Efficacy of Gabapentin in Treating Pain in Children with Severe Neurological Impairment

Protocol No. 2020GabTrial – Version 3.0 – October 4, 2020

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INVESTIGATOR AGREEMENT

Protocol Title:	Efficacy of Gabapentin in Treating Pain in Children with Severe Neurological Impairment
Protocol No:	2020GabTrial
Version No:	3.0

This clinical study will be conducted in accordance with applicable Health Canada regulations, ICH guidelines on current GCP, and the Declaration of Helsinki.

I confirm that I have read and understand this protocol and I agree to conduct this clinical study in accordance with the design and specific provisions of the protocol, with the exception of a change intended to eliminate an immediate hazard to participants. Any deviation from the study protocol will be documented in the case report form.

I agree to promptly report to the applicable ethics boards any changes in the research activity and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without prior ethics and sponsor approval, except where necessary to ensure the safety of study participants.

Dr. Hal Siden		04/10/2020
Name	Signature	Date

DISCLAIMERS

GCP Statement

This clinical study will be conducted in accordance with applicable Health Canada regulations, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on current Good Clinical Practice (GCP), and the Declaration of Helsinki.

Confidentiality Statement

This clinical study protocol contains information which is of a confidential, trade-secret or proprietary nature. The protocol is for the use of the Sponsor-Investigator and his designated representatives participating in the investigational trial. It is not to be disclosed to any other person or party without the prior written approval of the Sponsor-Investigator.

This protocol was developed based on the 2013 template developed by SPIRIT:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200-207.

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ 2013;346:e7586

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1. TRIAL SUMMARY

Title	Efficacy of Gabapentin in Treating Pain in Children with Severe Neurological Impairment
Brief title	Gabapentin Trial
Primary registry and trial number	2020GabTrial
Secondary identifying numbers	Clinical Trials.gov: NCT03464773 SCA-145104 RI MUHC Ref# 7733
Sources of monetary or material support	Canadian Institutes of Health Research (CIHR) SPOR Networks in Chronic Disease, CHILD-BRIGHT
Primary sponsor	Dr. Hal Siden
Study officials/Investigators	Dr. Hal Siden, Dr. Tim Oberlander, Dr. Julie Hauer, Erin Adams
Central contact	Anne-Mette Hermansen
Number of centers	1
Primary objective	Evaluate the effectiveness of gabapentin to decrease pain and irritability in children with SNI, when source of pain and irritability is attributed to neurological dysregulation and not to a nociceptive-inflammatory cause
Secondary objective	1. Identify the optimal dosing of gabapentin in reducing pain and irritability 2. Identify the latency time for gabapentin to show effectiveness 3. Evaluate the safety and tolerability of gabapentin
Exploratory objective	Evaluate whether parent/caregiver stress and function improve if gabapentin reduces child's pain and irritability
Interventions	Participants will receive liquid gabapentin, compounded from Teva-Gabapentin (gabapentin) 400 mg capsules (DIN 02244515). cf. below

Key eligibility criteria	Children 3 to 18 years old with severe neurological impairment who are experiencing pain and/or irritability of unknown origin (PIUO)
Study design	Repeat measures single cross-over trial (treatment and placebo)
Randomization	Computer-generated, simple randomization (starting with treatment or placebo). Each participant serves as their own control.
Target sample size	10
Study duration	Total study duration 12 months, participant study duration 4 months
Medication administration and dosing	Gabapentin capsules will be compounded with flavourings to create a 100 mg/mL oral solution. The starting dose will be 5 mg/kg/day as oral liquid or via g-, j-tube. The dose will be escalated as described in Section 6.2. The maximum dose is 60 mg/kg/day in participants < 15 kg, or 45 mg/kg/day (675 mg) in participants > 15 kg.
Primary outcomes	The pain and irritability score on the NCCPC-R through days 11-19 on active drug compared to placebo. An 11-point decrement in the NCCPC-R score with no rebound x 3 days is considered clinically meaningful minimum change (improvement)

Secondary outcomes	1. For patients who benefited from gabapentin, identification of the lowest dose that was effective in reducing pain scores, as shown by a 50% reduction in the NCCPC-R score compared to baseline during days 11-19 on active drug 2. For patients who benefited from gabapentin, identification of the maximal effect dosage as measured by the largest improvement in the NCPCC-R score compared to baseline during days 11-19 on active drug. 3. Identification of the latency time in days to the onset of maximum relief of pain and irritability as measured by the NCCPC-R score over days 0-19. 4. Adverse Events Collection demonstrates the AE on treatment arm do not exceed the frequency found in the Product Monograph for children receiving gabapentin.
Exploratory outcomes	PROMIS-57 scores on the treatment arm compared to the placebo arm.
Outcome measures	Primary: NCPCC-R Secondary: NCPCC-R, Adverse Events Collection Exploratory: PROMIS-57

2. INTRODUCTION

2.1. Background and Rationale

The rationale of this trial is to test the usefulness of gabapentin in reducing and resolving pain in children with developmental brain disorders, specifically those with severe neurological impairment (SNI). The trial is part of a larger program of research focused on the problem of ongoing, unexplained, and difficult-to-treat pain and irritability that many children with SNI, and their families, experience. Our program 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.

Severe Neurological Impairment (SNI)
SNI is an overarching descriptive term for children with significant health and functional 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.[1] 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.[2–4] 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.[5–9] Furthermore, the greater the degree of neurological impairment, the higher the prevalence of pain.[10]

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".[11] 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[12–14] and central or functional pain that arises entirely within the central nervous system, more recently termed 'nociplastic' pain.[15,16] 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.[17,18]

Pain is the most common symptom reported by the parents and caregivers of children with SNI,[19] 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.[20-25]

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).[26-28] Often, however, it is not clear what underlies the pain behavior as there is no clear inciting noxious event; our team has defined this entity of pain without an obvious source as Pain and Irritability of Unknown Origin (PIUO).[26]

Parents are experts in identifying pain behaviours in their own child, but consider their interpretation to be a complex and uncertain process.[29-31] 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.[32] 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.

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.[33,34] 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. Analgesics such as acetaminophen are used first and pain management may progress to powerful agents such as fentanyl and ketamine.[35] 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 clinicians cannot make the same assumptions and inferences about pain signals or responses as with the typical child, they need better tools to address pain in these children.

Our work to date has developed a more efficient, focused clinical pathway to evaluate children with SNI for all potential sources of nociceptive-inflammatory ("treatable") pain. We are currently conducting a multi-site randomized, controlled trial of this clinical pathway. Our objective is to reduce the "unknown" element of pain in these children, increasing the potential for treatment. Nevertheless, there are children, who at the end of a thorough evaluation guided by a clinical pathway, will still have PIUO. These children may benefit from adjuvant analgesics such as gabapentin.

Treating with Gabapentin

According to the US FDA product information (US FDA Neurontin (gabapentin) Prescribing Information. Revised: 10/2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020235s064_020882s047_021129s046lbl.pdf Accessed October 4, 2020), gabapentin is indicated for adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy. In Canada, however, gabapentin is authorized for use in adults only (> 18 years of age) as an antiepileptic agent and is not indicated for use in children. The precise mechanisms by which gabapentin produces its analgesic and antiepileptic actions are unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. Much is known about its activity at the molecular level and there is increasing understanding that it moderates nerve signals that include pain.[36] Gabapentin is notable for not being metabolized in humans; the parent compound is renally excreted with an elimination t1/2 of 5-7 hours.

