Project Title: A pilot clinical trial of a new neuromodulation device for acute attacks of migraine in children and adolescents visiting the emergency department

Clinicaltrials.gov Registration Identifier: NCT05102591

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1. General Information

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Investigator Agreement

By signing below, I confirm that I have read this protocol and agree to conduct this study in accordance with the procedures described in this protocol, with Good Clinical Practice and Health Canada Food & Drug Act, Part C, Division 5 of the Regulations: Drugs Trials Involving Human participants

Name of Principal Investigator (Print): Serena L. Orr, MD, MSc, FRCPC

Signature of Principal Investigator _____

Date: February 10th, 2023

Site Address

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2. Abbreviations

ACH - Alberta Children's Hospital

ADR – Adverse Drug Reaction

AE - Adverse event

CRF - Case report form

CHREB - Conjoint Health Research Ethics Board

ED - Emergency Department

KT – Knowledge Translation

NSAID - Non-Steroidal Anti-Inflammatory Drug

RCT - Randomized Controlled Trial

REDCap - Research Electronic Data Capture

REN - Remote Electrical Neuromodulation

RRN – Research Registered Nurse

SOP - Standard Operating Procedures

3. Study Summary

Title	A pilot clinical trial of a new neuromodulation device for acute attacks of migraine in children and adolescents visiting the emergency department
Short Title	A pilot clinical trial of a new neuromodulation device for acute attacks of migraine in children and adolescents
Protocol Number	N/A
Phase	
Methodology	Randomized, double-dummy, crossover randomized controlled trial
Study Duration	2 years
Study Center(s)	Single center: Alberta Children's Hospital Emergency Department
Objectives	To determine the feasibility, efficacy, and safety of treating children and adolescents reporting to the ED and suffering from an acute migraine attack with a remote electrical neuromodulation (REN) device in comparison to the standard of care emergency department migraine treatment (a combination of ketorolac and metoclopramide). The primary scientific objective is to determine if use of the REN device is feasible and acceptable in treating acute migraine attacks in the ED. If this objective is achieved, design of a fully-powered, phase 3 randomized controlled trial (RCT) will be implemented.
Number of Participants	40
Diagnosis and Main Inclusion Criteria	Children and adolescents suffering from an acute migraine attack and reporting to the emergency department at the Alberta Children's Hospital (ACH)
Study Product, Dose, Route, Regimen	Ketorolac (0.5 mg/kg, maximum 30 mg) Metoclopramide (0.15 mg/kg, maximum 10mg) REN device (modulated symmetrical biphasic square electrical pulse, modulated frequency of 100-120 Hz, pulse width of 400 μs, maximum of 40 mA)
Duration of administration	Single dose of ketorolac and metoclopramide in the emergency department. Single, 45-minute stimulation session with REN stimulation or sham stimulation in the emergency department.

Reference therapy	Normal saline placebo (0.9% sodium chloride, volume matched to that given to participants receiving ketorolac and metoclopramide) and sham REN stimulation Sham REN device (modulated symmetrical biphasic square electrical pulse, modulated frequency of ~0.083 Hz and a modulated pulse width of 40-550 μs)
Statistical Methodology	The primary outcome pertains to the recruitment rate for the duration of the study, which will be reported as the number of participants recruited/month. Our feasibility and acceptability outcomes will be summarized using appropriate descriptive statistics across both groups. For secondary efficacy outcomes, Chi square tests will be used to examine the association between each dichotomized outcome and treatment group. Adverse events will be presented descriptively in tabular form, with the frequency and percentage of each adverse event listed by the corresponding group.

4. Background Information and Clinical Data

Migraine in children and adolescents is a major public health problem. Migraine is a neurological disease characterized by severe and recurrent headaches.[1] It is the second most prevalent and disabling disease worldwide[2] affecting 1 in 10 children and adolescents (>800,000 in Canada).[3,4] At least 1/3 of migraine cases present in childhood or adolescence[5] and at least half persist into adulthood.[6–10] Migraine is considerably more prevalent[3] and resistant to preventive treatment in females,[11] though there is no sex difference in acute treatment response.[12] Unfortunately, migraine is one of the best examples of gender disparity in the allocation of research funds; it is one of the most underfunded chronic diseases and it is dominant in women.[13] The public health implications of migraine across the lifespan are enormous and include massive health care costs, loss of productivity at school and work, and impaired social functioning.[14–17] Compared to peers, children and adolescents with migraine experience higher rates of school absenteeism,[18–22] poorer academic performance,[23,24] fewer friendships,[25] and high disability in the home[18–22] and extra-curricular spheres.[18–22] Children and adolescents with migraine often present to the ED with acute attacks, where migraine accounts for up to ~30% of all pediatric ED visits for headache.[26] In Alberta, this translates to ~2,500 annual pediatric ED visits (Alberta Health Services data). Extrapolating expenditures from the US[27] to the Canadian context, the incremental cost of migraine in the pediatric ED would exceed CAD$ 100 million per year. Unsuccessful treatment of acute attacks of migraine in the ED may result in hospitalization, which costs ~USD$ 2,000 per day and has an average length of stay of 3.7 days.[28] Acute attacks of migraine are also severely disabling, as illustrated by these quotes from our qualitative study,[29] in which children, adolescents and their families were interviewed about their perspectives on recent ED visits:

"*It was just really really bad and we didn't know what else to do, because we'd already used Tylenol, naproxen and sleep, but it wasn't getting any better* " – Child with migraine[29]
"*It was debilitating in the sense that she was crying; she couldn't function anymore. It was just one of those things that, that particular moment on Monday morning, she just collapsed into my arms and said: Mummy, I can't do it*" – Parent of a child with migraine[29]

Children and adolescents need better treatments for refractory acute attacks of migraine. Patients, families, and health professionals from across Canada recently identified the need for better treatments to manage acute pain flares, such as acute attacks of migraine, as a top 10 research priority for Canadian pediatric chronic pain research[30] and for Canadian pediatric emergency medicine research.[31] Access to effective acute treatment options is of paramount importance; ineffective acute treatment leads to prolonged pain exposure, which has the biological underpinnings of central and peripheral sensitization and increases the risk of chronic migraine[32] (i.e., ≥15 headache days/month).[33] However, despite the importance of effective acute treatments, and the cost and disability associated with pediatric ED visits for acute attacks of migraine, evidence for how to manage migraine in this setting is lacking. Only three RCTs have investigated interventions in this setting, and all involved IV access.[34–36] The remaining studies on the management of children and adolescents presenting to the ED with acute attacks of migraine are limited to mostly small, uncontrolled, retrospective, observational studies.[37] The dearth of data in this area has led to a substantial amount of practice variation.[38] The lack of evidence-based treatment options may also be a factor in the continued inappropriate administration of opioids for children and adolescents presenting to the ED with acute attacks of migraine (up to 33% of these visits).[38–41] Given the link between adolescent chronic pain, including migraine, and the opioid crisis, improving treatment options in the ED has major public health implications.[42,43]

Based on the limited evidence, many centers have adopted protocols whereby children and adolescents who visit the ED with acute attacks of migraine are treated with an IV neuroleptic (metoclopramide or prochlorperazine) and an IV non-steroidal anti-inflammatory (ketorolac).[12,44–47] This combination of interventions is largely considered to be standard of care,[26,38] despite no rigorous evidence to support this practice.[37] Moreover, the reliance on IV interventions contradicts the preferences of a large proportion of patients: in a prior study, when we questioned children and adolescents with recent ED visits for migraine about their intervention preferences, approximately 50% expressed concern about IV interventions, with most of their concerns focused on IV-related pain.[29] The insertion of an IV requires a needle poke, which is known to be the most painful non-surgical procedure that children and adolescents experience in hospital.[48,49] Additionally, side effect rates with the neuroleptics (metoclopramide or prochlorperazine) are considerable, with up to 1/3 of patients experiencing extrapyramidal side effects including akathisia, which is an unpleasant movement disorder associated with restlessness and mental distress.[50–52] Furthermore, IV catheters themselves are associated with high

adverse event and failure rates in children and adolescents.[53] There are also substantial material and personnel costs associated with IV insertions and infusions.[54] Therefore, the current standard of care for managing children and adolescents visiting the ED with acute attacks of migraine poses concern to patients, and is associated with pain, significant and frequent side effects, and costs.

Emerging neuromodulation devices show promise for expanding acute treatment options. Over the past few years, there has been a growth in research investigating the efficacy and safety of non-invasive neuromodulation, which delivers electrical or magnetic stimulation to nerves or neural tissue, for the management of acute attacks of migraine.[55,56] Children and adolescents with migraine are also more interested in non-invasive neuromodulation devices to treat refractory acute attacks of migraine than they are in IV interventions; in an ongoing study where we are assessing the treatment preferences of children and adolescents with migraine (N=65 to date), our preliminary data suggest that more patients are interested in neuromodulation devices (26%) than in IV interventions (9%) for treating acute attacks that are refractory to swallowed pills (Orr lab; unpublished). Unfortunately, children continue to be excluded from acute migraine RCTs; all published RCTs evaluating non-invasive neuromodulation devices have excluded children and adolescents.[55,56] At present, there are 3 commercially available, non-invasive neuromodulation devices that effectively and safely treat acute attacks of migraine in adults.[57–59] Because none of these devices have a high level evidence in children, adolescents, nor in the ED setting, there is clinical equipoise as to which device would be most appropriate to study for treating children and adolescents visiting the ED with acute attacks. Given this equipoise, and our commitment to integrated knowledge translation (iKT) and patient engagement, we hosted a virtual patient engagement session on December 12th, 2020 to solicit feedback from patients about their appraisal of the device options. During this session, we engaged with adolescents (N=9) with migraine or chronic daily headache from across Canada (see patient research partner letter of support). The participants included individuals with disabilities, with diverse sexual orientations and gender identities, as well as racialized individuals. We presented the 3 device options to the group, along with plain language explanations of how they work, and the available safety and efficacy data from the adult literature. The majority (6/9) of the adolescents expressed a preference for trying the non-invasive Nerivio™ remote electrical neuromodulation (REN) device to treat an acute attack in the ED (Orr lab; unpublished). The adolescents were enthusiastic about a study that aims to investigate the REN device for the treatment of acute attacks of migraine in the ED, as illustrated by these quotes:

"*The Nerivio seemed appealing to me because of the fact that it's just like on your arm, like I feel I could move around a lot (…) as someone who is not particularly affected by needles, it still seems more appealing to me to have a device that just feels less invasive cuz then I can move around more*"
"*For me, I would rather come in and get the Nerivio on its own… I don't like the drug kind of stuff*"

We also presented this protocol to a large group of emergency medicine physicians and researchers on February 3rd 2021, at the Pediatric Emergency Research Canada (PERC) annual meeting. PERC is a well-established, highly productive, and award-winning national network of Canadian pediatric emergency medicine researchers with a track record of supporting successful multicenter phase III trials.[60] All meeting participants polled (N=44) indicated that they would use the REN device to treat children and adolescents with acute attacks of migraine in the ED if supportive evidence was available.

REN has a scientifically established mechanism of action and promising clinical data. REN stimulates C and Aδ nociceptive sensory nerves below their perceived pain thresholds, but above their depolarization thresholds, to induce a conditioned pain modulation response in the brain.[57] Conditioned pain modulation is a well-established endogenous analgesic mechanism that activates descending brain pathways that facilitate pain inhibitory effects.[61] By activating nociceptive sensory nerves in the arm, the REN device activates ascending spinothalamic pain pathways with collaterals in the brainstem, which concurrently activate descending brainstem pain inhibitory pathways. Ultimately, the activation of descending pain inhibitory pathways modulates incoming pain signals in the trigeminal nucleus caudalis arising from the acute attack of migraine, leading to an analgesic effect (see Figure 1).

