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A study protocol for two complementary trials of non-steroidal or opioid analgesia use for children aged 6 to 17 years with musculoskeletal injuries (The No OUCH Study)

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Title: A study protocol for two complementary trials of non-steroidal or opioid analgesia use for children aged 6 to 17 years with musculoskeletal injuries (The No OUCH Study)

Lay Title: Analgesia Use for Children with Musculoskeletal Injuries

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Author Contributions

Dr. Samina Ali (SA) developed and revised the protocol, co-drafted the protocol paper, and will operationalize the study. She chose the previously validated tools for measuring the primary and secondary efficacy outcomes (vNRS, VAS and FPS-R).

Manasi Rajagopal (MR) is the national study coordinator who contributed to study design, co-drafted the protocol paper and will operationalize the study.

Dr. Lawrence Richer (LR) and Dr. Christopher McCabe (CM) co-developed the novel study methodology and contributed to protocol revision

Dr. Andrew R. Willan (AW), Dr. Maryna Yaskina (MY), and Dr. Anna Heath (AH) led the statistical analysis planning and contributed to protocol revision.

Dr. Amy L. Drendel (ALD) is a fracture outcomes expert who contributed to determining the secondary outcomes for the study; she contributed to methodology and revised the protocol.

Dr. Serge Gouin (SG), Dr. Antonia Stang (AS), Dr. Scott Sawyer (DB), and Dr. Maala Bhatt (MB), as site leads for this study, reviewed and revised the protocol, with special input into the Methods section of the study.

Serena Hickes (SH) is a family representative who reviewed and provided input into the study protocol. She provided lived experience in patient-oriented outcomes.

Dr. Naveen Poonai (NP), Dr. Martin Offringa (MA), and Dr. Terry Klassen (TK) co-developed the methodology and revised the protocol.

All authors have approved this final version of the protocol. None of the authors have financial or other conflicts of interests as they pertain to this study and its involved recruitment sites.

ABSTRACT

Introduction. Musculoskeletal (MSK) injuries are a frequent cause for emergency department (ED) visits in children. MSK injuries are associated with moderate to severe pain in most children, yet recent research confirms that the management of children's pain in the ED remains inadequate. Clinicians are seeking better oral analgesic options for MSK injury pain with demonstrated efficacy and an excellent safety profile. This study aims to determine the efficacy and safety of adding oral acetaminophen or oral hydromorphone to oral ibuprofen and interpret this information within the context of parent/caregiver preference.

Methods and analysis. Using a novel preference-informed complementary trial design, two simultaneous trials are being conducted. Parents/caregivers of children presenting to the ED with acute limb injury will be approached and decide which trial they wish to participate in: an opioid-inclusive trial or a non-opioid trial. Both trials will follow randomized, double-blind, placebo-controlled, superiority-trial methodology and will enroll a minimum of 536 children across six Canadian pediatric EDs. Children will be eligible if they are 6 to 17 years of age and present to the ED with an acute limb injury and a self-reported verbal Numerical Rating Scale pain score ≥ 5. The primary objective is to determine the effectiveness of oral ibuprofen + oral hydromorphone versus oral ibuprofen + oral acetaminophen versus oral ibuprofen alone. Recruitment launched in April 2019.

Ethics and dissemination. This study has been approved by the Health Research Ethics Board (University of Alberta), and by appropriate ethics boards at all recruiting centers. Informed consent will be obtained from parents/guardians of all participants, in conjunction with assent from the participants themselves. Study data will be submitted for publication regardless of results. This study is funded through a Canadian Institutes of Health Research grant.

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Words: 295/ 300

Article Summary

Strengths and limitations of this study

1. Comparing the efficacy of adding oral acetaminophen or oral hydromorphone to oral ibuprofen for children's musculoskeletal injury, this study may lead to improved pediatric pain management in the emergency department.
2. This study employs a novel design involving two complementary, randomized controlled trials that will be run simultaneously.
3. Participating families will choose in which trial they wish to participate, thus engaging and empowering them as a key participant in healthcare research decision-making.
4. Given the current negative public opinion regarding opioids, we expect that some parents/caregivers will be hesitant to accept opioids thus leading to an imbalance in the pace of recruitment between the two trials.
5. Given the sample size, this study will not be able to provide definitive evidence regarding rare but serious adverse events.

BACKGROUND AND RATIONALE

Musculoskeletal (MSK) injuries are very common and are associated with moderate to severe pain for most children. [1, 2] Despite three decades of pain research in this area, recent evidence confirms that pediatric pain management in the emergency department (ED) is still suboptimal. [3-5] Previous studies have demonstrated that only 35% of children presenting to a pediatric ED with fractures or severe sprains received *any* analgesic. [6, 7] Further, a medical record review of two Canadian EDs showed unacceptably long delays in provision of initial analgesia, with children waiting a mean of 118 minutes to the provision of first analgesia. [6]

The American Academy of Pediatrics recommends acetaminophen, ibuprofen and opioids as the top three medication choices for the treatment of acute pain in children. [8] These are also the top three most commonly used ED for children with MSK injury. [3, 4, 6, 9, 10] However, there has recently been a concerted movement to limit opioid use in children, due, in large part, to the current Opioid Crisis.[11, 12] Clinicians are increasingly less likely to prescribe oral opioids to young children, and caregivers are increasingly less willing to administer them. [5] Coupled with the Opioid Crisis, the fear of adverse events, particularly respiratory depression and deep sedation, are another important reason to explain the reluctance of ED physicians to prescribe an opioid to children with moderate to severe pain. [13]

Clinicians are currently seeking optimal (and for many, non-opioid) oral analgesic options with the best efficacy and safety profile. It is known that the under-treatment of children's pain is partly due to a lack of evidence to support clinician decision-making in choosing the most effective medication. [4, 14] LeMay et al's recently published systematic review of MSK injury pain management concluded that an optimal analgesic agent or combination could not be identified at this time. [15] Very few pediatric studies of analgesic combination therapy for MSK injury exist, and extrapolation from adult data can be misleading, both in establishing the correct dose and in assessing child-specific pain reduction. [15-18] Previous research has demonstrated that a combination of oral morphine with ibuprofen was no more effective and was less safe than oral ibuprofen alone for children's suspected fracture pain. [16] Similarly, oxycodone was no more effective and was less safe than ibuprofen for post-discharge fracture pain. [19] There is some emerging work from non-ED settings to suggest that oral hydromorphone may be an effective alternative to oral morphine and oxycodone. [20, 21] Oral hydromorphone is a long-acting opioid analgesic with a duration of analgesic action of up to 4 hours and is more potent than oral morphine, but with fewer side effects. [22] Both oral hydromorphone and ibuprofen's peak analgesic action occurs at 60 minutes post administration.

The proposed study aims to determine if acetaminophen or hydromorphone, when added to ibuprofen, offers more clinical pain relief than ibuprofen alone, for children with an acute MSK injury. Further, it will determine if the combination of hydromorphone and ibuprofen is more clinically effective than the combination of acetaminophen with ibuprofen. This study, which will consist of two clinical trials, will inform health-care decisions by providing evidence for the effectiveness and safety of commonly prescribed

analgesic agents, and compare them to the most commonly used monotherapy, ibuprofen. [3, 6]

METHODS AND ANALYSIS

This study will be conducted with a novel preference-informed complementary trial design and is comprised of two simultaneous 'parallel' trials. Eligible parent/caregiver-child pairs will decide which trial they wish to participate in: a three-armed opioid-inclusive trial (the Opioid trial) or a two-armed non-opioid trial (the Non-Opioid trial). Once the family has chosen their preferred trial, conduct within each trial will follow traditional randomized, double-blind, parallel assignment, placebo-controlled superiority trial methodology. Study endpoints will be identical for both trials within this study. The study protocol is reported using the SPIRIT-PRO reporting guidelines. [23] (See Table 1 for study summary.)

Study Setting

This study will be conducted in six pediatric EDs across Canada: 1. Stollery Children's Hospital (Edmonton, Alberta) which will serve as the coordinating site, 2. Alberta Children's Hospital (Calgary, Alberta), 3. Winnipeg Children's Hospital (Winnipeg, Manitoba), 4. Children's Hospital at London Health Sciences Centre (London, Ontario), 5. CHEO (Ottawa, Ontario), and 6. Centre Hospitalier Universitaire Ste-Justine (Montreal, Quebec). The ED census for recruiting centers ranges from 30,000 to 80,000 patient visits per year. Study recruitment began on April 20, 2019 and is expected to be completed within 18 months.

Eligibility and Exclusion Criteria

Children will be eligible if they are 6 to 17 years of age, presenting to the ED with an acute limb injury (<24 hours old) that is neither obviously deformed nor having neuro-vascular compromise, and have a self-reported verbal Numerical Rating Scale pain score ≥ 5 at triage. This age group was chosen as fracture rarely occur under this age, and a consistent and validated pain measurement tool can be employed across this age category.

Children will be excluded if they meet any of the following criteria: (a) require immediate intravenous or intranasal pain medications (b) have known hypersensitivity to study medications, (c) receive acetaminophen or NSAID within three hours prior to recruitment, (d) receive opioids within one hour prior to recruitment, (e) parent/caregiver or child cognitive impairment precluding the ability to self-report pain or respond to study questions, (f) injury suspected to be due to non-accidental trauma or child abuse, (g) suspected multi-limb fracture, (h) chronic pain that necessitates daily analgesic use, (i)known hepatic or renal disease/dysfunction, (j) known bleeding disorder, (k) known pregnancy, (l) vomiting that precludes the ability to take oral medications, (m) parent/caregiver and/or child inability to communicate fluently in English or French in the absence of a native language interpreter, (n) parent/caregiver unavailable for follow-up, or (o) previous enrolment in this study.

Study Interventions and Rescue Medications

If a family chooses the **Opioid** trial, their child will be randomized to one of three treatment arms: (a) oral ibuprofen (10mg/kg, maximum 600mg) + acetaminophen placebo + hydromorphone placebo, OR
(b) oral ibuprofen (10mg/kg, maximum 600mg) + oral acetaminophen (15mg/kg, maximum 1000mg) + hydromorphone placebo, OR
(c) oral ibuprofen (10mg/kg, maximum 600mg) + acetaminophen placebo + oral hydromorphone (0.05mg/kg, maximum 5 mg).

If a family chooses the **Non-Opioid** trial, their child will be randomized to one of two treatment arms: (a) oral ibuprofen (10mg/kg, maximum 600mg) + acetaminophen placebo, OR
(b) oral ibuprofen (10mg/kg, maximum 600mg) + oral acetaminophen (15mg/kg, maximum 1000mg).

Given the consistent recommendations that ibuprofen be the first-line therapy for acute MSK injury pain, [15, 24-26] and the fact that it is the medication of choice for triage-initiated pain protocols at most Canadian pediatric EDs, [27] ibuprofen will serve as the comparator (standard of care) for both trials.

All study medications and placebos will be administered as a single oral dose in liquid form. No other medications will be administered as part of the study. However, enrolled patients will be eligible to receive additional analgesia at any time if requested by the child or family and/or deemed necessary by the clinical team. The treating physician will order rescue analgesia at their discretion. Any such co-interventions, including other non-pharmacologic interventions (e.g. ice, splinting) will be documented.

Randomization, Allocation Concealment, and Blinding
Randomization will be determined using a secure online centralized randomization tool hosted by the Women and Children's Health Research Institute (WCHRI, University of Alberta). [28] Participants will be allocated via a kit number. A statistician will oversee the generation of a randomized listing of the treatment by kit number using a 1:1:1 allocation scheme for the Opioid trial, and a 1:1 allocation scheme for the Non-Opioid trial. This will be further stratified by center using block-randomization with variable block sizes. These randomization lists, which will be sent directly by the statistician to the participating site's research pharmacy team, will be used by each participating site's research pharmacy to create pre-packaged, sequential study kits for each trial. Research nurses will then allocate the kits to enrolled participants in sequential fashion.

Study participants, research nurses (the outcome assessors), ED staff, and data analysts will all be blinded with respect to the intervention. In the rare occurrence where a treating physician needs to know what the child has received, the study blind can be broken by the clinical team for patient safety. The protocol for unblinding, if there is a risk to the participant whereby knowledge of the treatment arm will affect clinical decision-making, will involve the research nurse logging in to a secure web-based unblinding system with REDCap. However, only the treating physician will 'click' on the button to reveal the

study medications administered. Thus, parents/caregivers, children and research staff will remain blinded.

Recruitment and Data Collection

The patient's initial assessment upon arrival to the ED will be performed by a triage nurse. Triage nurses, research nurses, or their designate will identify potentially eligible participants. Research nurses will be present in enrolling EDs up to 16 hours a day to screen children and assess eligibility based on the inclusion and exclusion criteria outlined above. Research nurses will follow site-specific Research Ethics Board (REB) guidelines regarding approaching families for research studies. Verbal consent for screening will be obtained from families and documented. For eligible parent/caregiver-child pairs who express interest in study participation, an ED physician will confirm eligibility, and the research nurse or designate will complete consent and assent, as appropriate (Appendix 1).

After obtaining written informed consent from the parent/caregiver, and assent from the child where appropriate, the research nurse will determine the family's preference for study trial (ie. Opioid or Non-Opioid). If the family does not voice a preference, they will be enrolled in the Opioid trial as it contains all three possible medication combinations offered in the study. The research nurse will administer the study medications according to the randomization scheme for that chosen trial Figure 1). If a participant vomits within 30 minutes of drug administration, it will be repeated once in accordance with current clinical and research practice. [29] The parent/caregiver will be asked to complete a brief survey in the ED to explore their reasons for choosing their study trial (see Appendix 2 for case report form).

Following study drug administration, the research nurse will monitor the participant for up to 120 minutes, with safety and efficacy measures recorded at the time of recruitment (T-R), time of study drug administration (T-0), at 30 minutes, 60 minutes, 90 minutes and 120 minutes post-study drug administration (T-30, T-60, T-90, T-120 respectively), at the time of medical examination (T-ME) and as soon as possible following x-ray (T-XR). All study measures at T-30, T-60, T-90, and T-120 will be collected within 15 minutes of the designated time point (i.e. $\pm$ 15 minutes). All study measures for T-ME and T-XR will be collected within 30 minutes of the designated time point. If a patient is discharged prior to T-120, the study measures will be recorded one last time at the time of discharge.

Pain scores will be measured on the verbal Numerical Rating Scale (vNRS), Visual Analog Scale (VAS), and Faces Pain Scale-Revised (FPS-R) at each study time point. [30, 31] In addition, the research nurse will also evaluate the presence of adverse events (e.g. nausea, vomiting), record vital signs (pulse, blood pressure, respiratory rate, oxygen saturation) and evaluate sedation level using the Ramsay Sedation Scale (RSS). [32] Reporting of adverse events will be in keeping with Health Canada regulations and REB guidelines. Prior to their discharge from the ED, both the child and parent/caregiver will be asked to rate acceptability of the study medication received during the trial using a Likert scale. (Figure 2)

Two brief 10-minute follow-up surveys will be completed with the parent/caregiver following their child's discharge from the ED. Parents/caregivers will have the option of completing these over the phone or online via a secure email link. Non-responders to email contact and those who prefer phone follow-up will be called 3-5 times depending on local REB requirements. The first follow-up survey, conducted at 1-3 days post ED discharge, will determine the occurrence of any adverse events since discharge. The second follow-up survey will be completed at 1-2 weeks post ED discharge, to determine parent/caregiver comfort and satisfaction with at-home pain management and the extent of functional limitations for their child.

To achieve adequate participant enrolment to reach target sample size, we will monitor the monthly recruitment targets and have regular (every 4-8 week) team meetings to allow for timely implementation of procedural changes. There are no plans for patient follow-up beyond the two-week study period, given that only one dose of study medications will be administered. All study scripts and data collection tools will be available in English and French.

Outcome Measures

The Primary Efficacy Outcome will be the self-reported vNRS pain score at 60 minutes post study drug administration. The vNRS, ranging from 0 (no pain) to 10 (worst pain imaginable), is the most commonly used, responsive pain measurement tool for the study age group. [33] It has been successfully employed in several children's pain studies, [34, 35] and is validated for the age range of children included in this study. [36] The 60-minute primary outcome time point reflects the peak plasma concentration and clinical action of both oral hydromorphone and ibuprofen. [22, 37-39]

The Principal Safety Endpoint will be the proportion of children with adverse events related to study drug administration. Medication safety profiles influence parent/caregiver and patient willingness to adhere to medication regimens. [40] It has also been previously established that more safety data is urgently needed to inform clinical decision-making when using the study medications of interest. [24]

The Secondary Outcomes will include efficacy, safety and preference endpoints:

Secondary Efficacy Outcomes

1. A vNRS pain score <3 at T-60
2. A vNRS pain score reduction of at least 2 points out of 10 at T-60
3. Pain scores at study time-points (T-30, T-60, T-90, T-120, T-ME and T-XR).
4. ED length of stay
5. Missed fractures or dislocations
6. Rescue analgesic in the 60 minutes following administration of study medication
7. Time to effective analgesia, defined as the first vNRS pain score <3 post-intervention
8. Children's self-reported pain intensity on the VAS and the FPS-R at all study time-points

Secondary Safety Outcomes

1. Any serious adverse events during the study period, including apnea, cardiac arrest, or death
2. A Ramsay Sedation Score between 1 to 3
3. Each specific adverse event type (e.g., nausea, dizziness, itchiness) during the study period

Secondary Preference Outcomes

1. Parent/caregiver reasons for choosing the opioid or the non-opioid trial
2. Self-reported parent/caregiver and child satisfaction with pain relief and acceptability of study medications, using a previously employed 5-point Likert scale [41]
3. Physicians' in-ED preference of analgesics for the patient
4. Parent/caregiver comfort treating their child at home, as measured by a scale created by the study team [5]

Sample Size

The sample size for the three-armed opioid trial is 105 patients per arm, for a total of 315. The sample size for the two-armed non-opioid trial is 85 patients per arm, for a total of 170. Thus, the total for the No OUCH Study would be 485. To account for missing data for the primary outcome due to early withdrawal, the study will over-recruit by approximately 10%, for a target recruitment of approximately 540 patients. This sample size was determined based on a two-sided level of 0.05, a power of 0.95, a minimally clinically important difference (MCID) of 1.5 on the vNRS, an estimate of the standard deviation (SD) of the difference of 2.7, [42] and a Bonferroni correction to adjust for the three treatment comparisons. Based on previously conducted survey work, [43] an imbalance in recruitment pace between the opioid and non-opioid trials is expected. However, both trials will continue to recruit until the sample size is met for both. One trial will over-recruit to allow for completion of the other, without compromising the key preference-based study design. To ensure timely completion of the No-OUCH Study, we will monitor the recruitment rates and potentially update the randomization strategy if there is an extreme over-recruitment for one of the trials.

Statistical Methods

All analyses will adhere to the principle of intention-to-treat. There will be three treatment comparisons: (1) ibuprofen versus ibuprofen plus acetaminophen; (2) ibuprofen versus ibuprofen plus hydromorphone; (3) ibuprofen plus acetaminophen versus ibuprofen plus hydromorphone. Due to homogeneity in the trial end-points for the two complementary trials, we will consider a joint analysis across both the endpoints if the two patient populations are sufficiently similar. This will be determined using previously specified decision rules.

For each treatment comparison, the primary analysis will compare the mean vNRS reduction for pain scores at T-60. This comparison will be facilitated using a linear mixed model with the T-0 measure on the vNRS for pain as a covariate and a site-specific effect. We will consider whether the two trials can be analysed together used nested linear mixed models with and without a trial by treatment interaction term. If this interaction term is not significant then a single treatment effect will be estimated for each

comparison. A two-sided level of 0.05 will be used to declare significance. A Bonferroni -Holm correction will be used to adjust for the three treatment comparisons. The proportion of children with a self-reported of vNRS of less than 3 at 60 minutes, the proportion who require a rescue analgesic by 60 minutes and the proportion who experienced adverse events related to study drug administration will be analyzed using a Mantel Haenszel chi-squared test, stratified by site. All other outcomes will be summarised using appropriate descriptive statistics.

There will be no interim analyses of the efficacy endpoints, as it is very difficult to change practice based on the results from small samples, regardless of the p-value. The Data Safety Monitoring Board (DSMB) will be provided with a masked comparison between treatment groups with respect to the safety endpoints at the intervals of their choosing. The decision to stop the trial for safety reasons will be left to the discretion of the DSMB (See Appendix 3 for DSMB Charter). Interim analyses will also monitor the relative recruitment rate of the two trials. If insufficient participants are enrolled on either of the No OUCH trials, appropriate action will be taken to ensure sufficient power to conclude following the completion of the trials. Further information is available in the Statistical Analysis Plan, which will be published separately.

Health Economic Methods

The trial will also examine the relative cost-effectiveness of each of the medication options. The economic evaluation will take a healthcare perspective for the reference case, in line with CADTH guidance [44] and in secondary analyses will consider societal costs. Information will be collected on interventions during ED visit, in hospital medication costs, and follow up care from other health services, as well as on costs incurred by families in interacting with health services. Quality of life will be measured by asking parents/caregivers to report their child's quality of life using a 10-point numeric scale. The health economic analysis will estimate the expected cost per incremental change in quality of life and will use nonparametric bootstrapping methods to calculate uncertainty to assist in decision making about the value of providing different treatment strategies.

Patient and Public Involvement

The team's patient engagement partner (SH) has provided ongoing input on the study protocol and data collection tools. The study team was also supported by parent advisory groups at the ECHO (Evidence in Child Health to Enhance Outcomes) Research Program (Edmonton, Alberta) and TREKK (Translating Emergency Knowledge for Kids) (Winnipeg, Manitoba). Parent advisors reviewed and provided feedback on the wording, readability, sensitivity, flow and content of parent/caregiver surveys. Following recruitment completion, parent advisors will be engaged in focus groups to discuss study results and dissemination plans in the context of family-centered care.

Data Management

Data management services will be provided by the WCHRI data coordinating centre. Study data will be entered and managed using REDCap (Research Electronic Data Capture) tools hosted and supported by WCHRI.[45] WCHRI's REDCap installation is a

validated electronic, web-based data capture system housed in a secure data center at the University of Alberta.

Data will be entered directly into the study database or, in case of technical failure, it may be collected on paper and then digitally recorded in REDCap. Selected data elements will be validated electronically on an ongoing basis throughout the study and any discrepancies will be assigned to members of the study team for resolution. REDCap includes internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate (see Appendix 4 for data management plan).

Only limited identifiable data will be stored in REDCap (e.g. email address) for the purposes of completing follow-up surveys. Study participants' contact information will be stored securely at each clinical site for internal use during the study. Paper records (e.g., signed consent and assent forms) will be stored in a secure locked cabinet at each site, with limited access by the research team only. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Monitoring

Monitoring for quality and regulatory compliance will be performed by the University of Alberta's Quality Management in Clinical Research (QMCR) office. QMCR is an independent unit housed within the university's central administration that provides arms-length review of all University of Alberta sponsored trials, at least three times per year. Details of clinical site monitoring will be documented in a Clinical Monitoring Plan.

Safety oversight will be under the direction of a DSMB which will function independently of the investigators. This committee will be chaired by Dr. Garth Meckler (Division Head, BC Children's Hospital, Vancouver, British Columbia), and is composed of 5 individuals with expertise in trial methodology, epidemiology, biostatistics, and pediatric emergency medicine. The DSMB will meet at least semi-annually to assess safety and efficacy data and will operate under the rules of an approved charter/ terms of reference.

ETHICS AND DISSEMINATION

Based on previously conducted research with oral opioids, [16, 24, 46] nausea, mild dizziness, and drowsiness are expected to be possible non-serious adverse events in this study. There is a small potential risk of respiratory depression following the administration of any opioid, although the risk is notably greater with repeat dosing and intravenous administration. This risk will be minimized by using only a single oral dose and vigilantly monitoring the participant's vital signs and level of sedation during the study period, which extends for one hour past the peak action point of the drugs.

This study will be federally monitored by Health Canada, and approval has been granted for the conduct of this study (HC6-24-c220455). The Health Research Ethics Board Biomedical Panel at the University of Alberta has further approved this study

(Pro00073476). The five other participating centers acquired ethics approval from their local IRBs prior to commencing recruitment. Any protocol amendments will be submitted for Health Canada review and IRB approvals prior to implementation and will be added as an amendment to the clinicaltrials.gov registration. Institutional approvals from each participating pediatric ED will be obtained prior to beginning recruitment.

Public opinion regarding opioids is notably negative at this time, thus there is a hesitancy to accept opioids, even when they are felt to be clinically indicated. As such, it is expected that some parents/caregivers will be hesitant to accept opioids. [47-49] However, the study will leverage this opportunity to *understand* parent/caregiver perspectives and rationale for their decision-making. This valuable information can then inform knowledge translation of study results, educational initiatives and responsive healthcare provider prescribing of analgesia.

The study team plans to publish this trial in a high-impact, peer-reviewed journal and present the results at national and international meetings; authorship eligibility will be determined by employing the International Committee of Medical Journal Editors' recommended guidelines. [50] Statistical code and dataset can be made available upon request.

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Competing Interests None declared.

Patient Consent After assessing child eligibility based on the outlined inclusion/exclusion criteria, research nurses will obtain parent/caregiver consent (and assent for children 7 years and older) prior to recruitment of each patient. The research nurse will provide the parent/caregiver and child with both a verbal and written explanation of the study and an opportunity to review the information and consent/assent forms privately. They will then return shortly afterwards to answer any questions the family might have and obtain written consent and assent.

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Figures Legend

Figure 1. Study Interventions

Figure 2. Schedule of Study Measures

Table Legend

Table 1. WHO Trial Registration Data Set

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Table 1. WHO Trial Registration Data Set

Data Category	Information
Primary Registry and Trial Identifying Number	clinicaltrials.gov NCT03767933
Date of Registration in Primary Registry	December 7, 2018
Secondary Identifying Numbers	University of Alberta Research Ethics Board # Pro00073476
Source(s) of Monetary or Material Support	Canadian Institutes of Health Research SPOR Innovative Clinical Trials Grant (MYG-151207)
Primary Sponsor	University of Alberta
Secondary Sponsor(s)	-
Contact for Public Queries	Dr. Samina Ali 780.248.5575 sali@ualberta.ca
Contact for Scientific Queries	Dr. Samina Ali 780.248.5575 sali@ualberta.ca
Public Title	The No OUCH Study
Scientific Title	A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Study
Countries of Recruitment	Canada
Health Condition(s) or Problem(s) Studied	Acute musculoskeletal injury
Intervention(s)	**Opioid Trial**: A. Oral hydromorphone (0.05mg/kg, max 5mg) + Oral ibuprofen (10mg/kg, max 600mg) B. Oral acetaminophen (15mg/kg, max 1000mg) + Oral ibuprofen (10mg/kg, max 600mg) **Non-Opioid Trial**: Oral acetaminophen (15mg/kg, max 1000mg) + Oral ibuprofen (10mg/kg, max 600mg) (Comparator for both trials: Oral ibuprofen 10mg/kg, max 600mg)
Key Inclusion and Exclusion Criteria	To be eligible to participate in this study, an individual must meet all of the following criteria: 1.Child aged 6-17 years, 2. Presenting to the emergency department with an acute limb injury (<24 hours old) that is neither obviously deformed nor having neuro-vascular compromise (as assessed by the triage nurse), 3. Self-reported pain score ≥ 5 on the 0 to 10 verbal Numerical Rating Scale at triage Exclusion criteria include: 1. Deemed to require immediate intravenous (IV) or intranasal (IN) pain medications by the clinical team, 2. Previously known hypersensitivity to study medications, 3. Acetaminophen or NSAID use within 3 hours prior to recruitment, 4. Opioid use within 1 hour prior to recruitment, 5. Caregiver and/or child cognitive impairment precluding the ability to self-report pain or respond to study questions, 6. Injury suspected to be due to non-accidental trauma/ child abuse (as assessed by the triage nurse or reported by the family), 7. Suspected multi-limb fracture, 8. Chronic pain that necessitates daily analgesic use, 9. Hepatic or renal disease/dysfunction, 10.