In studies of gabapentin the main adverse effects are development of sedation and dizziness, ataxia, fatigue, and nystagmus in people 12 and older. In children aged 3-7 treated for epilepsy there was also a small increase, compared to controls of weight gain, susceptibility to viral ill ness, somnolence and hostility. (US FDA Neurontin (gabapentin) Prescribing Information. Revised: 10/2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020235s064_020882s047_021129s046lbl.pdf Accessed October 4, 2020),

Gabapentin was originally developed as an anti-convulsant. In the first 10 years of its use attempts were made to find its place as a monotherapy, and later an add-on therapy, for seizures. Starting in 1996 and continuing onward there was an explosion of interest in this drug as an analgesic, especially for neuropathic and chronic, complex pain.[37-39] Gabapentin is often used for these indications as it has a low adverse event profile and appears to provide clinical benefit in difficult-to-treat cases. Clinical use of gabapentin for these same indications of neuropathic and chronic pain, as well as pain and irritability, has extended to infants and children. In a longitudinal, prospective study of children with non-cancer life-threatening conditions, gabapentin was used by 13.8% of the subjects.[40]

Gabapentin was tested in 118 pediatric patients age 3 to 12 years with epilepsy. This study showed that gabapentin was significantly better than placebo. The drug's pharmacokinetics were established in 48 pediatric subjects between the ages of 1 month and 12 years. The dosing was tested with 253 pediatric subjects between 1 month and 13 years of age. A smaller study in pediatric patients age 1 month to 3 years compared dosing of 40 mg/kg/day gabapentin (N=38) with placebo (N=38) in patients who were receiving at least one marketed antiepileptic drug and had at least one partial seizure during the screening period, and this study showed no difference between product and placebo (Scientific Information, Teva Canada Ltd. https://www.tevacanada.com/globalassets/canada-ph2/product-monographs/teva-gabapentine-capsules-100-300-400-tablets-600-800mg_pm.pdf, accessed June 1st, 2020 and Product Information, Pfizer Canada Inc. https://www.pfizer.ca/sites/default/files/202005/Neurontin_PM_E_237475_2020.05.05.pdf accessed on June 1st, 2020).

The evidence base supporting the use of gabapentin for pain and irritability in infants and children with neurological impairment rests on case series publications describing a limited number of retrospective cases.[41-49] The lack of prospective, randomized studies, even for this commonly-used medication, underpins the rationale for this study.

The N-of-1 trial design chosen for this study is suitable for a small-scale study, the first randomized, placebo-controlled study in this population and for this indication (children with neurological impairment and potential neurological dysregulation). Results from this study are expected to be useful in the design of a much larger Randomized Clinical Trial (RCT) that will provide further information about the effectiveness, dosing and adverse effects of the medication.

2.2. Objectives

The primary objective of the trial is to evaluate the effectiveness of gabapentin to decrease pain and irritability in children with SNI, when the source of pain and irritability is attributed to neurological dysregulation (nociplastic pain), as measured by parent reported pain scores. This objective corresponds to the primary outcome listed in section 3.4.1.

We will compare the gabapentin versus placebo along an escalating dose range for both individual subjects and for the group. We will aggregate the results of the completed N-of-1 trials across all subjects to estimate the group level comparative effectiveness of gabapentin in reducing pain and irritability.

The secondary objectives are to:

1. Identify the optimal dosing of gabapentin in reducing pain and irritability (Corresponds to secondary outcomes 3.4.2 and 3.4.3).

2. Identify the latency time for gabapentin to show effectiveness (Corresponds to secondary outcome 3.4.4).

3. Evaluate the safety and tolerability of gabapentin (Corresponds to secondary outcome 3.4.5).

4. An Exploratory objective will be to evaluate whether parent/caregiver stress and function improve if gabapentin reduces children's pain and irritability. This objective corresponds to the Exploratory outcome listed in section 3.4.6.

2.3. Trial Design

With the small sample size and time needed to titrate up to an effective dose, this trial proposes to use a single randomized multiple-measures cross-over design (N-of-1), with results aggregated over several subjects. This design is well-suited to outcomes that are highly specific to each individual and not amenable to precise measurement across a large cohort. The heterogenous nature

of pain and irritability responses in children are more likely to be personally specific and characteristic, rather than generalizable. The behavioural pattern is reflected in the structure of the standard tools for pain assessment in SNI that rely upon a catalogue of behaviour patterns that differ from one child to the next.[3,29,50-52]

The proposed cross-over trial will use randomization and blinding of subjects and observers with placebo controls to reduce unexpected bias. A critical distinction is that each subject will serve as their own control and experiment, allowing for a finer assessment of the treatment efficacy within each patient.

In this trial, each patient will switch between gabapentin (G) and placebo (P). The sequence of whether G precedes P (GP) or P precedes G (PG) will be randomized by the study pharmacist, and neither the clinician nor the subject (parent/caregiver) will know the sequence.

Gabapentin is clinically started at a low dose and increased until either effectiveness is demonstrated or an upper limit dose, derived empirically, is reached. Based on work by Hauer and Solodiuk we have established a dose titration schedule that will reach a typically effective dose over 15 days (Hauer, personal communication).[44] Extensive expert opinion shows that in the setting of children with neurological irritability and pain, as opposed to functional chronic pain in other children/youth, the onset of pain relief is much more rapid than several weeks. Ref. 49 describes improvement in pain scores (NPASS) in a neonatal cohort at 14 days. In another study, an RCT of gabapentin in children, a stable dose was reached at 22 days, and clinical effect was seen within that time frame, even though the protocol continued to 30 days. [Effectiveness of Gabapentin on Chronic Irritability in Neurologically Impaired Children. ClinicalTrials.gov Identifier: NCT01675960. The trial was terminated due to slow recruitment (2 enrolled)]. In personal communication with the study PI, (Scott Schwantes), most of the effect was actually within 2 weeks and this is confirmed in his clinical practice. Julie Hauer, author of Ref 41, 43 and 44 concurs with this time frame, in personal communication. Parent-caregivers will administer either active gabapentin or placebo on the same schedule. When transitioning between gabapentin and placebo, in either direction, there will be a 3-day washout period. A study dosing table is shown in Section 3.3.

The primary variable assessed is the child's pain score. Pain and irritability will be measured using the Non-Communicating Children's Pain Checklist – Revised (NCCPC-R) at specified intervals throughout the randomized sequence of G : P. Additional measures of parent/caregiver burden and impact on their daily function will be undertaken weekly with the PROMIS-57, a tool adapted to measure the impact of the child's pain and irritability on parental functioning. This multi-dimensional tool assesses the parent/caregiver's stress, activity, function and sleep and is a proxy for the distress caused by the child's condition.

Other measures will be of usual, known side effects (e.g., sedation) and of any unexpected adverse events. Known side effects will be assessed regularly at the start, mid-point and end of each sequence via the Health Update. Unexpected adverse events will be tracked continuously.

3. METHODS

3.1. Study setting

The trial drug will be dispensed to participants to be administered by the parent/caregiver at home. Parents/caregivers of children with complex health issues are intimately familiar with these patients' daily routines and skilled at their care and can therefore be expected to administer the study drug according to protocol.

