNI. Furthermore, the greater the degree of neurological impairment, the higher the prevalence of pain.

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage.” Most people are familiar with nociceptive-inflammatory pain, in which an injury triggers nociceptive nerve activity followed by an inflammatory response (for example, from an everyday event such as stubbing a toe). There are several other types of pain, including direct nerve injury (neuropathic pain) that activates nerve pathways without accompanying inflammation and central or functional pain that arises entirely within the central nervous system. Some authors also hold that visceral pain from internal organs is itself a distinct category involving a specific physiology, but this is not always clear.
Pain is the most common symptom reported by the parents and caregivers of children with SNI, however, pain is notoriously difficult to identify, and therefore treat, in non-verbal children because their signals of distress are ambiguous and hard to decode. Typical distress behaviours include crying, tears, facial grimace, limb withdrawal, arching, hypertonicity, and decreased sleep. More mobile children may curl up into a ball, fling their arms or legs, or engage in self-injurious behaviour; they may even display decreased activity.

Children with SNI may experience nociceptive-inflammatory pain as a result of their specific medical condition (e.g. joint contractures) or from many procedures that they experience (e.g. injections). Often, however, it is not clear what underlies the pain behavior. Parents are experts in identifying pain behaviours in their own child, but consider their interpretation to be a complex and uncertain process. As well, while pain behaviours can be described by clinicians and parents, the behaviours themselves are subjective, ambiguous, and can reflect a variety of problems in addition to pain. Unless one witnesses an obvious nociceptive-inflammatory trigger such as an injury, parents and clinicians find it very difficult to ascribe all of the pain-like behaviours observed in children with SNI to pain as defined by the IASP. In this context, the term “pain” does not serve as a descriptive label. Therefore, we describe pain behaviour episodes using a less deterministic term, "pain and irritability," acknowledging that the behaviour is certainly negative in the eyes of the witnessing caregiver. Our team has defined this entity as Pain and Irritability of Unknown Origin (PIUO).

Addressing Assessment and Management of PIUO
As clinicians who care for these children, our goal is to improve the assessment and treatment of PIUO; yet there is no consensus among care providers about how best to approach PIUO. Lacking an explanation for the source leaves clinicians unable to treat the pain and increases a parent’s obstacles in providing care. Much is known about the assessment and treatment of both acute and chronic pain in typically developing children, from neonates to adolescents. While the treatment for an individual patient might pose significant clinical challenges (e.g. treating cancer pain in a toddler), the outlines of what to search for, the likely sources, and the starting points for treatment are clear. Care of a young child in pain begins with emotional-physical care such as hugging and soothing. We start medications with simple analgesics such as acetaminophen and progress to powerful agents such as fentanyl and ketamine. The sequence of interventions reflects knowledge of how the nervous system develops and responds to stimuli in the typical child. Children with SNI have marked differences in their nervous system because of differences in brain anatomy, injury to the developing brain, disruptions in healthy cell metabolism, or a host of other disruptions. Since we cannot make the same assumptions and inferences about pain signals or responses as we might in the typical child, we need better tools to address pain in these children.

Informed by our clinical and research experience, we have developed a new integrated clinical pathway called the PIUO Pathway, as a protocol to identify and treat underlying causes of pain and irritability in children with multiple disabilities and limited communication.
STUDY AIMS

Hypothesis
Our overall hypothesis is that children participating in the PIUO Pathway will experience improvement or resolution of PIUO as compared to children receiving treatment as usual.

Objectives
Our goal is to improve PIUO beyond what has been undertaken by the child's usual clinical teams. The primary outcome is improved pain control for non-verbal children with SNI as shown in a reduction of their pain and irritability scores for the pathway group compared to the control arm at week 10. Secondary outcomes include successful identification of common causes of pain and irritability in non-verbal children; decreased pain severity between baseline and the end of pathway (within 8 months post-baseline); improved family quality of life; ease of implementation of the PIUO Pathway for clinicians. We will also collect family feedback on the implementation of the PIUO Pathway.