	Bleeding disorder, 11. Known pregnancy, 12. Vomiting that precludes the ability to take oral medications (as determined by the family), 13. Caregiver and/or child inability to communicate fluently in English or French in the absence of a native language interpreter, 14. Caregiver unavailable for follow-up, or 15. Previous enrolment in the NO OUCH study
Study Type	Randomized, Double-Blind, Placebo-Controlled Superiority Trials
Date of First Enrollment	April 20,2019
Sample Size	536
Recruitment Status	Actively recruiting
Primary Outcome(s)	The **Primary Efficacy Outcome** will be the self-reported pain score at 60 minutes, using an 11-point 0-10 verbal Numerical Rating Scale (vNRS).
Key Secondary Outcomes	The **Principal Safety Endpoint** will be the proportion of children with adverse events related to study drug administration.
Ethics Review	University of Alberta Research Ethics Board # Pro00073476
Completion date	-
Summary Results	-
IPD sharing statement	De-identified data can be shared, on a case-by-case basis, upon discussion with the principal investigator.

Figure 1. Study Interventions

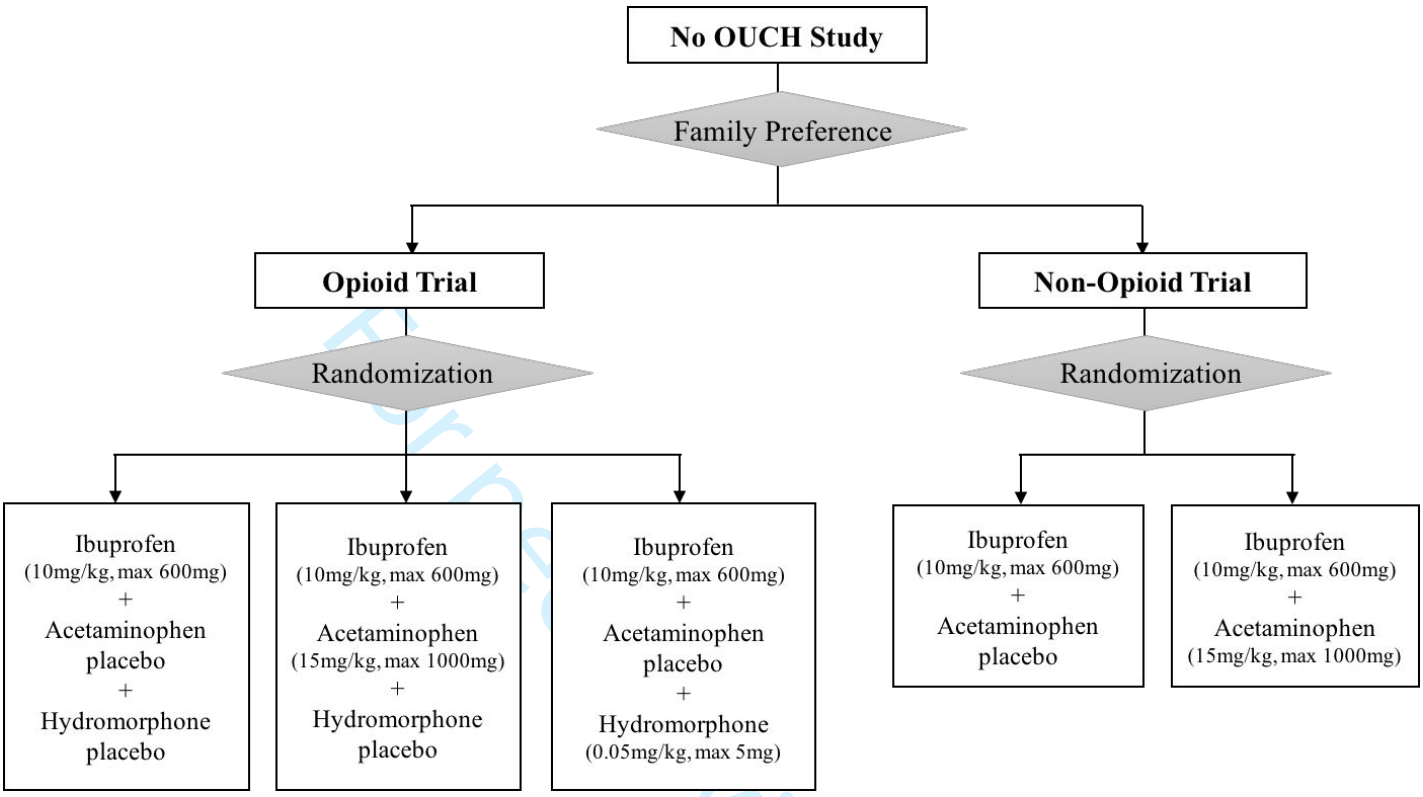
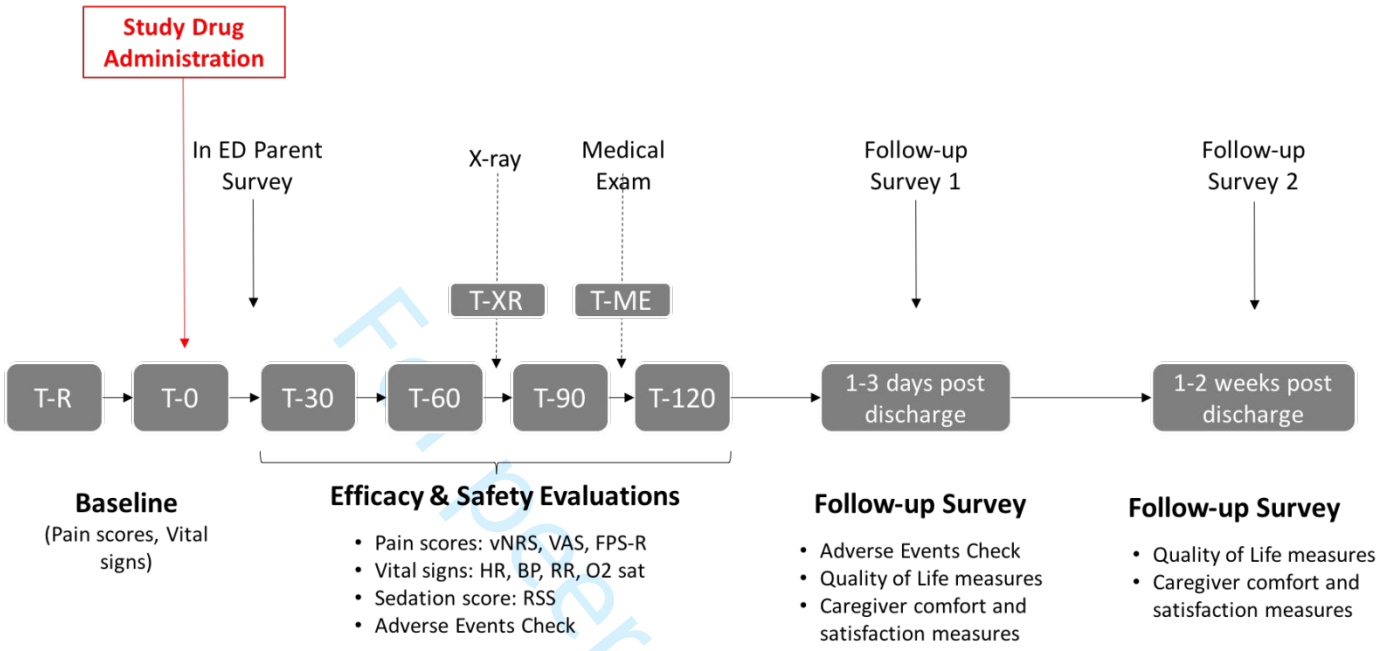


Figure 2. Schedule of Study Measures



vNRS=verbal Numerical Rating Scale; VAS=Visual Analog Scale; FPS-R=Faces Pain Scale-Revised; RSS=Ramsay Sedation Scale

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PARENT/GUARDIAN CONSENT FORM

Title of Study: A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries

Principal Investigator: Dr. Samina Ali (780) 248-5574
Research Coordinator: Ms. Manasi Rajagopal (780) 248-5440

Why am I being asked to consider this research study?
You are being asked if you and your child would like to be part of a research study. In this study, we are trying to determine the best ways to treat children's pain due to a limb injury. You are being asked to take part as your child may have pain due to an injury and is between 6 and 17 years old.

Before you make your decision one of the research team members will review this form with you. A copy of this sheet will be given to you to keep. If you would like more information, please feel free to ask. You are encouraged to ask questions if you feel anything needs to be made clearer. Please take the time to read this document carefully.

If your child is old enough to understand this information we would also like you to talk to them about being part of the study. If your child is 7 years of age or older, we would like you both to sign a form if you would like to participate in the study.

What is the reason for doing the study?
The purpose of this research study is to figure out which of three pain medicines best treats a child's pain. The pain medicines we are studying are ibuprofen (Advil/Motrin), acetaminophen (Tylenol/Tempra), and hydromorphone (Dilaudid). Ibuprofen and acetaminophen are the top two medicines used in the world and are approved for children's pain in Canada. Hydromorphone is used and approved for treating many kinds of children's pain in Canada, and we have received Health Canada approval to study it for the pain of limb injuries, since Canada has not yet approved it specifically for this problem. This study will help us figure out which pain medicine or combination of pain medicines works best for children with limb injuries. We would also like to understand the thoughts and feelings you have when making decisions about pain medication for your child.

This study is being conducted in six children's hospitals across Canada, and we will ask a total of over 500 children to be part of this study. Approximately 100 of these children will be recruited from the Stollery Emergency Department.

What will happen in the study?
If you agree to take part in this study, we will ask you to select which one of our two study groups you would like to be enrolled in: Group 1 OR Group 2. Regardless of which study you choose, your child will, at minimum, receive ibuprofen (Advil/Motrin) for their pain.

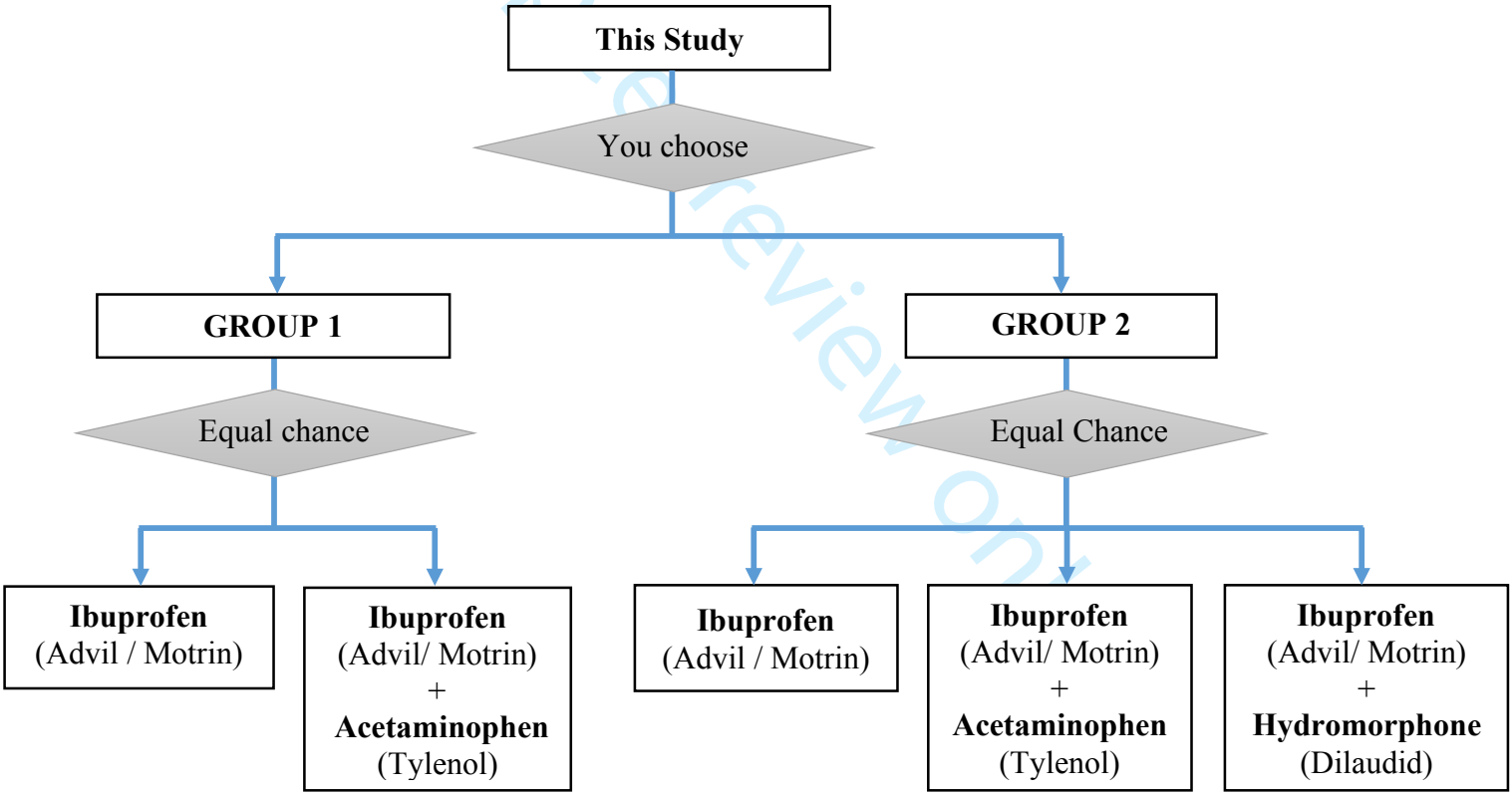
If you select **Group 1**, your child will have an equal chance of receiving one of the two medicine options below. This will be decided by the computer at random, so there is an equal chance of receiving either option, like the toss of a coin.

1. Oral liquid Ibuprofen (Advil/Motrin) only OR
2. Oral liquid Ibuprofen (Advil/Motrin) and oral liquid acetaminophen (Tylenol/Tempra)

If you select **Group 2**, your child will have an equal chance of receiving one of the following three medicine options:

1. Oral liquid Ibuprofen only (Advil/Motrin) OR
2. Oral liquid Ibuprofen (Advil/Motrin) and oral liquid acetaminophen (Tylenol/Tempra) OR
3. Oral liquid Ibuprofen (Advil/Motrin) and oral liquid hydromorphone (Dilaudid)

If you don't have a preference for a study group, we will assign you to Group 2, as this group includes all three of the options you might be offered when participating in this research study.



All children in the study will receive ibuprofen (Advil/Motrin), which is the standard medicine given to children for injury-related pain. Some children will also receive either acetaminophen (Tylenol/Tempra) or hydromorphone (Dilaudid). Neither the study nurse nor your doctor will know which combination of medicines your child has received for the study, but if we need to know this for medical reasons we can find out. After the study medicines have been given, your child may also get further medicines, which are not part of the study, as routinely recommended by the emergency doctor who is taking care of your child.

During the study your child will be monitored closely by the study nurse. The study nurse will measure your child's heart rate, breathing rate, blood pressure, oxygen levels, and pain levels every 30 minutes for up to 2 hours. They will also measure your child's pain when the doctor examines him/her and immediately following any X-ray procedures. If your child's medical care is finished before the 2-hour study period, and you are ready to leave, this is not a problem. Our research nurse will collect the measurements from your child one last time, and then you can go home, at your will. Participating in this study should NOT delay your leaving the emergency department or affect the timing of when the doctor will see you.

We will ask you to complete a short 5-minute questionnaire on an iPad, while you are in the emergency department today. This questionnaire will ask about your demographics, your child's injury and about your reasons for choosing your study group (ie. Group 1 vs. Group 2). We will also complete two 5-10 minute follow up surveys to see how your child is doing. You will have the option of completing these by email (we will send you a link through a secure online portal called REDCap) or over the phone. The survey will be done 24 hours after you leave the emergency department, and again 1 week after. After the two surveys are done, your part of this study is done.

What are the risks and discomforts?
Your child may experience side effects from participating in this study. Some side effects are known and listed below, but there may be risks in this study that are currently not known. If we find out anything new during the course of this study that may change your willingness to be in the study, we will tell you about these findings.

Based on our team's previous work, we expect nausea, mild dizziness, and tiredness to be possible non-serious common side effects. It is possible that your child might experience this. There is a very rare risk of serious drowsiness and low breathing rate following the use of any opioid medicine; this is extremely rare when the medicine is taken by mouth, like it is in this study. Even though such events are very rare, we want to make sure that your child is safe at all times. So, our research nurse will be watching your child closely for these effects and will even use an oxygen monitor to closely observe them. If such an event were to occur, the emergency team of doctors and nurses would take care of your child, as they are already present in the department.

Finally, there is an extremely rare risk of an allergic reaction to one of the study medicines.

What are the benefits to my child?
Your child may not benefit directly from being in the study, but you will be helping us understand how to best treat pain in children who come to the emergency department.

What happens if my child is injured because of this research?
If your child becomes ill or injured as a result of being in this study, he/she will receive necessary medical treatment, at no additional cost to you. By signing this consent form you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities. Contact the principal investigator, Dr. Samina Ali, at 780-248-5574, if your child has suffered an injury. If required, go to the emergency department right away.

Do I have to take part in the study?
Being in this study is your and your child's choice. If you decide to be in the study, you can change your mind and stop being in the study at any time by letting the research nurse know. This will in no way affect the care or treatment that your child is entitled to.

Can our participation in the study end early?
In addition to you being able to stop the study at any time, the study doctor may withdraw your child from this study for reasons such as:

- Your child is unable to tolerate the study medication
- The study doctor no longer feels this is the best option for your child

If your child is removed from this study, the research team will discuss the reasons with you and plans will be made for your child's continued care outside of the study.

Are there other choices to being in this research study?
If you choose not to take part in this study today, your child's doctors and nurses will decide what medicines to treat your child's pain with.

What will it cost me to participate?
There will be no costs to you to be in this study.

Will my information be kept private?
During the study, we will be collecting health data about your child. We will do everything we can to make sure that this data is kept private. No data relating to this study that includes your child's name will be released outside of the study doctor's office or published by the researchers. Sometimes, by law, we may have to release your information with your name in it so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your health information is kept private.

The study doctor/study staff will look at your child's personal health records held at the hospital, and/or kept by other health care providers that your child may have seen in the past (i.e. your family doctor). Any personal health information that we get from these records will be only what is needed for the study.

During research studies, it is important that the data we get is accurate. For this reason, your child's health data, including their name, may be looked at by people from: the research team, the study sponsor (University of Alberta), the University of Alberta auditors, clinical trial monitors, and Research Ethics Board, and Health Canada. By signing this consent form you are giving permission for the study doctor/staff to collect, use and disclose information about your child from his/her personal health records, as described above.

After the study is done, we will still need to securely store your health data that was collected as part of the study. In Canada, the law says we have to keep the data stored for 25 years after the end of the study. The data we collect will be stored, in Canada, on a system called REDCap. It will be accessible to and managed by, staff at the Women & Children's Health Research Institute

at the University of Alberta. If you leave the study, we will not collect new health information about you, but we will need to keep the data that we have already collected.

After study completion, your study data may be used again by other researchers. Any of your personal information (i.e. your name, address, telephone number) that can identify you will be removed or changed before files are shared with other researchers. Researchers that wish to use study data must 1) have their new study approved by an ethics board; 2) sign an agreement ensuring your confidentiality and restricting data use to only the approved study.

What if I have questions?
If you have any questions about the research now or later, please contact the principal investigator Dr. Samina Ali at 780 248 5574, or the research coordinator Ms. Manasi Rajagopal at 780 248 5440.

If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780-492-2615. This office is independent of the study investigators.

A copy of this sheet will be given to you to keep. This study is funded by the Canadian Institutes of Health Research and the Women and Children's Health Research Institute. The Institution and study doctor are getting money from the study sponsor to cover the costs of doing this study. You are entitled to request any details concerning this compensation from the Principal Investigator.

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CONSENT

Title of Study: A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries

Principal Investigator(s): Dr. Samina Ali **Phone Number:** 780 248 5574
Research Coordinator: Ms. Manasi Rajagopal **Phone Number:** 780 248 5440

	Yes	No
Do you understand that you and your child have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you and your child are free to leave the study at any time, without having to give a reason and without affecting your child's future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your child's records, including personally identifiable health information?	☐	☐

Who explained this study to you? _____

I agree for my child and I to take part in this study, and I have the legal authority to give this consent.

Signature of Parent or Guardian _____

(Printed Name) _____

Date: _____ Time: _____: _____ AM / PM
(circle one)

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____

Date: _____ Time: _____: _____ (24h clock)
(dd / mmm / yyyy)

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A SIGNED COPY GIVEN TO THE RESEARCH PARTICIPANT

UNIVERSITY OF ALBERTA

FACULTY OF MEDICINE & DENTISTRY
DEPARTMENT OF PEDIATRICS

CHILD ASSENT FORM

Title of Study: A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

Principal Investigator: Dr. Samina Ali **Phone Number:** (780) 248-5574

Study Coordinator: Ms. Manasi Rajagopal **Phone Number:** (780) 248-5440

We want to tell you about a research study we are doing. A research study is a way to learn new information about something. Children do not need to be in a research study if they don't want to.

Why am I being asked to be in this study?

We would like to find out more about what pain medicine works best for children with sprains or broken bones. You are being asked to join the study because you have pain due to an injury. Over 500 kids will take part in this study.

If I join the study, what will I have to do?

If you and your parent agree to take part, we will ask you to do a few things:

- First, we will ask you to take some pain medicines.
- Then, we will ask you to tell us about your pain, how you are feeling, and if you have any bad effects from the medicines we gave you.
- While you are in the emergency department, we will also check your heart rate and breathing.
- After you leave here, we will call or email your parents tomorrow and again after 1 week, to see how you are doing.

Will any part of the study hurt?

No, but sometimes kids can feel a little bit tired or sleepy after taking pain medicine. It is possible that you might feel this, but your parents and the research nurse will be there to help you, if this happens.

Will the study help me?

If you take part in this study, we hope the medicine we give you will help you. Even if you don't take part in the study, you can still ask your nurse for pain medicine, if you need it.

Will the study help others?

This study will help us figure out the best way to take care of kids' pain in the future.

What do I get for being in this study?

There are no direct cash or gifts for you for helping with this study.

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Can I say no?
Yes, of course, you do not have to be in the study. It's up to you. If you do join the study, you can change your mind and stop being part of it at any time. No one will upset if you decide you don't want to do this study or if you decide to stop part way through. You can tell your parents, your doctor or the research nurse if you want to quit. Before you say **yes or no** to being in this study, the research nurse will answer any questions you have. If you join the study, you can ask questions at any time.

What other choices do I have if I say no to this study?
If you choose not to be this study, your doctor and nurse will decide what pain medicines to give you. The three medicines that we are using in this study are the most commonly used medicines for this type of injury.

Do my parents know about this study?
This study was explained to your parents and they said that we could ask you if you want to be in it. You can talk this over with them before you decide.

Who will see information about me?
The information collected about you during this study will be kept safe. Nobody will know it except the people doing the research. The study information about you will NOT be given to your friends or teachers or anybody else.

What if I have any questions?
You can ask your mom or dad about anything you don't understand. You can also talk to the research nurse who is here, today. Dr. Samina Ali is the main doctor in charge of this study. If you have any questions about this study that you didn't think of now, either you can call or have your parents call her at 780 248 5574. You will be given a copy of this paper to keep.

Would you like to take part in this study?

☐ **Yes, I will be in this research study.** ☐ **No, I don't want to do this.**

Child's Name	Signature of Child	Date	_____: _____ am / pm (circle one)

☐ Assent was obtained verbally Age at the time of assent: _____ years

Person obtaining Assent	Signature	Date (dd/ mmm/yyyy)	_____: _____ (24h clock)

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ ____ ____ ____ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

REDCap Forms: Summary

Time Point / Section	
Screening	➢ Pre-Screening ➢ Eligibility ➢ Informed Consent ➢ Evaluation 1 (TR) ➢ Injury Details and Previous History ➢ Medical Oversight of Screening
T0 (Time of Study Drug Administration)	➢ Selection of Family Preference ➢ Study Drug Administration ➢ Evaluation 2 (T0) ➢ Evaluation Time point Calculator (will be programmed in REDCap) ➢ Contact Information Sheet ➢ In PED Caregiver Survey
T30	➢ Evaluation 3
T60	➢ Evaluation 4
T90	➢ Evaluation 5
T120	➢ Evaluation 6
TME (Time of Medical Exam)	➢ Evaluation 7
TXR (Time of X-Ray)	➢ Evaluation 8
PRE-Discharge	➢ ED Discharge Evaluation (only complete if discharged before 120 min) ➢ Pre-discharge Questions (complete with ALL families)
POST-Discharge	➢ Post-discharge Questions
Follow-up Survey 1 (24h)	➢ Call Log ➢ Follow-up Survey 1 (24h)
Follow-up Survey 2 (1-2w)	➢ Call Log ➢ Follow-up Survey 1 (1-2w)
Logs	➢ Concomitant and Rescue Medications ➢ Adverse Events ➢ Protocol Deviations ➢ Unanticipated Problems ➢ Early Withdrawal Form

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	___ ___ ___ - ___ ___ ___ ___ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Pre-Screening (electronic SEMO Log)

Site	☐ Edmonton AB (1) ☐ Calgary AB (2) ☐ Winnipeg MB (3) ☐ Montreal QC (4) ☐ London ON (5) ☐ Ottawa ON (6)	
Name of Research Nurse completing screening / enrolment	First and Last Name	
Date and Time of Triage	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)	
Age	_____ years	
Sex	☐ Male	☐ Female
Was the family approached for this study?	☐ Yes	☐ No
If NO, specify reason and STOP HERE.	☐ Family refused overall consent to be approached for research ☐ Legal guardian not present ☐ RA busy with another study ☐ Did not meet eligibility criteria, specify _____ ☐ Other, Specify _____	
If YES, continue to Eligibility.		

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ ____ ____ ____ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Eligibility

Was verbal consent for screening obtained from the family? ☐ Yes ☐ No

Inclusion Criteria

1. Child aged 6-17 years	☐ Yes	☐ No
2. Presenting to the emergency department with an acute limb injury (<24 hours old) that is neither obviously deformed nor having neuro-vascular compromise (as assessed by the triage nurse)	☐ Yes	☐ No
3. Self-reported pain score ≥ 5 on the 0 to 10 verbal Numerical Rating Scale (vNRS) at triage	☐ Yes	☐ No

Exclusion Criteria

1. Deemed to require intravenous (IV) or intranasal (IN) pain medications by the clinical team	☐ Yes	☐ No
2. Previously known hypersensitivity to study medications	☐ Yes	☐ No
3. Acetaminophen or non-steroidal anti-inflammatory medication (NSAID) use, within 3 hours prior to recruitment	☐ Yes	☐ No
4. Opioid use within 1 hour prior to recruitment	☐ Yes	☐ No
5. Caregiver and/or child cognitive impairment precluding the ability to self-report pain or respond to study questions	☐ Yes	☐ No
6. Injury suspected to be due to non-accidental trauma/ child abuse (as assessed by the triage nurse or reported by the family)	☐ Yes	☐ No
7. Suspected multi-limb fracture	☐ Yes	☐ No
8. Chronic pain that necessitates daily analgesic use	☐ Yes	☐ No
9. Hepatic or renal disease/dysfunction	☐ Yes	☐ No
10. Bleeding disorder	☐ Yes	☐ No
11. Known pregnancy	☐ Yes	☐ No
12. Vomiting that precludes the ability to take oral medications (as determined by the family)	☐ Yes	☐ No
13. Caregiver and/or child inability to communicate fluently in English or French in the absence of a native language interpreter	☐ Yes	☐ No
14. Caregiver unavailable for follow-up	☐ Yes	☐ No
15. Previous enrollment in study	☐ Yes	☐ No

REDCap to display if family is eligible or not based on above answers. RRN to confirm below.