3.2. Eligibility criteria

Inclusion criteria:

1) Any gender; 3 to 18 years old, inclusively
2) Gross Motor Functional Classification System (GMFCS53,54) score of 3, 4 or 5
3) Communication Function Classification System (CFCS55) level 4 or 5
4) A score C, D or E on the Pain Survey
5) Evidence of an evaluation using the PIUO Pathway showing no evidence for treatable sources (nociceptive-inflammatory) of pain and/or irritability symptoms

It is expected that most or all of the participants will be recruited from the participant cohort for the PIUO Study. If the child did not participate in the PIUO Study and has not undergone an evaluation using the PIUO Pathway, but is otherwise eligible, they may first go through the PIUO Pathway and may continue with the gabapentin trial if no evidence for sources of treatable pain are uncovered.

Exclusion criteria:

1) Patients with a known hypersensitivity/allergy to the study medication
2) Patients who are actively participating in another experimental therapy study for pain and/or irritability
3) Patients who are a poor medical risk because of other systemic diseases or active uncontrolled infections
4) Participants whose pain and or irritability is diagnosed through completion of the PIUO Pathway during the enrollment phase of the trial
5) Patients who score A or B on the Pain Survey
6) Patients who have an active source of nociceptive-inflammatory pain at the time of enrolment (e.g., post-operative pain)
7) Patients with active renal disease, known renal impairment or glomerular filtration rate < 60 mL/min/1.73 m2 (if known).
8) Patients with known significant hepatic impairment at the discretion of the investigator.
9) Patients with clinically relevant abnormal ECG (if available) at the discretion of the investigator.
10) Patients with diagnosis of sickle cell disease.

3.3. Interventions

Investigational Product Specifications

Generic Name: Gabapentin. Marketed Name: Teva-Gabapentin, DIN 02244515 (400 mg capsules)

Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but does not possess affinity for either GABAA or GABAB receptor.

Gabapentin binds with high affinity to the α2-δ (alpha-2-delta) subunit of voltage-gated calcium channels. Broad panel screening suggests it does not bind to other neurotransmitter receptors of the brain and does not interact with sodium channels.

Formulation, Storage and Handling
Teva-Gabapentin (gabapentin) 400 mg capsules contain gabapentin, colloidal silicon dioxide, lactose monohydrate, pregelatinized starch, and talc. Capsule shells may contain gelatin, titanium dioxide, yellow iron oxide, red iron oxide and blue ink.

Store capsules at room temperature between 15-30ºC.

For each study participant, 400 mg capsules will be compounded with OraPlus and OraSweet Sugar Free in a 1:1 ratio to create a 100 mg/mL oral liquid by the study site pharmacy. Similar-ly, placebo bottles will be prepared containing the same amount of OraPlus and OraSweet Sug-ar Free. The drug will be dispensed shortly after preparation.

The 100 mg/mL oral liquid will be supplied in bottles and should be stored at room temperature between 15-30ºC.

OraPlus and OraSweet Sugar Free are recommended as the compound solutions acceptable for all participants, including those with diabetes. For participants on a ketogenic diet it will be confirmed with the Neurological Care Centre, Ketogenic Diet program at BC Children's Hospital that the amount of OraPlus and OraSweet Sugar Free they will receive is safe, prior to dispensing (Lawren Fisher RD, personal communication, May 25th 2020)

Supply and Accountability
Teva-Gabapentin (gabapentin) 400 mg capsules are supplied as orange opaque cap and body hard gelatin capsules, size #0, with N and "400" printed in blue ink on opposing cap and body portions of the capsules.

Labeled and compounded 100 mg/mL study drug bottles will be supplied by the BC Children's Hospital pharmacy to study participants and drug accountability will be conducted by the same pharmacist.

Regimen, Administration and Duration

Summary: This study uses a rapid and safe dose escalation to the widely accepted therapeutic range where evaluation of response will be undertaken with frequent scoring. Different maximal doses are used for children < or ≥ 15 kg, based on pharmacokinetic data.[53] Doses are titrated to clinical effect or maximum target dose, whichever is lower. Once in the therapeutic range, doses change after 3 days if there is not an adequate reduction in symptoms. For any subject that obtains clinical benefit below maximal dose, then they will be held at that dose for the remainder of that period until such time as the scheduled wean begins. At the end of each treatment period there is a wash-out.

Starting Dose: The starting dose of gabapentin will be 5 mg/kg administered as oral liquid or via gastric or jejunal routes. On Day 1 of the study, the gabapentin will be administered once at bedtime and then increased according to the schedule shown in Table 1.

Dose Escalation: The dose will be increased every 3rd - 4th day in a step wise fashion of 13% - 50%, starting with the evening dose in order to accommodate sedation. The maximum dose for subjects will be as follows: < 15 kg to 60 mg/kg day and ≥15 kg to 45 mg/kg/day. Dose titration will be to a maximum target dose (based on weight as described, < 15 kg, > 15kg) or to clinical effect, whichever is lower. The dose escalation scheme is based upon expert consensus and personal communication with Scott Schwantes, Julie Hauer, and upon review with the BC Children's Hospital research pharmacist. .,[56].

Some children with PIUO and SNI have been given gabapentin empirically by their health care provider, often without any subsequent, detailed assessment of benefit. Many times, the medication is continued because of its low side-effect profile and overall safety compared with other analgesics. If a subject is currently on gabapentin at the time of enrolment, and the parent/caregiver wants an evaluation of its effectiveness, then the subject can be enrolled in this study with the following approach:

After appropriate enrolment and consent, the subject will be weaned off of gabapentin, in a stepwise manner with 25% reductions in dose every 3rd day. Once they are no longer on the active drug, they will be randomized to active drug or placebo like all other study participants.

Gabapentin Risks and Precautions

Risk minimization, management, and assessment procedures have been implemented in the study to minimize and assess potential risks to participants who participate in this clinical study with gabapentin. Components include: (1) specific study eligibility and exclusion criteria to ensure that participants who have underlying characteristics that potentially increase their risk for an adverse outcome are excluded. These include patients with a history of previous sensitivity to gabapentin. (2) Protocol-specific procedures for minimizing and managing AEs: sedation is the most common AE to gabapentin, and we will address this by titrating upwards on the dose every 3rd day, and always increasing the nighttime dose first; (3) overview surveillance by the independent Data Safety Monitoring Board; (4) ongoing follow-up throughout the study by research personnel twice weekly, coinciding with dose increases to check for AE as shown in the table below.

Refer to the TEVA-Gabapentin (gabapentin) TEVA Canada Product Monograph (DIN 02244515) for a detailed description of warnings, precautions, and adverse events: https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=68492

The following potential side effects occurred in clinical trials across ages 3-adults at rates higher than in placebo groups:

- Somnolence
- Dizziness
- Fatigue
- Nausea and/or Vomiting
- Increase Weight
- Emotional Lability
- Hostility
- Hyperkinesia
- Respiratory Infection
- Fever
- Swelling of limbs
- Gait disturbance

Implementation and adherence
The participant's parent or primary caregiver will administer the drug and track drug administration daily. They will be aided by written and verbal instructions by the pharmacist to dispense the correct dosage at the correct intervals. This counselling by the study pharmacist will take place in person, on site at the Baseline Visit. Adherence to the protocol will be accounted for via a daily tracker and measurement of drug use by the pharmacist. Participants will be pro-vided with the daily tracker to guide them administer the correct drug dose and will be instruct-ed in using the tracker at every drug administration. Upon completing the Sequence 1 and Sequence 2 participants will be instructed to return the bottles containing gabapentin or placebo and the pharmacist will measure the leftover drug against what was originally dispensed. In or-der to lessen the burden on study participants and ensure a timely return of the bottles, a secure courier service will be offered to participants who would be inconvenienced by returning the bottles to the study site.