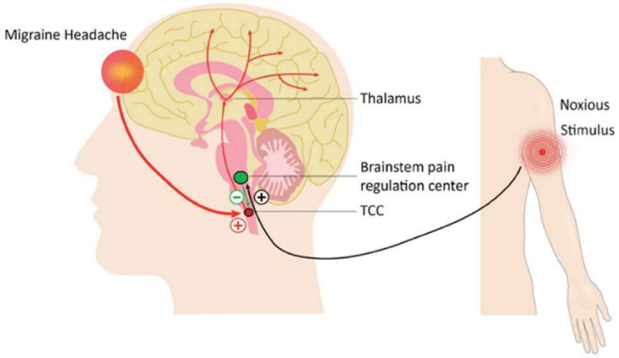

Figure 1. Schematic of the mechanism of action of REN[58]

Data from a phase III RCT have established the efficacy and safety of REN for the treatment of acute attacks of migraine in adults.[57] In this trial (N=252), 66.7% of participants randomized to REN achieved pain relief at 2 hours, as compared to 38.8% of participants in the sham stimulation group. Adverse events did not differ between the groups (15.1% of REN group vs. 11.9% of sham group p=0.581), only 2.7% had device-related adverse events, and no serious adverse events occurred.[57] In addition, comparison of data from the run-in phase whereby trial participants treated acute attacks with their usual care (i.e. at home oral medications), and data from the clinical trial period, showed that REN was more effective than usual care.[62] REN also appears to substantially reduce medication use, with 89.7% of the trial participants treating their attacks with REN alone in the open label

extension period.[63] In addition, a recently published open-label trial among 60 adolescents treating acute attacks of migraine in the home setting suggests that REN is safe and effective for use in adolescents.[64] Pain relief was achieved in 71% of participants at 2 hours. Importantly, only one participant (2.2%) experienced a device-related adverse event (transient pain in the arm), and no serious adverse events were reported. Further, the cost of REN is very low: each Nerivio™ REN device costs the equivalent of CAD$ 120 and provides 12 stimulation sessions (~ CAD$ 10/stimulation), making it a cost-effective option. While the FDA has recently approved use of the REN device for managing acute attacks of migraine in adolescents and adults based on this data, there is no current Health Canada indication for this device.

Based on this promising data, we believe that a trial evaluating REN in children and adolescents seeking ED care for refractory acute attacks of migraine has the potential to dramatically improve outcomes and patient experience. We propose a pilot RCT (N=40) that will determine the feasibility and acceptability of executing a phase III RCT, in which children and adolescents visiting the ED with acute attacks of migraine will be randomized to REN or standard of care IV treatment, and then crossed over to the other treatment arm if the initial intervention is not effective.

4.1. Name and Description of Investigational Agent

This study will examine the safety and efficacy of using the REN device, as compared to standard of care IV treatment with ketorolac and metoclopramide, to treat acute migraine attacks in children and adolescents reporting to the ED. The REN device is a battery-powered, wirelessly controlled neuromodulation device that attaches via armband to the upper arm. The REN device is controlled by a smartphone application and administers electrical stimulation to the local C and Aδ nociceptive sensory nerves of the upper arm. This stimulation is achieved using a symmetrical, biphasic, square pulse, modulated at a frequency between 100-120 Hz. Each pulse has a width of 400 μs and the user, via the smartphone application, can adjust the output current to apply a maximum of 40 mA. Each stimulation session occurs over 45 minutes and each device can administer up to 12 stimulation sessions. Ketorolac is a non-steroidal, anti-inflammatory medication indicated for acute pain management. Metoclopramide is a neuroleptic, benzamide-derived medication indicated for a variety of uses, such as a vomiting prophylactic.

Patients randomised to the REN group will receive 45 minutes of stimulation from the REN device (modulated frequency of 100-120 Hz and a pulse width of 400 μs) and will also receive normal saline though an IV. Patients randomised to the standard of care IV group will receive stimulation from a sham REN device, which will not administer the typical electrical stimulation (modulated frequency of ~ 0.083 Hz and a modulated pulse width of 40-550 μs), and will be given an IV ketorolac and IV metoclopramide, at a dose of 0.5 mg/kg (for a maximum 30 mg) and 0.15 mg/kg (for a maximum 10mg), respectively. Should participants not achieve enough pain relief to feel ready for discharge without further intervention at 2-hours post-intervention, then they will be crossed over to the

other treatment arm. This change to the protocol is being made after feedback from participants and potential participants about being concerned that should they be randomized to one arm, then they would not be eligible to receive the alternate treatment during their ED visit. Specifically, patients have expressed concerns they will not be able to receive the first-line standard of care treatment (ketorolac and metoclopramide) during their ED visit should they initially receive the active REN device and placebo IV medications.

4.2. Pre-Clinical Data on Ketorolac

Ketorolac is a cyclooxygenase-1 and cyclooxygenase-2 (COX-1/COX-2) inhibitor, a sub-class of NSAIDs designed to inhibit production of prostanoids, prostaglandins, and thromboxanes, which play key roles in inflammatory cascades in the body and in nociception. Limiting the release of these chemicals thereby limits activation of nociceptive neurons.[65] Ketorolac selectively inhibits COX-2 to limit pain and inflammation, as inhibition of COX-1 can result in gastrointestinal ulcers and bleeding. However, cardiovascular-related adverse event may be more common due to selective inhibition of COX-2.[66]

4.3. Pre-Clinical Data on Metoclopramide

Metoclopramide is a neuroleptic which acts as a dopamine antagonist; it is believed to block dopaminergic D-2 receptors, and can help to treat nausea and vomiting, and increase the absorption rate of other medications.[67] According to the product monograph, metoclopramide has been shown to induce catalepsy, elevate levels of plasma renin, prolactin, and aldosterone, increase dopamine turnover in the mesolimbic and striatal structures, and to antagonise apomorphine-induced stereotyped behaviours in rat models. Parenteral administration of metoclopramide has also been shown to decrease striatal acetylcholine levels in rat models. In other animal models, metoclopramide has been shown to modulate gastrointestinal motility by magnifying resting muscle tension and increasing the intensity of peristaltic movements. In vitro, metoclopramide influences the release of 3H-acetylcholine in striatal structures.

4.4. Pre-Clinical Data on the REN Device

The REN device modulates the pain response in the brain using conditioned pain modulation to trigger an analgesic effect. This mechanism is achieved by electrically stimulating the C and Aδ nociceptive sensory nerves in the upper arm, just below the perceived pain threshold and above the depolarization threshold. Precise activation of these sensory nerves further triggers ascending pain pathways within the spinothalamic tract and brain stem. These pathways further activate descending pain inhibitory pathways within the brain stem to modulate incoming pain signals and produce an analgesic effect.[57,68]

4.5. Known Risks and Benefits of Ketorolac to Human Participants

Many of the established side effects for ketorolac are related to chronic use rather than single doses. The product monograph for ketorolac provides a comprehensive list of possible side effects, including sweating, dizziness, nausea, vomiting, or pain at the

injection site. Rare and serious side effects that are possible include the development of stomach ulcers, bladder inflammation, a decrease in red or white blood cells, or allergic reactions (see product monograph in Appendix A). These rare and serious side effects typically only occur after prolonged usage and are exceptionally uncommon after receiving a single dose; we found no cases of any of these rare and serious adverse events after single use doses in children and adolescents with migraine.[12,44–47]

4.6. Known Risks and Benefits of Metoclopramide to Human Participants

The common side effects associated with metoclopramide may include drowsiness, dizziness, difficulty sleeping, bowel and stomach issues, and akathisia (physical and mental restlessness). Rare and serious side effects that are possible include Parkinsonian-like symptoms involving involuntary muscle and limb movements, and neuroleptic malignant syndrome which involves muscle rigidity, altered consciousness, and instability in heartbeat and blood pressure (see product monograph in Appendix B). Cardiac-related adverse events in healthy individuals are uncommon after a single dose or intermittent doses.[66]

4.7. Known Risks and Benefits of the REN device to Human Participants

The most common side effects associated with the REN device include feelings of warmth, redness, or pain in the arm. The less common side effects include numbness, itching, or tingling in the arm or hand, neck and shoulder pain, or muscle spasms. None of the current studies examining the REN device reported any serious device-related adverse events, and they reported very low (<5%) rates of moderate and less severe device-related adverse events. In addition, in the published studies using REN, there were very low rates of study withdrawal due to device-related adverse events.[57,62,64,68,69]

4.8. Description and Rationale for Dose, Route of Administration, and Single Administration of Ketorolac for this Indication

The dose of ketorolac that we have chosen (0.5mg/kg, maximum 30mg) is based on previous adult and pediatric migraine literature, where a dose of 0.5 mg/kg, up to a maximum of 10 mg to 40 mg, has been most commonly used.[35,44,47,51,70–74] Our chosen dosage is also in line with the Alberta Children's Hospital (ACH) emergency department protocol for treating acute attacks of migraine, which is considered to be local standard of care since it was released in 2021 (developed by Dr. Orr and emergency physician Dr. Joe MacLellan; Appendix C). Using IV as the route of administration was chosen to be consistent with procedures typically followed in the ED as per published studies[47,70,71] and as per the current ACH ED protocol. The pharmacokinetic properties of ketorolac support administration of a single dose to treat an acute migraine attack. Ketorolac is rapidly absorbed (maximum absorption in less than 1 hour) with a typical half-life of approximately 5 hours.[66] Single dose use is also safer; frequent administration of ketorolac (over 5-7 days) is also considered unsafe due to an increased risk of adverse events.[66]

4.9. Description and Rationale for Dose, Route of Administration, and Single Administration of Metoclopramide for this Indication

We chose our dose of metoclopramide (0.15 mg/kg, maximum 10mg) based on prior adult and pediatric migraine research[44,70,73,74] which typically administered 0.1-0.2 mg/kg, up to a maximum of between 10 mg and 20 mg. The dosage we are proposing is also identical to the dosage used in the ACH emergency department migraine protocol. Administration of metoclopramide through an IV was chosen to be consistent with procedures followed in the ED.[44,70,73,74] Single doses of metoclopramide have been shown to help relieve nausea and vomiting associated with acute attacks of migraine, and can also improve the absorption rate of other medications when administered concurrently.[66]

4.10. Description and Rationale for Usage and Single Administration of the REN device for this Indication

Using the REN device for a single, 45-minute session of electrical stimulation (modulated symmetrical biphasic square electrical pulse, modulated frequency of 100-120 Hz, pulse width of 400 μs, maximum of 40 mA) administered to the sensory nerves of the upper arm was chosen to comply with the manufacturers recommended usage, and in accordance with other REN device studies for the treatment of migraine.[57,62,64,68,69]

4.11. Conduct of the Trial

The trial will be conducted in compliance with the protocol submitted to the Conjoint Health Research Ethics Board (CHREB). It will follow the International Conference on Harmonization Good Clinical Practice standards[75] as described in the protocol. Any protocol deviation will only be implemented after approval from the CHREB, except for situations where immediate implementation of a protocol deviation is necessary to protect the trial participants from hazards or where the protocol deviation is logistic or administrative in nature, in which case the CHREB will be notified as soon as possible.

5. Trial Objectives and Purpose

5.1. Objectives

1) To determine the feasibility of comparing REN to the standard of care IV intervention (i.e., a combination of metoclopramide and ketorolac) for the treatment of children and adolescents visiting the ED with acute attacks of migraine.
2) To determine the acceptability of the study design and of using REN to treat children and adolescents visiting the ED with acute attacks of migraine.
3) To gather preliminary efficacy and safety data on the use of REN to treat children and adolescents visiting the ED with acute attacks of migraine.

5.2. Primary Research Question

1) Will a pilot double-dummy crossover RCT that compares remote electrical neuromodulation (REN) to standard of care IV interventions (metoclopramide +

ketorolac) for the treatment of acute attacks of migraine in children and adolescents (N=40) presenting to the ED be **feasible and acceptable**?

5.3. Secondary Research Questions

5.3.1. Recruitment Rate

The recruitment rate will be determined by taking a count of the number of participants recruited per month. Our target average is to recruit 1.5 participants per month.

5.3.2. Secondary Feasibility Measures

1) We will determine the proportion of participants who complete all measures for all follow-up time points. Our goal is to have 80% of participants complete all measures at each time point.
2) We will determine the proportion of eligible participants who are enrolled in the primary study (i.e., the study pertaining to ED treatment), relative to the total number of eligible participants who are approached in the ED. We aim to recruit 50% of the total number of eligible participants that are approached in the ED.
3) We will determine the proportion of participants who are enrolled in the study, relative to the total number of participants that are approached about the study in the ED. We aim to recruit 10% of individuals who are approached about the study.

5.3.3. Acceptability

1) We will determine the proportion of participants who report a "good" or "very good" global impression of change. This will be measured using a 7-point Likert scale, as recommended by the International Headache Society guidelines.[76] Our goal is to have 70% of participants reporting a "very much improved" or "much improved" global evaluation of treatment.
2) We will record feedback provided by participants on study acceptability for both the primary and secondary study. Our goal is to have most participants report that the study protocol is acceptable, as measured through specific questions at the 48-hour follow-up.
3) We will assess qualitative feedback provided by the ED staff, which will be collected by RRNs after completion of the 120-minute follow-up assessment. This feedback will be collected from the treating ED nurse and physician. Our goal is to have ED staff feedback centered on finding the study protocol acceptable.