Is family eligible for study?	☐ Yes	☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	___ ___ ___ - ___ ___ ___ ___ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Informed Consent

Has written informed consent been obtained?	☐ Yes ☐ No
If NO, specify reason and STOP HERE.	☐ Declined consent ☐ Declined assent ☐ Other, please specify _____
If YES, specify the date and time of Informed Consent:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Has a copy of the signed informed consent been given to the family?	☐ Yes ☐ No
If no, specify reason:	
Has written assent been obtained?	☐ Yes ☐ No ☐ No, but verbal assent was obtained and documented
If no, specify reason and STOP HERE.	
Has a copy of the signed assent been given to the family?	☐ Yes ☐ No
If no, specify reason:	
Permission to contact for future studies?	☐ Yes ☐ No
[Stollery Site ONLY] Would you be interested in being contacted, later, about a second related study? We want to better understand how parents make medical decisions for their children when they are injured and have pain.	☐ Yes ☐ No

If ALL the inclusion and exclusion criteria are met AND written consent and assent have been obtained, please proceed.

If NOT, please STOP here.

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	___ ___ ___ - ___ ___ ___ ___ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 1 (TR – Recruitment)

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	
Date and Time of evaluation # 1:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs: *Record triage vital signs here.* ***Please measure a new set of vital signs if triage time is ≥60 minutes from time of recruitment.***	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?"* *Note: say "hurt" or "pain" whichever seems right for a particular child*	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ ____ ____ ____ **(site)** **(screening number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Injury Details and Previous History

Date and Time of Injury:	_____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock)

Location of Primary Injury: Please select the location of the PRIMARY injury (pick ONE only)	
☐ Single or Multiple Fingers (if ONLY injury) ☐ Hand ☐ Wrist ☐ Forearm ☐ Elbow ☐ Upper Arm ☐ Shoulder ☐ Collarbone	☐ Single or Multiple Toes (if ONLY injury) ☐ Foot ☐ Ankle ☐ Lower leg ☐ Knee ☐ Thigh ☐ Hip

Concomitant Digit Injury:	
Is there a concomitant digit injury present **on the same limb**?	☐ Yes ☐ No
If yes, please select the location of the secondary injury (pick ONE only)	☐ Single or Multiple fingers ☐ Single or Multiple toes

Concomitant Medications Have any medications been given since the injury?	☐ Yes – (Fill out Concomitant Medication Form) ☐ No

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REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	___ ___ ___ - ___ ___ ___ ___ **(site)** **(screening number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Medical Oversight of Screening

Eligibility of the participant has been confirmed by:	☐ PI / Site Investigator (in person) ☐ PI / Site Investigator (by phone) ☐ Third party physician Purpose: to review the inclusion and exclusion criteria on this form and confirm that the patient meets the criteria listed.
If PI/ Site Investigator, specify: PI / Site Investigator Physician Name: Date and time of confirmation:	_____ _____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock)
If Third party physician, specify: Third party Physician Name: Date and time of confirmation:	_____ _____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock)

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ ____ ____ ____ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Selection of Family Preference

To Caregiver and Child: *"At this point, we need you to tell us which study group you would like to participate in: Group 1 or Group 2. Regardless of which study you choose, you / your child will, at minimum, receive ibuprofen (Advil) for their pain. Both groups include commonly used pain medicines for this type of pain, however Group 2 includes all three of the pain medicine options offered in this study. So, if you don't have a preference, we will assign you to Group 2.*

- *If you choose Group 2, you/your child will have an equal chance of receiving either:*
  - *Ibuprofen (Advil) AND placebos (inactive ingredient)*
  - *Ibuprofen (Advil) AND acetaminophen (Tylenol)*
  - *Ibuprofen (Advil) AND hydromorphone (Dilaudid)*

- *If you choose Group 1, you/your child will have an equal chance of receiving either:*
  - *Ibuprofen (Advil) AND placebo (inactive ingredient)*
  - *Ibuprofen (Advil) AND acetaminophen (Tylenol)*

To help you in making your choice, here is some more information about these medicines.

1. *Ibuprofen (Advil) is typically provided for the kind of injury you/your child has, but it may not always be strong enough to treat a child's pain.*
2. *When a child needs something stronger than ibuprofen (Advil) for their pain, acetaminophen (Tylenol) and opioid medicines like hydromorphone (Dilaudid) are the most commonly recommended pain killers to be added to the ibuprofen.*
3. *Please remember that if you feel that you/your child needs more pain medicine at any point during the study period, you or our research nurse can let your doctor know right away.*

- *Which study would you like to be a part of: Group 1 or Group 2?*

- [NOTE: If the family wishes to speak to a health care professional prior to making their study choice, the RA will then identify a clinical team member to aid them.]

Indicate family preference below:

☐ **Group 1:** Non-Opioid trial [N]
☐ **Group 2:** Opioid trial [O]
☐ No preference → Proceed to enroll in ☐ **Group 2:** Opioid trial [O]
☐ Family unable to reach consensus regarding preference. [If this is chosen, STOP enrolment now]

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ ____ ____ ____ **(site)** **(screening number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Once the **Preference Group** has been selected by the family, please retrieve the following study medication kit from your medication dispensing area:

Pharmacy Kit Number:

____ ____ ____ - ____ - ____ ____ ____

(site - preference group - patient number)

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Study Drugs Administration

Confirmed that the pharmacy kit is not expired?	☐ Yes ☐ No* *If "**NO**", check before proceeding*
Are the noted min. and max. temperatures of the drug storage fridge within the required ranges, today?	☐ Yes ☐ No* *If "**NO**", check temperatures before proceeding*
Weight:	_____kg ☐ Measured on scale ☐ Estimate provided by parent
Ibuprofen (40mg/ml) (up to **600 mg** maximum – **15 ml** maximum)	**Dose: 10 mg per kg** Calculation: _____kg x 10 = _____mg **Volume: 40mg = 1 ml** Calculation: _____mg ÷ 40mg/ml = _____ml **Volume actually dispensed to patient: _____ml**
Acetaminophen or Placebo (80mg/ml) (up to **1000 mg** maximum – **12.5 ml** maximum)	**Dose: 15 mg per kg** Calculation: _____kg x 15 = _____mg **Volume: 80mg = 1 ml** Calculation: _____mg ÷ 80 mg/kg = _____ml **Volume actually dispensed to patient: _____ml**

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	**____ ____ ____ - ____ - ____ ____ ____** **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Hydromorphone or Placebo (1mg/ml) (up to **5 mg** maximum – **5 ml** maximum) ONLY for participants enrolled in Group 2: Opioid trial	**Dose: 0.05 mg per kg** Calculation: _____kg x 0.05 = _____mg **Volume: 1 mg = 1 ml** Calculation: _____mg ÷ 1 mg/ml = _____ml **Volume actually dispensed to patient: _____ml**
*Dose calculation and dispensing in syringe must be verified by a second nurse:	Verified by: _____
Date and time of study drugs administration:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Has the participant taken the full dose of each syringe?	☐ Yes ☐ No* *If "**NO**", please comment*
Were all study drugs administered one after the other?	☐ Yes ☐ No* *If "**NO**", please comment*
Was dispensing of the study drugs recorded on the patient's clinical chart?	☐ Yes ☐ No* *If "**NO**", please comment*
Comments:	

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 2 (T0 – Immediately after Study Drug Administration)

Time due: dd/ mmm/ yyyy HH:MM ± 10 min

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	
Date and Time of evaluation # 2:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"*	_____/10
VAS *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"*	_____/100 mm
FPS-R *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?" Note: say "hurt" or "pain" whichever seems right for a particular child*	☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10
RSS	_____/6

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Contact Information Sheet

Child's Name:	_____ _____ First name Last name
Age:	_____ years
Sex:	☐Male ☐Female
Caregiver's Name:	_____ _____ First name Last name Specify relationship to child: _____
Preferred Mode of Contact:	☐Email ☐Phone
Email:	
Preferred Phone Number:	(_____) _____ - _____
Alternate Phone Number:	(_____) _____ - _____
Time for follow up call:	☐ AM ☐ PM Specify: _____

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

In PED Caregiver Survey

Your Information	
What is YOUR age, in years?	_____ years
What is YOUR sex?	☐ Male ☐ Female ☐ Other, specify: _____ ☐ Decline to answer
What is your home postal code? (1st 3 digits only)	__ __ __
What is your highest level of Education?	☐ Elementary School ☐ High School or some High School ☐ Diploma/Certificate ☐ Some Post-Secondary/University ☐ University/Professional Degree ☐ Decline to answer
What is your annual household income from all sources?	☐ Less than or equal to $25,000 ☐ $25,001 to $50,000 ☐ $50,001 to $75,000 ☐ $75,000 to $100,000 ☐ Greater than $100,000 ☐ Decline to answer

Injury Details	

How did your child's injury occur?	☐ Motor Vehicle Collision/ Road Traffic Accident
	☐ Sports Injury
	  ☐ Ice Hockey/ Hockey
	  ☐ Football
	  ☐ Soccer
	  ☐ Wrestling
	  ☐ Basketball
	  ☐ Gymnastics/ Cheerleading
	  ☐ Skiing/ Snowboarding
	  ☐ Biking
	  ☐ Other sport, specify: _____
	☐ Trampoline

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

	☐ Other play or activity ☐ Other Slip, Trip or Fall ☐ Other mechanism, specify: _____
Was the sports, play or activity supervised (ie. Were you or another adult there watching your child)?	☐ Yes ☐ No ☐ Unsure
Where did your child's injury occur?	☐ Sports Field/ Arena ☐ In School/ School playground ☐ Playground/ Park ☐ Home/ Friend's home ☐ Road ☐ Other, please specify: _____

Study Preference	
If they chose the Non-Opioid trial (Group 1): Please tell us your reason(s) for choosing **Group 1**, ie. the study with the possibility of receiving one of the following: o Ibuprofen only (Advil) o Ibuprofen (Advil) and Acetaminophen (Tylenol) *Choose all that apply*	☐ I do not believe my child's pain is/ will be severe enough to require an opioid medicine (Hydromorphone/ Dilaudid) ☐ I did not want my child to receive an opioid medicine ☐ I do not think my child is old enough to receive an opioid medicine ☐ I trust that both medicines in this study would work for my child, with their current level of pain ☐ I think my child will get better care if they are a part of this study (ex. they will get treated faster, get close care from the research nurse etc.) ☐ Other, please specify: _____
If they chose the Opioid trial (Group 2): Please tell us your reason(s) for choosing **Group 2**, ie. the study with the possibility of receiving one of the following: o Ibuprofen only (Advil) o Ibuprofen (Advil) and Acetaminophen (Tylenol) o Ibuprofen (Advil) and Hydromorphone (Dilaudid)	☐ I wanted to have the option of all 3 medicines, or combination of medicines, available to us ☐ I wanted/hoped that my child will receive the opioid medicine (Hydromorphone/ Dilaudid) specifically ☐ I believe that my child's pain is/ will be severe enough to require an opioid medicine ☐ I believe that the pain relief benefits of the opioid medicine are greater than any possible side effects ☐ I trust that any of the 3 options in this study would work for my child, with their current level of pain

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Choose all that apply	☐ I think my child will get better care if they are a part of this study (ex. they will get treated faster, get close care from the research nurse etc.) ☐ Participating in this study will help researchers learn more about the use of opioids for treating injury-related pain for children in the future ☐ Other, please specify: _____

Experience with Opioid Pain Medicines	
Have YOU ever been prescribed or given an opioid medicine by a health care provider, in a clinic or hospital? *Ex. Hydromorphone (Dilaudid), Morphine, Oxycodone (OxyContin, Percocet), Codeine, Fentanyl, Hydrocodone (Vicodin)*	☐ Yes ☐ No ☐ Unsure
Have any of your FAMILY MEMBERS ever been prescribed or given an opioid medicine by a health care provider, in a clinic or hospital? *Ex. Hydromorphone (Dilaudid), Morphine, Oxycodone (OxyContin, Percocet), Codeine, Fentanyl, Hydrocodone (Vicodin)*	☐ Yes ☐ No ☐ Unsure
If yes, was this family member a CHILD?	☐ Yes ☐ No ☐ Decline to Answer
Have you or a family member ever been diagnosed with a substance use disorder, or addiction to drugs/ alcohol?	☐ Yes ☐ No ☐ Unsure ☐ Decline to answer
If yes, can you please specify which drug(s)/ substances?	[Free text]

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 3 (T30 – 30 minutes after study drugs administration)

Time due: dd/ mmm/ yyyy HH:MM ± 15 min

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	☐ Patient discharged before specified evaluation time ☐ Other: _____
Date and Time of evaluation # 3:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?"* *Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 4 (T60 – 60 minutes after study drugs administration)

Time due: dd/ mmm/ yyyy HH:MM ± 15 min

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	☐ Patient discharged before specified evaluation time ☐ Other: _____
Date and Time of evaluation # 4:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?"* *Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 5 (T90 – 90 minutes after study drugs administration)

Time due: dd/ mmm/ yyyy HH:MM ± 15 min

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	☐ Patient discharged before specified evaluation time ☐ Other: _____
Date and Time of evaluation # 5:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?" Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

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REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 6 (T120 – 120 minutes after study drugs administration)

Time due: dd/ mmm/ yyyy HH:MM ± 15 min

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	☐ Patient discharged before specified evaluation time ☐ Other: _____
Date and Time of evaluation # 6:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?" Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

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REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 7 (TME, Time of Medical Examination)

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	
Date and Time of medical exam:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?"* *Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

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REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 8 (TXR – Time following X-Ray procedure +/- 30 minutes)

Did the patient have an X-ray?	☐ Yes ☐ No
If Yes, Was the post- X-ray evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	
Date and Time of X-ray:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Date and Time of evaluation # 8:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?" Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	**____ ____ ____ - ____ - ____ ____ ____** **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

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REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

ED Discharge Evaluation

ED Discharge Evaluation *(To be done only if discharged before 120 minutes)*	
Was the patient discharged before 120 minutes?	☐ Yes ☐ No
If Yes, Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	
Date and Time of ED Discharge:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?"* *Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	**____ ____ ____ - ____ - ____ ____ ____** **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Reason for early termination?	☐ Procedural sedation used for a reduction* ☐ Left ED prior to evaluation ☐ Left without being seen ☐ Other, please specify _____ * Fill out Concomitant Medication Form

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

PRE-Discharge Questions

Question for Research Nurse	
Which drug, or combination of drugs, do you think the child received for this study?	☐ Ibuprofen alone or ☐ Ibuprofen + Acetaminophen or ☐ Ibuprofen + Hydromorphone

Questions for Parent/ Caregiver	
Which drug, or combination of drugs, do you (parent/ caregiver) think your child received for this study?	☐ Ibuprofen alone or ☐ Ibuprofen + Acetaminophen or ☐ Ibuprofen + Hydromorphone
How do you feel about the pain treatment provided by the study medicine today?	☐ Very Satisfied ☐ Somewhat Satisfied ☐ Neutral ☐ Somewhat dissatisfied ☐ Very dissatisfied
Do you feel that that the medicines that your child received provided adequate/ enough pain relief for your child?	☐ Yes ☐ No ☐ Unsure
Would you accept the same medicine for your child, in the unlikely event of a similar injury in the future?	☐ Yes ☐ No ☐ Unsure
Why? Why Not?	Free Text

Questions for Child	
How happy were you with the pain treatment from the study medicine today?	☐ Very happy ☐ Somewhat happy ☐ Neutral ☐ Somewhat sad ☐ Very sad
Would you take the same medicine if you had the same injury again?	☐ Yes ☐ No

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REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

	☐ Unsure
Why? Why Not?	Free Text

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

POST-Discharge Questions

Questions for Treating ED Physician	
Which drug(s) would you have chosen to give this child?	☐ Ibuprofen alone or ☐ Ibuprofen + Acetaminophen or ☐ Ibuprofen + Hydromorphone ☐ other, please specify
Which drug(s) do you think that the child received?	☐ Ibuprofen alone or ☐ Ibuprofen + Acetaminophen or ☐ Ibuprofen + Hydromorphone

Unblinding	
Was the study unblinded during the ED visit?	☐ Yes, please explain. ☐ No

Co-Interventions

Were any interventions done during the ED visit? ☐ Yes* ☐ No

** If "**YES**", please fill out the table below*

Intervention	Administered?	Date and Time of Administration (dd/ mmm/ yyyy HH:MM)	Comments
Reduction of the fracture?	☐ Yes ☐ No		
Splint?	☐ Yes ☐ No		
Cast?	☐ Yes ☐ No		
Ice?	☐ Yes ☐ No		
Distraction?	☐ Yes ☐ No		
Other? Please specify: _____	☐ Yes ☐ No		

If a procedural sedation or a medication has been administered, please fill out the Concomitant Medication Form.

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	**____ ____ ____ - ____ - ____ ____ ____** **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Discharge Details	
Discharge Disposition	☐ Discharged Home ☐ Admitted ☐ Other, _____
Date and Time of Discharge	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Length of Stay in ED (calculated field):	_____ (hours, to one decimal place)
Final diagnosis at discharge (per MD):	
Radiologic Exams:	☐ Yes ☐ No
If yes, Date and Time of Radiologic Exam:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Final diagnosis from radiologist's report: (*From chart or electronic health care system)*	

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Follow-up Survey # 1 (1-3 days after discharge)

Call must be done in this time window

24 hours from discharge: _____:_____ (24 hour clock) Date: _____/_____/_____
dd mmm yyyy

72 hours from discharge: _____:_____ (24 hour clock) Date: _____/_____/_____
dd mmm yyyy

Follow-up Call Attempts:			
Number of call attempts made: ☐ 1 ☐ 2 ☐ 3 ☐ N/A – completed via email			
	Date and Time *(dd/ mmm/ yyyy HH:MM)*	**RA Initials**	**Comments**
Call # 1:	____/____/_____ ____:____		
Call # 2:	____/____/_____ ____:____		
Call # 3:	____/____/_____ ____:____		
24 hour Follow-up completed?: ☐ Yes ☐ No (Lost to follow-up)			
If YES, Continue…			

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

24 Hour Follow-up Survey

Adverse Effects and Side Effects	
After you were discharged from the emergency department, has your child experienced any adverse (bad) effects or side effects that you think are related to the pain medicines they got in the study?	☐ Yes ☐ No
If YES, please explain:	_____

Medication Uses	
After you were discharged from the emergency department, has your child taken any other medicines?	☐ Yes ☐ No
If YES, please specify:	_____

Home Pain Assessment	
Please rate your child's **overall** (average) pain experience in the last 24 hours, on a scale from 0-10, where 0=no pain and 10=the worst pain imaginable.	_____/10
Please rate your child's **worst** pain experienced in the last 24 hours, on a scale from 0-10, where 0=no pain and 10= the worst pain imaginable.	_____/10

Pain Related Function		
Did your child whine or complain more than usual in the last 24 hours?	☐ Yes	☐ No
Did your child play less than usual in the last 24 hours?	☐ Yes	☐ No
Did your child do the things they normally do in the last 24 hours?	☐ Yes	☐ No
Did your child act more quiet than usual in the last 24 hours?	☐ Yes	☐ No
Did your child have less energy than usual in the last 24 hours?	☐ Yes	☐ No
Did your child eat less than usual in the last 24 hours?	☐ Yes	☐ No
Did your child sleep less than usual in the last 24 hours?	☐ Yes	☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Did your child hold the sore part of the body in the last 24 hours?	☐ Yes ☐ No
Did your child moan or groan more than usual in the last 24 hours?	☐ Yes ☐ No
Did your child want to be close to you more than usual in the last 24 hours?	☐ Yes ☐ No
Total PPPM Score (Automatic Calculation – Hidden Field) =	0 - 10

Activity Score	
Rate your child's ability to perform their usual activities:	☐ A No limitation ☐ B Mild limitation ☐ C Severe limitation

At-Home Treatments		
Did your child use any of the following in the last 24 hours to help treat their pain?		
Ice?	☐ Yes	☐ No
Elevation (raising their sore body part)?	☐ Yes	☐ No
Distraction (such as iPad, movies, games)?	☐ Yes	☐ No
Please describe any other things that your child used to help treat the pain.	Free text	

Missed School and Work		
Did your child miss school and/or work in the last 24 hours?	☐ Yes	☐ No
Did YOU (caregiver/parent) miss work in the last 24 hours?	☐ Yes	☐ No

What Did Your Child Receive?
"We would like to let you know that your child received the following as their study drugs: [**A**dvil only OR **A**dvil and Tylenol OR **A**dvil and **D**ilaudid]. We will ask you about your thoughts in this when we email/ call you again in one week."

Do you have any other comments or concerns?
Thank you for completing this follow-up survey, we appreciate your participation in the No OUCH study! Without families like you, our research would not be possible. Your next (and last) follow-up survey will be in approximately 1 week.

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Follow-up Survey # 2 (1-2 weeks after discharge)

Call must be done in this time window

1 week from discharge: Date: _____/_____/_____
dd mmm yyyy

2 weeks from discharge: Date: _____/_____/_____
dd mmm yyyy

Follow-up Call Attempts:			
Number of call attempts made: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ N/A – completed via email			
	Date and Time *(dd/ mmm/ yyyy HH:MM)*	**RA Initials**	**Comments**
Call # 1:	____/____/_____ ____:____		
Call # 2:	____/____/_____ ____:____		
Call # 3:	____/____/_____ ____:____		
Call # 4:	____/____/_____ ____:____		
Call # 5:	____/____/_____ ____:____		
1 week Follow-up completed?: ☐ Yes ☐ No (Lost to follow-up)			
If YES, Continue…			

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

1-2 Week Follow-up Survey

Parent / Caregiver Satisfaction and Comfort Measures	
As you might remember, your child received _XXX__ in the emergency department, as part of this study. Did knowing what pain medicine(s) your child received in the study affect how you treated your child's pain at home?	☐ Yes ☐ No ☐ Unsure
Please explain:	Free text
How do you feel about the pain treatment provided by the medicines your child was given in the emergency department, as part of this study?	☐ Very Satisfied ☐ Somewhat Satisfied ☐ Neutral ☐ Somewhat dissatisfied ☐ Very dissatisfied
Please explain:	Free text
Do you feel that that the medicines that your child received in the emergency department, as part of this study provided adequate/ enough pain relief for your child?	☐ Yes ☐ No ☐ Unsure
Please explain:	Free text
Would you accept the same medicine for your child, in the unlikely event of a similar injury in the future?	☐ Yes ☐ No ☐ Unsure
Please explain:	Free text

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Since visiting the emergency department, has your child had contact with any of the following health services for any reason related to their injury:	
A. Family Doctor / General Practitioner? If YES, how many times?	☐ Yes ☐ No _____ times
B. Orthopedic Specialist? If YES, how many times?	☐ Yes ☐ No _____ times
C. Revisit to Emergency Department? If YES, how many times?	☐ Yes ☐ No _____ times
D. Other Health Professional (e.g. physiotherapist, chiropractor, naturopath, rehabilitation professional, etc)? If YES, please specify which kind of professional If YES, how many times?	☐ Yes ☐ No Open text _____ times

For any health care visits related to this injury (including your original visit to the emergency department), has your family:	
A. Driven yourself or been given a lift in someone else's car? If YES, how many times? If YES, estimated total cost of gas If YES, did you use paid parking? If YES, estimated total cost of parking	☐ Yes ☐ No _____ times _____$ ☐ Yes ☐ No _____$
B. Used Public Transport (e.g. bus, subway)? If YES, how many times? If YES, estimated total cost of using public transportation	☐ Yes ☐ No _____ times _____$
C. Used Taxi/Uber rides? If YES, how many times? If YES, estimated total cost of using this service	☐ Yes ☐ No _____ times _____$

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Additional Childcare Expenses	
A. Have you needed extra childcare for ANY of your children because of this injury (e.g. emergency department visit, other healthcare visits, child unable to go to school, etc)?	☐ Yes ☐ No
B. If YES, was it extra **unpaid** childcare (i.e. grandparents, neighbours) If YES, how many hours?	☐ Yes ☐ No _____ hours
C. If YES, was it extra **paid** childcare (i.e. babysitter, daycare)? If YES, how many hours? If YES, estimated total cost of for extra paid childcare	☐ Yes ☐ No _____ hours _____$

Since your emergency department visit ~1 week ago:	
How many days in total did your child use a pain medication, for injury-related pain?	_____ days
How many days in total did your child miss school and/ or work?	_____ days
How many days in total did your child not eat properly?	_____ days
How many nights in total did your child have disrupted/upset sleep?	_____ nights
How many days in total was your child unable to participate in their usual activities?	_____ days
How many days in total did YOU (or another caregiver) have to miss work from paid employment because of your child's injury?	_____ days
On a scale of 0 to 10 (where 0 means not at all affected and 10 means extremely affected), how much did this injury affect your child's quality of life?	0-10 numerical value
On a scale of 0 to 10 (where 0 means not at all affected and 10 means extremely affected), how much did this injury affect your quality of life?	0-10 numerical value

Do you have any additional comments or concerns about how this injury and the pain medicines that you used affected you or your child's quality of life?

Thank you for completing this final follow-up survey, we appreciate your participation in the No OUCH study! Without families like you, our research would not be possible.

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

CONCOMITANT AND RESCUE MEDICATIONS

Was a **rescue medication** given during the child's visit?	☐ Yes ☐ No
Were any other concomitant medications (other than the study drugs) given **during** the child's visit?	☐ Yes ☐ No
Were any concomitant medications given **after the child's** ED visit?	☐ Yes ☐ No

CONCOMITANT AND RESCUE MEDICATIONS							
Medication Name	**Indication**	**Rescue Medication? (Y/N)**	**Start Date & Time dd/mmm/yyyy HH:MM**	**Stop Date & Time dd/mmm/yyyy HH:MM (or Ongoing)**	**Dose**	**Route**	**Frequency**

Two Randomized Controlled Trials of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Study

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

ADVERSE EVENTS FORM

To be filled out by Research Nurse								To be filled out by Site Investigator			
No.	**Initial Report or Follow-up**	**Brief Description of Event**	**Onset Date & Time (dd/mmm/yyyy HH:MM)**	**Intensity grade:** 1. Mild 2. Moderate 3. Severe 4. Life-threatening 5. Fatal or Death	**Expected AE?** **Y / N**	**SAE?** **Y / N** **If YES, fill out SAE Form**	**Action Taken** 1. None 2. Medication 3. New or Prolonged Hospitalization 4. Procedure / Surgery 5. Other, specify	**Outcome** 1. Resolved 2. Resolved w/ sequalae 3. Ongoing 4. Death 5. Lost to f/u	**Date & Time Resolved (dd/mmm/yyyy HH:MM)**	**Relationship to Study** 1. Unrelated 2. Unlikely 3. Possible 4. Probable 5. Definite	**Site PI Initial**

Two Randomized Controlled Trials of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Study

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	___ ___ ___ - ___ - ___ ___ ___ **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

SERIOUS ADVERSE EVENTS FORM

Date and time Site Investigator and Site Research Coordinator were notified: *(to be completed by Research Nurse)*	_____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock)
To be completed by site RC / Investigator	
Date and time the local REB was notified:	_____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock) ☐ Not applicable *Local SAEs must be reported to REB if the event is serious, unexpected, **and** considered to be related or possibly related to the study. Local SAEs are to be reported to the REB (via email to REB coordinator) within 7 days of their discovery*
Date and time the lead site Principal Investigator was notified:	_____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock)
Follow up comments: *(to be completed by site Investigator)*	

Signature of Research Nurse: _____ Signature of Site Investigator: _____

Date: ___/_____/_____ Date: ___/_____/_____
dd mmm yyyy dd mmm yyyy

Two Randomized Controlled Trials of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Study

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

PROTOCOL DEVIATION FORM

Did any Protocol Deviations Occur? ☐ Yes ☐ No

Description of Protocol Deviation	Deviation Category/ Code*	Date Deviation Occurred (dd/mm/yyyy)	Time Deviation Occurred (HH:MM)	Date REB Notified (if applicable) (dd/mm/yyyy)	Date Sponsor Notified (if applicable) (dd/mm/yyyy)	Site PI Initial
1)				☐ Not applicable	☐ Not applicable	
2)				☐ Not applicable	☐ Not applicable	
3)				☐ Not applicable	☐ Not applicable	
4)				☐ Not applicable	☐ Not applicable	
5)				☐ Not applicable	☐ Not applicable	

Two Randomized Controlled Trials of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Study

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

***DEVIATION CATEGORIES / CODES:**

Safety (Category A)
1. Not reporting an SAE within 72 hours
2. AE/SAE is not reported to IRB

Informed Consent (Category B)
3. Failure to obtain informed consent
4. Consent form used was not current REB-approved version Consent form missing
5. Consent form missing
6. Consent form not signed and dated by participant
7. Consent form does not contain all required signatures

Eligibility (Category C)
8. Participant did not meet eligibility criterion
9. Randomization of an ineligible participant
10. Participant randomized prior to completing Baseline Assessment, etc.