Concealment mechanism
Both active drug and placebo will be masked in a liquid formulation, and administered via the same route (oral, direct gastric route, or direct jejunal route) depending on the subject's usual feeding approach. The label applied to the bottle will be blinded by the Research Pharmacy and identical flavouring will be added to the drug and placebo for additional masking.

Concomitant Care
Participants may receive any concomitant care, including medications, they wish during the trial. Due to their medical complexity it is expected that most participants will be doing so. Of specific consideration are:

- Aluminum and magnesium-based antacids reduce gabapentin bioavailability up to 20% (PrTEVA-GABAPENTIN Product Monograph (Capsules 100 mg, 300 mg, and 400 mg

Tablets 600 mg and 800 mg). Part III Consumer Information p. 29 Serious Warnings and Precautions. Teva Canada Limited. Date of Revision: August 25, 2020. Available at: https://www.tevacanada.com/globalassets/canada-ph2/product-monographs/gabapentine-capsules-100-300-400-tablets-600-800mg-teva-pm-aug25_2020-wis-eng.pdf. Accessed October 4, 2020). It is uncommon in the patient population and no patients will be on A1 or Mg containing antacids.

- The risk of serious side effects of respiratory depression with concomitant use with opioids is acknowledged (BC Children's Hospital Integrated Pain Service Gabapentin Information Sheet. Accessed at: http://www.bcchildrens.ca/Pain-Services-Site/Documents/BCCH1455Gabapentin.pdf. Retrieved on October 4, 2020). A minority of patients might be on opioids. Dose adjustments will be added when gabapentin is used with a concomitant opioid or other CNS depressant medication: the family will be advised to return to the previous stable, safe dose in the protocol, and the subject will remain at that dose with no further escalation for the duration of the trial arm. This schedule will be duplicated on the parallel arm (active drug or placebo) to maintain masking. The participants are highly monitored, often with continuous oxygen saturation monitoring and/or "baby-cam" devices observing them during sleep. During the daytime they are with family, or professional caregivers (aides, nurses, etc.). These individuals will be advised to watch for respiratory depression and sedation that occur well before fatal apnea, and how to respond.

While there are no prohibitions on concomitant care, any care or medications unrelated to the trial will be noted in the CRFs for each participant.

Participants are sometimes obtaining respite care at facilities with nursing and physician care. Medical reconciliation is done at each admission. Parents will be provided with a letter to share with these programs outlining the study, the drug being tested, and a 24-hour pager to contact for further information or concerns.

Table 1 Dosing Schedule

Active Participants < 15kg in mg per kg

Day	Morning mg/kg	Noon mg/kg	Evening mg/kg	Total mg/kg per day	% Change
1*	0	0	5	5	0
2	0	5	5	10	100%
3	5	5	5	15	50%
4	5	5	5	15	0%
5	5	5	10	20	**33%**
6	5	5	10	20	0%
7	5	5	10	20	0%
8	10	10	10	30	**50%**
9	10	10	10	30	0%
10	10	10	10	30	0%
11	13.3	13.3	13.3	40	**33%**
12	13.3	13.3	13.3	40	0%
13	13.3	13.3	13.3	40	0%
14	17	17	17	50	**25%**
15	17	17	17	50	0%
16	17	17	17	50	0%
17	20	20	20	60	20%
18	20	20	20	60	**0%**
19	20	20	20	60	0%
20	13.3	13.3	13.3	40	-33%
21	6.7	6.7	6.7	20	-50%
22	0	5	5	10	**-50%**
23	0	0	5	5	**-50%**
24	0	0	0	0	**-100%**
25	0	0	0	0	0%
Switch over*	-	-	-	-	-

*Day one or 26 if switching over, not both.

Active Participants > = 15kg in mg per day

Day	Morning mg	Noon mg	Evening mg	Total mg/kg per day	Total mg/day	% Change
1*	0	0	75	5	75	0
2	0	75	75	10	150	**100%**
3	75	75	75	15	225	**50%**
4	75	75	75	15	225	0%
5	100	100	100	20	300	**33%**
6	100	100	100	20	300	0%
7	100	100	100	20	300	0%
8	150	150	150	30	450	**50%**
9	150	150	150	30	450	0%
10	150	150	150	30	450	0%
11	200	200	200	40	600	**33%**
12	200	200	200	40	600	0%
13	200	200	200	40	600	0%
14	225	225	225	45	675	**13%**
15	225	225	225	45	675	0%
16	225	225	225	45	675	**0%**
17	225	225	225	45	675	**0%**
18	150	150	150	30	450	**-33%**
19	150	150	150	30	450	0%
20	100	100	100	20	300	**-33%**
21	100	100	100	20	300	**0%**
22	50	50	50	10	150	**-50%**
23	25	25	25	5	75	**-50%**
24	0	0	0	0	0	**-100%**
25	0	0	0	0	0	0%
Switch over*	-	-	-	-	-	-

*Day one or 26 if switching over, not both.

Inactive

Day	Morning mg/kg	Noon mg/kg	Evening mg/kg	Total mg/kg per day	% Change
1*	0	0	0	0	0%
2	0	0	0	0	0%
3	0	0	0	0	0%
4	0	0	0	0	0%
5	0	0	0	0	0%
6	0	0	0	0	0%
7	0	0	0	0	0%
8	0	0	0	0	0%
9	0	0	0	0	0%
10	0	0	0	0	0%
11	0	0	0	0	0%
12	0	0	0	0	0%
13	0	0	0	0	0%
14	0	0	0	0	0%
15	0	0	0	0	0%
16	0	0	0	0	0%
17	0	0	0	0	0%
18	0	0	0	0	0%
19	0	0	0	0	0%
20	0	0	0	0	0%
21	0	0	0	0	0%
22	0	0	0	0	0%
23	0	0	0	0	0%
24	0	0	0	0	0%
25	0	0	0	0	0%
Switch over*	0	0	0	0	0%

*Day one or 26 if switching over, not both.

3.4. Outcomes

1. Primary Outcome: The mean pain and irritability score on the NCCPC-R through days 11-19 on active drug compared to placebo.

An 11-point decrement in the NCCPC-R score with no rebound x 3 days is considered clinically meaningful minimum change (improvement).

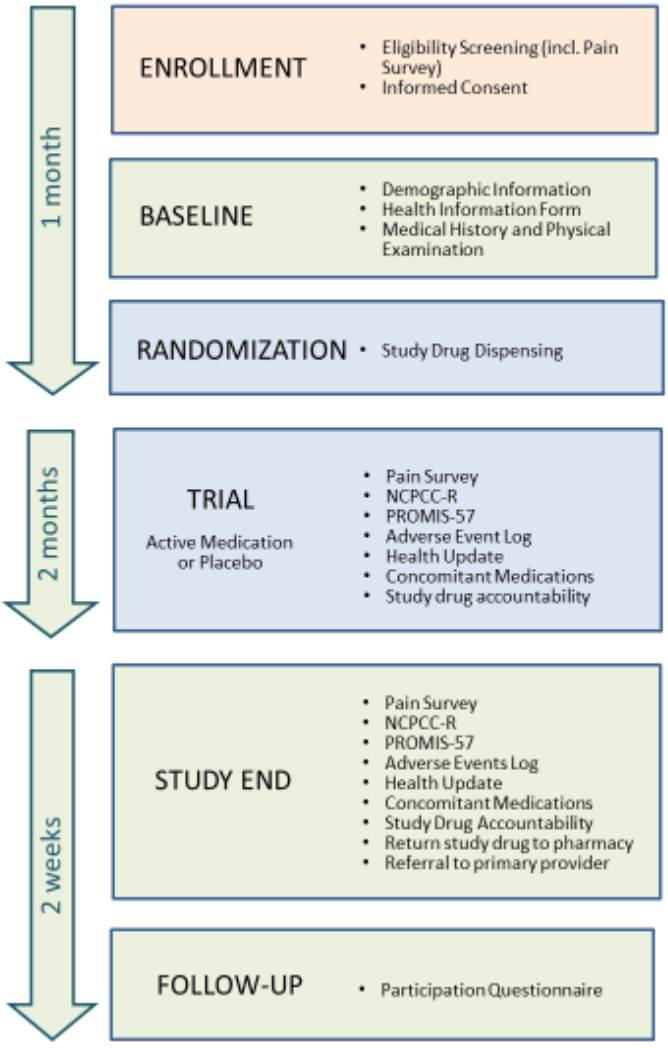
Secondary Outcomes:

2. For patients who benefited from gabapentin, identification of the lowest dose that was effective in reducing pain scores, as shown by a improvementin the NCCPC-R score compared to baseline during day 11-19 on active drug.
3. For patients who benefited from gabapentin, identification of the maximal effect dosage as measured by the largest improvement in the NCPCC-R score compared to baseline during days 11-19 on active drug.
4. Identification of the latency time in days to the onset of maximum relief of pain and irritability as measured by the NCCPC-R score over days 0-19.
5. Adverse Events Collection demonstrates the AE on treatment arm do not exceed the frequency found in the Product Monograph for children receiving gabapentin.

6. Exploratory Outcome: PROMIS-57 scores reported by parent/caregiver are improved on the treatment arm compared to the placebo arm.

3.5. Participant Timeline

Table 2: Participant Timeline



3.6. Sample size

We will enroll 10 participants in the gabapentin trial. In personalized trials, sample size refers to the number of assessments for each patient. As we had no prior data from which to estimate within patient day-to-day variability in pain scores nor an expected effect size for symptom reduction when comparing gabapentin to placebo in this population, we did not calculate statistical power a priori for the number of assessments per treatment period. Rather, the sample size for each personalized trial was based on collecting the maximal amount of data expected to be tolerable from the perspective of patient study burden. Ten participants is a sampling number based on current recruitment into the PIUO Study (REB #H16-03288) from which we expect to draw the majority of participants for this trial. This number, with the repeated measures obtained throughout the treatment periods should provide sufficient data to address the study goals.

3.7. Recruitment

Participants may be recruited from within the province of British Columbia exclusively. Recruitment will be via publicly displayed posters, social media channels, and referral from clinicians in accordance with ethical guidelines from the UBC Research Ethics Board (REB). Targeted recruitment will be made amongst participants in another health services study lead by the Sponsor, "Optimizing the Management of Pain and Irritability in Children with Severe Neurological Impairment" (The PIUO Study) (REB #H16-03288). Those participants in the PIUO Study who continue to experience unexplained pain and irritability despite thorough investigations and who have indicated in writing that they consent to receive information about research initiatives related to this issue, will be invited to take part in the trial.

3.8. Trial Procedures and Evaluations

Screening
Screening will be performed prior to the Baseline Visit as a preliminary assessment of the participant's eligibility. Screening will take place over the phone. The researchers will explain the study to the prospective participant in lay terms, including possible side effects of the therapy. The researchers will use the Eligibility Assessment to confirm whether the prospective participant is eligible. The Eligibility Assessment includes confirmation of the prospective participants':

- Age (must be between 3 and 18 years old)
- GMFCS level (must be 3, 4 or 5)
- CFCS level (must be 4 or 5)
- Pain Score (must be 3 or higher)*
- Pain Identification (must be PIUO, evidenced by a score of 3 or higher)*

* A Pain Score of 3 refers to the eligibility screening for the PIUO study, which potential participants may have participated in. The eligibility screening for the PIUO study includes a score to identify the pain as PIUO and a score to measure the persistence and distress level of the pain congruent with the Pain Survey scores of C, D, or E. In the eligibility screening these components are numerical scores.

If eligible, the prospective participant will be provided with the Consent Form. Upon receiving the signed Consent Form the researchers will schedule a Baseline Visit. Prior to the Baseline Visit the researchers will collect data from all medical records to fill out the Health Information Form. The data collected will be confirmed with the participant at the Baseline Visit. The participant will also receive the Demographic Information, the NCPCC-R and the POMIS-57 to complete immediately prior to the Baseline Visit.

Some children will already have completed evaluation via the PIUO Pathway, either as part of our current, ongoing study of children with PIUO, or by their primary provider who has used the PIUO

Pathway approach. These children will not need to undergo re-evaluation, but can move directly to the gabapentin trial.

If a subject who otherwise meets inclusion criteria has not undergone the evaluation for treatable, nociceptive-inflammatory causes of pain and irritability described by the PIUO Pathway, then we will conduct a PIUO Pathway evaluation first. If a treatable cause is identified, then the child will be referred back to their primary health care provider, and will not be enrolled in the gabapentin trial. If no treatable cause is found, then the child may continue onto the gabapentin trial. It is expected that undertaking a full PIUO Pathway evaluation may take 2-4 weeks time.

Baseline Visit
The Baseline Visit will be in person and will last approximately 2 hours. The following activities will be conducted prior to drug dispensing:

- Medical history: The participant will be asked to confirm findings in the Health Information Form. The following clinical information will also be collected for each participant:
  - Any pre-existing medical conditions/signs/symptoms as part of the medical history.
  - List of concomitant medications, dosage and date of treatment initiation
- Vital signs: Seated blood pressure (BP), heart rate (HR), respiration rate, oxygen saturation (SpO2), temperature, weight and height will be recorded.
- A head to toe physical exam will be performed
- The participant will be asked to complete the following at the Baseline Visit:
  - Demographic Information (Appendix 3)
  - Pain Survey (Appendix 5)
  - NCPCC-R (Appendix 7)
  - PROMIS-57 (Appendix 8)

In addition to reviewing all previous clinical work-up related to pain and irritability, we will establish a baseline for participants' expectations to the effectiveness of gabapentin. 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.[57] To evaluate the Impact of Expectations all families will be asked at the Baseline Visit if they expect participation in the trial will be of benefit to their child and at Follow Up they will be asked if the trial was of benefit to them and/or their child. They will also be asked after each sequence whether they believe their child received medication or placebo.

Randomization
Randomization will be undertaken by the study pharmacist, using a computer-generated randomization. Before the 2 periods (pair of active drug (G) or placebo (P)) the pharmacist will generate a random code indicating whether G or P is to be given first. The randomization table will be kept in the Research Pharmacy office, which has restricted access. In case of a serious adverse event and when necessary, the randomization of any one participant can be unmasked to the Principal Investigator. This will be done through direct contact between the pharmacist and the Principal Investigator.

Study Contacts
Contact with study participants during the trial will consist of online surveys and telephone check ins. Contacts will be scheduled to overlap with changes in dose. Each contact will last approximately 10 minutes. The following study tools will be used at study contacts (see table 4 for a schedule of assessments at the time of study contacts):

- Health Update (Appendix 6) (midway through each sequence and at study end)
- Pain Survey (Appendix) (only on the first or last day of each block, not both)
- NCCPC-R (Appendix 7)
- PROMIS-57 (Appendix 8)
- Adverse Events Log (Appendix 10)
- Concomitant Medications (Appendix 11)

When the participant begins Sequence 2, the drug will be dispensed again in person.