5.3.4. Efficacy

1) We will determine the proportion of participants who are pain free at: 1) 60 and 120 minutes (or at discharge if before 120 minutes) post-treatment in the ED (for both the initial assigned intervention and the crossover intervention where applicable).
2) We will determine the proportion of participants with sustained pain freedom after ED treatment. This will be measured according to which participants achieve pain freedom by the 120-minute time point (or at discharge if before 120

minutes) and maintain pain freedom until the 48-hour follow-up (for both the initial assigned intervention and the crossover intervention where applicable).
3) We will determine the proportion of participants who achieve headache relief at each time point in the ED (60 and 120 minutes post-treatment, or at discharge if before 120 minutes). We will examine these outcomes for both the initial assigned intervention and the crossover intervention where applicable. This outcome will be defined as those participants who experience a pain reduction from "severe" or "moderate" severity down to a "mild" or "no pain" severity, or those participants who experience a pain reduction from "mild" to "no pain" severity. This will be assessed using the 4-point pain severity scale.
4) We will determine the proportion of participants who are discharged from the ED and require no further intervention after both the initial assigned intervention and the crossover intervention where applicable.

5.3.5. Safety

1) We will determine the proportion of participants who report any adverse events. Adverse events will be assessed both in the ED as well as at the 48-hour follow-up.
2) We will determine the proportion of participants who report any serious adverse events. Serious adverse events will be assessed both in the ED as well as at the 48-hour follow-up.

5.4. Hypothesis

Based on the goals and research questions described above, we hypothesize that:

1) The study design will be feasible, achieving a recruitment rate similar to previous studies (~20 participants per year). This will allow for the pilot study to be scaled up to a fully powered, multicenter, phase III RCT where larger recruitment rates will be achievable and comparable to previous migraine treatment device trials (~120-250 participants, based on the non-inferiority margin and primary outcome).
2) The study design and the use of the REN device will be acceptable, as evidenced by quantitative and qualitative feedback from both participants and ED stakeholders.
3) We will not have the power to fully assess the safety and efficacy of the REN device, but preliminary data will be used to inform appropriate sample size and study design for a fully powered RCT.

6. Eligibility Criteria

6.1. Inclusion Criteria

Patients aged 8-18 years visiting the Alberta Children's Hospital (ACH) ED with an acute attack of migraine as per criteria B-E of the International Classification of Headache Disorders-3 criteria (ICHD-3):[33]

A. Headache attacks lasting at least 2 hours (untreated or unsuccessfully treated)[2;3]
B. Headache has at least two of the following four characteristics:
    a. Unilateral, bilateral, or frontotemporal location
    b. pulsating quality
    c. moderate or severe pain intensity
    d. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
C. Also has least one of the following:
    a. nausea and/or vomiting
    b. photophobia and phonophobia
D. Not better accounted for by another diagnosis in the opinion of the treating physician

Criterion A (at least 5 attacks) is not being used in this study because prior research has shown that removing criterion A increases the sensitivity of these criteria in the ED.[77,78] The patient and their caregiver will also be required to understand spoken and written English. In addition, potential participants will be required to have an upper arm circumference of at least 20 cm to ensure optimal device fit and safety.

6.2. Exclusion Criteria

Exclusion criteria include the following: allergy or contraindication to metoclopramide, ketorolac, or non-steroidal anti-inflammatories; implanted electrical device, congestive heart failure, severe cardiac or cerebrovascular disease, uncontrolled epilepsy (2 or more unprovoked seizures per year), abnormal skin on both upper arms (e.g., cancerous lesion on both upper arms, metallic implants on both upper arms, or abnormal physical sensation in both upper arms), febrile at triage, head trauma in the past 7 days, current secondary headache, previously enrolled in the study, pregnant or lactating.

For the pregnancy question, the screening research nurse will ask potential participants if they have reached menarche (had their first menstrual period). If they answer yes, then the parent(s)/guardian(s) will be asked to leave the room, and the potential participant will be directly asked if there is any potential that they are pregnant or lactating.

7. Study Design

7.1. Description

The proposed primary study will be a pilot RCT and will be designed as a randomized, double-dummy crossover study. Blinding will be maintained for the participant and the investigators throughout the study. The initial study design was a pilot parallel-group double-dummy study. However, as of February 10th, 2023, we have recruited at a rate of 1.0 participants/month vs. our target of 1.5 participants/month and we are below our 50% target for the proportion of eligible who enroll, at ~32%. Following feedback from participants and potential participants, we are proposing a study design change from a

parallel-group randomized controlled trial to a crossover trial; this change is being made to address participant/potential participant concerns expressed around the initial parallel-group design that precludes participants from receiving the non-assigned active intervention should the initial assigned intervention be ineffective. Specifically, patients have expressed concerns they will not be able to receive the first-line standard of care treatment (ketorolac and metoclopramide) during their ED visit should they initially receive the active REN device and placebo IV medications. Transitioning to a crossover trial will help to address these concerns and reflect a more patient-centered design.

7.2. Description of Study Stages

Forty children and adolescents will be recruited into the study from the ACH ED. Outpatients in Dr. Orr's neurology clinic may also receive information about the study in clinic in anticipation of possible future ED visits. Patients in clinic who verbally consent to receiving information about the study would have the study verbally described to them by either Dr. Orr or her RA, and the participant would have the option of taking a copy of the study brochure and study treatment summary documents home if they are interested. Upon arrival to the ED, potential participants (whether they are known to Dr. Orr as outpatients or not) will be triaged as per standard of care. Potential participants (i.e., those with a triage complaint of headache or migraine) will be asked by an agent of Alberta Health Services if they are willing to be approached regarding a research study. Potential participants who agree to hear about the study will then be approached by an ED-based research nurse who will seek verbal consent from the participant to be screened for the study. Demographic information will be recorded from each patient who provides verbal consent for screening, and this data will include sex, age, CTAS score, and date and time of triage). Written consent for the study will then be obtained by the research nurse after the patient has been screened for eligibility. Each participant will be enrolled in the study for approximately 48 hours, although each participant will only be assessed during their ED visit (duration is expected to be no more than 5 hours), and during a 48-hour follow-up after they have been discharged from the ED. The smartphone application used to control the REN device does collect de-identified data from the user, including treatment and symptom descriptions, actions performed within the application, and device information. This information is collected by the smartphone application and sent to the device manufacturer, Theranica Bio-Electronics Ltd. Instructions on how to use the device, the full End User License Agreement (EULA), and questions asked by the application can be found in Appendices D-H.

We expect each participant to be actively involved in the study for 2 to 5 hours in the ED (depending on whether or not they cross over), and for 48 hours post-intervention. Should they enter the crossover phase, their engagement time in the ED will be 4 to 5 hours. Assessments in the ED will either be completed electronically by the participant (with or without assistance from their parent and/or guardian if needed) or by the ED Research

Nurse, and the 48-hour follow-up will either be completed electronically or through a telephone call, whatever is most convenient for the participant.

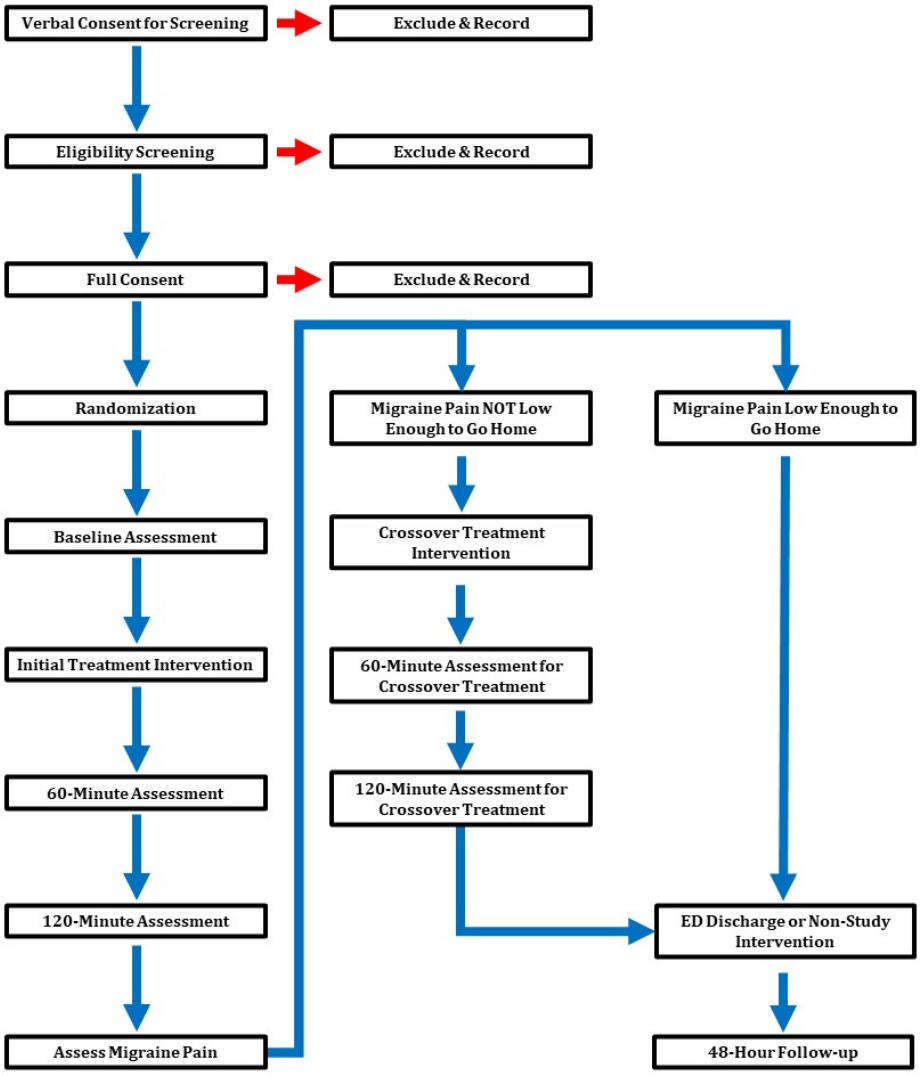

Figure 2. Study Flow Diagram

7.3. Screening

Patients presenting to the ACH ED with a triage complaint of migraine, headache, head pain, or symptoms in keeping with migraine aura will first be approached by an agent of Alberta Health Services who is not associated with the research study. This individual will request permission for the research team member to approach regarding the proposed study. If the potential participant agrees to learn more about the study, they will be approached by an ED-based research nurse who will seek verbal consent from the participant to be screened for the study, as per the procedure outlined above (in 7.2). The research nurse will be a member of the established ACH Pediatric Emergency Research Team (PERT), with study recruitment happening between the hours of 08:00 and 22:00. Specific recruitment times will vary based on the PERT nurse schedule for any given week,

but generally 4 PERT nurses, at 0.5 FTE each, are available 7 days per week to cover the hours between 08:00 and 22:00. Eligibility assessment will occur once the patient has been approached by an agent of Alberta Health Services and has verbally consented to screening. Demographic data will be recorded from each screened potential participant including age, sex, Canadian Triage and Acuity Scale (CTAS) scores, date and time of triage, and reason for non-enrollment (if applicable). If eligible, the study procedures will be explained to the patient and their family, and a responsible physician will review and confirm study eligibility. All ED physicians will receive training on the study protocol prior to involvement. In addition to the process above, at enrollment, the research nurse will ask the participant if they would like assistance with adjusting their environment for comfort purposes. These accommodations are being included in the protocol because many patients with migraine experience sensory sensitivities such as photophobia and phonophobia. The participant will be asked if they would like a pair of ear plugs to help with phonosensitivity, and they will be asked if they would like help to adjust the lights (i.e., turn off lights in the room) to help with photosensitivity. For those interested in ear plugs, the research nurse will provide the participant with a pair of basic ear plugs that will be purchased for the study. Finally, a study brochure will be available for participants to review electronically using their smartphones or using the ED research iPads, or physically by an ED-based research nurse while they are in the ED (after approach as described above). This brochure will be made available to participants through a QR code on the consent form, by showing them the brochure on an ED research iPad, or they will be provided with a physical copy while in the ED(see Appendix I) along with a one-page summary explaining the study treatments (Appendix J).

7.4. Randomization

Eligible and consenting participants will be randomized at a 1:1 ratio to initially receive:

1) the standard of care IV treatment for migraine in the ED (a combination of ketorolac and metoclopramide) and a sham REN device that will not administer therapeutic electrical stimulation

   or

2) the standard REN device that will administer the therapeutic electrical stimulation and IV fluid containing normal saline (i.e. placebo).