Protocol implementation (Category D)
11. Failure to keep IRB approval up to date
12. Participant receives wrong treatment
13. Use of unallowable concomitant treatments
14. Prescribed dosing outside protocol guidelines
15. Missed assessment
16. Assessment completed outside of protocol guidelines for timing

Other
17. Other, specify in log

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Unanticipated Problems (UP) Form

Date UP Identified:	_____/_____/_____ dd mmm yyyy
Identify UP: *(Give the UP a brief title)*	Open text
The Unanticipated Problem was unexpected in terms of nature, severity or frequency:	☐ Yes ☐ No
The Unanticipated Problem is possibly related to participation in the research:	☐ Yes ☐ No
The Unanticipated Problem suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized:	☐ Yes ☐ No
Briefly Describe the UP: *(Include additional or supplementary information as necessary. Include date of incident, date of discovery, describe harm or potential harm that occurred to subject(s), whether the incident is resolved, whether the subject(s) remains on study)*	Open text
What action was taken with the study as a result of the Unanticipated Problem? *(Check all that apply)*	☐ No action ☐ Revise protocol to eliminate apparent immediate hazards to subjects ☐ Modification of inclusion or exclusion criteria to mitigate newly identified risks ☐ Implementation of additional procedures for monitoring subjects ☐ Suspension of enrollment of new subjects ☐ Notify currently enrolled subjects ☐ Suspension of research procedures in currently enrolled subject ☐ Modification of consent documents to include a description of newly recognized risks (site and/or study wide)

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	**____ ____ ____ - ____ - ____ ____ ____** **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

	☐ Provision of additional information about newly recognized risks to previously enrolled subjects ☐ Other: _____
Is the Unanticipated Problem a serious adverse event?	☐ Yes ☐ No *If the Unanticipated Problem is a serious adverse event, submit this form and make sure that the adverse event form and Serious Adverse Event report have been completed and submitted as per local site policy.*
Was the Unexpected Problem reported to the sponsor?	☐ Yes ☐ No
If YES, Date UP reported to the sponsor:	_____/_____/_____ dd mmm yyyy
If NO, why was the UP not reported to the sponsor?	Open text
Was the Unexpected Problem reported to the local REB?	☐ Yes ☐ No
If YES, Date UP reported to the REB:	_____/_____/_____ dd mmm yyyy
If NO, why was the UP not reported to the REB?	Open text

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Early Withdrawal Form

Did participant withdraw from the study?	☐ Yes ☐ No
If YES: Date of Discontinuation:	_____/_____/_____ dd mmm yyyy
Reasons for Discontinuation:	☐ Adverse Event / Serious Adverse Event ☐ Death ☐ Withdrawal of Consent / Assent ☐ Protocol Violation, Specify _____ ☐ Other, Specify _____
If withdrew consent / assent: 1. Permission to use collected data? 2. Permission to conduct Chart Review? 3. Telephone follow up to continue?	☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No
Comments:	

Data and Safety Monitoring Board (DSMB) Charter

Protocol	Strategy for Patient Orientation Research (SPOR) Innovative Clinical Trials Multi-Year Grant
Nominated Principal Investigator:	Dr. Terry Klassen
Protocol title:	Innovation in Pediatric Trials (iPCT) Initiative
Sponsor:	CIHR - SPOR
DSMB Charter version:	3.5
DSMB Charter date:	January 18, 2019

1. Introduction

The purpose of this charter is to define the responsibilities of the SPOR Innovation in Pediatric Clinical Trials (iPCT) initiative's Data Safety Monitoring Board (DSMB), detail membership requirements, describe the data to be reviewed, delineate the meeting process, and outline the considerations and policies of the DSMB. The DSMB will act in an independent expert advisory capacity to monitor participant safety. The DSMB may wish to review this Charter at regular intervals to determine whether any changes are needed.

2. Organization and interactions

a. Membership of the DSMB

The DSMB consists of a Chair and 4-6 members with expertise in relevant (clinical) specialties for the study, including members who are knowledgeable about statistical methods for clinical research and analysis of research data. Other members should bring expertise in the clinical specialty the studies are conducted in (pediatric emergency medicine).

The DSMB Chair must be willing to make firm commitment to participate as Chair for the duration of the project.

The DSMB members are appointed by the Network Coordination Centre (NCC) Lead in consultation with the DSMB Chair and must meet the following requirements:

- Be willing to serve as a DSMB member for the duration of the project;
- Comply with the conflict of interest policy specified in this charter;

Although DSMB members are expected to serve for the full duration, in the unlikely event that a member is unable to continue participation, the reason will be documented, and a replacement member will be selected by the DSMB Chair. The new member must have comparable expertise and qualifications to the DSMB member she/he is replacing.

A list of members are mentioned in Appendix A.

b. Conflict of Interest

The DSMB must consist of individuals who are impartial, independent of the investigator(s) and who have no financial or scientific interest in the study that could impair the members' ability to objectively review study data as outlined below:

- DSMB members must not have any real or perceived scientific, financial, professional, personal, proprietary, or another conflict of interest related to the conduct, outcome, or impact of the study. DSMB members should preferably not be working at any of the participating sites.
- DSMB members must not be engaged in any simultaneously occurring competitive studies in any role that could pose a conflict of interest. DSMB members must also identify and disclose any concurrent service on other DSMBs of the same, related, or competing products;
- DSMB members must be independent of the sponsor, regulatory agencies, principal investigators, clinical care of the study participants, or any other capacity related to study operations. All DMSB members must disclose all possible conflicts of interest in writing before beginning service as a DSMB member.

c. Confidentiality

All materials, discussions, and proceedings of the DSMB are privileged and confidential. DSMB members agree to use this information exclusively to accomplish the responsibilities of the DSMB. No communication of the deliberations or recommendations of the DSMB, either written or oral, may occur except as required for the DSMB to fulfill its responsibilities. Individual DSMB members are expected to maintain confidentiality regarding the study outside the DSMB (including, but not limited to the investigators, REB, regulatory agencies, or sponsor) except as authorized by the DSMB.

If requested, this charter and accompanying list of Board members may be sent to a Research Ethics Board (REB). In the case, this charter will be marked as not for dissemination, and be sent by the Study Principal Investigator or the Network Manager to the REB Chair, with a cover letter. The SPOR - iPCT iniative does not release Board members' names in response to media inquiries until after publication of the main results of the study.

3. DSMB Responsibilities

The DSMB is responsible for safeguarding the interests of individuals participating in iPCT and approved related trials.

This responsibility will be implemented by providing recommendations for continuation or early termination of iPCT trials based on an assessment of safety. The DSMB may also make

recommendations related to the selection, recruitment or retention of participants, their management and adherence to protocol-specific regimens, and the procedures for data management and quality control.

The DSMB is advisory to the Study Principal Investigators and ultimately the iPCT Steering Committee. The DSMB is an independent board appointed by the NCC Lead and approved by the SPOR - iPCT Executive team.

The DSMB's responsibilities are to regularly monitor iPCT clinical trials, review and assess the performance of its operations, and make recommendations, as appropriate, to the Study Principal Investigator and, through the NCC lead, to the iPCT Steering Committee concerning:

- Protection of the safety and interests of the study participants;
- Review of the research protocol, informed consent documents, and plans for data safety and monitoring before initiation of study, - if needed - periodically during the study, and at the conclusion of the study;
- Conduct interim and final evaluation of the study, including safety data, participant recruitment, accrual and retention, risk versus benefit, and other factors that can affect study outcome, including aggregate and individual participant data related to safety.
- Review and evaluation of *ad hoc* safety issues concerning the study at the request of the Study Principal Investigator.
- Continuation, termination, or other modifications of the study based on the performance and observed beneficial or adverse effects of the study; and
- Amendments to the study protocol and consent forms, including whether any new data from other sources affect the equipoise of the study being monitored
- Operation according to the procedures described in this charter and all procedures of the DSMB.

4. DSMB Tasks

a. Before study opening

The DSMB will review completed protocols to assess that the monitoring plan ensures patient safety and research integrity. Consent and assent forms will be reviewed.

b. During the study

Once a study is open the protocol monitoring shall be facilitated at least semiannually (generally by conference calls) by submission of data summaries from the Data Coordinating Centre regarding each study to the Network Manager who sends these data summaries and available site monitoring reports to the DSMB Chair for preparation of the DSMB Report.

The primary responsibility of the DSMB is to monitor the study for participant safety. The DSMB will review the following safety and related data:

- Participant recruitment, accrual, retention, and withdrawal information;
- Adverse events (AEs) and serious adverse events (SAEs);
  - Tabulated by body system, intensity, seriousness, duration, treatment given, and the relationship to the study drug and study procedure
  - Comparison of events that occur between treatment arms
  - Individual events of particular concern
- Site monitoring reports;
- Any other safety-supporting data requested by the DSMB.

The DSMB will make a recommendation regarding the study continuation, termination, or modifications based on the review. Studies that are accruing poorly may be recommended to be placed into probationary status or closed.

Serious adverse events (SAEs) will be monitored by the DSMB Chair and must be reported by the Sponsor to the DSMB Chair via email **within seven working days** of learning of the event.

All participant withdrawals will be monitored by the DSMB Chair and must be reported by the Sponsor to the DSMB Chair via email **within two weeks** of learning of the withdrawal.

The DSMB may consider data from other studies or external sources during its deliberations, if available, as these results may have a profound impact on the status of the participants and design of the current study.

5. Meetings

a. Projected Schedule of Meetings

An initial meeting of the DSMB will be held before the start of the studies or as soon after that as possible for the members to:

- review the charter;
- receive an overview of study network activities;
- form an understanding of the protocol and definitions being used;
- establish a distribution and meeting schedule;
- review the study modification and termination guidelines; and

Subsequent DSMB meetings will be held to review and discuss study data according to the schedule as described in the table below.

Timeline	***Data Review by***
Biannually	Entire DSMB
Ad hoc (SAE)	Entire DSMB

b. *Ad Hoc* Meetings

An *ad hoc* meeting of the DSMB may be called at any time by the DSMB Chair or Study Principle Investigator if imminent participant safety issues arise. If a significant safety concern arises during the study, the DSMB Chair may convene a meeting to review safety and any other aspect of the study. Significant safety events may include, but are not limited to, the following:

- A death or life-threatening condition sustained by a participant, regardless of causality;
- An unexpected serious safety issue newly identified during the development program that could expose participants to unnecessary risks;
- Any other concern regarding participant safety raised by any DSMB member.

Proposed study amendments that significantly alter the treatment plan and deal with participant safety concerns will prompt an ad hoc meeting of the DSMB for review before implementation of changes. This may require suspension of enrollment pending DSMB review.

c. Meeting Format

DSMB meetings will be conducted by teleconference and facilitated by the DSMB Chair, consisting of an open session and a closed session. A quorum, defined as **four members of the DSMB including the DSMB Chair must be present to hold a DSMB meeting**.

Open Session

The open session may be attended by the investigator(s) and representatives of the Sponsor. Investigator and sponsor representatives may attend the open session with DSMB members. The Data Coordinating Centre provides a report for each study, containing: recruitment updates, compliance, withdrawals and other blinded data and non-confidential information regarding operational/logistical issues. This session gives the DSMB an opportunity to query an investigator about issues that have arisen during the review of safety data. Unblinded information will not be discussed in the open session.

Closed Session (if needed)

The closed session will be restricted to attendance by the DSMB members, and a recorder (NCC administrator) for the review of an interim analysis, prepared by the Methods Core.

At the closed session, study blinding may be broken. Closed sessions also consist of a review of the recommendations the DSMB wishes to make to the investigator and a formal vote.

d. Voting

DSMB recommendations will be agreed upon by formal majority vote. In the event of a split vote, the DSMB Chair will cast the deciding vote.

6. DSMB Considerations and policies

a. Stopping Rules

After considering the information in the open and closed session DSMB report, the DSMB will determine whether the study should continue as planned, proceed with modifications, or be terminated. The justification to terminate the study may be due to the DSMB's analysis that there are overwhelming safety issues. If the DSMB votes to terminate the study, the Network Manager will prepare a final study report for the DSMB, and a final DSMB meeting will be held. The DSMB's recommendations at the final DSMB meeting may include continuing action items to the investigator based on the final review.

b. Meeting Minutes

Minutes of DSMB meetings will be kept in two parts: open session and closed session.

Open Session

Open session meeting minutes include (at a minimum):

- Protocol number, study title, version;
- DSMB meeting date;
- Copy of the open session agenda;
- A list of attendees, including DSMB members and any others present, listing their professional title and role at the meeting;
- A list of attendees who have been unblinded to any data;
- Information reviewed and related discussion during the open session, including rationale for recommendations provided by voting DSMB members;
- A copy of the DSMB recommendation letter.

The DSMB Recorder is responsible for recording and generating meeting minutes of both open and closed sessions.

Draft minutes of open sessions will be sent to the DSMB Chair for review and approval within three working days of the meeting. The draft minutes will be reviewed by the DSMB Chair within seven working days, and final minutes of the open session will be distributed to the DSMB

members and the investigator within ten working days of the DSMB meeting. Final minutes will be distributed to DSMB members by PDF version sent by secure email.

Closed Session

Draft minutes of closed sessions will be sent to the DSMB Chair for review and approval within one working day of the DSMB meeting. The draft minutes will be reviewed by the DSMB Chair within three working days, and final minutes of the closed session will be distributed only to the DSMB members within five working days of the DSMB meeting. Final minutes will be distributed to DSMB members by PDF version sent by secure email.

Closed session meeting minutes will not be divulged beyond the DSMB until after the study is closed unless either:

- The DSMB voting members approve the release to preserve the integrity of the study and the safety of participants; or
- Health Canada –Therapeutic Product Directorate requires disclosure.

The investigator, Network Manager and sponsor will receive a complete copy of the open and closed session meeting minutes at the completion of the study.

7. Report to DSMB

a. Responsibility for Preparing DSMB Data Reports (open session)

The report is prepared by the DCC, and sent to the DSMB Chair three weeks before the planned meeting.

b. Responsibility for Preparing DSMB Interim analysis (closed session)

The report is prepared by the Methods Core, and sent to the DSMB Chair three weeks before the meeting.

a. Content of the Reports to the DSMB

The DSMB chair will prepare the report to include two DSMB parts – open session and (if available) closed session.

- *Open Session Report*: The open session report presents data only in aggregate and focuses on study conduct issues, like accrual and withdrawal rates, eligibility rates, reasons for ineligibility and discussion of blinded materials. To protect the blind participant-specific data and treatment group data are not presented in the open session report.
- *Closed Session Report*: In the event of serious adverse events or significant protocol violations, the DSMB may bequest closed session reports that include unblinded comparative statistical outputs.The closed session reports include unblinded comparative

statistical outputs. The closed session report is considered confidential and must be destroyed at the conclusion of the meeting.

b. Distribution of the Report to the DSMB

Reports to the DSMB are distributed to DSMB members two weeks before a scheduled meeting. The report is dated and provided to individual DSMB members in PDF format sent by secure email.

c. DSMB Reports to Investigator

Following each meeting, the DSMB will issue a confidential report separate from the minutes of the open and closed sessions that will be sent to the investigator. The report includes a summary of the open session discussion, does not include unblinded data or discussion of the unblinded data, and provides the DSMB's recommendations accompanied by clear, concise rationale for them. The report should contain sufficient information to explain the rationale for any specific actions by the DSMB without jeopardizing conduct or scientific integrity of the study (unblinding). If no recommendations are made, the report may simply state, "The DSMB recommends that the study continues as planned."

The report should be presented to the investigator both in writing and orally. The DSMB Chair communicates directly with the investigator to allow them the opportunity to ask questions and discuss any recommendations. If the report does include DSMB recommendations for changes or termination of the study, the report must include a minimum amount of data such that the investigator can make a reasoned decision in response to the recommendation.

If the investigator accepts the recommendations of the DSMB, the investigator will be responsible for implementing the actions in response. In the event the study must be amended, the investigator will prepare and submit the amendment to the DSMB and REB for approval before implementing amendment changes.

If the investigator rejects the DSMB's recommendations, the investigator must provide the DSMB with a written explanation of their decision and supporting rationale within one working day. If the DSMB has recommended that the study is stopped, but the investigator decides to continue the study, the investigator will inform all concerned regulatory authorities of its decision to continue the study despite the DSMB's recommendation. Public disclosure of the decision to stop the study is at the discretion of the investigator. The DSMB will not make any public announcements.

8. Other

a. Amendments to the DSMB Charter

This DSMB charter can be amended as needed during the study. All amendments will be documented with sequential version numbers and revision dates and will be recorded in the open session DSMB meeting minutes. Each revision will be reviewed and agreed upon by the DSMB.

b. Archiving

All DSMB documentation and records will be retained in sealed envelopes in the Sponsor Study File by the National Coordinating Centre for 25 years after completion of the study. Access to archived data will be controlled by the sponsor, which will release the information only as specified in this charter or as required by law.

Appendix A – DSMB members

Voting members

Member name	*Conflicts of interest*
Garth Meckler (chair)	
Mark Roback	
Anupam Kharbanda	
Eyal Cohen	
Lise Nigrovic	

Ex-officio (non-voting)

NCC Lead: Dr. Geert W. 't Jong

Network Manager: Tannis Erickson

Appendix B – Definitions

Study Principal Investigator: The investigator who is primarily responsible for a trial.

SPOR Principal Investigator: The investigator designated as Primary Investigator on the SPOR application (Dr. Klassen).

iPCT Steering Committee: Executive committee consisting of the study leads (PIs) and the leads within each core (Network Coordinating Centre; Data Coordinating Centre; Methods Core)

Study Details			
Study Title:	No-OUCH A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials		
Investigator:	Dr. Samina Ali	**Code:**	00073476
Sponsor:	University of Alberta		
Document History			
Version	**Date**	**Reason For Change**	
1	20 Mar 2019	Initial draft	

Introduction

This document defines the data management approach for the named study. Specifically it defines data sources, data handling practice and relevant additional documentation.

Document Control

This document is to be authorized by WCHRI DCC Team Lead, their designee or a senior manager within the Women & Children's Health Research Institute (WCHRI). The study sponsor (sponsor-initiated studies) and/or Principal Investigator (investigator-initiated studies) should also review and authorize the production version and any subsequent modifications.

Following authorization a read-only 'controlled' copy will be created and the document will be allocated a version number. Subsequent changes will be authorized (see above) and the version number incremented. Each authorized version will be retained on file for audit purposes.

Study Title

A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

Study Overview

This study will be comprised of two Phase 2, six-centre, randomized, double-blind, placebo-controlled trials that will be run simultaneously. The primary objective of this study is to determine the effectiveness of a combination of opioid and non-opioid oral analgesic medications (PO ibuprofen + PO acetaminophen; PO ibuprofen + PO hydromorphone; PO ibuprofen alone) for the acute pain management of children with an acute musculoskeletal (MSK) limb injury.

The study aims to recruit 536 children, aged 6-17 years, presenting to one of six Canadian pediatric emergency departments (EDs) with an acute MSK injury (<24 hours old) of a single limb over a period of 18 months.

Participants who participate in the Opioid Trail will receive either single-dose:

A. Oral hydromorphone (0.05mg/kg, max 5mg) + Oral ibuprofen (10mg/kg, max 600mg), OR

B. Oral acetaminophen (15mg/kg, max 1000mg) + Oral ibuprofen (10mg/kg, max 600mg), OR

C. Oral ibuprofen (10mg/kg, max 600mg)

Participants who participate in the Non-Opioid Trial will receive either single-dose:

A. Oral acetaminophen (15mg/kg, max 1000mg) + Oral ibuprofen (10mg/kg, max 600mg), OR

B. Oral ibuprofen (10mg/kg, max 600mg)

Pain scores, any adverse events, level of sedation, and vital signs will be recorded every 30 minutes, for up to 120 minutes following study drug administration. Participants will also receive two follow-up questionnaires, either by email or telephone, at 24 hours and 1 week post discharge from the ED.

For inclusion and exclusion criteria see the study protocol.

Primary Efficacy Variables

Primary Efficacy Endpoint will be the self-reported pain score at 60 minutes, using a 0-10 verbal Numerical Rating Scale (vNRS).

Variable: pain_vnrs at the 60 minute mark

Secondary Efficacy Variables

The Secondary Efficacy Endpoints will include:

Endpoint	Variable Name
1. the proportion of patients with a vNRS pain score <3 at 60 minutes	pain_vnrs at the 60 minute mark
2. the proportion of patients with a vNRS pain score reduction of at least 2 points out of 10 at 60 minutes	pain_vnrs at the 60 minute mark
3. between group differences in pain scores at study time-points (T-30,T-60,T-90, T-120, T-Medical Exam and T-Xray)	pain_vnrs, pain_fpsr and pain_vas at all timepoints
4. self-reported caregiver and child satisfaction with pain relief and acceptability of study medications, using a previously employed 5 point Likert scale	qp_rate qp_relief qc_rate qc_same folup2_ratetx folup2_ratetx_expl folup2_relief folup2_relief_expl
5. ED length of stay	pscr_triage disch_dt
6. frequency of missed fractures or dislocations	disch_mddx disch_raddx
7. the proportion of children administered a rescue analgesic in the 60 minutes following administration of study medication	cm_sd cm_st cm_ed cm_et
8. time to effective analgesia, defined as the first vNRS pain score <3 post-intervention	pain_vnrs

9. children's self-reported pain intensity on the Visual Analog Scale (VAS) and the Faces Pain Scale-Revised (FPS-R) at all study times	pain_vas pain_fpsr

Safety Data

Principal Safety Endpoint will be the proportion of children with any adverse events related to study drug administration.

Secondary Safety Endpoints will include 1. the proportion of children with any serious adverse events during the study period, 2. the proportion of children in each study group with a Ramsay Sedation Score (RSS) score between 1 to 3, and 3. the proportion of children with each specific adverse event type during the study period.

Patient Numbers

The sample size for the three-armed Opioid Trial is 105 patients per arm, for a total of 315. For the two-armed Non-Opioid Trial, a sample of 85 patients per arm, for a total of 170. Thus, the grand total for the No OUCH Study would be 485. In order to account for patients who are excluded from primary analyses due to missing data for the primary (efficacy) outcome and to adjust for loss to follow-up, the sites will recruit approximately 10% more, for a target recruitment of approximately 536 patients. However, in order to preserve the patient preference aspect of this study, which allows families to choose which trial they would like to participate in, we will over-recruit one trial in order to allow the second to achieve its sample size.

Study Timelines

Participants are enrolled, if eligible, in the ED. Once the drug is administered, patient assessments are implemented in the ED at T0, T30, T60, T90 and T120 time points. Assessments are also collected at the time of the medical examination, time of x-rays and at discharge. Two follow-ups conducted either by phone or online survey to be completed at 1-3 days post discharge and 1-2 weeks post discharge. Total study period: 14 days for all outcome data.

First Participant visit: April 2019

Last Participant visit: expected April 2021

Ethics Status

This is a Health Canada regulated clinical trial that requires REB approval at participating sites. It is required to be GCP-compliant and undertaken on a validated installation of REDCap.

Data Sources

All data entry will be performed at the sites by trained research staff, with exception of the survey data which will be entered directly by the parents. Source Documents include medical records. Some data will be collected directly from the study participants and under these circumstances REDCap is considered the source document.

Standard Operating Procedures

Data management work performed by WCHRI will be undertaken using the current version of WCHRI SOPs.

Scope of Work

WCHRI staff will perform the following tasks:

Database build, data management activities, delivery of data for analysis, preparation of DSMB reports.

Data Collection Mode

Data will be collected electronically (any transcription from paper will be performed at the study sites. WCHRI will not receive copies of paper CRFs or source documents.)

CRF Design

Data collection forms have been developed by the Principal Investigator and her staff with minimal input from WCHRI.

Data Collection System

Data will be entered into REDCap by personnel at the study sites.

Randomization and Unblinding

For Randomization and Unblinding specifics, see the protocol.

Randomization of participants will occur outside of REDCap. Should unblinding be required, this will be performed through the study unblinding project in REDCap. In addition, 1-3 days AFTER The primary outcome measures are collected, the study arm assigned to the patient will be revealed.

Study Monitoring

Monitoring will be performed by staff from the University of Alberta Quality Management in Clinical Research (QMCR) according to their monitoring plan.

Document Tracking

WCHRI will not be handling paper documents for this study.

Data Entry

The Study sites will complete electronic CRFs contained within the data collection system (REDCap) based on the contents of the patient records and other data sources.

Data Handling

Data handling practices for this study are documented in the study's data handling manual. This document will be updated throughout the study as practices are refined and as new situations arise. Specifically, this document covers issues such as data handling conventions, self-evident corrections, data query practice and will also serve to log data handling exceptions.

Data Quality

The approach to data quality is based on key points contained within ICH GCP. These are:

- Complete Minimal missing values
- Accurate Database values match original observation
- Precise Units and measurability clearly understood
- Timely Minimal time between observation and recording

- Verifiable Independent assessment or monitoring
- Traceable Actions taken are logged

The above points will be ensured as follows:

Data Validation and Queries

Electronic data collection forms will be programmed with online validation checks (also known as edit checks). Based on an understanding of the data collection forms these checks will:

- Alert data entry users to missing data
- Check that numeric variables and dates are within reasonable ranges
- Check for consistency within the data

Entered data will be subject to visual and electronic validation by data management staff according to an approved data validation plan. Issues that arise will be notified to the sites as queries, for resolution.

Data issues will be entered into the data capture system in the form of queries/discrepancies. Sites will respond to the queries, directly in the data collection system. Query responses will be reviewed by data management staff and closed once the issue has been resolved.

Source Document Verification

This will be performed by study monitors according the approved monitoring plan.

Serious Adverse Events

Serious adverse events (SAEs) are to be reported to the sponsor *(and/or PI for investigator-initiated studies)* and ethics board, by the sites, as defined in the study protocol. Periodically the sponsor (or PI) will forward copies of SAE reports to WCHRI for reconciliation with the CRF data.

Data Coding

Adverse events will be coded with MedDRA by WCHRI staff. A formal coding review will be undertaken by an authorized individual prior to database lock or delivery for interim analysis.

Data Extract and Delivery

Data will be extracted into SAS data sets for delivery to the study statistician.

Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB). The DMSB will operate under the rules of an approved charter which will outline all terms of reference, as well as the frequency of meetings, that will be reviewed at the organizational meeting of the DSMB. Prior to each DSMB meeting, the study statistician shall prepare reports with interim data for presentation to the DSMB.

The following timelines will need to be met in order to have enough time to prepare and submit the report to the DSMB.

- Data quality review will be performed 6-8 weeks prior to the data of the planned DSMB meeting and any necessary queries raised.
- Study sites will be asked to review and respond to queries within 1-2 weeks

- 4-5 weeks before the DSMB meeting data will be exported and provided to the statistician for preparation of the DSMB reports.

Archiving and Destruction

After study completion all study materials will be returned to the Principal Investigator / Sponsor for archiving.