Follow up
Two weeks past Study End the randomization sequence for individual participants will be unblinded and shared with the participants along with their individual results. The results will be presented numerically and graphically. Graphs showing the outcomes over time on the medication and placebo arms, summarizing the dosage used at individual outcome points will be provided. This will allow participants to make decisions regarding continuing gabapentin (in consultation with their primary caregiver) and is in keeping the Strategies for Patient Oriented Research (SPOR) principles that this clinical care trial is based on. At this time, the participant's caregiver will also be given the opportunity to provide feedback to the research team via the Participation Questionnaire (Appendix 9).

For any participant that experiences a SAE, there will be an initial contact at the time of the event and appropriate evaluation undertaken by the physician investigator. Another safety follow-up visit will be scheduled within 7 days following the final study visit to review the event. Additional follow-up may be done based on the investigator's medical judgment.

Missed visits
If a participant misses a scheduled study visit or contact with prior permission, the researchers will try to contact him/her and schedule a visit as soon as possible. Participants who stop taking the study medication for any reason will be asked to complete the Final Study Visit.

Withdrawal from trial
A participant may be withdrawn from the trial due to the following reasons including, but not limited to:

- Participant's request
- Severe Adverse Events (SAE) and/or other safety reasons
- A new health condition appears that is suspected to require care or medications prohibited by the protocol

- It is in the participant's best interest according to the Investigator's clinical judgment

Participants are free to withdraw from the study at any time and for whatever reason, specified or unspecified, and without prejudice to his or her medical care by a physician.

All premature discontinuations and their causes must be documented by the Investigator on the appropriate CRF pages. The reason for, and date of, the discontinuation, and the date of the last dose of the study medication, must be recorded in the appropriate section of the CRF. While the treatment with the investigational product will discontinue if a participant withdraws from the trial, participants not completing the entire study should be fully evaluated (i.e., last study contact and follow up procedures performed), wherever possible.

Withdrawn participants will be replaced via ongoing recruitment in order to meet the goal of obtaining data from 10 participants completing the trial.

Early termination visit
If a participant withdraws or is removed from the trial for any reason prior to the completion of the trial, the reason for, and date of, the discontinuation, and date of the last dose of study drug, must be recorded in the appropriate section of the Case Report Form (CRF).

At the time of discontinuation, every effort should be made to ensure that: (1) Procedures and evaluations scheduled for the End of Study are performed, including the assessment of AEs. (2) Study drugs are returned and inventoried. (3) Study staff make an appointment for a safety follow-up visit if required.

3.9. Data Management

Data Collection
Data will be collected on CRFs during screening and at all the study visits/contacts. 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. However, as surveys will be sent via e-mail to participants, e-mail addresses will be collected and linked to the participant study ID within REDCap in order to facilitate data collection. 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.

Detailed aspects of data handling will be laid out in the Data Management Plan.

Source Documents
The Investigator must maintain adequate and accurate source documents upon which CRFs for each participant are based. They are to be separate and distinct from CRFs except for cases in which the Sponsor has pre-determined that direct data entry into specified pages of the participant's CRF is appropriate. These records should include detailed notes on:

- Oral and written communication with participant and caregiver regarding the study treatment (risks/benefits)
- Participation in trial and signed and dated informed consent forms
- Inclusion and exclusion criteria details
- Visit dates
- Adverse events and concomitant medication
- Results of relevant examinations
- Participant's exposure to any concomitant therapy (start/stop dates, dosing details)
- Reason for premature discontinuation (if applicable)
- Enrollment number
- Compliance/noncompliance protocol deviation information

Record Retention
The Investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for 25 years, in accordance with applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and the Sponsor-Investigator notified. The Investigator should ensure that no destruction of medical records occurs without the written approval of the Sponsor-Investigator. Data kept within the REDCap database will be deleted only upon request by the Sponsor, in accordance with this protocol

3.10. Statistical Methods

All data will be entered into a REDCap database, either directly from participants using a web-based entry system, or for those using paper, transferred from data collection sheets by a research assistant. The study cohort will be described in tables with descriptive statistics (mean, median and standard deviation) where appropriate. The primary method of analyzing the data was by systematic visual graphing of the pain scale over the exposure/placebo conditions. This is the method recommended by the CONSORT collaboration, extension for N-of-1 studies (CENT).[58]

Data analysis for the primary outcome will be conducted within each N-of-1 trial and will also be aggregated across trials using measurements taken on days 11-19.

For each individual, the pain and irritability score on the NCCPC-R will be calculated over days 11-19 for both the treatment and control periods. These means will then be compared statistically using a Bayesian model, reporting the posterior mean difference using a non-informative prior for the means and variance. The posterior probability that the mean of the treatment is greater than the mean of the control will also be reported. Because of the use of non-informative priors, this analysis is very similar to a t-test.

We will also aggregate the means across participants using Bayesian linear mixed models in order to compare the average effect of the treatment as well as obtain better estimates of each individual's effect through borrowing of strength from others' data.

Additional analyses
Secondary outcomes will be assessed as follows:

- For each patient who benefits from gabapentin, the lowest dose that was effective in reducing pain scores will be calculated as the lowest dose that gives at least an 11 point reduction with no rebound over 3 days in the NCCPC-R score compared to baseline during day 11-19 on active drug. The set of lowest doses will be summarized descriptively.
- For each patient who benefits from gabapentin, the maximal effect dose will be calculated as the dose that gives the largest improvement in the NCPCC-R score compared to baseline during days 11-19 on active drug. The set of lowest doses will be summarized descriptively.
- The latency time in days to the onset of maximum relief of pain and irritability as measured by the NCCPC-R score will be the day that gives the largest improvement in the NCPCC-R score compared to baseline during days 0-19 on active drug. The set of latency times will be summarized descriptively.
- Adverse Events will be compared between treatment arms descriptively.
- PROMIS-57 scores reported by parent/caregiver will be computed for each patient on each arm by averaging the scores taken on days 12, 16 and 19 and comparing these mean scores. The differences in mean scores between the treatment and placebo arms will be summarized descriptively.

Analysis population and missing data
For the primary outcome, any missing days will be excluded from calculation of the mean.

For secondary outcomes, missing values will be disregarded in the sense that only observed values will be used to compute the lowest dose, maximal effect dose, latency time and PROMIS-57 mean scores.

Analyses will use the intent-to-treat principle meaning that observations in a period will be ascribed to the treatment to which that period was randomized.

3.11. Data Monitoring

Formal Committee
The Gabapentin Trial will be monitored by a Data Safety Monitoring Board (DSMB), nestled under the Research Network CHILD-BRIGHT, sponsoring this trial. The DSMB will review the reports created by the study team on a bi-annual basis. Based on review of the reports, the DSMB may consider making recommendations on the adverse events, protocol deviations and ongoing monitoring of the data as assembled. The duties, activities and referential framework for the DSMP will be laid out in the Data Safety Monitoring Plan.

Monitoring
The study site agrees to allow the Sponsor-Investigator's monitor(s) direct access to the study records and medical records from those patients enrolled in the clinical study as well as drug accountability records. Monitoring for this study will consist of data management review focused on erroneous data, illogical entries, and missing data, and on central monitoring of clinical and operational data reviewed for outliers and trends. On-site monitoring will be targeted based on the results of data management and of central monitoring reviews. A site initiation, with the presence of the site monitor, will ensure that best Good Documentation Practices (GDP) are set up. A site visit when half of the participants have been enrolled and at study close out will follow the site initiation and ensure that GDP is being followed and that reporting on protocol deviations or adverse events during the trial has been done when necessary.
Plans for Site Monitoring are laid out in the Data Safety Monitoring Plan.