At 120-minutes post-intervention, and if not already discharged, participants will be asked if they feel ready to go home without further intervention. Should they respond “yes” to this question at either the 60-minute or 120-minute time point, they will be discharged from the ED in consultation with their treating physician. Should they respond “no” to this question at both the 60-minute and 120-minute time points, they will be crossed over at 2 hours to the alternate treatment arm. The randomization sequence will be prepared by a statistician who will have no role in the recruitment or clinical care of the participants. The

sequence will be sent to the pharmacy and will not be accessible to anyone involved in the study or care of the participant.

The pharmacy will maintain a list with the randomization code and the corresponding treatment allocation order. Only the pharmacy will be able to link the randomization to the treatment allocation order. Where necessary, the ED clinical staff and study investigators will also be given access to this information to ensure the health and safety of the participant, should any adverse events requiring intervention and/or treatment discontinuation occur (i.e., in these cases, the clinical personnel will ask the pharmacy for the treatment allocation order associated with the given randomization code, which will allow them to unblind clinical and/or research personnel to what intervention(s) the participant received for participant safety and/or clinical treatment purposes).

7.5. Baseline Assessment

A baseline assessment will comprise additional demographics (beyond those in the screening questions), a headache history, and a past medical history (see Appendix K-N). Efficacy and safety measures will also be recorded at baseline (see Appendix L and M for baseline measures).

7.6. Study Intervention Administration and Efficacy Assessments

Following consent, screening, and baseline assessment, the initial study intervention will be administered. A fluid bolus, to help alleviate potential dehydration, may also be administered at the discretion of the attending ED physician if it is felt to be clinically indicated (i.e., if the patient is clinically dehydrated). Study medications will be stored in the access restricted ED research fridge, and one study package at a time will be stored in the ED research office (i.e., each package will contain an "Initial Treatment" part and a "Crossover Treatment" part; the "Initial Treatment" part will comprise two vials containing either metoclopramide and ketorolac, or normal saline and normal saline, which will be stored in the ED research fridge, and one device, either sham or active, which will be stored in the ED research office in a locked cupboard. The "Crossover Treatment" part will contain the alternate vials and device for crossover should it be necessary. For each package, the medication vials and the corresponding device will be labeled with "Initial Treatment" vs. "Crossover Treatment" and the given randomization code. The study intervention(s) will be administered by the ED research nurse. Once the study package is used, another study package will be ordered from research pharmacy so that the ED supply is replenished. For participants not requiring crossover, the "Crossover Treatment" part of the study kits will be sent back to Pharmacy for handling and possible reuse in the next kit if not expired.

Efficacy and safety assessments will be completed by participants and administered by the ED research nurse at 60 and 120 minutes (or at discharge if before 120 minutes) following each treatment (Appendix N). We will allow for a 30-minute time window around each of the timed assessments in the ED to account for any small deviations regarding when the assessments are completed. Pain severity will be measured using the 11-point pain numerical rating scale, which is a well-established self-reported pain scale that has a strong

recommendation to use in children aged 6-18 years with acute pain based on a recent systematic review.[79] To align with International Headache Society (IHS)[76,80] and FDA guidelines for migraine trials,[81] we will also use the 4-point pain severity scale (0=none, 1=mild, 2=moderate, 3=severe), and participants will be asked about their most bothersome migraine associated symptom for the current attack, and whether it is present or not. For safety, participants will be asked about adverse events, and these will be defined according to the Good Clinical Practice of the International Conference on Harmonization. Using these measures, secondary efficacy and safety outcomes will be reported, in accordance with the IHS[76,80] and FDA guidelines.[81] If participants experience nausea or vomiting following the study intervention, the treating physician will manage the nausea or vomiting at their discretion. If participants experience adverse events at any time point in the ED, the treating physician will manage the adverse events. If participants are experiencing ongoing pain that they are requesting intervention for after the initial 120-minute assessment (following the first assigned intervention), then they will be crossed over to the alternate treatment arm. If participants are experiencing ongoing pain that they are requesting intervention for after the 60-minute post-crossover assessment, the ED physician will determine ongoing management at their discretion, and may administer additional interventions to manage the pain before the 120-minute post-crossover assessment. In cases where participants do receive additional pain interventions before the 120-minute post-crossover assessment, the intervention and the timing of its delivery will be recorded. If participants are not feeling well enough to be discharged home after the 60-minute post-crossover assessment, the treating physician will determine ongoing management at their discretion.

7.7. Follow-Up

Participants will be offered the option of completing their follow-up via a self-administered electronic questionnaire sent through Research Electronic Data Capture (REDCap), or over the phone with a research assistant. If they choose the option of the self-administered electronic questionnaire, they will receive an email with a link to the REDCap-administered questionnaire at 48 hours post-intervention. Should they not complete the given questionnaire within 12 hours, a reminder email will be sent. Should they fail to complete the given questionnaire within 24 hours of the reminder, the research assistant will contact them over the telephone for the follow-up. We will allow for 36-hour time window for data collection around the 48-hour outcome time point to ensure feasibility and ease of participation in the study.

For participants selecting the option of telephone follow-up, the research assistant will call the patient for a follow-up telephone-administered questionnaire approximately 48 hours post-interventions (see Appendix O and P). In the event where it is not possible to contact a patient for follow-up over the telephone after several attempts, follow-up questionnaires will be emailed to the participant through REDCap, with 12-hour reminders as described above. Because some questions posed in the 48-hour follow-up pertain to participants rating their experience of the study and study personnel, part of the 48-hour assessment

will be completed electronically even where participants select the option of telephone follow-up. In these instances, the study research assistant who calls participants will complete the telephone questions, then ask participants how they would like to receive the remaining questions electronically (i.e., over email or via text message).

When an adverse event is reported during follow-up on one of the electronic questionnaires, the participant may be contacted over the telephone to clarify details pertaining to the adverse event, where needed to clarify the nature and severity of the adverse event.

Where clinically relevant information is reported at follow-up (e.g., occurrence of new concerning neurological symptoms), the research assistant will contact Dr. Orr to discuss the information. Dr. Orr will then decide how to proceed in handling the information and making a management plan for the participant where applicable.

Participants who complete the 48-hour follow-up questionnaires will be sent a $20 electronic gift card of their choice via email.

7.8. Chart Review

The research assistant will review the participants' charts 7 days or later after discharge to record any return visits to the ED and hospital admissions. Return visits will be coded as either headache-related or unrelated (see Appendix Q). Charts will also be reviewed for a period encompassing up to 6 months after the 48-hour follow-up to record any return visits to the ED and hospital admissions.

7.9. Study Endpoints

7.9.1. Primary Outcome

The primary outcome for this pilot study involves assessment of the feasibility of using the REN device to treat children and adolescents suffering from acute migraine attacks in the ED. The primary feasibility outcome will be determined based on the recruitment rate, defined as the number of participants enrolled per month. Our target is to have an average recruitment rate of 1.5 participants per month. Feasibility will be used as the primary outcome, along with the secondary outcomes, to provide preliminary data to help design and optimize a fully powered, phase III RCT.

7.9.2. Secondary Outcomes

Secondary outcomes will relate to the feasibility, acceptability, efficacy, and safety of using the REN device.

Secondary feasibility outcomes will involve:

- The proportion of participants who complete all assessments at each time point (baseline, 60, 120 minutes or at discharge if before 120 minutes, 60 and 120 minutes post-crossover, where applicable, and 48-hours).

- The proportion of screened eligible participants who are subsequently enrolled in the study.
- The proportion of approached potential participants who subsequently decide to enroll in the study.

The acceptability outcomes involve:
- The proportion of participants who report a global impression of change as "very much improved" or "much improved".
- Participant feedback regarding study acceptability
- ED staff feedback provided

Efficacy and safety outcomes will assess the proportion of participants who:
- are pain-free following the 60 and 120-minute assessments (or at discharge if before 120 minutes), and 60 and 120-minute post-crossover assessments after treatment.
- maintain pain-freedom following the 120-minute assessment (or at discharge if before 120 minutes) or the 120-minute post-crossover assessment and up to the 48-hour follow-up after treatment.
- experience headache relief after treatment.
- are free of their most bothersome migraine-associated symptom after treatment.
- Receive additional interventions for pain prior to the 120-minute post-crossover assessment
- are discharged from the ED and require no further intervention after the initial assigned treatment or after the crossover treatment.
- experience adverse events.
- experience serious adverse events.

7.10. Study Design and Protocol

We propose to carry out a pilot RCT to determine the feasibility and acceptability of implementing a double-dummy, crossover RCT protocol. Though treatment carry-over effects can occur in cross-over design,[76] it is standard in the literature to expect both REN and the IV medications (metoclopramide and ketorolac) to have had effect by 2 hours (this is the standard time point at which acute interventions are assessed as per international trial guidelines)[76], and we feel that there will be adequate washout with this design without significant contamination from treatment carry over effects, while balancing the need for timely further intervention should the first intervention not provide adequate pain relief. We also considered the possibility of a futility design, however the lack of adequate historical control data[82] preclude a futility design.

In this pilot study, 40 children and adolescents (N=40) visiting the ED with acute attacks of migraine will be randomized to REN, or to standard of care IV treatment (i.e. a combination of metoclopramide and ketorolac), and crossed over to the alternate treatment arm if they have not had adequate pain relief at 2-hours post-intervention. Each group will also receive

a blinded control in each phase of the trial (either normal saline through the IV for the REN group, or sham stimulation for the standard of care IV group). Design will adhere to International Headache Society[76] and CONSORT[83] trial guidelines. A trained ED-based research nurse from the established ACH Pediatric Emergency Research team (PERT) will assess eligibility of identified patients who are present during PERT research nursing hours, from 8:00 to 22:00, 7 days per week. This will occur following placement in a treatment room and prior to, or just following ED physician assessment. If potentially eligible, the study procedures will be explained to the family and the responsible physician will review and confirm all eligibility criteria and their support for participant recruitment. All ED physicians potentially enrolling patients into the study will be trained on the study protocol.

Consenting participants will be randomized at a 1:1 ratio to either REN or standard of care IV treatment as their initial treatment allocation, with the option to cross over to the alternate treatment arm at 2-hours post-initial treatment should they not feel that they have had adequate pain relief. The allocation sequence will be prepared by a statistician with no role in recruitment or clinical care. The allocation sequence will be sent to the pharmacy and will not be accessible to anyone involved in the study or care. The pharmacist will prepare study intervention kits with two parts for each participant: the "Initial Treatment" part will contain either IV metoclopramide (0.15 mg/kg, maximum 10 mg), ketorolac (0.5 mg/kg, maximum 30 mg), and a sham stimulation device, or normal saline placebo and REN with the Nerivio™ device, and the "Crossover Treatment" part will contain the alternate components. Regarding preparation of study kits, each kit will contain six elements: four medication vials, and two devices. The pharmacist will direct transfer either a metoclopramide solution and a ketorolac solution into two separate vials, and will direct transfer normal saline into two separate vials. The pharmacist will label these vials with the randomization code and which part of the kit they belong to ("Initial Treatment" or "Crossover Treatment"). Two devices (active and sham) will also be sent with the study kit, labelled as to which part of the kit they correspond to ("Initial Treatment" or "Crossover Treatment") and labelled with the randomization code.

The REN device (Figure 3) is a wearable, battery-operated neuromodulation device that is applied to the arm using an armband and wirelessly controlled by a smartphone software application. The REN device delivers electrical stimulation to local C and Aδ nociceptive sensory nerves using a modulated symmetrical biphasic square pulse, with a modulated frequency of 100-120 Hz, a pulse width of 400 μs, and with participant-adjusted output current to a maximum of 40 mA. Stimulation occurs over 45 minutes.[57] During stimulation, participants will also have the option of watching a video consisting of guided imagery, education about migraine, and guided relaxation, which is embedded into the device's smartphone application. The REN assignment will comprise active stimulation and normal saline (0.9% sodium chloride solution) placebo that will appear identical in appearance and volume to the medications given to the comparison group. The normal saline solution will be transferred to vials by the research pharmacy in the same volumes as those planned

for the active metoclopramide and ketorolac solutions (i.e., for ketorolac 1.4 mL of normal saline, and for metoclopramide 2.4 mL of normal saline). The placebo ketorolac solution (i.e., 1.4 mL of normal saline) will be transferred from the vial to a syringe and will be administered to participants, in the appropriate volume to mimic the weight-based dosing of ketorolac (30 mg/mL solution concentration, with target dose of 0.5 mg/kg, maximum 30 mg or 1 mL maximum), using a direct IV push. The placebo metoclopramide solution (i.e., 2.4 mL of normal saline) will be transferred from the vial to a 50 mL mini bag of normal saline and will be administered to participants, in the appropriate volume to mimic the weight-based dosing of metoclopramide (5 mg/mL solution concentration, with target dose of 0.15 mg/kg, maximum 10 mg or 2 mL maximum), over 15-30 minutes. Please see Table 1 for details on the interventions administered to each group.