Electronic data will be retained in WCHRI secure systems until such time as these systems are decommissioned or until the Principal Investigator requests their deletion.

Tasks and Responsibilities

These are summarized in the following table:

Task	Responsibility	Notes
CRF design	PI	
Database configuration	WCHRI	
Database documentation	WCHRI	
Database acceptance testing	WCHRI / PI	
Monitoring	CRU	
Document flow and tracking	N/A	
Data entry	Study sites	
Data validation	WCHRI	
Discrepancy resolution	Study sites	
Data extract	WCHRI	
Analysis database creation	WCHRI	
DSMB Reports	WCHRI	
Study materials archiving	Study sites / PI	
Data archiving	PI	

Authorization:

Author: (Signature) Pamela Marples **Date:** 12 Apr 2019

Authorized by: (PI or Sponsor) Dr. Samina Ali **Date:** 15 April 2019

Reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Table 1
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	3
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	14
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or	12-13

		groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	8
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10 and Figure 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8-9
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10 And Appendix 2 for Case Report Form
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10

Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-13 And Appendix 3 for data management plan
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13 and Appendix 4 for DSMB charter
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-11

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13-14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9, 14, and Appendix 1
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12-13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	3 and 14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Table 1
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in	14

		results databases, or other data sharing arrangements), including any publication restrictions	
3Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14 and Table 1
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Reporting checklist for protocol of a clinical trial (SPIRIT-PRO Elaborations only).

		SPIRIT-PRO Elaboration	Page Number
Roles and responsibilities: contributorship	#5a	Specify the individual(s) responsible for the PRO content of the trial protocol.	3
Background and rationale	#6a	Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.	10-11
Background and rationale	#7	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	10-11
Trial Design	#10	Specify any PRO-specific eligibility criteria (eg, language/reading requirements or prerandomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.	7
Interventions: adherence	#12	Identify the PRO endpoint as the primary, secondary (and if so - whether a key/important secondary), or an exploratory endpoint. Specify the PRO concepts/ domains used to evaluate the intervention (eg, overall health- related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.	10-11
Interventions: concomitant care	#13	Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not pre-randomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple	10-11, Figure 2

		questionnaires, whether order of administration will be standardized.	
Outcomes	#14	When a PRO is the primary end point, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses.	11
Methods	#18a(i)	Justify the PRO instrument to be used and describe domains, number of items, recall period, instrument scaling and scoring (eg, range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.	10
Data collection	#18a(ii)	Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other).	9, 12
Data collection	#18a(iii)	Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.	10
Data collection	#18a(iv)	When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available.	N/A
Data collection	#18b(i)	Specify PRO data collection and management strategies for minimizing avoidable missing data.	9-10

Data Collection	#18b(ii)	Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.	9
Statistics	#20a	State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error.	11-12
Statistics	#20c	State how missing data will be described and outline the methods for handling missing items or entire assessments (eg, approach to imputation and sensitivity analyses).	11-12
Data monitoring	#22	State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; eg, in the participant information sheet and consent form.	N/A as single dose administration study

BMJ Open

A study protocol for two complementary trials of non-steroidal or opioid analgesia use for children aged 6 to 17 years with musculoskeletal injuries (The No OUCH Study)

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Keywords:	Pain management < ANAESTHETICS, Paediatric orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, ACCIDENT & EMERGENCY MEDICINE

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Title: A study protocol for two complementary trials of non-steroidal or opioid analgesia use for children aged 6 to 17 years with musculoskeletal injuries (The No OUCH Study)

Lay Title: Analgesia Use for Children with Musculoskeletal Injuries

Authorship: Samina Ali[1,2,*], Manasi Rajagopal[1], Terry P. Klassen[3,4], Lawrence Richer[1,2], Christopher McCabe[5,6], Andy Willan[7,8], Maryna Yaskina[2], Anna Heath[9], Amy L. Drendel[10], Martin Offringa[11], Serge Gouin[12], Antonia S. Stang[13], Scott Sawyer[14], Maala Bhatt[15], Serena Hickes[4] and Naveen Poonai[16,17], on behalf of the KidsCAN PERC Innovative Pediatric Clinical Trials No OUCH Study Team

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Keywords: pain, analgesia, fracture, musculoskeletal injury, pediatrics, emergency medicine, opioid

Trial Protocol Version 22/08/2019
Trial Registration: clinicaltrials.gov NCT03767933
WHO Trial Registration Data Set: See Table 1

Word Count: 4000/ 4000 words

ABSTRACT

Introduction. Musculoskeletal (MSK) injuries are a frequent cause for emergency department (ED) visits in children. MSK injuries are associated with moderate to severe pain in most children, yet recent research confirms that the management of children's pain in the ED remains inadequate. Clinicians are seeking better oral analgesic options for MSK injury pain with demonstrated efficacy and an excellent safety profile. This study aims to determine the efficacy and safety of adding oral acetaminophen or oral hydromorphone to oral ibuprofen and interpret this information within the context of parent/caregiver preference.

Methods and analysis. Using a novel preference-informed complementary trial design, two simultaneous trials are being conducted. Parents/caregivers of children presenting to the ED with acute limb injury will be approached and decide which trial they wish to participate in: an opioid-inclusive trial or a non-opioid trial. Both trials will follow randomized, double-blind, placebo-controlled, superiority-trial methodology and will enroll a minimum of 536 children across six Canadian pediatric EDs. Children will be eligible if they are 6 to 17 years of age and present to the ED with an acute limb injury and a self-reported verbal Numerical Rating Scale pain score ≥ 5. The primary objective is to determine the effectiveness of oral ibuprofen + oral hydromorphone versus oral ibuprofen + oral acetaminophen versus oral ibuprofen alone. Recruitment launched in April 2019.

Ethics and dissemination. This study has been approved by the Health Research Ethics Board (University of Alberta), and by appropriate ethics boards at all recruiting centers. Informed consent will be obtained from parents/guardians of all participants, in conjunction with assent from the participants themselves. Study data will be submitted for publication regardless of results. This study is funded through a Canadian Institutes of Health Research grant.

Trial registration number: NCT03767933, First registered December 07, 2018

Words: 296/ 300

Article Summary

Strengths and limitations of this study

1. This study employs a novel design involving two simultaneously run, complementary, randomized controlled trials.
2. Participating families will choose in which trial they wish to participate, thus engaging and empowering them as a key participant in healthcare research decision-making.
3. This study will collect preference and opinion data from families, in order to better understand their analgesic decision-making for their children.
4. We expect that some parents/caregivers will be hesitant to accept opioids thus leading to an imbalance in the pace of recruitment between the two trials.
5. Given the sample size, this study will not be able to provide definitive evidence regarding rare but serious adverse events.

INTRODUCTION

Musculoskeletal (MSK) injuries are very common and are associated with moderate to severe pain for most children. [1, 2] Despite three decades of research in this area, recent evidence confirms that pediatric pain management in the emergency department (ED) is still suboptimal. [3-5] Previous studies have demonstrated that only 35% of children presenting to a pediatric ED with fractures or severe sprains received *any* analgesic. [6, 7]

The American Academy of Pediatrics recommends acetaminophen, ibuprofen and opioids as the top three medication choices for the treatment of acute pain in children. [8] These are also the top three most commonly used analgesics for children with MSK injury. [3, 4, 6, 9, 10] However, there has recently been a concerted movement to limit opioid use in children, due, in large part, to the current Opioid Crisis.[11, 12] Clinicians are increasingly less likely to prescribe oral opioids to young children, and caregivers are increasingly less willing to administer them. [5] The fear of adverse events, particularly respiratory depression and deep sedation, are other important reasons to explain the reluctance to prescribe an opioid to children with moderate to severe pain. [13]

Clinicians are currently seeking optimal (and for many, non-opioid) oral analgesic options with the best efficacy and safety profile. It is known that the under-treatment of children's pain is partly due to a lack of evidence to support clinician decision-making in choosing the most effective medication. [4, 14] A recently published systematic review of MSK injury pain management concluded that an optimal analgesic approach could not be identified at this time. [15] Very few pediatric studies of analgesic combination therapy for MSK injury exist, and extrapolation from adult data can be misleading, both in establishing the correct dose and in assessing effect. [15-18] Research has demonstrated that a combination of oral morphine with ibuprofen was no more effective and was less safe than oral ibuprofen alone for children's MSK pain. [16] Two clinical trials of oral morphine versus ibuprofen have shown that oral morphine was not superior to ibuprofen alone. [19, 20] Similarly, oxycodone was no more effective and was less safe than ibuprofen for post-discharge fracture pain. [21] Further, tramadol, hydrocodone, and codeine are not recommended for widespread use in children due to safety concerns. [22-25] There is some emerging work from non-ED settings to suggest that oral hydromorphone may be an effective alternative to oral morphine and oxycodone. [26, 27] Oral hydromorphone is a long-acting opioid analgesic with a duration of action up to 4 hours and is more potent than oral morphine, but with fewer side effects. [28] Both oral hydromorphone and ibuprofen's peak analgesic action occurs at 60 minutes post administration.

The proposed study aims to determine if acetaminophen or hydromorphone, when added to ibuprofen, offers more clinical pain relief than ibuprofen alone, for children with an acute MSK injury. Further, it will determine if the combination of hydromorphone and ibuprofen is more clinically effective than the combination of acetaminophen with ibuprofen. This study, which will consist of two clinical trials, will inform health-care decisions by providing evidence for the effectiveness and safety of commonly prescribed

analgesic agents, and compare them to the most commonly used monotherapy, ibuprofen. [3, 6]

METHODS AND ANALYSIS

This study will be conducted with a novel preference-informed complementary trial design and is comprised of two simultaneous 'parallel' trials. Eligible parent/caregiver-child pairs will decide which trial they wish to participate in: a three-armed opioid-inclusive trial (the Opioid trial) or a two-armed non-opioid trial (the Non-Opioid trial). Once the parent/caregiver and child have chosen their preferred trial, conduct within each trial will follow traditional randomized, double-blind, parallel assignment, placebo-controlled superiority trial methodology. Study endpoints will be identical for both trials within this study. The study protocol is reported using the SPIRIT-PRO reporting guidelines. [29] (See Table 1.)

Table 1. WHO Trial Registration Data Set

Data Category	Information
Primary Registry and Trial Identifying Number	clinicaltrials.gov NCT03767933
Date of Registration in Primary Registry	December 7, 2018
Secondary Identifying Numbers	University of Alberta Research Ethics Board # Pro00073476
Source(s) of Monetary or Material Support	Canadian Institutes of Health Research SPOR Innovative Clinical Trials Grant (MYG-151207)
Primary Sponsor	University of Alberta
Secondary Sponsor(s)	-
Contact for Public Queries	Dr. Samina Ali 780.248.5575 sali@ualberta.ca
Contact for Scientific Queries	Dr. Samina Ali 780.248.5575 sali@ualberta.ca
Public Title	The No OUCH Study
Scientific Title	A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Study
Countries of Recruitment	Canada
Health Condition(s) or Problem(s) Studied	Acute musculoskeletal injury
Intervention(s)	**Opioid Trial**: A. Oral hydromorphone (0.05mg/kg, max 5mg) + Oral ibuprofen (10mg/kg, max 600mg) B. Oral acetaminophen (15mg/kg, max 1000mg) + Oral ibuprofen (10mg/kg, max 600mg) **Non-Opioid Trial**: Oral acetaminophen (15mg/kg, max 1000mg) + Oral ibuprofen (10mg/kg, max 600mg) (Comparator for both trials: Oral ibuprofen 10mg/kg, max 600mg)

Key Inclusion and Exclusion Criteria	To be eligible to participate in this study, an individual must meet all of the following criteria: 1.Child aged 6-17 years, 2. Presenting to the emergency department with an acute limb injury (<24 hours old) that is neither obviously deformed nor having neuro-vascular compromise (as assessed by the triage nurse), 3. Self-reported pain score ≥ 5 on the 0 to 10 verbal Numerical Rating Scale at triage Exclusion criteria include: 1. Deemed to require immediate intravenous (IV) or intranasal (IN) pain medications by the clinical team, 2. Previously known hypersensitivity to study medications, 3. Acetaminophen or NSAID use within 3 hours prior to recruitment, 4. Opioid use within 1 hour prior to recruitment, 5. Caregiver and/or child cognitive impairment precluding the ability to self-report pain or respond to study questions, 6. Injury suspected to be due to non-accidental trauma/ child abuse (as assessed by the triage nurse or reported by the family), 7. Suspected multi-limb fracture, 8. Chronic pain that necessitates daily analgesic use, 9. Hepatic or renal disease/dysfunction, 10. Bleeding disorder, 11. Known pregnancy, 12. Vomiting that precludes the ability to take oral medications (as determined by the family), 13. Caregiver and/or child inability to communicate fluently in English or French in the absence of a native language interpreter, 14. Caregiver unavailable for follow-up, or 15. Previous enrolment in the No OUCH study
Study Type	Randomized, Double-Blind, Placebo-Controlled Superiority Trials
Date of First Enrollment	April 20, 2019
Sample Size	536
Recruitment Status	Actively recruiting
Primary Outcome(s)	The **Primary Efficacy Outcome** will be the self-reported pain score at 60 minutes, using an 11-point 0-10 verbal Numerical Rating Scale (vNRS).
Key Secondary Outcomes	The **Principal Safety Endpoint** will be the proportion of children with adverse events related to study drug administration.

Ethics Review	University of Alberta Research Ethics Board # Pro00073476
Completion date	-
Summary Results	-
IPD sharing statement	De-identified data can be shared, on a case-by-case basis, upon discussion with the principal investigator.

Study Setting
This study will be conducted in six pediatric EDs across Canada: 1. Stollery Children's Hospital (Edmonton, Alberta) (coordinating site), 2. Alberta Children's Hospital (Calgary, Alberta), 3. Winnipeg Children's Hospital (Winnipeg, Manitoba), 4. Children's Hospital at London Health Sciences Centre (London, Ontario), 5. CHEO (Ottawa, Ontario), and 6. Centre Hospitalier Universitaire Ste-Justine (Montreal, Quebec). The annual ED census for recruiting centers ranges from 30,000 to 80,000 patient visits. Study recruitment began on April 20, 2019 and is expected to be completed within 18 months.

Eligibility and Exclusion Criteria
Children will be eligible if they are 6 to 17 years, presenting to the ED with an acute limb injury (<24 hours old) that is neither obviously deformed nor having neuro-vascular compromise, and have a self-reported verbal Numerical Rating Scale pain score ≥ 5 at triage. This age group was chosen as fractures rarely occur under this age, and a consistent and validated pain measurement tool can be employed across this age range.

Children will be excluded if they meet any of the following criteria: (a) require immediate intravenous or intranasal pain medications (b) have known hypersensitivity to study medications, (c) receive acetaminophen or NSAID within three hours prior to recruitment, (d) receive opioids within one hour prior to recruitment, (e) parent/caregiver or child cognitive impairment precluding the ability to self-report pain or respond to study questions, (f) injury suspected to be due to non-accidental trauma or child abuse, (g) suspected multi-limb fracture, (h) chronic pain that necessitates daily analgesic use, (i) known hepatic or renal disease/dysfunction, (j) known bleeding disorder, (k) known pregnancy, (l) vomiting that precludes the ability to take oral medications, (m) parent/caregiver and/or child inability to communicate fluently in English or French in the absence of a native language interpreter, (n) parent/caregiver unavailable for follow-up, or (o) previous enrolment in this study.

Study Interventions and Rescue Medications
If a family chooses the **Opioid** trial, their child will be randomized to one of three treatment arms: (a) oral ibuprofen + acetaminophen placebo + hydromorphone placebo, OR (b) oral ibuprofen + oral acetaminophen+ hydromorphone placebo, OR
(c) oral ibuprofen + acetaminophen placebo + oral hydromorphone.

If a family chooses the **Non-Opioid** trial, their child will be randomized to one of two treatment arms: (a) oral ibuprofen + acetaminophen placebo, OR (b) oral ibuprofen + oral acetaminophen.

Ibuprofen will be dosed as 10mg/kg (maximum 600 mg), acetaminophen as 15mg/kg (maximum 1000 mg), and oral hydromorphone as 0.05mg/kg (maximum 5 mg).

Given the consistent recommendations that ibuprofen be the first-line therapy for acute MSK injury pain, [15, 30-32] and the fact that it is the medication of choice for triage-initiated pain protocols at most Canadian pediatric EDs, [33] ibuprofen will serve as the comparator (standard of care) for both trials.

All study medications and placebos will be administered as a single oral dose in liquid form. No other medications will be administered as part of the study. However, enrolled patients will be eligible to receive additional analgesia at any time if requested and/or deemed necessary by the clinical team. The treating physician will order rescue analgesia at their discretion. Any such co-interventions, including non-pharmacologic interventions (e.g. ice, splinting) will be documented.

Randomization, Allocation Concealment, and Blinding

Randomization will be determined using a secure online centralized randomization tool hosted by the Women and Children's Health Research Institute (WCHRI, University of Alberta). [34] Participants will be allocated via a kit number. A statistician will oversee the generation of a randomized listing of the treatment by kit number using a 1:1:1 allocation scheme for the Opioid trial, and a 1:1 allocation scheme for the Non-Opioid trial. This will be further stratified by center using block-randomization with variable block sizes. These randomization lists, which will be sent directly by the statistician to the participating site's research pharmacy team, will be used by each participating site's research pharmacy to create pre-packaged, sequential study kits for each trial. Research nurses will then allocate the kits to enrolled participants in sequential fashion.

Study participants, research nurses (the outcome assessors), ED staff, and data analysts will all be blinded with respect to the intervention. In the rare occurrence where a treating physician feels that knowing what the child has received will impact further clinical care, the study blind can be broken by the clinical team for patient safety. The protocol for unblinding will involve the research nurse logging in to a secure web-based unblinding system with REDCap. However, only the treating physician will 'click' on the button to reveal the study medications administered. Thus, parents/caregivers, children and research staff will remain blinded.

Recruitment and Data Collection

The patient's initial assessment upon arrival to the ED will be performed by a triage nurse. Triage nurses, research nurses, or their designate will identify potentially eligible participants. Research nurses will be present in enrolling EDs up to 16 hours a day to screen children and assess eligibility based on the inclusion and exclusion criteria outlined above. Research nurses will follow site-specific Research Ethics Board (REB)

guidelines regarding approaching families for research studies. Verbal consent for screening will be obtained from families and documented. For eligible parent/caregiver-child pairs who express interest in study participation, an ED physician will confirm eligibility, and the research nurse or designate will complete consent and assent, as appropriate (Appendix 1).

After obtaining written informed consent from the parent/caregiver, and assent from the child where appropriate, the research nurse will determine preference for study trial (ie. Opioid or Non-Opioid). In keeping with the ethical requirements of the involved Canadian institutions, we will have consent forms for parent/caregivers, assent forms for children, and mature minor consent forms for both accompanied and unaccompanied youth who are deemed to be mature minors. All of these forms are written in a manner to reflect the reading and comprehension capacity of the target groups. If the parent/caregiver and child pair do not voice a trial preference, they will be enrolled in the Opioid trial as it contains all three possible medication combinations offered in the study, as outlined in the consent form. The research nurse will administer the study medications according to the randomization scheme for that chosen trial (Figure 1). If a participant vomits within 30 minutes of drug administration, it will be repeated once in accordance with current clinical and research practice. [35] The parent/caregiver will be asked to complete a brief survey in the ED to explore their reasons for choosing their study trial (see Appendix 2).

Following study drug administration, the research nurse will monitor the participant for up to 120 minutes, with safety and efficacy measures recorded at the time of recruitment (T-R), time of study drug administration (T-0), at 30 minutes, 60 minutes, 90 minutes and 120 minutes post-study drug administration (T-30, T-60, T-90, T-120 respectively), at the time of medical examination (T-ME) and as soon as possible following x-ray (T-XR). All study measures at T-30, T-60, T-90, and T-120 will be collected within 15 minutes of the designated time point (i.e. $\pm$ 15 minutes). All study measures for T-ME and T-XR will be collected within 30 minutes of the designated time point. If a patient is discharged prior to T-120, the study measures will be recorded one last time at the time of discharge.

Pain scores will be measured on the verbal Numerical Rating Scale (vNRS), Visual Analog Scale (VAS), and Faces Pain Scale-Revised (FPS-R) at each study time point. [36, 37] In addition, the research nurse will also evaluate the presence of adverse events (e.g. nausea, vomiting), record vital signs (pulse, blood pressure, respiratory rate, oxygen saturation) and evaluate sedation level using the Ramsay Sedation Scale (RSS). [38] Reporting of adverse events will be in keeping with Health Canada regulations and REB guidelines. Prior to their discharge from the ED, both the child and parent/caregiver will be asked to rate acceptability of the study medication received during the trial using a Likert scale. (Figure 2)

Two brief 10-minute follow-up surveys will be completed with the parent/caregiver following their child's discharge from the ED. Parents/caregivers will have the option of completing these over the phone or online via a secure email link. Non-responders to email contact and those who prefer phone follow-up will be called 3-5 times depending

on local REB requirements. The first follow-up survey, conducted at 1-3 days post ED discharge, will determine the occurrence of any adverse events since discharge. The second follow-up survey will be completed at 1-2 weeks post ED discharge, to determine parent/caregiver comfort and satisfaction with at-home pain management and the extent of functional limitations for their child.

To achieve adequate participant enrolment to reach target sample size, we will monitor the monthly recruitment targets and have regular (every 4-8 week) team meetings to allow for timely implementation of procedural changes. There are no plans for patient follow-up beyond the two-week study period, given that only one dose of study medications will be administered. All study scripts and data collection tools will be available in English and French.

Outcome Measures

The Primary Efficacy Outcome will be the self-reported vNRS pain score at 60 minutes post study drug administration. The vNRS, ranging from 0 (no pain) to 10 (worst pain imaginable), is the most commonly used, responsive pain measurement tool for the study age group. [39] It has been successfully employed in several children's pain studies, [40, 41] and is validated for the age range of children included in this study. [42] The 60-minute primary outcome time point reflects the peak plasma concentration and clinical action of both oral hydromorphone and ibuprofen. [28, 43-45]

The Principal Safety Endpoint will be the proportion of children with adverse events related to study drug administration. Medication safety profiles influence parent/caregiver and patient willingness to adhere to medication regimens. [46] It has also been previously established that more safety data is urgently needed to inform clinical decision-making when using the study medications of interest. [30]

The Secondary Outcomes will include efficacy, safety and preference endpoints:

Secondary Efficacy Outcomes

1. A vNRS pain score <3 at T-60
2. A vNRS pain score reduction of at least 2 points out of 10 at T-60
3. Pain scores at study time-points (T-30, T-60, T-90, T-120, T-ME and T-XR).
4. ED length of stayRescue analgesic in the 60 minutes following administration of study medication
5. Time to effective analgesia, defined as the first vNRS pain score <3 post-intervention
6. Children's self-reported pain intensity on the VAS and the FPS-R at all study time-points

Secondary Safety Outcomes

1. Any serious adverse events during the study period, including apnea, cardiac arrest, or death
2. A Ramsay Sedation Score between 1 to 3
3. Each specific adverse event type (e.g., nausea, dizziness, itchiness) during the study period

4. Missed fractures or dislocations

Secondary Preference Outcomes

1. Parent/caregiver reasons for choosing the opioid or the non-opioid trial
2. Self-reported parent/caregiver and child satisfaction with pain relief and acceptability of study medications, using a previously employed 5-point Likert scale [47]
3. Physicians' in-ED preference of analgesics for the patient
4. Parent/caregiver comfort treating their child at home, as measured by a scale created by the study team [5]

Sample Size

The sample size for the three-armed opioid trial is 105 patients per arm, for a total of 315. The sample size for the two-armed non-opioid trial is 85 patients per arm, for a total of 170. Thus, the total for the No OUCH Study would be 485. To account for missing data for the primary outcome due to early withdrawal, the study will over-recruit by approximately 10%, for a target recruitment of approximately 540 patients. This sample size was determined based on a two-sided level of 0.05, a power of 0.95, a minimally clinically important difference (MCID) of 1.5 on the vNRS, an estimate of the standard deviation (SD) of the difference of 2.7, [48] and a Bonferroni correction to adjust for the three treatment comparisons. Based on previously conducted survey work, [49] an imbalance in recruitment pace between the opioid and non-opioid trials is expected. However, both trials will continue to recruit until the sample size is met for both. One trial will over-recruit to allow for completion of the other, without compromising the key preference-based study design. To ensure timely completion of the No-OUCH Study, we will monitor the recruitment rates and potentially update the randomization strategy if there is an extreme over-recruitment for one of the trials.

Statistical Methods

All analyses will adhere to the principle of intention-to-treat. There will be three treatment comparisons: (1) ibuprofen versus ibuprofen plus acetaminophen; (2) ibuprofen versus ibuprofen plus hydromorphone; (3) ibuprofen plus acetaminophen versus ibuprofen plus hydromorphone. Due to homogeneity in the trial end-points for the two complementary trials, we will consider a joint analysis across both the endpoints if the two patient populations are sufficiently similar. This will be determined using the following specified decision rules.

For each treatment comparison, the primary analysis will compare the mean vNRS reduction for pain scores at T-60. This comparison will be facilitated using a linear mixed model with the T-0 measure on the vNRS for pain as a covariate and a site-specific effect. We will consider whether the two trials can be analysed together used nested linear mixed models with and without a trial by treatment interaction term. If this interaction term is not significant then a single treatment effect will be estimated for each comparison. A two-sided level of 0.05 will be used to declare significance. A Bonferroni -Holm correction will be used to adjust for the three treatment comparisons. The proportion of children with a self-reported of vNRS of less than 3 at 60 minutes, the proportion who require a rescue analgesic by 60 minutes and the proportion who

experienced adverse events related to study drug administration will be analyzed using a Mantel Haenszel chi-squared test, stratified by site. All other outcomes will be summarised using appropriate descriptive statistics.

There will be no interim analyses of the efficacy endpoints, as it is very difficult to change practice based on the results from small samples, regardless of the p-value. The Data Safety Monitoring Board (DSMB) will be provided with a masked comparison between treatment groups with respect to the safety endpoints at the intervals of their choosing. The decision to stop the trial for safety reasons will be left to the discretion of the DSMB (See Appendix 3 for DSMB Charter). Interim analyses will also monitor the relative recruitment rate of the two trials. If insufficient participants are enrolled on either of the No OUCH trials, appropriate action will be taken to ensure sufficient power to conclude following the completion of the trials. Further information is available in the Statistical Analysis Plan, which will be published separately.

Health Economic Methods

The trial will also examine the relative cost-effectiveness of each of the medication options. The economic evaluation will take a healthcare perspective for the reference case, in line with CADTH guidance [50] and in secondary analyses will consider societal costs. Information will be collected on interventions during ED visit, in hospital medication costs, and follow up care from other health services, as well as on costs incurred by families in interacting with health services. Quality of life will be measured by asking parents/caregivers to report their child's quality of life using a 10-point numeric scale. The health economic analysis will estimate the expected cost per incremental change in quality of life and will use nonparametric bootstrapping methods to calculate uncertainty to assist in decision making about the value of providing different treatment strategies.

Patient and Public Involvement

The team's patient engagement partner (SH) has provided ongoing input on the study protocol and data collection tools. The study team was also supported by parent advisory groups at the ECHO (Evidence in Child Health to Enhance Outcomes) Research Program (Edmonton, Alberta) and TREKK (Translating Emergency Knowledge for Kids) (Winnipeg, Manitoba). Parent advisors reviewed and provided feedback on the wording, readability, sensitivity, flow and content of parent/caregiver surveys. Following recruitment completion, parent advisors will be engaged in focus groups to discuss study results and dissemination plans in the context of family-centered care.

Data Management

Data management services will be provided by the WCHRI data coordinating centre. Study data will be entered and managed using REDCap (Research Electronic Data Capture) tools hosted and supported by WCHRI.[51] WCHRI's REDCap installation is a validated electronic, web-based data capture system housed in a secure data center at the University of Alberta.