Justification
PIUO is a source of stress for children and families. Research undertaken by our team and by others over the last fifteen years has described the manifestations of pain and irritability in children with SNI, developed assessment tools, explored its causes, and recorded the impact on families. With this study, we are moving forward to intervention. Many of the team members in this study are clinicians with leadership roles in programs providing care to children with SNI. Therefore findings from this study, in the form of clinical guidelines, may be rapidly translated into practice.

We have verified the importance of this research through years of focus on this issue. We developed the PIUO Pathway based on best evidence from the literature and expert opinion and performed a pilot observational study in 10 non-verbal children with SNI. The children ranged in age from 5 to 17 years and their SNI had a wide variety of causes, with high degrees of medical complexity and communication impairment. The children were recruited from community pediatric practices and all were followed by hospital sub-specialists. Our results were surprising: while it might be assumed that evaluation for pain and irritability would be thorough and revealing, just the opposite occurred in these children. We found that:

- No child in the pilot study had been fully evaluated for PIUO before enrolling. PIUO assessment was conducted in a disorganized, scatter-shot manner, with each child receiving only partial elements of a comprehensive evaluation.
- Even multiple attempts by diverse care teams were unable to resolve PIUO. Children continued to experience PIUO despite assessments by 6 to 14 different clinical teams and primary care providers prior to enrolment.
- Pediatric symptom management experts could not agree on treatment strategies. For example, there was a complete lack of consensus about optimal pharmacotherapy for PIUO.
- For pilot study participants, PIUO was resolved for 63% in ~13 weeks (median). These children had shown signs of PIUO for 1-2 years prior to study entry, but our stepwise
evaluation and treatment sequence (led by an RN and MD) resolved it for nearly two-thirds of the children in 1-25 weeks.

If our current study confirms the outcomes from our pilot study - that the PIUO Pathway can be useful in addressing the vexing problem of PIUO in children with SNI, the results will create the first-ever systemized practice guideline to treating pain in this challenging and vulnerable population based on a solid evidence base. Ultimately, such guidelines will streamline pain management for this population and improve the children and their families’ well-being. The results will inform families, front-line clinicians, and researchers about better ways to address one of the most troubling symptoms occurring in children with complex, incurable conditions.

**STUDY DESIGN**

Interventions for resolving PIUO are time and resource intensive. They require a focused approach to assessing all the underlying possibilities for the PIUO and addressing each potential source of pain one at a time. Tackling PIUO requires systematic, comprehensive, process-oriented thinking applied by an interdisciplinary team with flexibility in terms of approach and time. There have been recommendations in the literature about how to approach the problem of PIUO in children with SNI, but these recommendations have never been subjected to systematic evaluation as complex interventions, for example by following an integrated clinical pathway. Integrated clinical pathways (also called "care pathways” or “critical pathways”) are structured, sequenced approaches guiding the delivery of healthcare, often with a multidisciplinary perspective. They provide algorithms to be followed in the assessment and treatment of conditions, but are not intended to be rigidly followed; instead, integrated clinical pathways delineate a foundation for a clinician’s approach to a complex problem, thereby avoiding inefficiencies in evaluation or resource use. Integrated clinical pathways are a form of Complex Interventions and have been developed for sickle cell pain, childhood asthma, appendicitis, autoimmune conditions, inborn errors of metabolism, and cerebrospinal fluid shunt management. Despite their complexity, integrated clinical pathways are appropriate interventions for evaluation by Randomized Controlled Trial (RCT). RCTs of integrated clinical pathways have been proposed and/or completed for complex, multi-factorial patient problems including lung disease, heart failure, gastrointestinal surgery, stroke, and hip fractures.

In this study, we will use a waitlist-controlled RCT design, with 120 children randomized to PIUO Pathway or waitlist (standard care) treatment arms. This design was chosen strategically, with consideration of both the special pediatric population being studied and the ethical inappropriateness of randomly assigning children to a placebo group when pain is the target condition.

The Study Sequence, Events Grid and a detailed depiction of the PIUO Pathway are shown in Appendix 1, 1a and 1b.