Early Termination of the Trial
As part of their duties to ensure that research participants are protected, the institutional REB or other government organizations may discontinue the study at any time. Regulatory authorities and the Sponsor-Investigator retain the authority to suspend additional enrollment for the entire study as applicable.

3.12. Safety/Harms

The safety analyses will include all data with no exclusions allowed because of protocol deviations.

Definition of Adverse Events
An AE is any untoward medical occurrence in a patient or clinical investigation participant, administered a study medication/intervention, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) study medication/intervention, whether or not related to the medicinal (investigational) study medication/intervention.

During each contact with the participant and the participant's caregiver, information on AEs will be gathered and documented accordingly. AEs will be graded as mild, moderate, severe or life threatening and assessed by causality as probably related, possibly related, unlikely to be related or not related to the study drug.

Other clinically significant AEs are those that cause the study participant discomfort or interfere with normal functions such as feeding, sleep, activity, etc. In this study these are likely to be the new onset of known side effects of gabapentin, as listed in the Health Update, or any other events that the parent-caregiver is concerned about.

Definition of Serious Adverse Events
An SAE is defined as an AE meeting one of the following criteria at any dose:

- Results in death during the period of protocol-defined surveillance

- Is a life-threatening event (defined as a participant at immediate risk of death at the time of the event)
- Results in in-patient hospitalization or prolongation of existing hospitalization during the period of protocol-defined surveillance
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions)

Any other important medical event that may not result in one of the above outcomes, may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Participants will be monitored during the 108-day study period for SAEs. If an SAE is ongoing at the time a participant discontinues/completes the study, the SAE will be followed until the Investigator agrees that the event is satisfactorily resolved, becomes chronic, or that no further follow-up is required.

Stable chronic conditions which are present prior to clinical trial entry and do not worsen are not considered AEs and will be accounted for in the participant's medical history.

Relationship to Treatment
For all collected AEs (including SAEs), the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment.

In some circumstance, an AE will require the unblinding of the trial. The study pharmacist will inform the Study Medical Monitor as to whether the active medication or the placebo was in use. The Medical Monitor can then advise the Investigator as to whether the subject should be withdrawn from the study, a modification made in the drug schedule, or no action needs to be taken.

The degree of certainty about causality will be graded using the categories below:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not related: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Intensity

The Intensity (severity) for each AE (including SAE) will be graded according to the RN or MD who examines and evaluates the participant, given the clinical team's experience with severely disabled children, as mild, moderate or severe and potentially life-threatening.

Reporting

Only SAEs that meet the definition of an unanticipated problem (i.e. unexpected, related and involving greater risk) are required to be reported to the DSMB, the institutional REB and Health Canada. Expected, unrelated and/or non-serious adverse events will not be reported to the DSMB and the institutional REB. Reportable SAEs will be reported within 24 hours of the site becoming aware of the event.

Should a clinically significant AE occur, the Study Medical Monitor will be notified. The monitor will require unblinding by the study pharmacist. The Investigator will be advised by the Medical Monitor and review with the parent/caregiver. Modifications may need to be made in the study sequence, for example, extending the time between dose increases. Any modifications in the protocol will be reflected on both the gabapentin and placebo arms.

Any AE that occurs between the time that a study participant is enrolled and the time that s/he departs the study at the end of the final study visit (or at the time of early discontinuation of the participant from the study for any reason) will be captured and recorded. At each contact with the participant, the investigator (or designate) must seek information on AEs by specific questioning and, as appropriate, by examination.

AEs that have been reported by the study participant will be followed-up for duration, intensity and possible recurrence.

All AEs (including SAEs) will be followed until resolution or until the investigator and the Medical Monitor agree that the AE has resolved, stabilized or become chronic and no further follow-up is required.

In the case of a Suspected Unexpected Serious Adverse Reactions (SUSARs) the Sponsor will expedite the reporting of the event to investigator(s), institutions(s), ethics board(s), and Health Canada per published guidelines. If the adverse reaction is not documented in the Product Monographs (new occurrence) and is thought to be related to the study treatment, the study sponsor may urgently require further information from the investigator for regulatory reporting.

4. ETHICS AND DISSEMINATION

4.1. Research Ethics Approval

The UBC Research Ethics Board (REB) will review the protocol and all appropriate study documentation to safeguard the rights, safety, and well-being of the participants. The study will be conducted only when and where ethics approval has been obtained. A copy of the protocol (including protocol amendments), all versions of informed consent forms, other information to be completed by participants such as survey instruments or questionnaires, and any proposed advertising/recruitment materials must be reviewed and approved by the UBC REB prior to implementation of the trial. The investigator will be responsible for obtaining REB approval of the annual Continuing Review and any protocol modifications throughout the duration of the study.

This study will be conducted in accordance with the guidelines of the University of British Columbia Research Ethics Board and the principles in the Tri-Council Statement on research conduct. The Investigators will be thoroughly familiar with the appropriate use of the study treatment as described in the protocol and the Teva-Gabapentin Product Monograph.

4.2. Protocol Deviations

Minor deviations from the drug sequence (see Dosing Schedule) will be permitted without the prior written approval of the REB if, in the Investigator's opinion, it is required to enable a participant to continue in the trial. An example would be extending the time between dose titration increases if the subject (parent/caregiver) believes it would improve minor side effects. Parallel adjustments would be made in the gabapentin and placebo sequences to preserve blinding. These deviations will be reported to the Data Safety Monitoring Board (DSMB).

Major deviations in the study protocol will not occur without REB approval except when the modification is needed to eliminate an immediate hazard or hazards to participants. Any deviations that may affect a participant's informed consent, especially those increasing potential risks, must receive prior approval from the REB unless performed to remove an immediate safety risk to the participants. In this case it will be reported to the REB, and the DSMB immediately thereafter. Any departures from the protocol must be documented.

4.3. Informed Consent Process

All participants will be given detailed oral and written information about the study prior to enrollment. A Consent Form describing in detail the study medication and study procedures and risks will be given to each participant (caregiver). Each participant will have sufficient opportunity to

discuss the study, have all of their questions addressed and consider the information in the Consent Form prior to agreeing to participate in the trial. Participants must sign the Consent Form prior to any study procedures being done specifically for the trial. Participants may withdraw consent at any time during the course of the study without prejudice. The Consent Form will be signed and dated by the participant and the person obtaining consent, from the study team. The original signed informed consent form will be retained in the participant's study files and a copy will be provided to the participant.

4.4. Confidentiality

All participant-related information including Case Report Forms, evaluation forms, reports, clinical notes etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only accessible to research staff. Participants will be identified only by means of a coded number specific to each participant. All computerized databases will identify participants by numeric codes only and will be password protected.

4.5. Access to Data

Upon request, and in the presence of the investigator or his representative, participant records will be made available to the study sponsor, monitoring groups representative of the study sponsor, representatives of funding groups, and applicable regulatory agencies for the purpose of verification of clinical trial procedures and/or data, as is permissible by local regulations.

4.6. Ancillary and Post-Trial Care

Participants may have access to gabapentin after completing the study through their primary healthcare provider.

5. STUDY ADMINISTRATION

5.1. Key contacts

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5.2. Funders

Child-Bright Network (SCA-145104)
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5.3. Trial Committees

Data Coordination Center (DCC): Development and maintenance of REDCap database.