Data will be entered directly into the study database or, in case of technical failure, it may be collected on paper and then digitally recorded in REDCap. Selected data elements will be validated electronically on an ongoing basis throughout the study and any discrepancies will be assigned to members of the study team for resolution. REDCap includes internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate (see Appendix 4 for data management plan).

Only limited identifiable data will be stored in REDCap (e.g. email address) for the purposes of completing follow-up surveys. Study participants' contact information will be stored securely at each clinical site for internal use during the study. Paper records (e.g., signed consent and assent forms) will be stored in a secure locked cabinet at each site, with limited access by the research team only. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing REB, institutional policies, or sponsor requirements.

Monitoring

Monitoring for quality and regulatory compliance will be performed by the University of Alberta's Quality Management in Clinical Research (QMCR) office. QMCR is an independent unit housed within the university's central administration that provides arms-length review of all University of Alberta sponsored trials, at least three times per year. Details of clinical site monitoring will be documented in a Clinical Monitoring Plan.

Safety oversight will be under the direction of a DSMB which will function independently of the investigators. This committee will be chaired by Dr. Garth Meckler and is composed of 5 individuals with expertise in trial methodology, epidemiology, biostatistics, and pediatric emergency medicine. The DSMB will meet at least semi-annually to assess safety and efficacy data and will operate under the rules of an approved charter/ terms of reference.

ETHICS AND DISSEMINATION

Based on previously conducted research with oral opioids, [16, 20, 30] nausea, mild dizziness, and drowsiness are expected to be possible non-serious adverse events in this study. There is a small potential risk of respiratory depression following the administration of any opioid, although the risk is notably greater with repeat dosing and intravenous administration. This risk will be minimized by using only a single oral dose and vigilantly monitoring the participant's vital signs and level of sedation during the study period, which extends for one hour past the peak action point of the drugs.

This study will be federally monitored by Health Canada, and approval has been granted for the conduct of this study (HC6-24-c220455). The Research Ethics Board at the University of Alberta has further approved this study (Pro00073476). The five other participating centers acquired ethics approval from their local REBs prior to commencing recruitment. Any protocol amendments will be submitted for Health Canada review and REB approvals prior to implementation and will be added as an amendment to the

clinicaltrials.gov registration. Institutional approvals from each participating pediatric ED will be obtained prior to beginning recruitment.

Public opinion regarding opioids is notably negative at this time, thus there is a hesitancy to accept opioids, even when they are felt to be clinically indicated. As such, it is expected that some parents/caregivers will be hesitant to accept opioids. [52-54] However, the study will leverage this opportunity to *understand* parent/caregiver perspectives and rationale for their decision-making. This valuable information can then inform knowledge translation of study results, educational initiatives and responsive healthcare provider prescribing of analgesia.

The study team plans to publish this trial in a high-impact, peer-reviewed journal and present the results at national and international meetings; authorship eligibility will be determined by employing the International Committee of Medical Journal Editors' recommended guidelines. [55] Statistical code and dataset can be made available upon request.

Competing Interests None declared.

Patient Consent After assessing child eligibility based on the outlined inclusion/exclusion criteria, research nurses will obtain parent/caregiver consent (and assent for children 7 years and older) prior to recruitment of each patient. The research nurse will provide the parent/caregiver and child with both a verbal and written explanation of the study and an opportunity to review the information and consent/assent forms privately. They will then return shortly afterwards to answer any questions parent/caregiver or child might have and obtain written consent and assent.

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AUTHORS' CONTRIBUTIONS

Dr. Samina Ali (SA) developed and revised the protocol, co-drafted the protocol paper, and will operationalize the study. She chose the previously validated tools for measuring the primary and secondary efficacy outcomes (vNRS, VAS and FPS-R).

Manasi Rajagopal (MR) is the national study coordinator who contributed to study design, co-drafted the protocol paper and will operationalize the study.

Dr. Lawrence Richer (LR) and Dr. Christopher McCabe (CM) co-developed the novel study methodology and contributed to protocol revision

Dr. Andrew R. Willan (AW), Dr. Maryna Yaskina (MY), and Dr. Anna Heath (AH) led the statistical analysis planning and contributed to protocol revision.

Dr. Amy L. Drendel (ALD) is a fracture outcomes expert who contributed to determining the secondary outcomes for the study; she contributed to methodology and revised the protocol.

Dr. Serge Gouin (SG), Dr. Antonia Stang (AS), Dr. Scott Sawyer (DB), and Dr. Maala Bhatt (MB), as site leads for this study, reviewed and revised the protocol, with special input into the Methods section of the study.

Serena Hickes (SH) is a family representative who reviewed and provided input into the study protocol. She provided lived experience in patient-oriented outcomes.

Dr. Naveen Poonai (NP), Dr. Martin Offringa (MA), and Dr. Terry Klassen (TK) co-developed the methodology and revised the protocol.

All authors have approved this final version of the protocol. None of the authors have financial or other conflicts of interests as they pertain to this study and its involved recruitment sites.

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Figures Legend

Figure 1. Study Interventions

Figure 2. Schedule of Study Measures

Table Legend

Table 1. WHO Trial Registration Data Set

Figure 1. Study Interventions

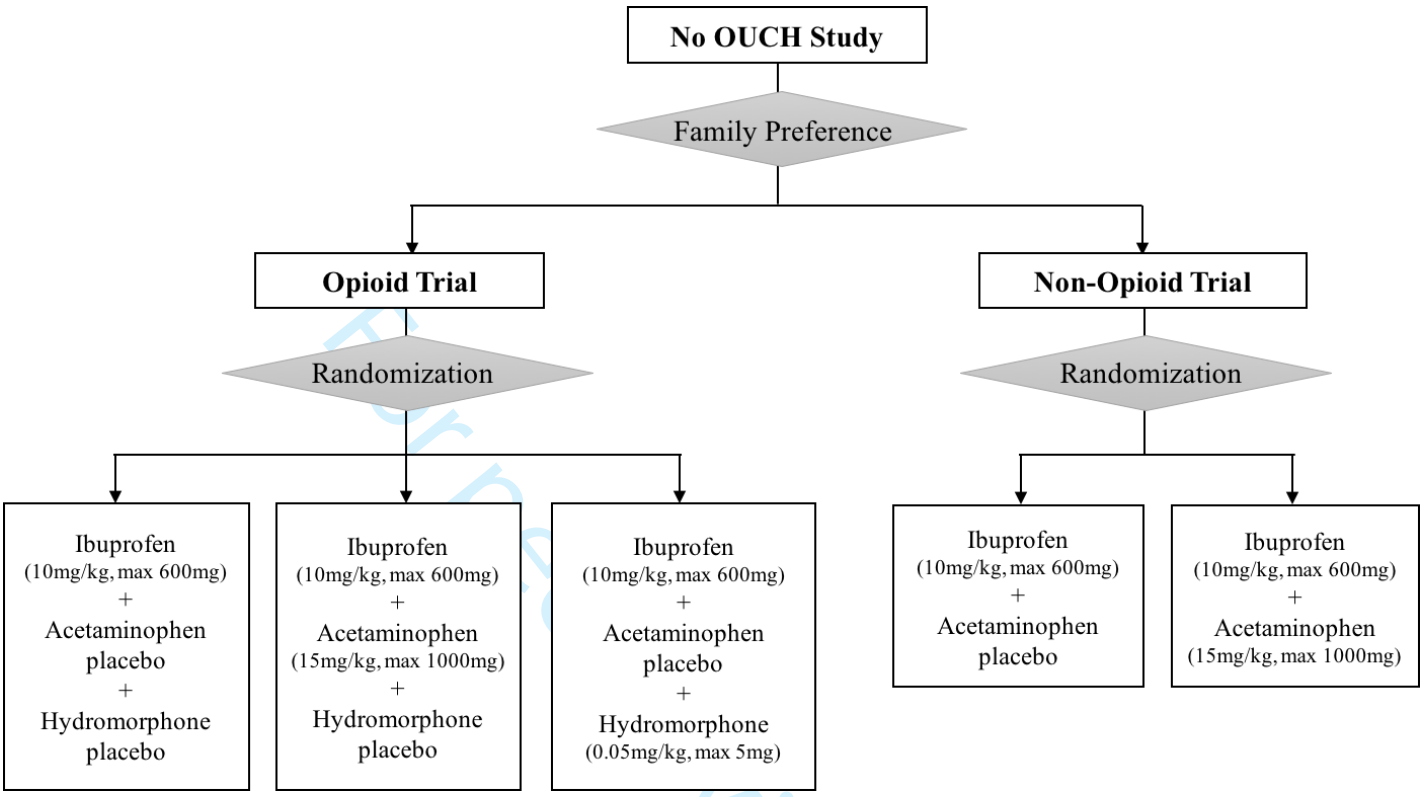
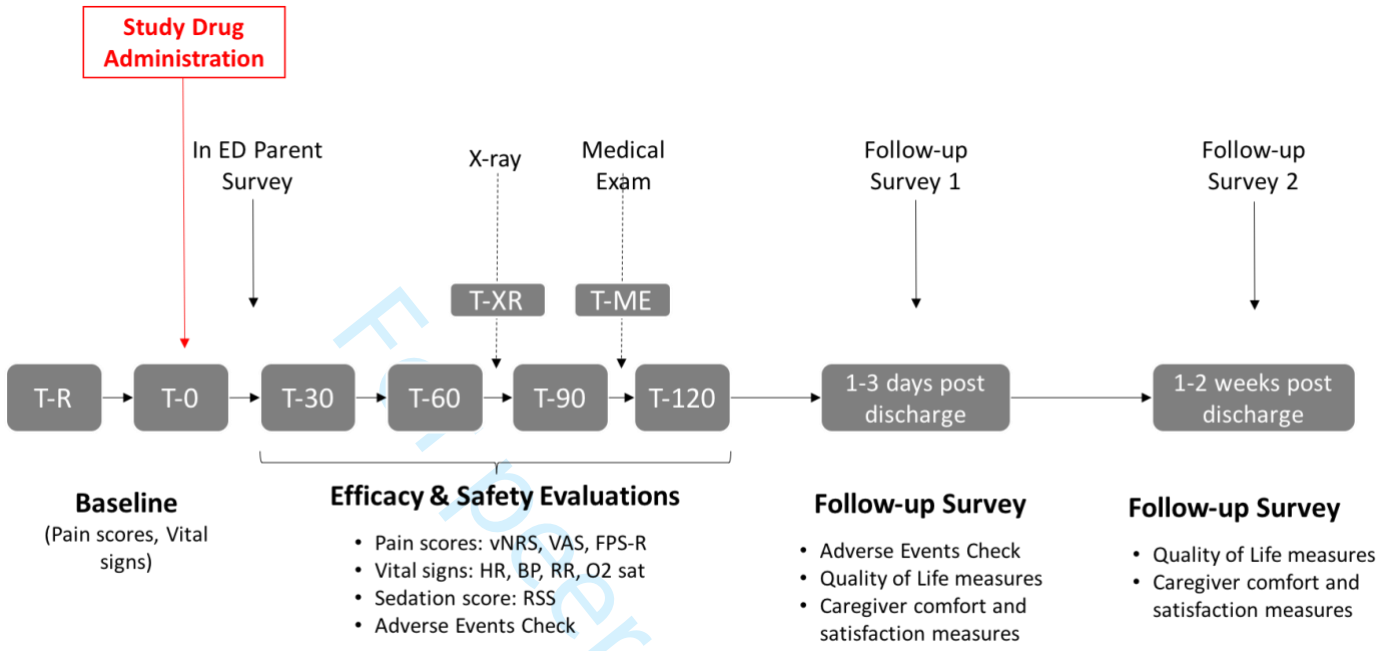


Figure 2. Schedule of Study Measures



vNRS=verbal Numerical Rating Scale; VAS=Visual Analog Scale; FPS-R=Faces Pain Scale-Revised; RSS=Ramsay Sedation Scale

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PARENT/GUARDIAN CONSENT FORM

Title of Study: A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries

Principal Investigator: Dr. Samina Ali (780) 248-5574
Research Coordinator: Ms. Manasi Rajagopal (780) 248-5440

Why am I being asked to consider this research study?
You are being asked if you and your child would like to be part of a research study. In this study, we are trying to determine the best ways to treat children's pain due to a limb injury. You are being asked to take part as your child may have pain due to an injury and is between 6 and 17 years old.

Before you make your decision one of the research team members will review this form with you. A copy of this sheet will be given to you to keep. If you would like more information, please feel free to ask. You are encouraged to ask questions if you feel anything needs to be made clearer. Please take the time to read this document carefully.

If your child is old enough to understand this information we would also like you to talk to them about being part of the study. If your child is 7 years of age or older, we would like you both to sign a form if you would like to participate in the study.

What is the reason for doing the study?
The purpose of this research study is to figure out which of three pain medicines best treats a child's pain. The pain medicines we are studying are ibuprofen (Advil/Motrin), acetaminophen (Tylenol/Tempra), and hydromorphone (Dilaudid). Ibuprofen and acetaminophen are the top two medicines used in the world and are approved for children's pain in Canada. Hydromorphone is used and approved for treating many kinds of children's pain in Canada, and we have received Health Canada approval to study it for the pain of limb injuries, since Canada has not yet approved it specifically for this problem. This study will help us figure out which pain medicine or combination of pain medicines works best for children with limb injuries. We would also like to understand the thoughts and feelings you have when making decisions about pain medication for your child.

This study is being conducted in six children's hospitals across Canada, and we will ask a total of over 500 children to be part of this study. Approximately 100 of these children will be recruited from the Stollery Emergency Department.

What will happen in the study?
If you agree to take part in this study, we will ask you to select which one of our two study groups you would like to be enrolled in: Group 1 OR Group 2. Regardless of which study you choose, your child will, at minimum, receive ibuprofen (Advil/Motrin) for their pain.

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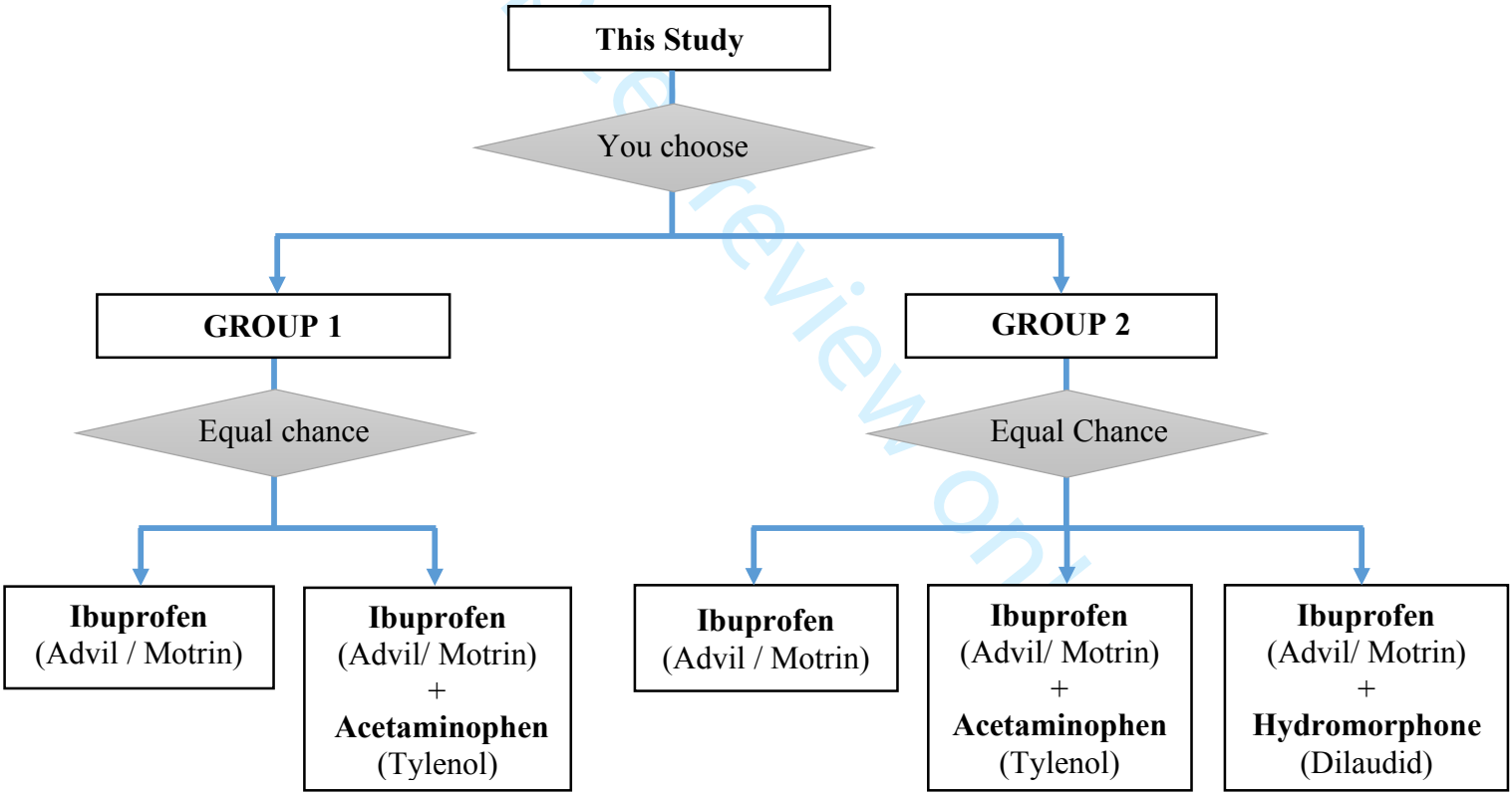
If you select **Group 1**, your child will have an equal chance of receiving one of the two medicine options below. This will be decided by the computer at random, so there is an equal chance of receiving either option, like the toss of a coin.

1. Oral liquid Ibuprofen (Advil/Motrin) only OR
2. Oral liquid Ibuprofen (Advil/Motrin) and oral liquid acetaminophen (Tylenol/Tempra)

If you select **Group 2**, your child will have an equal chance of receiving one of the following three medicine options:

1. Oral liquid Ibuprofen only (Advil/Motrin) OR
2. Oral liquid Ibuprofen (Advil/Motrin) and oral liquid acetaminophen (Tylenol/Tempra) OR
3. Oral liquid Ibuprofen (Advil/Motrin) and oral liquid hydromorphone (Dilaudid)

If you don't have a preference for a study group, we will assign you to Group 2, as this group includes all three of the options you might be offered when participating in this research study.



All children in the study will receive ibuprofen (Advil/Motrin), which is the standard medicine given to children for injury-related pain. Some children will also receive either acetaminophen (Tylenol/Tempra) or hydromorphone (Dilaudid). Neither the study nurse nor your doctor will know which combination of medicines your child has received for the study, but if we need to know this for medical reasons we can find out. After the study medicines have been given, your child may also get further medicines, which are not part of the study, as routinely recommended by the emergency doctor who is taking care of your child.

During the study your child will be monitored closely by the study nurse. The study nurse will measure your child's heart rate, breathing rate, blood pressure, oxygen levels, and pain levels every 30 minutes for up to 2 hours. They will also measure your child's pain when the doctor examines him/her and immediately following any X-ray procedures. If your child's medical care is finished before the 2-hour study period, and you are ready to leave, this is not a problem. Our research nurse will collect the measurements from your child one last time, and then you can go home, at your will. Participating in this study should NOT delay your leaving the emergency department or affect the timing of when the doctor will see you.

We will ask you to complete a short 5-minute questionnaire on an iPad, while you are in the emergency department today. This questionnaire will ask about your demographics, your child's injury and about your reasons for choosing your study group (ie. Group 1 vs. Group 2). We will also complete two 5-10 minute follow up surveys to see how your child is doing. You will have the option of completing these by email (we will send you a link through a secure online portal called REDCap) or over the phone. The survey will be done 24 hours after you leave the emergency department, and again 1 week after. After the two surveys are done, your part of this study is done.

What are the risks and discomforts?
Your child may experience side effects from participating in this study. Some side effects are known and listed below, but there may be risks in this study that are currently not known. If we find out anything new during the course of this study that may change your willingness to be in the study, we will tell you about these findings.

Based on our team's previous work, we expect nausea, mild dizziness, and tiredness to be possible non-serious common side effects. It is possible that your child might experience this. There is a very rare risk of serious drowsiness and low breathing rate following the use of any opioid medicine; this is extremely rare when the medicine is taken by mouth, like it is in this study. Even though such events are very rare, we want to make sure that your child is safe at all times. So, our research nurse will be watching your child closely for these effects and will even use an oxygen monitor to closely observe them. If such an event were to occur, the emergency team of doctors and nurses would take care of your child, as they are already present in the department.

Finally, there is an extremely rare risk of an allergic reaction to one of the study medicines.

What are the benefits to my child?
Your child may not benefit directly from being in the study, but you will be helping us understand how to best treat pain in children who come to the emergency department.

What happens if my child is injured because of this research?
If your child becomes ill or injured as a result of being in this study, he/she will receive necessary medical treatment, at no additional cost to you. By signing this consent form you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities. Contact the principal investigator, Dr. Samina Ali, at 780-248-5574, if your child has suffered an injury. If required, go to the emergency department right away.

Do I have to take part in the study?
Being in this study is your and your child's choice. If you decide to be in the study, you can change your mind and stop being in the study at any time by letting the research nurse know. This will in no way affect the care or treatment that your child is entitled to.

Can our participation in the study end early?
In addition to you being able to stop the study at any time, the study doctor may withdraw your child from this study for reasons such as:

- Your child is unable to tolerate the study medication
- The study doctor no longer feels this is the best option for your child

If your child is removed from this study, the research team will discuss the reasons with you and plans will be made for your child's continued care outside of the study.

Are there other choices to being in this research study?
If you choose not to take part in this study today, your child's doctors and nurses will decide what medicines to treat your child's pain with.

What will it cost me to participate?
There will be no costs to you to be in this study.

Will my information be kept private?
During the study, we will be collecting health data about your child. We will do everything we can to make sure that this data is kept private. No data relating to this study that includes your child's name will be released outside of the study doctor's office or published by the researchers. Sometimes, by law, we may have to release your information with your name in it so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your health information is kept private.

The study doctor/study staff will look at your child's personal health records held at the hospital, and/or kept by other health care providers that your child may have seen in the past (i.e. your family doctor). Any personal health information that we get from these records will be only what is needed for the study.

During research studies, it is important that the data we get is accurate. For this reason, your child's health data, including their name, may be looked at by people from: the research team, the study sponsor (University of Alberta), the University of Alberta auditors, clinical trial monitors, and Research Ethics Board, and Health Canada. By signing this consent form you are giving permission for the study doctor/staff to collect, use and disclose information about your child from his/her personal health records, as described above.

After the study is done, we will still need to securely store your health data that was collected as part of the study. In Canada, the law says we have to keep the data stored for 25 years after the end of the study. The data we collect will be stored, in Canada, on a system called REDCap. It will be accessible to and managed by, staff at the Women & Children's Health Research Institute

at the University of Alberta. If you leave the study, we will not collect new health information about you, but we will need to keep the data that we have already collected.

After study completion, your study data may be used again by other researchers. Any of your personal information (i.e. your name, address, telephone number) that can identify you will be removed or changed before files are shared with other researchers. Researchers that wish to use study data must 1) have their new study approved by an ethics board; 2) sign an agreement ensuring your confidentiality and restricting data use to only the approved study.

What if I have questions?
If you have any questions about the research now or later, please contact the principal investigator Dr. Samina Ali at 780 248 5574, or the research coordinator Ms. Manasi Rajagopal at 780 248 5440.

If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780-492-2615. This office is independent of the study investigators.

A copy of this sheet will be given to you to keep. This study is funded by the Canadian Institutes of Health Research and the Women and Children's Health Research Institute. The Institution and study doctor are getting money from the study sponsor to cover the costs of doing this study. You are entitled to request any details concerning this compensation from the Principal Investigator.

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CONSENT

Title of Study: A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries

Principal Investigator(s): Dr. Samina Ali **Phone Number:** 780 248 5574
Research Coordinator: Ms. Manasi Rajagopal **Phone Number:** 780 248 5440

	Yes	No
Do you understand that you and your child have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you and your child are free to leave the study at any time, without having to give a reason and without affecting your child's future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your child's records, including personally identifiable health information?	☐	☐

Who explained this study to you? _____

I agree for my child and I to take part in this study, and I have the legal authority to give this consent.

Signature of Parent or Guardian _____

(Printed Name) _____

Date: _____ Time: _____: _____ AM / PM
(circle one)

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____

Date: _____ Time: _____: _____ (24h clock)
(dd / mmm / yyyy)

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A SIGNED COPY GIVEN TO THE RESEARCH PARTICIPANT

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CHILD ASSENT FORM

Title of Study: A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

Principal Investigator: Dr. Samina Ali **Phone Number:** (780) 248-5574

Study Coordinator: Ms. Manasi Rajagopal **Phone Number:** (780) 248-5440

We want to tell you about a research study we are doing. A research study is a way to learn new information about something. Children do not need to be in a research study if they don't want to.

Why am I being asked to be in this study?

We would like to find out more about what pain medicine works best for children with sprains or broken bones. You are being asked to join the study because you have pain due to an injury. Over 500 kids will take part in this study.

If I join the study, what will I have to do?

If you and your parent agree to take part, we will ask you to do a few things:

- First, we will ask you to take some pain medicines.
- Then, we will ask you to tell us about your pain, how you are feeling, and if you have any bad effects from the medicines we gave you.
- While you are in the emergency department, we will also check your heart rate and breathing.
- After you leave here, we will call or email your parents tomorrow and again after 1 week, to see how you are doing.

Will any part of the study hurt?

No, but sometimes kids can feel a little bit tired or sleepy after taking pain medicine. It is possible that you might feel this, but your parents and the research nurse will be there to help you, if this happens.

Will the study help me?

If you take part in this study, we hope the medicine we give you will help you. Even if you don't take part in the study, you can still ask your nurse for pain medicine, if you need it.

Will the study help others?

This study will help us figure out the best way to take care of kids' pain in the future.

What do I get for being in this study?

There are no direct cash or gifts for you for helping with this study.

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Can I say no?
Yes, of course, you do not have to be in the study. It's up to you. If you do join the study, you can change your mind and stop being part of it at any time. No one will upset if you decide you don't want to do this study or if you decide to stop part way through. You can tell your parents, your doctor or the research nurse if you want to quit. Before you say **yes or no** to being in this study, the research nurse will answer any questions you have. If you join the study, you can ask questions at any time.

What other choices do I have if I say no to this study?
If you choose not to be this study, your doctor and nurse will decide what pain medicines to give you. The three medicines that we are using in this study are the most commonly used medicines for this type of injury.

Do my parents know about this study?
This study was explained to your parents and they said that we could ask you if you want to be in it. You can talk this over with them before you decide.

Who will see information about me?
The information collected about you during this study will be kept safe. Nobody will know it except the people doing the research. The study information about you will NOT be given to your friends or teachers or anybody else.

What if I have any questions?
You can ask your mom or dad about anything you don't understand. You can also talk to the research nurse who is here, today. Dr. Samina Ali is the main doctor in charge of this study. If you have any questions about this study that you didn't think of now, either you can call or have your parents call her at 780 248 5574. You will be given a copy of this paper to keep.

Would you like to take part in this study?