**STUDY SITES**

In order to use an RCT to assess the effectiveness of the PIUO Pathway, we need a large number of participants - more than can be found in one center. Therefore, with the help of colleagues we
RECRUITMENT

Participants
Children aged 6 months to 18 years with SNI (from any cause) with unexplained pain and irritability and whose cognitive or communication impairments prevent determination of pain location, cause, and type will be eligible to participate.

Eligibility
Inclusion criteria: Eligible children will have cognitive impairment or be non-verbal and have severe levels of disability equivalent to Gross Motor Functional Classification System (GMFCS) scores of 3, 4 or 5. Eligible children will score $\geq 3$ on two scales administered via an Eligibility Screening (Appendix 2) that measure persistence and distress level the child is experiencing as well as identifies the type of pain and irritability as PIUO – with no obvious cause or explanation. The score of $\geq 3$ on the scale measuring pain persistence and distress level confirms that the child is experiencing pain and irritability more than “a little” on “some days”. The parent will confirm that the experience of pain and irritability has been present within the last month of the eligibility screening, although we recognize that some children will have experienced PIUO for much longer. The score of $\geq 3$ on the pain identification scale indicates that the child has unexplained pain and irritability (as opposed to, for example, ongoing pain due to a known cause such as esophagitis). Parents should have sufficient English/French language skill, or have access to assistance, to participate in the clinic visits and complete survey tools. The Child will also have a score of 4 or 5 on the Communication Function Classification System (CFCS).

Exclusion criteria: Children will be excluded if they are not within the specified age range; have the communication capabilities and cognitive development to localize their pain or have an explained and treatable cause of pain and irritability.

Randomization
Participants will be randomized to start the PIUO Pathway or to the waitlist control arm. The list of random allocations will be generated at WCHRI’s DCC centre using REDCap. An automated audit trail of all transactions, including assigned study identification number, treatment allocation, and time and date of the transaction will be recorded by REDCap. Randomization will be stratified by site and using permuted blocks of sizes 2 and 4.

Sample Size
The sample size calculation was based on the anticipated treatment difference between PIUO Pathway arm and waitlist control arm in the period between 8 and 12 weeks. As stipulated in the section on primary outcomes (page 12) a patient will be considered a success if they are judged to be in the lowest two pain categories (A or B) on consecutive visits beginning at weeks 8, 10 or
12. We anticipate that a 25% response to treatment during this period would be the minimal required to be viewed as clinically important, and we believe that a 25% response rate is achievable. The response rate during this period in the waitlist control is assumed to be zero, although we have set it at 5% to be cautious. To achieve 80% power using a two-tailed alpha=0.05 using the Fisher’s exact conditional test for comparing proportion, we require 57 patients per group. The Site Leads confirm that this number is readily obtainable within the proposed timeline.

Recruitment Procedures

It is anticipated that the same recruitment procedures will be followed at all four sites. However, minor modifications may be necessary for compliance with the individual ethics board at those institutions. Recruitment will be amongst outpatients, however if a child is hospitalized after enrolment, s/he can remain on the study.

Families will be made aware of the study via the following two channels:

1. A letter (Appendix 7) will be sent on behalf of the Principal Investigator, by the Site Leads to respective community pediatricians and sub-specialty clinics where children with SNI often receive care (e.g., Neurology, Complex Care, Orthopaedics, etc.). The letter invites them to refer patients to the study.

2. Study advertisements (Appendix 8 and 9) will be placed on websites and social media sponsored by our hospitals, research institutes and community partners (e.g. Research4kids database at HSC, Rare Disease Foundation’s website etc.) in compliance with the REB’s social networking guidelines. Paper ads will be placed on bulletin boards near clinics. These advertisements will inform potentially interested participants of how to contact the study team.