Figure 2. The REN Device*

**Image from: www.theranica.com*

The comparison assignment will comprise a combination of pharmaceutical interventions that are considered to be the standard of care for treating children and adolescents visiting the ED with migraine: IV ketorolac (0.5 mg/kg, maximum 30 mg) and IV metoclopramide (0.15 mg/kg, maximum 10 mg).[26,38] As per ACH ED protocols, ketorolac solution (concentration = 30 mg/mL) will be transferred from the vial provided by the pharmacy to a syringe and will be administered to participants, at the appropriate weight-based dose (0.5 mg/kg, maximum 30 mg or 1 mL), using a direct IV push. The ketorolac solution will thus be undiluted and administered over 1-5 minutes, averaging 2-3 minutes. Metoclopramide solution (5 mg/mL) will be transferred from the vial provided by the pharmacy to a 50 mL mini bag of normal saline (0.9% sodium chloride), and will be administered to participants, at the appropriate weight-based dose (0.15 mg/kg, maximum 10 mg or 2 mL) over 15-30 minutes (see Table 1). IV fluid boluses are often co-administered with these interventions,[36,38] but there is no evidence that this approach is effective in children and adolescents, and there is evidence that IV fluid boluses are ineffective for the treatment of adults visiting the ED with acute attacks of migraine.[84] Therefore, we will not co-administer an IV fluid bolus in this trial, unless the treating physician feels that it is clinically indicated for dehydration. In this case, the treating ED

physician will order the IV fluid bolus at their discretion. In addition, though there have been more data reported on the use of prochlorperazine for treating migraine in children and adolescents,[12,44,45] it is no longer available in Canada, and metoclopramide, which is a neuroleptic with a similar mechanism of action, has replaced its use. The comparison assignment will also comprise sham stimulation that will be low enough that it cannot induce conditioned pain modulation, the mechanism of action of REN, but it will be perceptible and similar to the sensation induced by the active REN device. As with the active stimulation assignment, during stimulation, participants in the sham stimulation group will also have the option of watching a video consisting of guided imagery, education about migraine, and guided relaxation, which is embedded into the device's smartphone application. The sham stimulation parameters will mirror those from the published trial in adults (modulated frequency of ~ 0.083 Hz and a modulated pulse width of 40-550 μs), where the validity of this sham protocol was established.[57] These sham parameters are designed to induce a sensation that will be perceptible to participants, similar to stimulation from the active REN device, but at a frequency that is low enough so as to not modulate the nociceptive sensory nerves.

Table 1. Interventions Administered During Each Assignment

Intervention	Standard of Care Assignment	REN Assignment
Vial #1	Metoclopramide: • Concentration of solution in vials kept in fridge: 5 mg/mL • Volume of solution in vials kept in fridge: 2.4 mL • Administration: Transfer appropriate volume of solution to 50 mL mini bag of normal saline (0.9% NaCl) for target dose of 0.15 mg/kg, maximum 10 mg of metoclopramide (2 mL), and administer as infusion over 15-30 minutes	Normal saline (0.9% NaCl): • Concentration of solution in vials kept in fridge: N/A • Volume of solution in vials kept in fridge: 2.4 mL • Administration: Transfer appropriate volume of solution to 50 mL mini bag of normal saline (0.9% NaCl) for target dose of 0.15 mg/kg, maximum 10mg of metoclopramide (2mL), and administer as infusion over 15-30 minutes
Vial #2	Ketorolac: • Concentration of solution in vials kept in fridge: 30 mg/mL • Volume of solution in vials kept in fridge: 1.4 mL • Administration: Transfer appropriate volume of solution to syringe for target dose of 0.5 mg/kg, maximum	Normal saline (0.9% NaCl): • Concentration solution in vials kept in fridge: N/A • Volume of solution in vials kept in fridge: 1.4 mL • Administration: Transfer appropriate volume of solution to syringe for target dose of 0.5 mg/kg, maximum 30 mg of

	30 mg of ketorolac (1 mL), and administer as a direct IV push over 1-5 minutes	ketorolac (1 mL), and administer as a direct IV push over 1-5 minutes
Device	Sham device: • Parameters: Modulated frequency of ~ 0.083 Hz and a modulated pulse width of 40-550 µs • Duration: 45 minutes of stimulation	Active device: • Parameters: Modulated frequency of 100-120 Hz, a pulse width of 400 µs, with participant-adjusted output current to a maximum of 40 mA • Duration: 45 minutes of stimulation

The study kits will be stored in the ED (with medications in fridge) and labelled as per Health Canada regulations. The study interventions will not be labeled with intervention information, so that the research and clinical staff can remain blinded to the interventions. The PERT research nurse will administer the assigned interventions to participants. Efficacy and safety outcomes will be measured at baseline, 60, and 120 minutes, and 48 hours post-intervention. For participants who cross over, additional 60-minute and 120-minute post-crossover assessments will occur. Participants, the ED research nurse, and the clinical team will remain blinded to the interventions.

Participants with significant relief prior to the initial or post-crossover 120-minute assessment may be discharged from the ED, rather than being asked to remain in the ED until the next assessment. For such participants, an additional time point for data collection will occur at discharge. Additionally, the ED research nurse will electronically schedule the next assessment questions to be sent to the participant through REDCap at 120 minutes after the last intervention via text message or email, contingent on the participant's preferred method of contact. Reminders for the 120-minute assessment will also be scheduled in REDCap and will be sent every 30 minutes (up to 3 times) after the assessment was initially sent to the participant. Where the participant does not complete these questions post-discharge, the discharge questions will be used in lieu of the 120-minute questions to measure the 120-minute outcomes (after initial or post-crossover assessment).

The smartphone application used to control the REN device does collect data from the user, including treatment and symptom descriptions, actions performed within the application, and device information. This information is collected by the smartphone application and sent to the device manufacturer. The full End User License Agreement (EULA) that describes this data collection can be found in Appendix G. The application will be accessed on a study device (e.g., iPad), using a study account, and participants will not be asked to enter data directly into the device, as all outcome data will be collected through REDCap.

Therefore, participants will not have to use their own device to participate, and will only enter data into the application if they choose to.

7.11. Measures

In order to compare enrolled to non-enrolled individuals, we will record basic demographic data on all individuals approached for the study, including: age, sex, Canadian Triage and Acuity Scale (CTAS) score, date and time of triage, and where, applicable, reason for non-enrollment. The primary outcome for this pilot trial will pertain to feasibility. All feasibility and acceptability outcomes are described in previous sections, along with targets, that were established using data from prior similar trials.[34–36,85]

Participants will be asked to report on the main efficacy and safety measures at each outcome measurement time point (baseline, 60, and 120 minutes, 60 minutes and 120 minutes post-crossover where applicable, or at discharge if before 120 minutes after the last intervention, and 48 hours). Pain severity will be measured using the 11-point pain numerical rating scale, which is a well-established self-reported pain scale that has a strong recommendation to use in children aged 6-18 years with acute pain based on a recent systematic review.[79] To align with International Headache Society (IHS)[76,80] and FDA guidelines for migraine trials,[81] we will also use the 4-point pain severity scale (0=none, 1=mild, 2=moderate, 3=severe), and participants will be asked about their most bothersome migraine associated symptom for the current attack, and whether it is present or not (see Appendix L, N, and O). For safety, participants will be asked about adverse events, and these will be defined according to the Good Clinical Practice of the International Conference on Harmonization. Using these measures, secondary efficacy and safety outcomes will be reported, in accordance with the IHS[76,80] and FDA guidelines.[81]

In addition to these efficacy and safety measures, we will measure:

1. **Treatment expectancy**: We will measure treatment expectancy in both the participant and the parent at baseline using two questions, one referring to expectancy in relation to the study device, and one referring to expectancy in relation to the standard of care IV medications (see Appendix L and M). These questions have been designed specifically for this study and have not been previously piloted or validated.
2. **Expected magnitude of pain relief**: At baseline, we will ask both the participant and their parent about what level of pain they would deem acceptable prior to discharge. We have designed two questions for this purpose (see Appendix L and M). These have been designed specifically for this study and have not been previously piloted or validated.
3. **State pain catastrophizing**: Both the participant and an accompanying parent or guardian will be asked to complete the 3-item State Pain Catastrophizing Scale for Children (SPCS-C) at baseline. The State Pain Catastrophizing Scale for Children (SPCS-C) is a shorter derivative of the Pain Catastrophizing Scale for Children (PCS-

C) and has been found to be reliable and valid in the pediatric chronic pain population (see Appendix L and M).[86] Questions in the PCS-C will refer to the child/participant's pain (ie. Participants will answer question about their own pain and the parent/guardian will answer questions about their child's pain).

4. **State anxiety**: Both the participants and a parent/guardian will also be asked to complete the short-form, 6-item State-Trait Anxiety Inventory (STAI-6) at baseline. The STAI-6 contains six items from the 20 state-related items of the State-Trait Anxiety Inventory (STAI), and has been validated in both adult[87,88] and pediatric clinical populations.[89–92] The STAI was developed to assess both current (state) and general (trait) levels of anxiety, with the state and trait measures each containing 20 items.[93] The STAI-6 is based on the state-related items and was developed for settings that are time sensitive, making such a scale ideal for the emergency department.[87] Appendix L and M shows the items used in the STAI-6.
5. **Participant global impression of change**: At the 120-minute (or at discharge if before 120 minutes) and 48-hour time points, the participants will be asked to report their global impression of change using a single item question, rated on a 7-point Likert scale that ranges from "very much improved" to "very much worse" (see Appendix N and O).
6. **Data on baseline demographics, headache history, and medical history**: At baseline or any time during the participant's stay in the ED, the research nurse will ask participants a series of questions aimed at ascertaining their demographics, headache history, and medical history. These questions are listed on the baseline data collection form that will be completed by the research nurse (see Appendix K).
7. **Disposition outcomes**: The research nurse will also enter data into REDCap with regards to the participants' disposition outcomes (e.g., whether the patient was discharged from the ED without further intervention, what other interventions were administered according to the ED physician between the 60- and 120-minute post-crossover assessments and after study interventions, etc). These questions are listed on the baseline data collection form that will be completed by the research nurse (see Appendix K).
8. **Additional questions at 48-hour follow-up**: In addition to the main efficacy and safety measures as outline above, at the 48-hour follow-up questionnaire, participants will be asked about headache recurrence, medication use at home, migraine-related disability, impressions of the study interventions received, and to provide feedback on their study experience. The study feedback questions were mostly derived from a prior published survey.[94] All of these questions are listed on the 48-hour feedback data collection form (see Appendix P).

Based on feedback from our patient engagement, we will offer each participant the option of selecting their preferred reporting method for initial outcomes in the ED (i.e., electronic surveys completed by the participant, or data collected from the research nurse and entered into REDCap on behalf of the participant). For the 48-hour outcomes, participants will choose between electronic or telephone follow-up, as per our prior study.[85]

Qualitative feedback will also be collected from the nurses and physicians who are treating the participants in the ED (see Appendix R). The PERT nurse will approach the treating clinicians towards or at the end of each participant's involvement in the primary study to solicit verbal or written feedback from them. These clinical staff will be asked: 1. "Did you have any concerns with the study?", and 2) "Do you have any suggestions for improvement of the study?". For those providing verbal feedback, the PERT nurse will transcribe the feedback and place it into REDCap. For those providing written feedback, they will have the option of writing it down on a paper form, or being sent an emailed or text messaged REDCap link.

8. Expected Duration of Participant Participation

Participants will remain in the ED for variable lengths of time, which will largely be dependent on the time needed to effectively treat and manage their acute migraine attack. Further interventions will be administered at the discretion of the attending ED physician if participants do not experience a significant reduction in pain 60-120 minutes after receiving the crossover study intervention. We expected participants will remain in the ED on an average of 2-5 hours, depending on whether they cross over or not.

Following discharge from the ED, participants will then complete an electronic or telephone follow-up 48 hours post-intervention. We expect this follow-up to take between 15-30 minutes. Participation in the study will end once this 48-hour follow-up has been completed.