☐ **Yes, I will be in this research study.** ☐ **No, I don't want to do this.**

Child's Name	Signature of Child	Date	_____: _____ am / pm (circle one)

☐ Assent was obtained verbally Age at the time of assent: _____ years

Person obtaining Assent	Signature	Date (dd/ mmm/yyyy)	_____: _____ (24h clock)

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ ____ ____ ____ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

REDCap Forms: Summary

Time Point / Section	
Screening	➢ Pre-Screening ➢ Eligibility ➢ Informed Consent ➢ Evaluation 1 (TR) ➢ Injury Details and Previous History ➢ Medical Oversight of Screening
T0 (Time of Study Drug Administration)	➢ Selection of Family Preference ➢ Study Drug Administration ➢ Evaluation 2 (T0) ➢ Evaluation Time point Calculator (will be programmed in REDCap) ➢ Contact Information Sheet ➢ In PED Caregiver Survey
T30	➢ Evaluation 3
T60	➢ Evaluation 4
T90	➢ Evaluation 5
T120	➢ Evaluation 6
TME (Time of Medical Exam)	➢ Evaluation 7
TXR (Time of X-Ray)	➢ Evaluation 8
PRE-Discharge	➢ ED Discharge Evaluation (only complete if discharged before 120 min) ➢ Pre-discharge Questions (complete with ALL families)
POST-Discharge	➢ Post-discharge Questions
Follow-up Survey 1 (24h)	➢ Call Log ➢ Follow-up Survey 1 (24h)
Follow-up Survey 2 (1-2w)	➢ Call Log ➢ Follow-up Survey 1 (1-2w)
Logs	➢ Concomitant and Rescue Medications ➢ Adverse Events ➢ Protocol Deviations ➢ Unanticipated Problems ➢ Early Withdrawal Form

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	___ ___ ___ - ___ ___ ___ ___ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Pre-Screening (electronic SEMO Log)

Site	☐ Edmonton AB (1) ☐ Calgary AB (2) ☐ Winnipeg MB (3) ☐ Montreal QC (4) ☐ London ON (5) ☐ Ottawa ON (6)	
Name of Research Nurse completing screening / enrolment	First and Last Name	
Date and Time of Triage	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)	
Age	_____ years	
Sex	☐ Male	☐ Female
Was the family approached for this study?	☐ Yes	☐ No
If NO, specify reason and STOP HERE.	☐ Family refused overall consent to be approached for research ☐ Legal guardian not present ☐ RA busy with another study ☐ Did not meet eligibility criteria, specify _____ ☐ Other, Specify _____	
If YES, continue to Eligibility.		

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ ____ ____ ____ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Eligibility

Was verbal consent for screening obtained from the family? ☐ Yes ☐ No

Inclusion Criteria

1. Child aged 6-17 years	☐ Yes	☐ No
2. Presenting to the emergency department with an acute limb injury (<24 hours old) that is neither obviously deformed nor having neuro-vascular compromise (as assessed by the triage nurse)	☐ Yes	☐ No
3. Self-reported pain score ≥ 5 on the 0 to 10 verbal Numerical Rating Scale (vNRS) at triage	☐ Yes	☐ No

Exclusion Criteria

1. Deemed to require intravenous (IV) or intranasal (IN) pain medications by the clinical team	☐ Yes	☐ No
2. Previously known hypersensitivity to study medications	☐ Yes	☐ No
3. Acetaminophen or non-steroidal anti-inflammatory medication (NSAID) use, within 3 hours prior to recruitment	☐ Yes	☐ No
4. Opioid use within 1 hour prior to recruitment	☐ Yes	☐ No
5. Caregiver and/or child cognitive impairment precluding the ability to self-report pain or respond to study questions	☐ Yes	☐ No
6. Injury suspected to be due to non-accidental trauma/ child abuse (as assessed by the triage nurse or reported by the family)	☐ Yes	☐ No
7. Suspected multi-limb fracture	☐ Yes	☐ No
8. Chronic pain that necessitates daily analgesic use	☐ Yes	☐ No
9. Hepatic or renal disease/dysfunction	☐ Yes	☐ No
10. Bleeding disorder	☐ Yes	☐ No
11. Known pregnancy	☐ Yes	☐ No
12. Vomiting that precludes the ability to take oral medications (as determined by the family)	☐ Yes	☐ No
13. Caregiver and/or child inability to communicate fluently in English or French in the absence of a native language interpreter	☐ Yes	☐ No
14. Caregiver unavailable for follow-up	☐ Yes	☐ No
15. Previous enrollment in study	☐ Yes	☐ No

REDCap to display if family is eligible or not based on above answers. RRN to confirm below.

Is family eligible for study?	☐ Yes	☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	___ ___ ___ - ___ ___ ___ ___ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Informed Consent

Has written informed consent been obtained?	☐ Yes ☐ No
If NO, specify reason and STOP HERE.	☐ Declined consent ☐ Declined assent ☐ Other, please specify _____
If YES, specify the date and time of Informed Consent:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Has a copy of the signed informed consent been given to the family?	☐ Yes ☐ No
If no, specify reason:	
Has written assent been obtained?	☐ Yes ☐ No ☐ No, but verbal assent was obtained and documented
If no, specify reason and STOP HERE.	
Has a copy of the signed assent been given to the family?	☐ Yes ☐ No
If no, specify reason:	
Permission to contact for future studies?	☐ Yes ☐ No
[Stollery Site ONLY] Would you be interested in being contacted, later, about a second related study? We want to better understand how parents make medical decisions for their children when they are injured and have pain.	☐ Yes ☐ No

If ALL the inclusion and exclusion criteria are met AND written consent and assent have been obtained, please proceed.

If NOT, please STOP here.

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ ____ ____ ____ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 1 (TR – Recruitment)

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	
Date and Time of evaluation # 1:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs: *Record triage vital signs here.* ***Please measure a new set of vital signs if triage time is ≥60 minutes from time of recruitment.***	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?"* *Note: say "hurt" or "pain" whichever seems right for a particular child*	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ ____ ____ ____ **(site)** **(screening number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Injury Details and Previous History

Date and Time of Injury:	_____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock)

Location of Primary Injury: Please select the location of the PRIMARY injury (pick ONE only)	
☐ Single or Multiple Fingers (if ONLY injury) ☐ Hand ☐ Wrist ☐ Forearm ☐ Elbow ☐ Upper Arm ☐ Shoulder ☐ Collarbone	☐ Single or Multiple Toes (if ONLY injury) ☐ Foot ☐ Ankle ☐ Lower leg ☐ Knee ☐ Thigh ☐ Hip

Concomitant Digit Injury:	
Is there a concomitant digit injury present **on the same limb**?	☐ Yes ☐ No
If yes, please select the location of the secondary injury (pick ONE only)	☐ Single or Multiple fingers ☐ Single or Multiple toes

Concomitant Medications Have any medications been given since the injury?	☐ Yes – (Fill out Concomitant Medication Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	___ ___ ___ - ___ ___ ___ ___ **(site)** **(screening number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Medical Oversight of Screening

Eligibility of the participant has been confirmed by:	☐ PI / Site Investigator (in person) ☐ PI / Site Investigator (by phone) ☐ Third party physician Purpose: to review the inclusion and exclusion criteria on this form and confirm that the patient meets the criteria listed.
If PI/ Site Investigator, specify: PI / Site Investigator Physician Name: Date and time of confirmation:	_____ _____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock)
If Third party physician, specify: Third party Physician Name: Date and time of confirmation:	_____ _____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock)

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ ____ ____ ____ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Selection of Family Preference

To Caregiver and Child: *"At this point, we need you to tell us which study group you would like to participate in: Group 1 or Group 2. Regardless of which study you choose, you / your child will, at minimum, receive ibuprofen (Advil) for their pain. Both groups include commonly used pain medicines for this type of pain, however Group 2 includes all three of the pain medicine options offered in this study. So, if you don't have a preference, we will assign you to Group 2.*

- *If you choose Group 2, you/your child will have an equal chance of receiving either:*
  - *Ibuprofen (Advil) AND placebos (inactive ingredient)*
  - *Ibuprofen (Advil) AND acetaminophen (Tylenol)*
  - *Ibuprofen (Advil) AND hydromorphone (Dilaudid)*

- *If you choose Group 1, you/your child will have an equal chance of receiving either:*
  - *Ibuprofen (Advil) AND placebo (inactive ingredient)*
  - *Ibuprofen (Advil) AND acetaminophen (Tylenol)*

To help you in making your choice, here is some more information about these medicines.

1. *Ibuprofen (Advil) is typically provided for the kind of injury you/your child has, but it may not always be strong enough to treat a child's pain.*
2. *When a child needs something stronger than ibuprofen (Advil) for their pain, acetaminophen (Tylenol) and opioid medicines like hydromorphone (Dilaudid) are the most commonly recommended pain killers to be added to the ibuprofen.*
3. *Please remember that if you feel that you/your child needs more pain medicine at any point during the study period, you or our research nurse can let your doctor know right away.*

- *Which study would you like to be a part of: Group 1 or Group 2?*

- [NOTE: If the family wishes to speak to a health care professional prior to making their study choice, the RA will then identify a clinical team member to aid them.]

Indicate family preference below:

☐ **Group 1:** Non-Opioid trial [N]
☐ **Group 2:** Opioid trial [O]
☐ No preference → Proceed to enroll in ☐ **Group 2:** Opioid trial [O]
☐ Family unable to reach consensus regarding preference. [If this is chosen, STOP enrolment now]

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Screening ID	Enrolment Date
PI: Dr. Samina Ali	___ ___ ___ - ___ ___ ___ ___ (site) (screening number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Once the **Preference Group** has been selected by the family, please retrieve the following study medication kit from your medication dispensing area:

Pharmacy Kit Number:

___ ___ ___ - ___ - ___ ___ ___

(site - preference group - patient number)

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	**____ ____ ____ - ____ - ____ ____ ____** **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Study Drugs Administration

Confirmed that the pharmacy kit is not expired?	☐ Yes ☐ No* *If "**NO**", check before proceeding*
Are the noted min. and max. temperatures of the drug storage fridge within the required ranges, today?	☐ Yes ☐ No* *If "**NO**", check temperatures before proceeding*
Weight:	_____kg ☐ Measured on scale ☐ Estimate provided by parent
Ibuprofen (40mg/ml) (up to **600 mg** maximum – **15 ml** maximum)	**Dose: 10 mg per kg** Calculation: _____kg x 10 = _____mg **Volume: 40mg = 1 ml** Calculation: _____mg ÷ 40mg/ml = _____ml **Volume actually dispensed to patient: _____ml**
Acetaminophen or Placebo (80mg/ml) (up to **1000 mg** maximum – **12.5 ml** maximum)	**Dose: 15 mg per kg** Calculation: _____kg x 15 = _____mg **Volume: 80mg = 1 ml** Calculation: _____mg ÷ 80 mg/kg = _____ml **Volume actually dispensed to patient: _____ml**

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	**____ ____ ____ - ____ - ____ ____ ____** **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Hydromorphone or Placebo (1mg/ml) (up to **5 mg** maximum – **5 ml** maximum) ONLY for participants enrolled in Group 2: Opioid trial	**Dose: 0.05 mg per kg** Calculation: _____kg x 0.05 = _____mg **Volume: 1 mg = 1 ml** Calculation: _____mg ÷ 1 mg/ml = _____ml **Volume actually dispensed to patient: _____ml**
*Dose calculation and dispensing in syringe must be verified by a second nurse:	Verified by: _____
Date and time of study drugs administration:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Has the participant taken the full dose of each syringe?	☐ Yes ☐ No* *If "**NO**", please comment*
Were all study drugs administered one after the other?	☐ Yes ☐ No* *If "**NO**", please comment*
Was dispensing of the study drugs recorded on the patient's clinical chart?	☐ Yes ☐ No* *If "**NO**", please comment*
Comments:	

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 2 (T0 – Immediately after Study Drug Administration)

Time due: dd/ mmm/ yyyy HH:MM ± 10 min

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	
Date and Time of evaluation # 2:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"*	_____/10
VAS *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"*	_____/100 mm
FPS-R *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?" Note: say "hurt" or "pain" whichever seems right for a particular child*	☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10
RSS	_____/6

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Contact Information Sheet

Child's Name:	_____ _____ First name Last name
Age:	_____ years
Sex:	☐Male ☐Female
Caregiver's Name:	_____ _____ First name Last name Specify relationship to child: _____
Preferred Mode of Contact:	☐Email ☐Phone
Email:	
Preferred Phone Number:	(_____) _____ - _____
Alternate Phone Number:	(_____) _____ - _____
Time for follow up call:	☐ AM ☐ PM Specify: _____

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

In PED Caregiver Survey

Your Information	
What is YOUR age, in years?	_____ years
What is YOUR sex?	☐ Male ☐ Female ☐ Other, specify: _____ ☐ Decline to answer
What is your home postal code? (1st 3 digits only)	__ __ __
What is your highest level of Education?	☐ Elementary School ☐ High School or some High School ☐ Diploma/Certificate ☐ Some Post-Secondary/University ☐ University/Professional Degree ☐ Decline to answer
What is your annual household income from all sources?	☐ Less than or equal to $25,000 ☐ $25,001 to $50,000 ☐ $50,001 to $75,000 ☐ $75,000 to $100,000 ☐ Greater than $100,000 ☐ Decline to answer

Injury Details	

How did your child's injury occur?	☐ Motor Vehicle Collision/ Road Traffic Accident
	☐ Sports Injury
	  ☐ Ice Hockey/ Hockey
	  ☐ Football
	  ☐ Soccer
	  ☐ Wrestling
	  ☐ Basketball
	  ☐ Gymnastics/ Cheerleading
	  ☐ Skiing/ Snowboarding
	  ☐ Biking
	  ☐ Other sport, specify: _____
	☐ Trampoline

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

	☐ Other play or activity ☐ Other Slip, Trip or Fall ☐ Other mechanism, specify: _____
Was the sports, play or activity supervised (ie. Were you or another adult there watching your child)?	☐ Yes ☐ No ☐ Unsure
Where did your child's injury occur?	☐ Sports Field/ Arena ☐ In School/ School playground ☐ Playground/ Park ☐ Home/ Friend's home ☐ Road ☐ Other, please specify: _____

Study Preference	
If they chose the Non-Opioid trial (Group 1): Please tell us your reason(s) for choosing **Group 1**, ie. the study with the possibility of receiving one of the following: o Ibuprofen only (Advil) o Ibuprofen (Advil) and Acetaminophen (Tylenol) *Choose all that apply*	☐ I do not believe my child's pain is/ will be severe enough to require an opioid medicine (Hydromorphone/ Dilaudid) ☐ I did not want my child to receive an opioid medicine ☐ I do not think my child is old enough to receive an opioid medicine ☐ I trust that both medicines in this study would work for my child, with their current level of pain ☐ I think my child will get better care if they are a part of this study (ex. they will get treated faster, get close care from the research nurse etc.) ☐ Other, please specify: _____
If they chose the Opioid trial (Group 2): Please tell us your reason(s) for choosing **Group 2**, ie. the study with the possibility of receiving one of the following: o Ibuprofen only (Advil) o Ibuprofen (Advil) and Acetaminophen (Tylenol) o Ibuprofen (Advil) and Hydromorphone (Dilaudid)	☐ I wanted to have the option of all 3 medicines, or combination of medicines, available to us ☐ I wanted/hoped that my child will receive the opioid medicine (Hydromorphone/ Dilaudid) specifically ☐ I believe that my child's pain is/ will be severe enough to require an opioid medicine ☐ I believe that the pain relief benefits of the opioid medicine are greater than any possible side effects ☐ I trust that any of the 3 options in this study would work for my child, with their current level of pain

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Choose all that apply	☐ I think my child will get better care if they are a part of this study (ex. they will get treated faster, get close care from the research nurse etc.) ☐ Participating in this study will help researchers learn more about the use of opioids for treating injury-related pain for children in the future ☐ Other, please specify: _____

Experience with Opioid Pain Medicines	
Have YOU ever been prescribed or given an opioid medicine by a health care provider, in a clinic or hospital? *Ex. Hydromorphone (Dilaudid), Morphine, Oxycodone (OxyContin, Percocet), Codeine, Fentanyl, Hydrocodone (Vicodin)*	☐ Yes ☐ No ☐ Unsure
Have any of your FAMILY MEMBERS ever been prescribed or given an opioid medicine by a health care provider, in a clinic or hospital? *Ex. Hydromorphone (Dilaudid), Morphine, Oxycodone (OxyContin, Percocet), Codeine, Fentanyl, Hydrocodone (Vicodin)*	☐ Yes ☐ No ☐ Unsure
If yes, was this family member a CHILD?	☐ Yes ☐ No ☐ Decline to Answer
Have you or a family member ever been diagnosed with a substance use disorder, or addiction to drugs/ alcohol?	☐ Yes ☐ No ☐ Unsure ☐ Decline to answer
If yes, can you please specify which drug(s)/ substances?	[Free text]

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 3 (T30 – 30 minutes after study drugs administration)

Time due: dd/ mmm/ yyyy HH:MM ± 15 min

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	☐ Patient discharged before specified evaluation time ☐ Other: _____
Date and Time of evaluation # 3:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?"* *Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 4 (T60 – 60 minutes after study drugs administration)

Time due: dd/ mmm/ yyyy HH:MM ± 15 min

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	☐ Patient discharged before specified evaluation time ☐ Other: _____
Date and Time of evaluation # 4:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?"* *Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 5 (T90 – 90 minutes after study drugs administration)

Time due: dd/ mmm/ yyyy HH:MM ± 15 min

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	☐ Patient discharged before specified evaluation time ☐ Other: _____
Date and Time of evaluation # 5:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?" Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 6 (T120 – 120 minutes after study drugs administration)

Time due: dd/ mmm/ yyyy HH:MM ± 15 min

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	☐ Patient discharged before specified evaluation time ☐ Other: _____
Date and Time of evaluation # 6:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?" Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 7 (TME, Time of Medical Examination)

Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	
Date and Time of medical exam:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?"* *Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Evaluation # 8 (TXR – Time following X-Ray procedure +/- 30 minutes)

Did the patient have an X-ray?	☐ Yes ☐ No
If Yes, Was the post- X-ray evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	
Date and Time of X-ray:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Date and Time of evaluation # 8:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?" Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	**____ ____ ____ - ____ - ____ ____ ____** **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

ED Discharge Evaluation

ED Discharge Evaluation *(To be done only if discharged before 120 minutes)*	
Was the patient discharged before 120 minutes?	☐ Yes ☐ No
If Yes, Was this evaluation completed?	☐ Yes ☐ No
If Yes, continue. If No, specify reason:	
Date and Time of ED Discharge:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Vital Signs:	HR: _____ bpm RR: _____ rpm Sat: _____ % BP: _____ / _____ mmHg
Pain and Sedation Scores: **vNRS** *"On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain you can imagine, what is your pain level now?"* **VAS** *"What is your pain level on this sliding scale, where 0 means absence of pain and 100 is the worst pain you have ever experienced?"* **FPS-R** *"These faces show how much something can hurt. This face (point to left most face) shows no pain. The faces show more and more pain (point from left to right) up to this one (point to right most face) – it shows very much pain. Can you point to the face that shows how much you hurt right now?"* *Note: say "hurt" or "pain" whichever seems right for a particular child* **RSS**	_____/10 _____/100 mm ☐ 0 ☐ 2 ☐ 4 ☐ 6 ☐ 8 ☐ 10 _____/6
Any adverse events or side effects? *If "**YES**", complete a separate entry for each AE on the AE Form. Do not suggest any AEs to the participant; let him/ her answer spontaneously.*	☐ Yes – (Fill out Adverse Events Form) ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Reason for early termination?	☐ Procedural sedation used for a reduction* ☐ Left ED prior to evaluation ☐ Left without being seen ☐ Other, please specify _____ * Fill out Concomitant Medication Form

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

PRE-Discharge Questions

Question for Research Nurse	
Which drug, or combination of drugs, do you think the child received for this study?	☐ Ibuprofen alone or ☐ Ibuprofen + Acetaminophen or ☐ Ibuprofen + Hydromorphone

Questions for Parent/ Caregiver	
Which drug, or combination of drugs, do you (parent/ caregiver) think your child received for this study?	☐ Ibuprofen alone or ☐ Ibuprofen + Acetaminophen or ☐ Ibuprofen + Hydromorphone
How do you feel about the pain treatment provided by the study medicine today?	☐ Very Satisfied ☐ Somewhat Satisfied ☐ Neutral ☐ Somewhat dissatisfied ☐ Very dissatisfied
Do you feel that that the medicines that your child received provided adequate/ enough pain relief for your child?	☐ Yes ☐ No ☐ Unsure
Would you accept the same medicine for your child, in the unlikely event of a similar injury in the future?	☐ Yes ☐ No ☐ Unsure
Why? Why Not?	Free Text

Questions for Child	
How happy were you with the pain treatment from the study medicine today?	☐ Very happy ☐ Somewhat happy ☐ Neutral ☐ Somewhat sad ☐ Very sad
Would you take the same medicine if you had the same injury again?	☐ Yes ☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

	☐ Unsure
Why? Why Not?	Free Text

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

POST-Discharge Questions

Questions for Treating ED Physician	
Which drug(s) would you have chosen to give this child?	☐ Ibuprofen alone or ☐ Ibuprofen + Acetaminophen or ☐ Ibuprofen + Hydromorphone ☐ other, please specify
Which drug(s) do you think that the child received?	☐ Ibuprofen alone or ☐ Ibuprofen + Acetaminophen or ☐ Ibuprofen + Hydromorphone

Unblinding	
Was the study unblinded during the ED visit?	☐ Yes, please explain. ☐ No

Co-Interventions

Were any interventions done during the ED visit? ☐ Yes* ☐ No

** If "**YES**", please fill out the table below*

Intervention	Administered?	Date and Time of Administration (dd/ mmm/ yyyy HH:MM)	Comments
Reduction of the fracture?	☐ Yes ☐ No		
Splint?	☐ Yes ☐ No		
Cast?	☐ Yes ☐ No		
Ice?	☐ Yes ☐ No		
Distraction?	☐ Yes ☐ No		
Other? Please specify: _____	☐ Yes ☐ No		

If a procedural sedation or a medication has been administered, please fill out the Concomitant Medication Form.

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	**____ ____ ____ - ____ - ____ ____ ____** **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Discharge Details	
Discharge Disposition	☐ Discharged Home ☐ Admitted ☐ Other, _____
Date and Time of Discharge	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Length of Stay in ED (calculated field):	_____ (hours, to one decimal place)
Final diagnosis at discharge (per MD):	
Radiologic Exams:	☐ Yes ☐ No
If yes, Date and Time of Radiologic Exam:	_____/_____/_____ dd mmm yyyy _____:_____ (24 hour clock)
Final diagnosis from radiologist's report: (*From chart or electronic health care system)*	

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REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Follow-up Survey # 1 (1-3 days after discharge)

Call must be done in this time window

24 hours from discharge: _____:_____ (24 hour clock) Date: _____/_____/_____
dd mmm yyyy

72 hours from discharge: _____:_____ (24 hour clock) Date: _____/_____/_____
dd mmm yyyy

Follow-up Call Attempts:			
Number of call attempts made: ☐ 1 ☐ 2 ☐ 3 ☐ N/A – completed via email			
	Date and Time *(dd/ mmm/ yyyy HH:MM)*	**RA Initials**	**Comments**
Call # 1:	____/____/_____ ____:____		
Call # 2:	____/____/_____ ____:____		
Call # 3:	____/____/_____ ____:____		
24 hour Follow-up completed?: ☐ Yes ☐ No (Lost to follow-up)			
If YES, Continue…			

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

24 Hour Follow-up Survey

Adverse Effects and Side Effects	
After you were discharged from the emergency department, has your child experienced any adverse (bad) effects or side effects that you think are related to the pain medicines they got in the study?	☐ Yes ☐ No
If YES, please explain:	_____

Medication Uses	
After you were discharged from the emergency department, has your child taken any other medicines?	☐ Yes ☐ No
If YES, please specify:	_____

Home Pain Assessment	
Please rate your child's **overall** (average) pain experience in the last 24 hours, on a scale from 0-10, where 0=no pain and 10=the worst pain imaginable.	_____/10
Please rate your child's **worst** pain experienced in the last 24 hours, on a scale from 0-10, where 0=no pain and 10= the worst pain imaginable.	_____/10

Pain Related Function		
Did your child whine or complain more than usual in the last 24 hours?	☐ Yes	☐ No
Did your child play less than usual in the last 24 hours?	☐ Yes	☐ No
Did your child do the things they normally do in the last 24 hours?	☐ Yes	☐ No
Did your child act more quiet than usual in the last 24 hours?	☐ Yes	☐ No
Did your child have less energy than usual in the last 24 hours?	☐ Yes	☐ No
Did your child eat less than usual in the last 24 hours?	☐ Yes	☐ No
Did your child sleep less than usual in the last 24 hours?	☐ Yes	☐ No

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Did your child hold the sore part of the body in the last 24 hours?	☐ Yes ☐ No
Did your child moan or groan more than usual in the last 24 hours?	☐ Yes ☐ No
Did your child want to be close to you more than usual in the last 24 hours?	☐ Yes ☐ No
Total PPPM Score (Automatic Calculation – Hidden Field) =	0 - 10

Activity Score	
Rate your child's ability to perform their usual activities:	☐ A No limitation ☐ B Mild limitation ☐ C Severe limitation

At-Home Treatments	
Did your child use any of the following in the last 24 hours to help treat their pain?	
Ice?	☐ Yes ☐ No
Elevation (raising their sore body part)?	☐ Yes ☐ No
Distraction (such as iPad, movies, games)?	☐ Yes ☐ No
Please describe any other things that your child used to help treat the pain.	Free text

Missed School and Work	
Did your child miss school and/or work in the last 24 hours?	☐ Yes ☐ No
Did YOU (caregiver/parent) miss work in the last 24 hours?	☐ Yes ☐ No

What Did Your Child Receive?
"We would like to let you know that your child received the following as their study drugs: [**A**dvil only OR **A**dvil and Tylenol OR **A**dvil and **D**ilaudid]. We will ask you about your thoughts in this when we email/ call you again in one week."

Do you have any other comments or concerns?
Thank you for completing this follow-up survey, we appreciate your participation in the No OUCH study! Without families like you, our research would not be possible. Your next (and last) follow-up survey will be in approximately 1 week.

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Follow-up Survey # 2 (1-2 weeks after discharge)

Call must be done in this time window

1 week from discharge: Date: _____/_____/_____
dd mmm yyyy

2 weeks from discharge: Date: _____/_____/_____
dd mmm yyyy

Follow-up Call Attempts:			
Number of call attempts made: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ N/A – completed via email			
	Date and Time *(dd/ mmm/ yyyy HH:MM)*	**RA Initials**	**Comments**
Call # 1:	____/____/_____ ____:____		
Call # 2:	____/____/_____ ____:____		
Call # 3:	____/____/_____ ____:____		
Call # 4:	____/____/_____ ____:____		
Call # 5:	____/____/_____ ____:____		
1 week Follow-up completed?: ☐ Yes ☐ No (Lost to follow-up)			
If YES, Continue…			

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

1-2 Week Follow-up Survey

Parent / Caregiver Satisfaction and Comfort Measures	
As you might remember, your child received _XXX__ in the emergency department, as part of this study. Did knowing what pain medicine(s) your child received in the study affect how you treated your child's pain at home?	☐ Yes ☐ No ☐ Unsure
Please explain:	Free text
How do you feel about the pain treatment provided by the medicines your child was given in the emergency department, as part of this study?	☐ Very Satisfied ☐ Somewhat Satisfied ☐ Neutral ☐ Somewhat dissatisfied ☐ Very dissatisfied
Please explain:	Free text
Do you feel that that the medicines that your child received in the emergency department, as part of this study provided adequate/ enough pain relief for your child?	☐ Yes ☐ No ☐ Unsure
Please explain:	Free text
Would you accept the same medicine for your child, in the unlikely event of a similar injury in the future?	☐ Yes ☐ No ☐ Unsure
Please explain:	Free text

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Since visiting the emergency department, has your child had contact with any of the following health services for any reason related to their injury:	
A. Family Doctor / General Practitioner? If YES, how many times?	☐ Yes ☐ No _____ times
B. Orthopedic Specialist? If YES, how many times?	☐ Yes ☐ No _____ times
C. Revisit to Emergency Department? If YES, how many times?	☐ Yes ☐ No _____ times
D. Other Health Professional (e.g. physiotherapist, chiropractor, naturopath, rehabilitation professional, etc)? If YES, please specify which kind of professional If YES, how many times?	☐ Yes ☐ No Open text _____ times

For any health care visits related to this injury (including your original visit to the emergency department), has your family:	
A. Driven yourself or been given a lift in someone else's car?	☐ Yes ☐ No
If YES, how many times?	_____ times
If YES, estimated total cost of gas	_____$
If YES, did you use paid parking?	☐ Yes ☐ No
If YES, estimated total cost of parking	_____$
B. Used Public Transport (e.g. bus, subway)?	☐ Yes ☐ No
If YES, how many times?	_____ times
If YES, estimated total cost of using public transportation	_____$
C. Used Taxi/Uber rides?	☐ Yes ☐ No
If YES, how many times?	_____ times
If YES, estimated total cost of using this service	_____$

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REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Additional Childcare Expenses	
A. Have you needed extra childcare for ANY of your children because of this injury (e.g. emergency department visit, other healthcare visits, child unable to go to school, etc)?	☐ Yes ☐ No
B. If YES, was it extra **unpaid** childcare (i.e. grandparents, neighbours) If YES, how many hours?	☐ Yes ☐ No _____ hours
C. If YES, was it extra **paid** childcare (i.e. babysitter, daycare)? If YES, how many hours? If YES, estimated total cost of for extra paid childcare	☐ Yes ☐ No _____ hours _____$

Since your emergency department visit ~1 week ago:	
How many days in total did your child use a pain medication, for injury-related pain?	_____ days
How many days in total did your child miss school and/ or work?	_____ days
How many days in total did your child not eat properly?	_____ days
How many nights in total did your child have disrupted/upset sleep?	_____ nights
How many days in total was your child unable to participate in their usual activities?	_____ days
How many days in total did YOU (or another caregiver) have to miss work from paid employment because of your child's injury?	_____ days
On a scale of 0 to 10 (where 0 means not at all affected and 10 means extremely affected), how much did this injury affect your child's quality of life?	0-10 numerical value
On a scale of 0 to 10 (where 0 means not at all affected and 10 means extremely affected), how much did this injury affect your quality of life?	0-10 numerical value

Do you have any additional comments or concerns about how this injury and the pain medicines that you used affected you or your child's quality of life?