All potentially interested participants will receive a phone call from the Study Research Nurse who will provide a brief explanation of the study and administer the Eligibility Screening Checklist (Appendix 2). If a child is eligible and the parents or legal guardians wish to participate, the Study Research Nurse will obtain consent by providing the family with a Consent Form (Appendix 3) to be reviewed, signed and returned within two weeks, provided that all the family’s questions and concerns have been answered. For communication purposes the Study Research Nurse will collect contact information from participants, including their addresses and phone numbers. This information will be stored separately from study data, under lock and key. Email addresses will be collected in order to send REDCap surveys to participants and will be kept with contact information. Email addresses will also be stored in the same project database as participant survey responses within the REDCap database. This juxtaposition of data elements is required by the REDCap software in order that survey invitations may be emailed to the study participants at specific time points. All study data generated by online survey will be stored in the same secure manner as the study data, as outlined on page 15. IP addresses will not be collected as part of the completion of online surveys. In cases where a parent is unwilling or unable to access email for the online surveys, a paper copy of the surveys will be provided as an alternate for their convenience.
**STUDY SEQUENCE**

For a visual of the Study Sequence, see Appendix 1, 1a and 1b. Study procedures and tools are described separately and in detail below.

Following recruitment, there will be a brief “run-in” period to establish a baseline for all participants. To this end, the Study Research Nurse will review the child’s health record and information obtained from community practitioners (with family consent) detailing previous clinical investigations and treatments for pain and irritability. These include laboratory tests, imaging, and interventional and surgical procedures that were directed towards addressing pain and irritability. We will collect consultation reports to enhance the information provided in the parent history. The results of this record will be compared with the recommendations of the PIUO Pathway in order to avoid any duplication or unnecessary repetition of assessment or treatment. Based on our previous pilot study many children will likely have had some, but not all, elements of the PIUO Pathway completed. The Study Research Nurse will mail out the Consent Form to participants and include instructions on how to answer three questionnaires that will be send to the participant via e-mail as REDCap surveys, once consent has been obtained. The questionnaires are: The Baseline Non Communicating Children’s Pain Checklist Revised (NCCPC-R), the Face, Legs, Activity, Cry and Consolability (FLACC) and the Patient reported Outcomes Measures Information System Pain Survey (PROMIS-57). A survey to obtain basic demographic information from the participating family will also be send out via REDCap. The participant is to mail back the signed consent form in a pre-stamped return envelope.

The Study Research Nurse will meet with participants for a baseline interview, ideally at a time that coincides with other appointments at the hospital. At the baseline interview, the Study Research Nurse will administer the Health Information Form (Appendix 4), confirm the information collected from the child’s health record and confirm the child’s GMCFS score based on the assessment at the Eligibility Screening as well as evaluate the child’s CFCS level. The Study Research Nurse will administer the Pain Survey and collect the, NCCPC-R, FLACC and the (PROMIS-57) which have been mailed out prior to the baseline interview. PROMIS-57 will be completed again at week 10 of the study and upon completion of the Pathway as well as at Follow Up 8 weeks post Pathway completion. The Pain Survey and the FLACC will be repeated at Follow Up as well.

In addition to reviewing all previous work up related to pain and irritability, we will establish a baseline for participants’ expectations to the effectiveness of the PIUO Pathway. Pain is highly modifiable by psychological factors such as beliefs and expectations, which may influence treatment response (via placebo analgesia). This is especially important in this context of children with SNI where caregivers play a key role in assessment and management of pain and a placebo-by-proxy effect might occur based on the parents’ perceptions/behavior. To evaluate the Impact of Expectations all families will be asked at the outset and at the end of the Pathway if they expect that participation will be of benefit to them and/or their child.

After the baseline has been established, children will then be randomly assigned to (1) PIUO Pathway arm with immediate intervention or (2) waitlist control arm. Data will be collected on pain and irritability and health during the waitlist period for control subjects in the same way as for those on the immediate intervention arm.
Children assigned to the immediate PIUO Pathway arm will start with Step 1 right after randomization. The waitlist control arm will be ten weeks in duration and then children will cross over to Step 1 of the PIUO Pathway. For participants on either arm, starting at enrolment, the Study Research Nurse will administer a Pain Survey and provide a consultation (Appendix 5 and 5b) every two weeks by phone. The Research Nurse can be contacted by the family for consultation at any time during the study (standard working hours) in between the scheduled bi-weekly phone call. The Pain Survey tool measures pain and irritability persistence and distress level through a composite score of two questions asking parents to report on their child’s experience and behavior within the last two weeks. The tool is taken from the Washington Group Extended Question Set on Functioning (WGES-F) developed by a United Nations commission on disability statistics and is intended to capture a measure of physical impairment along with questions on pain, fatigue and depression. The extended set of questions has been adopted by the United Nations as a scale to measure disability at an epidemiological level and the two-question pain set has been shown to demonstrate validity in an adult population. These two questions on pain (“how much pain did you have” and “how bad is the pain”) have been adapted for use with children and are included in the study as markers of pain persistence and distress.