9. Study Medication

9.1. Study Medication Description

The study interventions will consist of either a one-time dose of the standard of care IV medications: a combination of ketorolac and metoclopramide, or electrical stimulation from the REN device. Ketorolac will be administered at a dose of 0.5 mg/kg, up to a maximum of 30 mg, and metoclopramide will be administered at a dose of 0.15 mg/kg, up to a maximum of 10 mg. The standard of care medications will be prepared at the ACH research pharmacy and sent down in vials to the ED research office, to be kept in the ED research fridge. The REN device will administer electrical stimulation to the upper arm over 45 minutes, using a modulated frequency of 100-120 Hz, a pulse width of 400 μs, and a maximum output current of 40 mA. The REN device is manufactured by Theranica Bio-Electronics, Ltd.

9.2. Placebo Description

The placebo IV medication consists of normal saline that is matched in volume to the weight-based volume that would be given if the participant were received the standard of care IV medications. The sham REN device uses a pulse frequency of about 0.083 Hz, and a

modulated 40-550μs pulse width. These settings differ from the active REN device but are designed to create a sensation similar to the active REN device without stimulating the nociceptive sensory nerves in the arm. These parameters were chosen based on previous RCT studies using the active and sham REN devices.[57]

9.3. Accountability Procedures and Storing

The ketorolac and metoclopramide suspensions will be stored in vials within the AHS-maintained research fridge of the ACH ED. This fridge is wirelessly monitored and maintained at a range of 2-8°C as per the recommended pharmacy guidelines for storage of the investigational products. The fridge is locked, along with the research office containing the fridge, and only relevant and trained study staff have access. The saline placebo suspensions (one for ketorolac and metoclopramide) will also be stored in the research fridge, in vials identical to those used to store ketorolac and metoclopramide. Ketorolac and metoclopramide vials will remain stable for 9 days while in the fridge and both medications will be labelled with their respective expiration dates. The saline placebos will also be labelled with expiration dates matched to the expiration dates of ketorolac or metoclopramide (see Appendix S-U for label templates). After the expiration date, remaining vials will be destroyed in compliance with the research pharmacy's standard operating procedures (SOP) for the destruction of investigational drugs, which are compliant with the guidelines as set out in ICH.[75]

The ketorolac, metoclopramide, and placebo vial labeling will be compliant with Health Canada Division 5 Food and Drug Regulation clinical trial labeling guidelines (see Appendix S-U for labels).

The active and sham REN devices will be stored in the pharmacy, and devices (a sham and an active device) will be sent down with the kits (i.e., medication vials and devices, divided into "Initial Treatment" and "Crossover Treatment" parts to reflect the crossover design), to be stored in a locked access-controlled cupboard in the ED research office. The devices will not be labelled as active or sham; they will only be identified with randomization codes and the part of the kit they correspond to ("Initial Treatment" or "Crossover Treatment" that corresponds to their paired medication vials in the kits) so that blinding of both research personnel and staff is maintained. This office is locked and compliant with Health Canada regulations.

Throughout the study recruitment period, pre-printed orders will be sent to the pharmacy to ensure that a consistent stock of study treatments is maintained in the ED fridge. One-two study kits will be maintained in the fridge at a time. When the pharmacist receives an order for a study kit, they will then check the randomization scheme and prepare the appropriate kit, with "Initial Treatment" being either a ketorolac, metoclopramide, and a sham REN device, or a normal saline and an active REN device, according to the randomization code, and "Crossover Treatment" being the alternate intervention. When a participant is randomized to the study, the current study treatment in the ED research

office will be used and a new kit will be ordered by Dr. Orr's research team following kit use. If the kit expires before use, then the expired kit will be sent to pharmacy for disposal, and a new kit will be ordered and delivered to the ED research office. For kits where only the "Initial Treatment" part was used (i.e., the participant did not require crossover), then the unused part of the kit ("Crossover Treatment") will be sent to pharmacy for handling (either disposal or reuse in the next kit depending on expiry date). The pharmacy will maintain a list documenting kit preparation with the information as follows: randomization number associated with kit, date of kit preparation, person who prepared the kit, person who checked the kit. The pharmacy will also maintain a copy of the randomization scheme. The research nurse will document the randomization number on their baseline case report form, which will include participant identifying information, and which will be linked in REDCap to the participant's record ID form that will include contact information (see Appendix V). Thus, in the case where unblinding is required for participant safety reasons, the research team will reach out to the Alberta Children's Hospital inpatient pharmacy with the randomization code assigned to the participant and the pharmacy personnel will be able to report which study intervention(s) were administered to that participant.

Study packages will be kept in the ED research office: each device (sham vs. active) and each medication package (placebo vs. active) will be labelled with "Initial Treatment" or "Crossover Treatment", a randomization code, and a label. Medication packages (placebo and active) will be kept in the ED research office fridge and will comprise vials of metoclopramide, ketorolac, and normal saline placebo. Devices will be stored in the ED research office, outside of the fridge. Each medication package will have the same randomization code and "Initial Treatment" or "Crossover Treatment" labels as one of the devices, so that the appropriate device can be linked to the appropriate medication package during each phase of the study. When a participant consents and is randomized, a PERT nurse will prepare the "Initial Treatment" study interventions for the participant according to their randomization code and the kit part. The PERT nurse will draw the study interventions from the vials in the corresponding medication packages, which will be labeled in compliance with Health Canada Division 5 Food and Drug Regulation clinical trial labeling guidelines, into either a syringe or a normal saline mini bag. The corresponding appropriate REN device for the "Initial Treatment" part (either active or sham, depending on the randomization code) will also be obtained from the research office by the PERT nurse. The PERT nurse will then bring both the prepared IV interventions and the corresponding device to the participant for administration, along with an iPad that will contain the application that is required to connect with the device and allow the user to initiate treatment and control the stimulation intensity. Where an IV catheter has not already been put in place by the clinical team, an IV catheter will be placed by either the clinical team or the research nurse into the participant at this time. The IV interventions (metoclopramide and ketorolac or normal saline, depending on group assignment), will be administered to the participants through the IV catheter as is detailed in 7.10 and Table 1 above. The device (active or sham, depending on group assignment) will be placed on the participant's chosen arm by the PERT nurse, and connected to either the participant's (or

their parent or guardian's) smartphone (after downloading the REN application): https://play.google.com/store/apps/details?id=app.theranica.neriviomigra&hl=en_CA&gl=US), or to an iPad from the ED. The PERT nurse will teach the participant how to control the intensity of electrical stimulation, and participants will be offered the option of controlling the stimulation intensity themselves using their chosen smart device (i.e., their own vs. the study iPad), or having either a parent/guardian or the PERT nurse control the stimulation intensity.

At 120-minutes post-"Initial Treatment" intervention, participants will be asked if they feel ready to go home without further intervention. If they answer "yes", they will be discharged home. If they answer "no", they will be crossed over to the "Crossover Treatment" intervention.

Medications that are not administered to patients will be sent back to the research pharmacy for destruction according to the research pharmacy's SOPs for destruction of investigational products. REN devices that are not used, and not worn, by participants will be returned to the research office. REN devices that have been unused will be sent back to the manufacturer.

Drug accountability forms will be completed and stored in the pharmacy and records will be maintained in accordance with Health Canada Division 5 Food and Drug Regulation guidelines. An accountability log will also be maintained in the ED research office to document dispensation of the study kits to the participants.

9.4. Monitoring for Participant Compliance

We expect few compliance issues once participants are fully informed and have consented to participate in the study. The combination IV treatment of ketorolac and metoclopramide, or saline, will only be administered as a one-time dose, and both the active and sham REN devices will only administer a single, 45-minute session in the study. The study treatments will also be administered by the attending ED research nurse. Should participants wish to discontinue their participation in the study (e.g., due to adverse events, no meaningful reduction in pain, spending too much time in the ED), the treating ED research nurse and physician will withdraw the participant from the study and administer further treatment, as needed and at their discretion. Compliance issues are expected to be more likely between ED discharge and the 48-hour follow-up. Completion and withdrawal rates will be carefully monitored and recorded to properly determine the feasibility and acceptability of the study design.

10. Statistical Procedures

10.1. Sample Size

We expect to recruit 40 participants over two years to the study, averaging 1.5 participants per month. Given that this is a pilot study, data regarding recruitment rates will be used to help inform and design a fully-powered, multi-center phase III RCT study in the future.

10.2. Outcome Analysis Plan

Demographic data for each screened participant will be collected and will include: age, sex, Canadian Triage and Acuity Scale (CTAS) scores, date and time of triage, and reasons for non-enrollment (if applicable). This demographic data will be summarised and described in tabular form. The primary outcome measures of this pilot study pertain to feasibility while the secondary outcomes measures relate to feasibility, acceptability, efficacy, and safety of using the REN device to treat child and adolescent acute migraine attacks in the ED.

Our feasibility and acceptability outcomes will be summarized using appropriate descriptive statistics across both groups. Participant global evaluations of treatment from the 7-point Likert scale will be dichotomized into good (i.e., "good" or "very good" global impression of change) and poor ("minimally improved", "no change", "minimally worse", "much worse", and "very much worse"), and Likert scale-based responses to the questions on the "Participant Protocol Feedback Form" will be dichotomized into agree ("strongly agree" or "agree), and disagree ("neutral", "disagree", "strongly disagree"). These responses will be reported as proportions. Chi square tests will be used to examine the association between each (dichotomized) outcome and treatment group. Qualitative feedback from the "Participant Protocol Feedback Form" and feedback from treating physicians and nurses will be coded independently by two researchers using a content-driven immersion process, whereby concept and theme elements will be extracted as content units. Open coding will be used, with inductive and logical reasoning applied to identify rival means of categorizing the data. A codebook will be kept and updated iteratively.[95–97]

Secondary outcomes will pertain to efficacy and safety. We will calculate the proportion of patients in each group who achieve each dichotomous efficacy outcome. We will also calculate adverse event rates and serious adverse event rates in each group. All planned analyses comparing treatment groups will be exploratory, and this data will be used to guide our sample size calculations for a phase III trial.

10.3. Sex and Gender Analyses

We will measure and report sex and gender. We will assess sex with the question: "What sex was assigned at birth?" and options will be "male", "female" or "other (please describe)". Gender will be assessed with the question: "What gender do you currently identify with?" and options will be "male", "female", "unknown", "I prefer not to disclose", "not listed, I identify as (please describe)". These sex and gender questions are derived from the NIH core common data elements for headache. We expect that approximately

75% of the sample will be female, based on the sex distribution of prior similar studies.[34,36,85] We have no a priori expectation regarding the gender distribution, as this has not been measured in prior studies. We hypothesize that there will be no significant differences in trial acceptability by sex or gender, but we will compare our acceptability outcome results by sex and gender using chi square tests.

10.4. Race, Indigenous, and Visible Minority Analyses

We will measure race, Indigenous, and visible minority status with questions derived from the Canadian Community Health Survey, and from CIHR's Equity, Diversity, and Inclusion Questionnaire, respectively (see form to be completed by research nurse in Appendix K). We hypothesize that there will be no significant differences in trial acceptability by race, Indigenous, or visible minority status, but we will compare the groups' acceptability results using chi square tests.

10.5. Sample Size Analyses

We are planning a sample of size of 40 participants, to acquire adequate data on feasibility and acceptability, and preliminary efficacy and safety data to help inform the sample size and design of a future fully powered RCT. Determining if we can recruit at the rate of ~1.5 participants/month will also help to determine the feasibility of scaling to a fully powered, multicenter phase III RCT.