Team Lead Clinical Research Informatics: Rick Watts

Data Safety Monitoring Board (DSMB). The DSMB comprises a group of 4 subject-matter experts and 1 biostatistician. They are:

Dr. Deborah Hirtz (Chair of the DSMB)
Dr. Amy Houtrow
Dr. Andy Willan (biostatistician)
Dr. Thierry Lacaze
Dr. Paige Church
Dr. Beatrice Latal (non-voting member)

Medical Monitor: Ran Goldman, MD

6. APPENDICES

6.1. List of Appendices

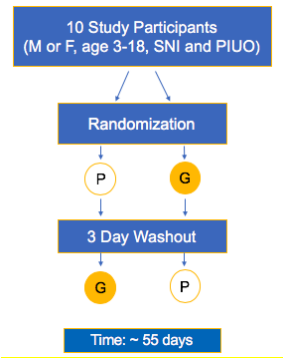
Appendix 7 NCCPC-R
Appendix 8 PROMIS-57
Appendix 9 Participant Questionnaire
Appendix 9b Pre-Participation Questionnaire
Appendix 10 Adverse Events Log
Appendix 11 Concomitant Medications

6.2. Schedule of Enrolment, Interventions, and Assessments

Gabapentin Trial Diagrams and Summaries
Table 3 shows which assessments happen during specific phases of the trial. Table 4 shows the exact timepoint assessments are administer

Trial Design Summary

- Repeated Measures Single Cross-Over Trial (Treatment and Placebo)
- We will recruit 10 study participants. These participants will have completed the PIUO Pathway without resolution of pain. They will have severe neurological impairment and unexplained, untreated pain.
- The study participants will be randomized to treatment or placebo arms. This first session will take 25 days. During this time the treatment arm gabapentin dose will be slowly increased until an effective dose or maximum dose (60mg/kg/day) is reached, whichever comes first.
- The participants will then undergo a three-day long washout period, where neither drug nor placebo will be administered.
- Following this, the participants that were on placebo previously will switch to gabapentin treatment and those who were on gabapentin treatment will switch to placebo. This will again go on for 25 days, with the gabapentin dose increasing throughout.
- NCCPC-R, PROMIS-57 and Pain Surveys will be administered throughout the trial to obtain data.
- The total participant time will be around 55 days.
- The diagram below depicts the Gabapentin trial design.



N-of-1 Design
The Gabapentin Trial will use an N-of-1 design. This means that each participant will be his or her own experiment, acting as both treatment and placebo participants. In an N-of-1 trial, each participant's treatment data is compared to his or her own placebo data, and the results are specific to

the individual participant. A small "N" such as 10 (as we are going to recruit for the Gabapentin Trial) can provide an adequate amount of data when using an N-of-1 design because 10 separate data sets and results will be produced. Multiple N-of-1 trials that are conducted on similar patients taking similar drugs can be amalgamated to give broader results.

N-of-1 trials allow for the development of personalized medicine, which is ideal when working with a population of high heterogeneity, such as children with severe neurological impairment. Each of the participants will be unique in his or her own physical and emotional health needs. An N-of-1 trial allows the researcher to determine if treatment is effective in a specific individual, as well as the optimal dose, tolerability and potential side effects of the treatment for that individual. A standard cross-over trial may elicit the answer to the question of "Does drug X relieve pain in children with severe neurological impairment?" but an N-of-1 trial can answer the question of "Does 10mg/kg of drug X relieve pain in a 10-year-old female whose severe neurological impairment is caused by Rett Syndrome?".

The diagram below depicts a sample N-of-1 trial with five participants. Each colour represents an individual participant, and their cause of severe neurological impairment is listed on the right. Each participant will trial the treatment (in our case Gabapentin) and the placebo, in randomized order. The results (check mark = pain resolved and "X" = pain not resolved) are also coloured in to show that the results are specific to the individual. For example, the treatment that worked for the participant with Rett Syndrome may have been 30 mg/kg/day of drug X, while the effective treatment for the participant with cerebral palsy may have been 15mg/kg twice a day, because he/she was overly sensitive to the sedative effects of drug X and required a lower dose.

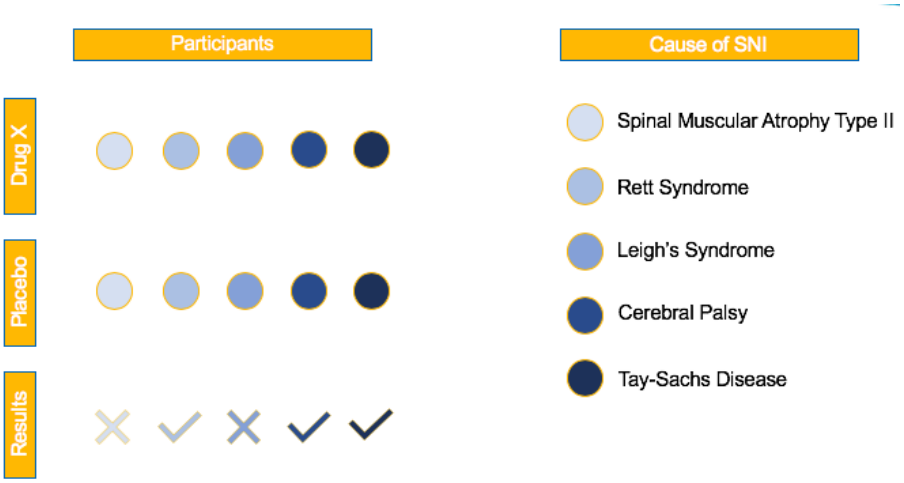


Table 3: Gabapentin Trial Events Schedule

Study Phase	Screening and Enrollment	Baseline Visit	Sequence 1	Study Visit	Sequence 2	Study End	Follow Up
Study Time Point	- 4 to 0 weeks	Day 1 of Period 1	Day 1 – 26 of Period 1	Day 1 of Period 2	Day 1 – 26 of Period 2	Day 26 of Period 2	1 week post Study End
Eligibility Assessment	X						
Informed Consent	X						
Demographic Information		X*					
Health Information Form		X*					
Medical History		X*					
Physical Exam		X*					
Pre-Participation Questionnaire		X					
Randomization		X					
Study Drug Dispensing		X		X			
Pain Survey			X		X	X	
NCCPC-R			X		X	X	
PROMIS-57			X		X	X	
Adverse Events Log			X		X	X	

Health Update			X		X	X	
Concomitant Medications			X		X	X	
Study Drug Accountability				X		X	
Participation Questionnaire							X

*If the child participated in the PIUO Study within the last 6 months these items will already be completed and only a Health Update is necessary to complete prior to drug dispensing. If the child did not participate in the PIUO Study all items will be completed and the PIUO Pathway will be implemented prior to drug dispensing. If a treatable cause for the child's PIUO is uncovered, the child will be withdrawn from the gabapentin trial.

Table 4: Medication and Placebo Assessment Schedule for all subjects

Day	Health Update	Concomitant Medications	NCCPC-R	Pain Survey	PROMIS-57
1	X	X	X	X	X
2					
3					
4					
5			X	X	
6					
7					
8			X		
9					
10					
11	X		X		
12			X	X	X
13			X		
14			X		
15			X		
16			X	X	X
17			X		
18			X		

19			X	X	X
20					
21					
22			X		
23					
24					
25					
Switch Over*	X	X	X	X	X

*Day 1 or 26 if switching over, not both

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