The RN Consultation has a two-fold objective: 1) To gather clinical information to assist the study team in assessing and treating the child’s PIUO and 2) to provide the parent with a consultation in regards to any measurements they might take or have taken to relieve their child’s PIUO. The clinical information relevant in this regard includes any changes in health, medications or interventions outside the study (including care provided by community physicians, therapists, and alternative medicine practitioners) that might impact PIUO.

Once on the PIUO Pathway (regardless of starting arm) children will receive the intervention until the condition improves/resolves or until 6 months have passed, whichever comes first. There will be a follow-up assessment 2 months after the child successfully completes the PIUO Pathway with resolution or improvement, or if not then at 8 months following the start of Step 1, whichever comes first.

Efficiency of the PIUO Pathway will be measured by tracking time needed, and number of investigations required, for those patients who turn out to have an identifiable cause for pain and irritability. Parents will be given a chance to provide feedback on the study and their participation at a follow up interview over the phone, answering questions detailed in the Family Feedback Form (Appendix 11)

**STUDY PROCEDURES**

*The PIUO Pathway*

The PIUO Pathway focuses on eliminating undiagnosed, but treatable sources of PIUO. It targets PIUO in an intentional, focused, timely sequential order of standardized steps with physician and dedicated nurse support. The PIUO Pathway is implemented by clinicians (MD and RN) with expertise in treating pain in children. A key element is the ongoing and frequent contact between families and clinicians to coordinate tests and treatments along the PIUO Pathway and to monitor
results or adverse events (see Data Monitoring Plan for handling and reporting of adverse events).

As shown in Appendix 1b, the PIUO Pathway has 2 steps (described in detail below). Each participant proceeds through the PIUO Pathway as long as their pain persists, but may not go through all steps of the PIUO Pathway in case their pain is resolved at any stage.

- Step 1 is a thorough history and patient evaluation, including directed testing.
- Step 2 is a series of screening tests to further explore any potential underlying disease or injury not apparent based on history and physical examination.

**Step 1** begins with a detailed History and Physical Examination (Hx&PE). This includes a pain history to identify known and unknown sources of past and current pain, and a recording of previous assessments and treatments directed towards pain.\(^51\) The history will include a record of medications, surgical interventions, physical and behavioural interventions from allopathic and alternative/complementary approaches. If families have any detailed observations demonstrating their child's PIUO episodes (e.g. diary or video); these will be reviewed by the study clinician. Clinician assessment of those observations will be considered clinical data, but the media will not become part of the dataset. The MD Assessment to be undertaken in Step 1 is outlined in full in Appendix 6. Appendix 6b constitutes a summary of the assessment to be filled out by the SRN. While the MD Assessment will be used as clinical data to assess and treat the participants’ pain and irritability, the Summary Sheet will contain research data to be entered into REDCap. The data to be collected regards whether the MD Assessment was carried out thoroughly by the MD, rather than the results of the assessment.

In Step 1, any information gained may then lead to directed testing with imaging or laboratory studies. As an example of directed testing, if the child has pain with transfers into a wheelchair the physician may order an x-ray to rule out hip dislocation. Any findings from directed testing (or screening testing as described below) will be shared with the child’s usual care team (i.e. primary team) via the standard reporting system available at each study site (paper and/or electronic record). Findings related to pain sources will be managed by the Site Lead clinician, whereas incidental findings will be referred for management by the child’s usual care team.