11. Safety and Adverse Events

11.1. Safety Assessments of Ketorolac

Below is a list of the most commonly reported adverse events in the pediatric and adult research involving single-dose ketorolac. Because ketorolac will be administered in the ED under the supervision of a treating ED physician, treatment of these possible adverse events will be at the discretion of the treating ED physician:

Dizziness: One study examining the treatment of adult migraine using ketorolac found that 7% of patients reported feelings of dizziness.[73] Several other studies examining single-dose ketorolac have also reported dizziness as a common adverse event with rates at approximately 10%, 17%, and 10% respectively.[98–100]

Nausea: A common adverse event among many single-dose ketorolac studies, whether migraine-related or not, is nausea, with rates varying between less than 1% to 67%[47,98–104]

Vomiting: Several studies using ketorolac for non-migraine related pain treatment have reported instances of vomiting, varying from 8% to 42%.[98–100,103]

Drowsiness: Several studies of adult and pediatric migraine treatment have reported drowsiness in less than 1% to as much as 38% of participants.[47,73,98–102,105]

Injection-site Pain: Between 2% and 21% of participants reported pain at the injection site after receiving IV ketorolac.[99,104,105]

Gastrointestinal: Gastrointestinal issues, including bloating, dyspepsia, and heartburn, have been reported in a couple studies, with 2% to 7% of participants reporting gastrointestinal-related adverse events.[73,104]

Increased Risk of Bleeding: Rarely, events of bleeding have been reported after a single dose of intravenous ketorolac, though these reports have come predominantly from studies of ketorolac given perioperatively in surgical patients.[98,106,107]

11.2. Safety Assessments of Metoclopramide

Below is a list of the possible adverse events that may occur when using a single dose of metoclopramide, as described in several studies using a single dose of metoclopramide as treatment in adult and pediatric populations. Because metoclopramide will be administered in the ED under the supervision of a treating ED physician, treatment of these possible adverse events will be at the discretion of the treating ED physician:

Akathisia: Movement disorders such as akathisia have been commonly reported by several adult and pediatric migraine studies, with rates varying from 5% to 32%.[73,108–112]

Dizziness: Feelings of dizziness were also commonly reported in many adult and pediatric migraine studies. Between approximately 1% and 13% of participants reported feeling dizzy after receiving a single dose of metoclopramide.[66,73,74,109,110]

Drowsiness: Along with dizziness, drowsiness was reported in 13% and 38% of adult and pediatric headache participants.[73,74,109,110,113]

Nausea: Several studies reported nausea following a single dose of metoclopramide, with rates between less then 1% to 15%.[74,111,114]

Gastrointestinal: Several gastrointestinal issues, including vomiting and dyspepsia, were reported by about 1% of participants in some studies.[73,74,111]

Dystonic Reactions: Very rarely (< 0.1%) after a single dose of metoclopramide, a dystonic reaction can occur (a sustained muscle contraction).[115,116]

11.3. Safety Assessments of the REN Device

The current literature exploring the use of the REN device in treating adult and pediatric migraine has reported either no or very low (< 5%) device-related adverse events. All adverse events resolved within 48 hours and none were considered serious. Below is a list of the reported adverse events from the literature. If any of these adverse events occur in the ED and are considered intolerable to the participant, the participant will have the option of stopping stimulation or notifying their treating ED physician who can decide on

treatment at their discretion. For adverse events occurring at home, participants will have the option of presenting back to the ED or consulting with their family physician if these adverse events are intolerable or serious:

Warmth Sensation: Two studies with adult migraine participants indicated that about 2.4% of participants reported feeling a warm sensation when using the REN device.[57,62]

Arm/Hand Numbness: A single study examining adult migraine had 0.8% of participants report numbness in the arm or hand when using the REN device to treat their migraines.[57]

Arm/Hand Redness: Two adult migraine studies indicated that 1.6% of participants reported redness in their hand or upper arm when using the REN device.[57,62]

Arm/Hand Pain: One adult migraine study and one pediatric migraine study reported that approximately 2% of participants reported pain in their hand or arm when using the REN device.[57,64] However, both studies indicate that this pain was temporary, considered to be mild, and resolved within 24 hours without the need for medical intervention.

Itching: One adult migraine study had a single participant (0.8%) report an itching feeling when using the REN device.[57]

Muscle Spasms: The same study as described above also had a single participant (0.8%) experience muscle spasms when using the REN device.[57]

11.4. Methods and Timing of Safety Assessments and Follow-Up

For the study, assessment of adverse events will occur at each time point while the participant is in the ED (60 and 120 minutes, 60 and 120 minutes post-crossover intervention, or at discharge if before the initial or post-crossover 120 minute time point). The participant will also be asked to indicate if they have experienced any adverse events when they are contacted for the 48-hour follow-up assessment. Participants who indicate they have experienced adverse events will be asked to describe the adverse events, either in writing if completing the electronic assessment or verbally if completing the assessment over the phone. Participants who complete the assessment electronically, and indicate they have experienced adverse events of concern (i.e., that require more information or follow-up), will be contacted by phone to obtain more information about the adverse events. The Qualified Investigator or co-investigator will determine if each adverse event is related to the investigational product.

Any participants that report experiencing adverse events prior to being discharged from the ED will only have the option of completing the 48-hour follow-up over the phone, rather than electronically. This will be done to ensure that all reported adverse events are thoroughly described during the 48-hour follow-up. Further follow-ups beyond the initial 48-hours will occur as needed should any adverse events not stabilize or resolve prior to

the 48-hour follow-up. How and when further follow-ups occur will be at the discretion of the Qualified Investigator. If deemed necessary by the Qualified Investigator, in-person follow-ups may be required to ensure the health and safety of participants.

11.5. Definitions Pertaining to Adverse Events

Starting from the time participants provide informed consent until the conclusion of the 48-hour follow-up, adverse events will be monitored and recorded. Adverse events will be described according to the definitions provided by the International Conference on Harmonization (ICH E2A topic):

Adverse event: Any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Adverse drug reaction: Any response to a drug, biologic, or natural health product which is noxious and unintended, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function. A reaction, as opposed to an adverse event, is characterized by the fact that a causal relationship between the product and the occurrence is suspected (i.e. judged to be at least a reasonably possibility).

Important medical events are those that may not be immediately life-threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent a serious outcomes. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Unexpected adverse drug reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. the Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Unanticipated problem: Any incident, experience, or that meets **all** the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:

    - the research procedures that are described in the protocol-related documents, such as the CHREB-approved research protocol and informed consent document, or the Investigator Brochure
    - the characteristics of the research participant population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the [investigational product(s)] or procedures involved in the research)
- Suggests that the research places research participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious adverse event: Adverse events will be classified as serious or non-serious. A serious adverse event is defined as any adverse event that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

The **severity** of an adverse event will be determined by the investigator, who should use the following definitions when assessing the intensity of an adverse event:

- **MILD**: Participant is aware of symptoms or has minor findings but tolerates them well and no or minimal intervention required
- **MODERATE**: Participant experiences enough symptoms or findings to require intervention
- **SEVERE**: Participant experiences symptoms or findings that require significant intervention

An event will be qualified as **unexpected** when the specificity or severity of the event is not consistent with the package inserts or investigational brochure for the drugs under study.

Causality will be determined by the following question, where an affirmative answer designates the event as a suspected adverse reaction: Is there a reasonable possibility that the drug caused the event? ''Reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the specific adverse event being assessed.

In relation to the **identification of adverse events**, some participants in this study will have pre-existing medical conditions and those pre-existing conditions will not be considered as adverse events. New events that occur or the worsening in frequency or

intensity of pre-existing conditions will be reported as adverse events (Schedule of Events). All reportable events as defined above, determined to be an adverse event based on physical examination, laboratory findings, or other means will be recorded in the source documents and entered in the CRF. Each event will be recorded on an adverse event CRF starting after first dose of study drug has been delivered. The investigator will provide date of onset and resolution, severity, action(s) taken, changes in study drug dosing, causality to study drug, and outcome.

For **follow-up of adverse events, a**ny safety event that is identified at the last assessment (or an early termination) will be recorded on the CRF with the status of the safety event noted. All serious suspected adverse reactions and serious adverse reactions will be followed until resolution or until the patient is medically stable.

11.6. Recording and Reporting of Adverse Events

All adverse events, adverse drug reactions and unanticipated problems will be recorded on the electronic adverse event data collection form (see Appendix W), which will be stored in REDCap. Only adverse drug reactions that are ***both*** serious and unexpected are subject to expedited reporting to Health Canada.

Expedited reporting of reactions which are serious but expected is not required. Expedited reporting is also inappropriate for serious events from clinical investigations that are considered unrelated to the study product, whether or not the event is expected.

During this trial, the sponsor (University of Calgary) will inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada:

- where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information
- where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information
- within 8 days after having informed Health Canada of the adverse drug reaction (ADR), submit as complete a report as possible which includes an assessment of the importance and implication of any findings

Each ADR which is subject to expedited reporting will be reported individually in accordance with the data element(s) specified in the Health Canada / ICH Guidance Document *E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*. The Council for International Organization of Medical Sciences (CIOMS) form 1 will be used for reported serious and unexpected adverse events (see Appendix X).

In situations when causality assessment and determination of expectedness is not straightforward, the report will be submitted in the expedited manner and the relevant issues will be outlined in a cover letter. Final reports of fatal or life-threatening reactions

will include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs.

In addition to the above, if any additional situations arise, appropriate scientific and medical judgment will be applied to determine if rapid communication to Health Canada is required. For example, information that might influence the risk-benefit assessment of a drug, or that would be sufficient to consider changes in drug administration, or in the overall conduct of a clinical trial, represent such situations where rapid communication to Health Canada will occur; including:

- for an "expected" serious ADR, an increase in the rate of occurrence which is judged clinically important.
- a significant hazard to the patient population, such as lack of efficacy with a drug used in treating a life-threatening disease.
- a major safety finding from a newly completed animal study.

As per the ICH Good Clinical Practice Guidelines stipulations, the Conjoint Health Research Ethics Board will establish, document in writing and follow procedures for:

- Determining the frequency of continuing review as appropriate (including adverse drug reactions and adverse events).
- Requiring that the **Investigator** should promptly report to the CHREB.
    - Changes increasing the risk to participants and/or significantly affecting the conduct of the trial.
    - All adverse drug reactions that are both serious and unexpected.
    - New information may adversely affect the safety of the participant or the conduct of the trial.

In additions to the reporting to Health Canada as described above, all serious adverse events that occur at the Alberta Children's Hospital along with any adverse events that are both serious and unexpected, will be reported to the CHREB.

With regards to device-related adverse events, serious adverse events related to the REN (Nerivio™) device will be reported to Health Canada, the CHREB, and the manufacturer and importer within 72 hours of discovery. This includes cases in which the incident:

a. is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use, and

b. has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur.

In these cases, a preliminary and a final report in respect of the incident will be submitted:

a. within 10 days after the manufacturer or importer of a medical device becomes aware of an incident, if the incident has led to the death or a serious deterioration in the state of health of a patient, user or other person, or

b. within 30 days after the manufacturer or importer of a medical device becomes aware of an incident, if the incident has not led to the death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur.

11.7. Treatment Discontinuation

In the study, participants will receive either a one-time dose of a combination of metoclopramide and ketorolac, or a single 45-minute electrical stimulation session from the REN device, or each intervention should they enter the crossover phase, and placebo treatment/sham device. However, participants will be able to withdraw from the study at any point. At the discretion of the attending ED research nurse and physician, further treatments will be administered to participants who withdraw from the study to ensure proper treatment and management of pain and symptoms associated with an acute migraine attack.

11.8. Premature Study Discontinuation for Individual Participants

A participant will be permanently discontinued from the study when:

- Consent is withdrawn by the participant (ie. the participant requests to discontinue their participation)
- The investigator believes that ongoing participation in the trial will either pose a significant risk to the participant, invalidate the results of the study or involve a high risk of self-harm
- Loss to follow-up involving absence of all feasibility, acceptability, efficacy, and safety assessments, and follow-up assessments, for any reason

11.9. Protocol Deviations and Violations

A protocol deviation is defined as any modification or alteration of the CHREB approved protocol. A major deviation is defined as a modification or alteration of the REB approved protocol involving a potential impact on the participants' safety, rights, welfare, or a potential impact on the integrity of the data. A minor deviation is defined as a modification or alteration of the CHREB approved protocol involving no significant impact on the study.

No deviations from the protocol will occur prior to having received written permission from CHREB, except where required to protect participants from hazards or where the deviation is limited to a logistical or administrative aspect of the trial. In such instances, CHREB will be notified as soon as possible about the deviation.

12. Data Handling and Record Keeping

12.1. Data Collection

For the study, data collected for participants in the ED will either be collected electronically or by the ED research nurse, depending on how the participants wants to complete the assessments. Depending on the participant's preference, data from the 48-hour follow-up will either be collected electronically or will be collected during a telephone call by the research assistant. Participants, the research nurse, and the research assistant will be blind to the randomized treatment group and will be asked to report and assess all outcomes. All data, whether collected electronically or otherwise, will be transferred into a dedicated, validated REDCap database.

REDCap is a secure, web-based application hosted by the Clinical Research Unit in the Faculty of Medicine at the University of Calgary that is compliant with ICH Good Clinical Practice Guidelines section 5.5.3. REDCap is designed for the purposes of capturing data for research studies. REDCap provides:

- an intuitive interface for data entry (with data validation)
- 128-bit encryption between the data entry client and the server (https)
- audit trails for tracking data manipulation and export procedures
- automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R)
- procedures for importing data from external sources
- advanced features, such as branching logic and calculated fields

12.2. Confidentiality

All participant information will be kept strictly confidential. Study data will be entered into an electronic data capture system, REDCap, as described above. All data entered into REDCap will be de-identified and coded using a numeric code only. Access to REDCap is password-encrypted and only granted to research staff.