If Step 1 is unrevealing, **Step 2** consists of a series of screening tests. The screening tests are designed to look for sources of pain that would not necessarily be revealed in a careful Hx&PE or directed testing. If any screening test has already been completed within 6 months prior to the participant enrolling in the PIUO Pathway, it is not repeated, unless the pain and irritability symptoms have changed since the test was done. The exception is the Hx&PE, which is always done at the Step 1 visit by the study team. The utility of the step approach is provided by a study that used directed tests and screening to assess PIUO in a limited and more expensive workup with nuclear medicine imaging.\(^52\)

The 4 PIUO standard screening tests are:

1. Urinalysis/Urine Culture
2. Ultrasound - abdominal
3. Gastric pH (if G-tube present)
4. Bloodwork  (CBC, Alkaline Phosphatase, ALT/AST, Bilirubin, C reactive protein, Electrolytes – Na, K, Ca, Mg, Cl and PO4, GGT, Lipase, IgA TTG)

Although the above screens are standard of care, the order of these tests (e.g. performing Hx & PE) then Step 1 tests, and then moving to Step 2 screens is a novel approach being tested here. If Step 2 imaging or exams were required as part of Step 1, then they will not be repeated at Step 2.

**DATA COLLECTION TOOLS**

All Instruments to be used for data collection will be available in English and French or an interpreter will be available when the tool is used:

Eligibility and Baseline

- The Gross Motor Function Classification Scale (GMFCS) establishes levels of function for individuals with cerebral palsy, based on self-initiated movement. This is a widely used, standard tool for determining functional levels and has been rigorously validated.\(^53,54\) GMFCS scores will be one element in establishing initial eligibility for the study, and will also be a part of the data analysis.

- The Communication Function Classification System classifies the everyday communication performance of an individual into one of five levels. The CFCS is a validated tool that will be used in conjunction with the GMFCS to describe the ability, or lack thereof, in our population to communicatively locate and describe their pain and irritability to caregivers and care providers.\(^55\) We expect our participants to fall within category IV and V.

- The Faces, Legs, Activity, Cry and Consolability (FLACC) observational pain assessment tool has been widely used to measure pain intensity in young children who cannot self-report a pain score and shows reasonable interrater reliability for children with different levels of cognitive impairment.\(^56\) A sample item on this scale is scored by the parents as a possible score of 0-2, and there are 5 items (Face, Leg, Activity, Cry and Consolability) that add up to a total pain score between 0-10. Reliability and validity of this scale are previously reported, specifically for children with post-operative pain.\(^57\)

- The Non-Communicating Children's Pain Checklist-Revised (NCCPC-R) will describe each child’s typical pain and irritability behaviours at baseline. The NCCPC-R was designed to assess pain in children with cognitive impairment. Psychometric properties are well established.\(^58\) Score results on the NCCPC-R are internally consistent, significantly related to pain intensity ratings provided by caregivers, consistent over time, sensitive to pain, and specific to pain. Results of the NCCPC-R will provide parents, the study team and clinicians with a common understanding of the child's individualized pain and irritability behaviour.

Primary Outcomes

- The Pain Survey tool will measure pain and irritability persistence and distress level throughout the study. A quick, two question assessment, the pain survey is taken from the
Washington group Extended Question Set on Functioning (WGES-F) and is adapted here for use in children. The pain question set has been shown to have good validity and is able to correlate with other pain measurements in adults.\textsuperscript{50} Although this two-question pain survey is simple, it is sufficiently informative so as to be of use in describing a child’s pain, without unduly burdening parents with an overload of questions every two weeks. Pain Surveys will be completed biweekly throughout the Study as described below. Participants will be deemed to have had a positive outcome if they score in category A or B (see Appendix 5) on two consecutive visits. We will compare those who have a positive response on weeks 8, 10 and 12 between intervention and waitlist group.

- PROMIS-57 (Patient Reported Outcomes Measures Information System) is a multi-dimensional tool that will assess parents’ well-being in the face of their child’s chronic pain and irritability. This assessment is one of the two primary outcome of this project. PROMIS-57 was developed as part of an initiative of the US Department of Health and Human Services to establish a common set of patient reported outcome measures (www.healthmeasure.net). The PROMIS tools are found to be valid and reliable. There is a Canadian PROMIS coordinator as well, and support is available for translation and adaption to the REDCap database which we will be using. There are several PROMIS tools assessing various elements of adult and child health and well-being. The PROMIS-57 tool assesses across the following domains: physical function, anxiety, depression, fatigue, sleep, social participation, and pain interference in daily activity. While we cannot attribute all changes in quality of life to improvement in the child’s pain and irritability, we will analyze to look for high degrees of correlation.