Upon request, participant records will be made available to the sponsor (University of Calgary), Health Canada or other applicable regulatory agencies.

12.3. Record Retention

Study records will be retained for 15 years in accordance with Division 5 of Health Canada's Food and Drug Regulations.

13. Quality Control and Quality Assurance

13.1. Study Monitoring Plan

The study will comply with the ICH Good Clinical Practice Guidelines, the requirements of the CHREB and Division 5 of Health Canada's Food and Drug Regulations.

A study binder detailing all standard operating procedures and including a copy of the protocol will be kept on site and accessible to all research personnel. Prior to trial commencement, the site investigators will give a presentation to the research personnel outlining the study protocol, documentation, and reporting procedures.

Research personnel will maintain study records that are complete, legible, and accurate so as to allow for appropriate interpretation, reporting and verification of study records.

Monitoring for this protocol will be coordinated by the sponsor-investigator. A study monitor will monitor the study regularly. The plan will consist of monitoring for CHREB and regulatory compliance on-site and remotely, to ensure that the rights and well-being of participants are protected and reported data are accurate, complete, and verifiable from source documents, along with the trial being conducted in compliance with the currently approved protocol and other applicable regulatory requirements. The peer monitoring activities will consist of, but not be limited to verification of:

- the investigator has adequate qualifications and resources.
- the investigational product(s) are stored, supplied, returned/disposed as per protocol and applicable regulatory requirement(s).
- the investigator follows the approved protocol and all protocol amendments.
- the written informed consent was obtained before each participant's participation and was re-consented when amendments were made in the trial.
- the investigator receives current protocol amendments, all documents, and all trial supplies needed to conduct the trial properly.
- the investigator and the investigator's trial staff are adequately informed about the trial.
- the investigator and the investigator's trial staff are performing the specified trial functions in accordance with the protocol and written agreements.
- the investigator is enrolling only eligible participants.
- the participant recruitment rate.
- the source documents and the other trial records are accurate, complete, and kept up-to-date and maintained.
- the investigator provides all the required reports, notification, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated and identify the trial.

- checking the accuracy and completeness of the electronic CRF entries, source documents and other trial-related material.
- informing the investigator of any electronic CRF entry error, omission, or illegibility in writing.
- determining whether all adverse events are appropriately reported within the time periods required by GCP, the protocol, the CHREB, the sponsor, and applicable regulatory requirements.
- determining whether the investigator is maintaining the essential documents.
- communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

13.2. Safety Monitor

The study's safety monitor will be a neurologist with extensive clinical trial experience from the Hotchkiss Brain Institute at the University of Calgary (or someone with comparable experience with clinical trials who practices within Canada, should the identified individual have to cease their duties for personal or other reasons). This individual will review the protocol prior to initiation of recruitment. Should this individual have concerns about the protocol, they will bring those concerns up to the study team and suggest appropriate actions. After this individual has approved the protocol and recruitment has begun, they will review study progress and data as necessary thereafter, if safety issues arise.

Any safety concerns raised by clinical or research staff will be reported to the safety monitor by the investigators in a written report as soon as possible. All serious adverse events will be brought to the attention of the safety monitor immediately by the Qualified Investigator, who will also send a report to Health Canada (see section 11.4), as applicable. Once safety issues have been brought to the attention of the safety monitor, should the safety monitor review the data and identify concerning trends in adverse events or should a serious adverse event requiring unblinding occur, they will contact the research pharmacists and the research team, at their discretion, to access participant information if required for safety reasons. The safety monitor will make recommendations regarding early trial termination. Should the safety monitor decide for early trial termination or should they identify major concerns relating to safety in relation to the trial, the safety monitor will prepare a written report and communicate the plans or findings both verbally and in written form to the study investigators.

13.3. Ethical Considerations

13.3.1. General Principles

This trial will be carried out according to the principles outlined in the Declaration of Helsinki,[117] the ICH Good Clinical Practice Guidelines[75] and the Division 5 of Health Canada's Food and Drug Regulations. The institutional policies of the CHREB will also be followed.

Prior to initiating the study, written approval from the CHREB will be sought. Protocol deviations will only be implemented following approval from the CHREB, except where the investigators are concerned about potential hazards to the participants or where the deviations are logistical or administrative in nature.

13.3.2. Clinical Equipoise

While most of the research determining the effectiveness of the REN device to treat acute migraine attacks has been done in adult populations,[57,62,68,69,118] there is more recent work suggesting the REN device can effectively treat acute migraine attacks in children and adolescents at home.[64] However, there is a lack of evidence demonstrating the effectiveness of the REN device in treating acute migraine attacks in children and adolescents who are reporting to the ED. Recent research has focused on participants who were trained to treat their migraine attacks with the REN device at home, often using the device to treat multiple attacks across several weeks. Given that the nature of an acute migraine attack in the ED likely differs from acute attacks in non-ED settings[38,50] it is unclear how the migraine attack, and participants themselves, will respond to the REN device as ED treatment. As such, there is much uncertainty in how feasible, acceptable, effective, and safe the REN device will be when treating a pediatric population suffering from acute migraine attacks in an ED setting. The use of a placebo treatment and a sham device is crucial for comparing the REN device to standard of care treatments. (i.e., ketorolac and metoclopramide).

13.3.3. Informed Consent

Informed consent will be sought from all participants who are deemed to be capable of consenting (i.e., mature minors 14 years of age of over who want to and are capable of consenting on their own behalf). Additionally, informed assent will be sought from participants who are not deemed to be capable of consenting. Where participants are not deemed to be capable of consenting, the parent or guardian will carry out informed consent in their place. All elements pertinent to consent and assent will be explained verbally to the parents and participants by the PERT research nurse. Parents and participants will also be provided with a written informed consent form, and in applicable cases, with a written assent form. The consent and assent forms comply with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans[119] (see Appendix Y-AC). The consent and assent discussions and forms use simple language, written and expressed at grade levels recommended by the CHREB. Participants and their parents will receive a detailed explanation about potential harms incurred by the study, namely about potential side effects of metoclopramide, ketorolac, and the REN device, and delayed treatment of the acute migraine attack should the study interventions be ineffective. Anticipated benefits will also be discussed:

1) Direct benefits: Participants may potentially avoid side effects associated with a single-dose, IV administration of ketorolac and metoclopramide. They will also receive a $20 e-gift card of their choice upon completion of the 48-hour follow-up.

2) Indirect benefits: Participants will be involved in research to explore a non-IV, non-medication treatment to manage acute migraine attacks in children and adolescents reporting to the ED, potentially allowing for future patients to avoid the side effects associated with a single-dose, IV administration of ketorolac and metoclopramide.

13.3.4. Privacy and Confidentiality

Participant information will be coded using study identification numbers. Participant data will be entered into the REDCap study database using the study identification numbers. The Record ID form in REDCap will contain participants' names, dates of birth, and contact information. The purpose of this will be to identify participants for follow-up and to have adequate identifying and contact information available for the purposes of following up on adverse events as needed. The password-protected access to REDCap is granted to research staff only and is monitored by the Clinical Research Unit in the Faculty of Medicine at the University of Calgary. REDCap is housed in servers located in Canada and is firewall protected. Only the pharmacists carrying out randomization will have access to the participants' group assignments in case there are adverse reactions that require unblinding. The allocation list maintained by pharmacy will not contain identifiable information, but will contain the participant randomization code. This code will be used to identify participants for unblinding if needed for safety reasons (i.e., the randomization code assigned to the participant will be entered into REDCap, where identifying and contact information will also be stored, and this code will be linked to the assignment information provided by pharmacy).

14. Budget and Finance

This study is funded by a Canadian Institutes of Health Research Early Career Investigator Grant in Maternal, Reproductive, Child & Youth Health (funding reference number = 177445), and through Dr. Orr's start-up funds from the University of Calgary Department of Pediatrics and the Alberta Children's Hospital Research Institute. We have partnered with Theranica Bioelectrics Ltd for this study, who will also be offering 5,000$ of in-kind contributions towards to study in the form of active and sham REN devices for the trial. For knowledge translation, we have also partnered with SKIP, TREKK and the Alberta SPOR Support Unit's (AbSPORU) KT and patient engagement platforms, each of whom have contributed to design of our KT plan and who are providing in-kind support for our KT plans. The total estimated cost for this study will be 35,000$ of in-kind support, and 236,603.60$ of cash costs, over the planned 3 year study period (2 years of recruitment, and 1 year of preparation and study completion). Details regarding our budget are available in Appendix AD.

15. Publication Plan

A manuscript will be submitted for publication to a peer-reviewed medical journal and at least one conference abstract will be submitted for presentation. The listed investigators will participate in the drafting, review and dissemination of the manuscript and abstracts. Authors will be required to meet authorship criteria as laid out in the International Committee of Medical Journal Editors Guidelines (ICMJE).

16. Knowledge Translation Plan

16.1. Patients and Families

We will engage with patients throughout all study phases as part of our knowledge translation (KT) plan. We have already engaged with patients through our preliminary treatment preferences survey and our virtual patient engagement session, as previously described. During these endeavours, we received feedback from patient knowledge users that has directly informed the proposed project regarding device preferences and optimizing study design. We evaluated our patient engagement session using the Public and Patient Engagement Evaluation Tool (PPEET),[120] and found that this tool was easy to implement, and that it demonstrated clearly that the participants felt engaged and supported (Orr lab; unpublished).

To facilitate our ongoing patient engagement strategy and implementation, we have partnered with Solutions for Kids in Pain (SKIP), a knowledge mobilization network for which co-investigator Dr. Birnie is Assistant Scientific Director. SKIP has offered an in-kind contribution of 15,000$ and we will have engaged with a knowledge broker and patient engagement coordinator from SKIP to further develop and carry out our patient engagement strategy. We are also working with the Alberta SPOR Support Unit's (AbSPORU) KT and patient engagement platforms to optimize our KT and patient engagement strategies. We have identified two patient partners to engage with us regularly throughout the study to inform study design, execution, and translation for greater impact (e.g. recruitment, readability/understandability of materials, sharing of study findings). The patient partners will receive payment for their collaboration in accordance with SKIP's guidelines on patient partner reimbursement (i.e., 500$/year for each year of involvement with the study). The patient partners will also help to co-facilitate another patient engagement session once the pilot trial is complete to plan next steps (i.e., planning a multicenter trial and how to disseminate the pilot trial results in a patient-centered manner). We will again use the PPEET[120] to evaluate patient engagement at this stage.

For end-of-grant KT, our goal is to inform patients and families about our preliminary results and plans for future research. To achieve this, we will continue to work with SKIP and the AbSPORU, and we will also be working with Translating Emergency Knowledge for Kids (TREKK; www.trekk.com), a knowledge mobilization network focused on pediatric

emergency medicine that will be providing us with 5,000$ of in-kind support. We will leverage the SKIP, the AbSPORU, and the TREKK networks of partners and knowledge users (patients, caregivers, health professionals, decision-makers, and policymakers) to mobilize our study findings (e.g., webinars, media articles).

16.2. Research community and health care professionals

We are engaging with pediatric emergency researchers regularly through Pediatric Emergency Research Canada (PERC).[60] At the recent PERC annual meeting (February 3rd 2021), we presented our pilot protocol and engaged with pediatric ED researchers for feedback, which we have integrated into the proposal. We also presented to pediatric ED nurses and physicians at ACH to solicit their feedback. These engagements occurred during the May 6, 2021 Research Steering Committee meeting and the June 8, 2021 Quality Improvement Committee meeting. Feedback obtained from these meetings has been incorporated into the current protocol.

For our end-of-grant KT plan, we aim to disseminate the results of our pilot trial to the research community and to health care professionals, and to engage them in future plans arising from this pilot trial (i.e., if feasibility and acceptability are demonstrated, we will engage these knowledge users in multicenter RCT design and execution). To achieve these goals, we will publish the results of this pilot trial in an open access journal to disseminate our key findings and messages. We will present these results at local, national, and international clinical rounds and research conferences, including the PERC annual meeting and the American Headache Society annual meeting. We will engage clinicians and researchers through the SKIP and TREKK networks. National and international engagement will also occur through consultation with the Pediatric Canadian Headache Network (PeCaHN: https://headachesociety.ca/pecahn/), a national group of pediatric headache experts led by Dr. Orr, and the American Headache Society, of which NPA Dr. Orr is an emerging leader.

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