**ANALYSIS**

The primary analytic strategy is based on the assumption that it will take some time after the screening period (weeks 0-2), the onset of randomization (week 2-3) and the Pathway initiation (weeks 4-10 in the Pathway group) for the intervention to have its full impact. As well, to determine the impact relative to the Waitlist group, the comparison must take place before the intervention is delivered to the Waitlist group (i.e. prior to cross-over). Thus, the primary analysis will focus on the measurements taken at weeks 8, 10, and 12.

The primary outcome is a change in Pain Survey score, moving a child from any high pain and irritability score (C, D, and E), to a low score (A, B) for 2 continuous reporting periods. A level B score (“little pain” on “some days”) is clinically acceptable in this health challenged population, although not ideal. Previous work has indicated that complete absence of pain is not always achievable in this population.\textsuperscript{3, 33}

The primary comparison will use a Fisher’s exact test to compare the proportion of patients achieving a successful outcome in the period starting between week 10 and 12. We will also perform an adjusted analysis using logistic regression and treating the baseline category as a covariate.

In addition, we will compare the Pathway groups on each domain of the PROMIS-57 instrument at week 10. The dependent measures will be the domain scores at week 10, the covariates will be the scores at baseline of each domain, and the independent variable be will the Pathway group.
Multiple linear regression will be used to evaluate the intervention differences. In the primary analysis, all participants measured on week 10 will be included. Multiple imputation will be used in a sensitivity analysis to include participants without measures on week 10.

As a secondary analysis, we will determine whether the intervention had an effect in the Waitlist group by comparing their measurements on the pain outcomes at week 14, 16 and 18 with their week 10 measurements (just before they cross over to the Pathway).

**DATA STORAGE**

Participants will be assured that all collected information will be kept strictly confidential. Non-identifying participant ID numbers assigned to each participant will be used on all written forms and identifying information will be locked in secure file cabinets and/or will be password protected on computers. All paper documents and data will be kept for 5 years following completion of the study and then destroyed. All procedures will be in accordance with the ethical guidelines at the participating institutions and applications for research ethics boards at all sites will be completed prior to study commencement.

The Research Coordinator in Vancouver will retain an electronic file with paper backup copies of the Master List of all the participants. This list will contain participants’ names, their unique Participants ID number and contact information. The Master List of participants will remain in a locked research office at the Vancouver site and the electronic file will be password protected to restrict access to study staff. The electronic file and backup paper copies of the Master list of all participants will be destroyed 5 years after completion of the study. Paper copies of the site lists will be maintained under lock-and-key control at each site, accessible by only the Study Research Nurse at that site. The paper and electronic site lists will never leave the separate sites and will be destroyed at completion of the data collection portion of the study. These lists are necessary to enable accurate collection of follow-up data.

Original versions of the signed consent forms will be retained at the site in which the participant was recruited and will be kept under lock and key. Similarly, paper copies of the study tools administered at each site along with study notes made by the Study Research Nurse or Site Leads or any other source documents will remain there under lock and key.

Data from source documents will entered and validated in a REDCap database for which special privacy and security measures are in place. All data entered into REDCap will be de-identified and collected data will only be viewed by study team members granted specific rights. REDCap has the capacity to store ‘live’ data for multiple, ongoing study databases simultaneously where each individual study database has the option of supporting multiple centers. The REDCap database will be provided by the CHILD-BRIGHT Data Coordinating Centre (DCC) which is managed by the Women & Children’s Health Research Institute at the University of Alberta. The database itself is housed on secure servers hosted in a secure data Centre in the basement of the University of Alberta Hospital behind the MEDIT firewall. The REDCap database will be annulled and the electronic data deleted 5 years after the study has been completed.
REFERENCES