Thank you for completing this final follow-up survey, we appreciate your participation in the No OUCH study! Without families like you, our research would not be possible.

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

CONCOMITANT AND RESCUE MEDICATIONS

Was a **rescue medication** given during the child's visit?	☐ Yes ☐ No
Were any other concomitant medications (other than the study drugs) given **during** the child's visit?	☐ Yes ☐ No
Were any concomitant medications given **after the child's** ED visit?	☐ Yes ☐ No

CONCOMITANT AND RESCUE MEDICATIONS							
Medication Name	**Indication**	**Rescue Medication? (Y/N)**	**Start Date & Time dd/mmm/yyyy HH:MM**	**Stop Date & Time dd/mmm/yyyy HH:MM (or Ongoing)**	**Dose**	**Route**	**Frequency**

Two Randomized Controlled Trials of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Study

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

ADVERSE EVENTS FORM

To be filled out by Research Nurse								To be filled out by Site Investigator			
No.	**Initial Report or Follow-up**	**Brief Description of Event**	**Onset Date & Time (dd/mmm/yyyy HH:MM)**	**Intensity grade:** 1. Mild 2. Moderate 3. Severe 4. Life-threatening 5. Fatal or Death	**Expected AE?** **Y / N**	**SAE?** **Y / N** **If YES, fill out SAE Form**	**Action Taken** 1. None 2. Medication 3. New or Prolonged Hospitalization 4. Procedure / Surgery 5. Other, specify	**Outcome** 1. Resolved 2. Resolved w/ sequalae 3. Ongoing 4. Death 5. Lost to f/u	**Date & Time Resolved (dd/mmm/yyyy HH:MM)**	**Relationship to Study** 1. Unrelated 2. Unlikely 3. Possible 4. Probable 5. Definite	**Site PI Initial**

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REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

SERIOUS ADVERSE EVENTS FORM

Date and time Site Investigator and Site Research Coordinator were notified: *(to be completed by Research Nurse)*	_____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock)
To be completed by site RC / Investigator	
Date and time the local REB was notified:	_____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock) ☐ Not applicable *Local SAEs must be reported to REB if the event is serious, unexpected, **and** considered to be related or possibly related to the study. Local SAEs are to be reported to the REB (via email to REB coordinator) within 7 days of their discovery*
Date and time the lead site Principal Investigator was notified:	_____/_____/_____ _____:_____ dd mmm yyyy (24 hour clock)
Follow up comments: *(to be completed by site Investigator)*	

Signature of Research Nurse: _____ Signature of Site Investigator: _____

Date: ___/_____/_____ Date: ___/_____/_____
dd mmm yyyy dd mmm yyyy

Two Randomized Controlled Trials of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Study

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

PROTOCOL DEVIATION FORM

Did any Protocol Deviations Occur? ☐ Yes ☐ No

Description of Protocol Deviation	Deviation Category/ Code*	Date Deviation Occurred (dd/mm/yyyy)	Time Deviation Occurred (HH:MM)	Date REB Notified (if applicable) (dd/mm/yyyy)	Date Sponsor Notified (if applicable) (dd/mm/yyyy)	Site PI Initial
1)				☐ Not applicable	☐ Not applicable	
2)				☐ Not applicable	☐ Not applicable	
3)				☐ Not applicable	☐ Not applicable	
4)				☐ Not applicable	☐ Not applicable	
5)				☐ Not applicable	☐ Not applicable	

Two Randomized Controlled Trials of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Study

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

***DEVIATION CATEGORIES / CODES:**

Safety (Category A)
1. Not reporting an SAE within 72 hours
2. AE/SAE is not reported to IRB

Informed Consent (Category B)
3. Failure to obtain informed consent
4. Consent form used was not current REB-approved version Consent form missing
5. Consent form missing
6. Consent form not signed and dated by participant
7. Consent form does not contain all required signatures

Eligibility (Category C)
8. Participant did not meet eligibility criterion
9. Randomization of an ineligible participant
10. Participant randomized prior to completing Baseline Assessment, etc.

Protocol implementation (Category D)
11. Failure to keep IRB approval up to date
12. Participant receives wrong treatment
13. Use of unallowable concomitant treatments
14. Prescribed dosing outside protocol guidelines
15. Missed assessment
16. Assessment completed outside of protocol guidelines for timing

Other
17. Other, specify in log

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Unanticipated Problems (UP) Form

Date UP Identified:	_____/_____/_____ dd mmm yyyy
Identify UP: *(Give the UP a brief title)*	Open text
The Unanticipated Problem was unexpected in terms of nature, severity or frequency:	☐ Yes ☐ No
The Unanticipated Problem is possibly related to participation in the research:	☐ Yes ☐ No
The Unanticipated Problem suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized:	☐ Yes ☐ No
Briefly Describe the UP: *(Include additional or supplementary information as necessary. Include date of incident, date of discovery, describe harm or potential harm that occurred to subject(s), whether the incident is resolved, whether the subject(s) remains on study)*	Open text
What action was taken with the study as a result of the Unanticipated Problem? *(Check all that apply)*	☐ No action ☐ Revise protocol to eliminate apparent immediate hazards to subjects ☐ Modification of inclusion or exclusion criteria to mitigate newly identified risks ☐ Implementation of additional procedures for monitoring subjects ☐ Suspension of enrollment of new subjects ☐ Notify currently enrolled subjects ☐ Suspension of research procedures in currently enrolled subject ☐ Modification of consent documents to include a description of newly recognized risks (site and/or study wide)

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	**____ ____ ____ - ____ - ____ ____ ____** **(site - preference group - patient number)**	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

	☐ Provision of additional information about newly recognized risks to previously enrolled subjects ☐ Other: _____
Is the Unanticipated Problem a serious adverse event?	☐ Yes ☐ No *If the Unanticipated Problem is a serious adverse event, submit this form and make sure that the adverse event form and Serious Adverse Event report have been completed and submitted as per local site policy.*
Was the Unexpected Problem reported to the sponsor?	☐ Yes ☐ No
If YES, Date UP reported to the sponsor:	_____/_____/_____ dd mmm yyyy
If NO, why was the UP not reported to the sponsor?	Open text
Was the Unexpected Problem reported to the local REB?	☐ Yes ☐ No
If YES, Date UP reported to the REB:	_____/_____/_____ dd mmm yyyy
If NO, why was the UP not reported to the REB?	Open text

A study of Non-Steroidal Or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

REB # :	Study ID	Enrolment Date
PI: Dr. Samina Ali	____ ____ ____ - ____ - ____ ____ ____ (site - preference group - patient number)	__ __ / __ __ __ / 2 0 __ __ dd mmm yyyy

Early Withdrawal Form

Did participant withdraw from the study?	☐ Yes ☐ No
If YES: Date of Discontinuation:	_____/_____/_____ dd mmm yyyy
Reasons for Discontinuation:	☐ Adverse Event / Serious Adverse Event ☐ Death ☐ Withdrawal of Consent / Assent ☐ Protocol Violation, Specify _____ ☐ Other, Specify _____
If withdrew consent / assent: 1. Permission to use collected data? 2. Permission to conduct Chart Review? 3. Telephone follow up to continue?	☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No
Comments:	

Data and Safety Monitoring Board (DSMB) Charter

Protocol	Strategy for Patient Orientation Research (SPOR) Innovative Clinical Trials Multi-Year Grant
Nominated Principal Investigator:	Dr. Terry Klassen
Protocol title:	Innovation in Pediatric Trials (iPCT) Initiative
Sponsor:	CIHR - SPOR
DSMB Charter version:	3.5
DSMB Charter date:	January 18, 2019

1. Introduction

The purpose of this charter is to define the responsibilities of the SPOR Innovation in Pediatric Clinical Trials (iPCT) initiative's Data Safety Monitoring Board (DSMB), detail membership requirements, describe the data to be reviewed, delineate the meeting process, and outline the considerations and policies of the DSMB. The DSMB will act in an independent expert advisory capacity to monitor participant safety. The DSMB may wish to review this Charter at regular intervals to determine whether any changes are needed.

2. Organization and interactions

a. Membership of the DSMB

The DSMB consists of a Chair and 4-6 members with expertise in relevant (clinical) specialties for the study, including members who are knowledgeable about statistical methods for clinical research and analysis of research data. Other members should bring expertise in the clinical specialty the studies are conducted in (pediatric emergency medicine).

The DSMB Chair must be willing to make firm commitment to participate as Chair for the duration of the project.

The DSMB members are appointed by the Network Coordination Centre (NCC) Lead in consultation with the DSMB Chair and must meet the following requirements:

- Be willing to serve as a DSMB member for the duration of the project;
- Comply with the conflict of interest policy specified in this charter;

Although DSMB members are expected to serve for the full duration, in the unlikely event that a member is unable to continue participation, the reason will be documented, and a replacement member will be selected by the DSMB Chair. The new member must have comparable expertise and qualifications to the DSMB member she/he is replacing.

A list of members are mentioned in Appendix A.

b. Conflict of Interest

The DSMB must consist of individuals who are impartial, independent of the investigator(s) and who have no financial or scientific interest in the study that could impair the members' ability to objectively review study data as outlined below:

- DSMB members must not have any real or perceived scientific, financial, professional, personal, proprietary, or another conflict of interest related to the conduct, outcome, or impact of the study. DSMB members should preferably not be working at any of the participating sites.
- DSMB members must not be engaged in any simultaneously occurring competitive studies in any role that could pose a conflict of interest. DSMB members must also identify and disclose any concurrent service on other DSMBs of the same, related, or competing products;
- DSMB members must be independent of the sponsor, regulatory agencies, principal investigators, clinical care of the study participants, or any other capacity related to study operations. All DMSB members must disclose all possible conflicts of interest in writing before beginning service as a DSMB member.

c. Confidentiality

All materials, discussions, and proceedings of the DSMB are privileged and confidential. DSMB members agree to use this information exclusively to accomplish the responsibilities of the DSMB. No communication of the deliberations or recommendations of the DSMB, either written or oral, may occur except as required for the DSMB to fulfill its responsibilities. Individual DSMB members are expected to maintain confidentiality regarding the study outside the DSMB (including, but not limited to the investigators, REB, regulatory agencies, or sponsor) except as authorized by the DSMB.

If requested, this charter and accompanying list of Board members may be sent to a Research Ethics Board (REB). In the case, this charter will be marked as not for dissemination, and be sent by the Study Principal Investigator or the Network Manager to the REB Chair, with a cover letter. The SPOR - iPCT iniative does not release Board members' names in response to media inquiries until after publication of the main results of the study.

3. DSMB Responsibilities

The DSMB is responsible for safeguarding the interests of individuals participating in iPCT and approved related trials.

This responsibility will be implemented by providing recommendations for continuation or early termination of iPCT trials based on an assessment of safety. The DSMB may also make

recommendations related to the selection, recruitment or retention of participants, their management and adherence to protocol-specific regimens, and the procedures for data management and quality control.

The DSMB is advisory to the Study Principal Investigators and ultimately the iPCT Steering Committee. The DSMB is an independent board appointed by the NCC Lead and approved by the SPOR - iPCT Executive team.

The DSMB's responsibilities are to regularly monitor iPCT clinical trials, review and assess the performance of its operations, and make recommendations, as appropriate, to the Study Principal Investigator and, through the NCC lead, to the iPCT Steering Committee concerning:

- Protection of the safety and interests of the study participants;
- Review of the research protocol, informed consent documents, and plans for data safety and monitoring before initiation of study, - if needed - periodically during the study, and at the conclusion of the study;
- Conduct interim and final evaluation of the study, including safety data, participant recruitment, accrual and retention, risk versus benefit, and other factors that can affect study outcome, including aggregate and individual participant data related to safety.
- Review and evaluation of *ad hoc* safety issues concerning the study at the request of the Study Principal Investigator.
- Continuation, termination, or other modifications of the study based on the performance and observed beneficial or adverse effects of the study; and
- Amendments to the study protocol and consent forms, including whether any new data from other sources affect the equipoise of the study being monitored
- Operation according to the procedures described in this charter and all procedures of the DSMB.

4. DSMB Tasks

a. Before study opening

The DSMB will review completed protocols to assess that the monitoring plan ensures patient safety and research integrity. Consent and assent forms will be reviewed.

b. During the study

Once a study is open the protocol monitoring shall be facilitated at least semiannually (generally by conference calls) by submission of data summaries from the Data Coordinating Centre regarding each study to the Network Manager who sends these data summaries and available site monitoring reports to the DSMB Chair for preparation of the DSMB Report.

The primary responsibility of the DSMB is to monitor the study for participant safety. The DSMB will review the following safety and related data:

- Participant recruitment, accrual, retention, and withdrawal information;
- Adverse events (AEs) and serious adverse events (SAEs);
  - Tabulated by body system, intensity, seriousness, duration, treatment given, and the relationship to the study drug and study procedure
  - Comparison of events that occur between treatment arms
  - Individual events of particular concern
- Site monitoring reports;
- Any other safety-supporting data requested by the DSMB.

The DSMB will make a recommendation regarding the study continuation, termination, or modifications based on the review. Studies that are accruing poorly may be recommended to be placed into probationary status or closed.

Serious adverse events (SAEs) will be monitored by the DSMB Chair and must be reported by the Sponsor to the DSMB Chair via email **within seven working days** of learning of the event.

All participant withdrawals will be monitored by the DSMB Chair and must be reported by the Sponsor to the DSMB Chair via email **within two weeks** of learning of the withdrawal.

The DSMB may consider data from other studies or external sources during its deliberations, if available, as these results may have a profound impact on the status of the participants and design of the current study.

5. Meetings

a. Projected Schedule of Meetings

An initial meeting of the DSMB will be held before the start of the studies or as soon after that as possible for the members to:

- review the charter;
- receive an overview of study network activities;
- form an understanding of the protocol and definitions being used;
- establish a distribution and meeting schedule;
- review the study modification and termination guidelines; and

Subsequent DSMB meetings will be held to review and discuss study data according to the schedule as described in the table below.

Timeline	***Data Review by***
Biannually	Entire DSMB
Ad hoc (SAE)	Entire DSMB

b. *Ad Hoc* Meetings

An *ad hoc* meeting of the DSMB may be called at any time by the DSMB Chair or Study Principle Investigator if imminent participant safety issues arise. If a significant safety concern arises during the study, the DSMB Chair may convene a meeting to review safety and any other aspect of the study. Significant safety events may include, but are not limited to, the following:

- A death or life-threatening condition sustained by a participant, regardless of causality;
- An unexpected serious safety issue newly identified during the development program that could expose participants to unnecessary risks;
- Any other concern regarding participant safety raised by any DSMB member.

Proposed study amendments that significantly alter the treatment plan and deal with participant safety concerns will prompt an ad hoc meeting of the DSMB for review before implementation of changes. This may require suspension of enrollment pending DSMB review.

c. Meeting Format

DSMB meetings will be conducted by teleconference and facilitated by the DSMB Chair, consisting of an open session and a closed session. A quorum, defined as **four members of the DSMB including the DSMB Chair must be present to hold a DSMB meeting**.

Open Session

The open session may be attended by the investigator(s) and representatives of the Sponsor. Investigator and sponsor representatives may attend the open session with DSMB members. The Data Coordinating Centre provides a report for each study, containing: recruitment updates, compliance, withdrawals and other blinded data and non-confidential information regarding operational/logistical issues. This session gives the DSMB an opportunity to query an investigator about issues that have arisen during the review of safety data. Unblinded information will not be discussed in the open session.

Closed Session (if needed)

The closed session will be restricted to attendance by the DSMB members, and a recorder (NCC administrator) for the review of an interim analysis, prepared by the Methods Core.

At the closed session, study blinding may be broken. Closed sessions also consist of a review of the recommendations the DSMB wishes to make to the investigator and a formal vote.

d. Voting

DSMB recommendations will be agreed upon by formal majority vote. In the event of a split vote, the DSMB Chair will cast the deciding vote.

6. DSMB Considerations and policies

a. Stopping Rules

After considering the information in the open and closed session DSMB report, the DSMB will determine whether the study should continue as planned, proceed with modifications, or be terminated. The justification to terminate the study may be due to the DSMB's analysis that there are overwhelming safety issues. If the DSMB votes to terminate the study, the Network Manager will prepare a final study report for the DSMB, and a final DSMB meeting will be held. The DSMB's recommendations at the final DSMB meeting may include continuing action items to the investigator based on the final review.

b. Meeting Minutes

Minutes of DSMB meetings will be kept in two parts: open session and closed session.

Open Session

Open session meeting minutes include (at a minimum):

- Protocol number, study title, version;
- DSMB meeting date;
- Copy of the open session agenda;
- A list of attendees, including DSMB members and any others present, listing their professional title and role at the meeting;
- A list of attendees who have been unblinded to any data;
- Information reviewed and related discussion during the open session, including rationale for recommendations provided by voting DSMB members;
- A copy of the DSMB recommendation letter.

The DSMB Recorder is responsible for recording and generating meeting minutes of both open and closed sessions.

Draft minutes of open sessions will be sent to the DSMB Chair for review and approval within three working days of the meeting. The draft minutes will be reviewed by the DSMB Chair within seven working days, and final minutes of the open session will be distributed to the DSMB

members and the investigator within ten working days of the DSMB meeting. Final minutes will be distributed to DSMB members by PDF version sent by secure email.

Closed Session

Draft minutes of closed sessions will be sent to the DSMB Chair for review and approval within one working day of the DSMB meeting. The draft minutes will be reviewed by the DSMB Chair within three working days, and final minutes of the closed session will be distributed only to the DSMB members within five working days of the DSMB meeting. Final minutes will be distributed to DSMB members by PDF version sent by secure email.

Closed session meeting minutes will not be divulged beyond the DSMB until after the study is closed unless either:

- The DSMB voting members approve the release to preserve the integrity of the study and the safety of participants; or
- Health Canada –Therapeutic Product Directorate requires disclosure.

The investigator, Network Manager and sponsor will receive a complete copy of the open and closed session meeting minutes at the completion of the study.

7. Report to DSMB

a. Responsibility for Preparing DSMB Data Reports (open session)

The report is prepared by the DCC, and sent to the DSMB Chair three weeks before the planned meeting.

b. Responsibility for Preparing DSMB Interim analysis (closed session)

The report is prepared by the Methods Core, and sent to the DSMB Chair three weeks before the meeting.

a. Content of the Reports to the DSMB

The DSMB chair will prepare the report to include two DSMB parts – open session and (if available) closed session.

- *Open Session Report*: The open session report presents data only in aggregate and focuses on study conduct issues, like accrual and withdrawal rates, eligibility rates, reasons for ineligibility and discussion of blinded materials. To protect the blind participant-specific data and treatment group data are not presented in the open session report.
- *Closed Session Report*: In the event of serious adverse events or significant protocol violations, the DSMB may bequest closed session reports that include unblinded comparative statistical outputs.The closed session reports include unblinded comparative

statistical outputs. The closed session report is considered confidential and must be destroyed at the conclusion of the meeting.

b. Distribution of the Report to the DSMB

Reports to the DSMB are distributed to DSMB members two weeks before a scheduled meeting. The report is dated and provided to individual DSMB members in PDF format sent by secure email.

c. DSMB Reports to Investigator

Following each meeting, the DSMB will issue a confidential report separate from the minutes of the open and closed sessions that will be sent to the investigator. The report includes a summary of the open session discussion, does not include unblinded data or discussion of the unblinded data, and provides the DSMB's recommendations accompanied by clear, concise rationale for them. The report should contain sufficient information to explain the rationale for any specific actions by the DSMB without jeopardizing conduct or scientific integrity of the study (unblinding). If no recommendations are made, the report may simply state, "The DSMB recommends that the study continues as planned."

The report should be presented to the investigator both in writing and orally. The DSMB Chair communicates directly with the investigator to allow them the opportunity to ask questions and discuss any recommendations. If the report does include DSMB recommendations for changes or termination of the study, the report must include a minimum amount of data such that the investigator can make a reasoned decision in response to the recommendation.

If the investigator accepts the recommendations of the DSMB, the investigator will be responsible for implementing the actions in response. In the event the study must be amended, the investigator will prepare and submit the amendment to the DSMB and REB for approval before implementing amendment changes.

If the investigator rejects the DSMB's recommendations, the investigator must provide the DSMB with a written explanation of their decision and supporting rationale within one working day. If the DSMB has recommended that the study is stopped, but the investigator decides to continue the study, the investigator will inform all concerned regulatory authorities of its decision to continue the study despite the DSMB's recommendation. Public disclosure of the decision to stop the study is at the discretion of the investigator. The DSMB will not make any public announcements.

8. Other

a. Amendments to the DSMB Charter

This DSMB charter can be amended as needed during the study. All amendments will be documented with sequential version numbers and revision dates and will be recorded in the open session DSMB meeting minutes. Each revision will be reviewed and agreed upon by the DSMB.

b. Archiving

All DSMB documentation and records will be retained in sealed envelopes in the Sponsor Study File by the National Coordinating Centre for 25 years after completion of the study. Access to archived data will be controlled by the sponsor, which will release the information only as specified in this charter or as required by law.

Appendix A – DSMB members

Voting members

Member name	*Conflicts of interest*
Garth Meckler (chair)	
Mark Roback	
Anupam Kharbanda	
Eyal Cohen	
Lise Nigrovic	

Ex-officio (non-voting)

NCC Lead: Dr. Geert W. 't Jong

Network Manager: Tannis Erickson

Appendix B – Definitions

Study Principal Investigator: The investigator who is primarily responsible for a trial.

SPOR Principal Investigator: The investigator designated as Primary Investigator on the SPOR application (Dr. Klassen).

iPCT Steering Committee: Executive committee consisting of the study leads (PIs) and the leads within each core (Network Coordinating Centre; Data Coordinating Centre; Methods Core)

Study Details			
Study Title:	No-OUCH A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials		
Investigator:	Dr. Samina Ali	**Code:**	00073476
Sponsor:	University of Alberta		

Document History

Version	**Date**	**Reason For Change**
1	20 Mar 2019	Initial draft

Introduction

This document defines the data management approach for the named study. Specifically it defines data sources, data handling practice and relevant additional documentation.

Document Control

This document is to be authorized by WCHRI DCC Team Lead, their designee or a senior manager within the Women & Children's Health Research Institute (WCHRI). The study sponsor (sponsor-initiated studies) and/or Principal Investigator (investigator-initiated studies) should also review and authorize the production version and any subsequent modifications.

Following authorization a read-only 'controlled' copy will be created and the document will be allocated a version number. Subsequent changes will be authorized (see above) and the version number incremented. Each authorized version will be retained on file for audit purposes.

Study Title

A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

Study Overview

This study will be comprised of two Phase 2, six-centre, randomized, double-blind, placebo-controlled trials that will be run simultaneously. The primary objective of this study is to determine the effectiveness of a combination of opioid and non-opioid oral analgesic medications (PO ibuprofen + PO acetaminophen; PO ibuprofen + PO hydromorphone; PO ibuprofen alone) for the acute pain management of children with an acute musculoskeletal (MSK) limb injury.

The study aims to recruit 536 children, aged 6-17 years, presenting to one of six Canadian pediatric emergency departments (EDs) with an acute MSK injury (<24 hours old) of a single limb over a period of 18 months.

Participants who participate in the Opioid Trail will receive either single-dose:

A. Oral hydromorphone (0.05mg/kg, max 5mg) + Oral ibuprofen (10mg/kg, max 600mg), OR

B. Oral acetaminophen (15mg/kg, max 1000mg) + Oral ibuprofen (10mg/kg, max 600mg), OR

C. Oral ibuprofen (10mg/kg, max 600mg)

Participants who participate in the Non-Opioid Trial will receive either single-dose:

A. Oral acetaminophen (15mg/kg, max 1000mg) + Oral ibuprofen (10mg/kg, max 600mg), OR

B. Oral ibuprofen (10mg/kg, max 600mg)

Pain scores, any adverse events, level of sedation, and vital signs will be recorded every 30 minutes, for up to 120 minutes following study drug administration. Participants will also receive two follow-up questionnaires, either by email or telephone, at 24 hours and 1 week post discharge from the ED.

For inclusion and exclusion criteria see the study protocol.

Primary Efficacy Variables

Primary Efficacy Endpoint will be the self-reported pain score at 60 minutes, using a 0-10 verbal Numerical Rating Scale (vNRS).

Variable: pain_vnrs at the 60 minute mark

Secondary Efficacy Variables

The Secondary Efficacy Endpoints will include:

Endpoint	Variable Name
1. the proportion of patients with a vNRS pain score <3 at 60 minutes	pain_vnrs at the 60 minute mark
2. the proportion of patients with a vNRS pain score reduction of at least 2 points out of 10 at 60 minutes	pain_vnrs at the 60 minute mark
3. between group differences in pain scores at study time-points (T-30,T-60,T-90, T-120, T-Medical Exam and T-Xray)	pain_vnrs, pain_fpsr and pain_vas at all timepoints
4. self-reported caregiver and child satisfaction with pain relief and acceptability of study medications, using a previously employed 5 point Likert scale	qp_rate qp_relief qc_rate qc_same folup2_ratetx folup2_ratetx_expl folup2_relief folup2_relief_expl
5. ED length of stay	pscr_triage disch_dt
6. frequency of missed fractures or dislocations	disch_mddx disch_raddx
7. the proportion of children administered a rescue analgesic in the 60 minutes following administration of study medication	cm_sd cm_st cm_ed cm_et
8. time to effective analgesia, defined as the first vNRS pain score <3 post-intervention	pain_vnrs

9. children's self-reported pain intensity on the Visual Analog Scale (VAS) and the Faces Pain Scale-Revised (FPS-R) at all study times	pain_vas pain_fpsr

Safety Data

Principal Safety Endpoint will be the proportion of children with any adverse events related to study drug administration.

Secondary Safety Endpoints will include 1. the proportion of children with any serious adverse events during the study period, 2. the proportion of children in each study group with a Ramsay Sedation Score (RSS) score between 1 to 3, and 3. the proportion of children with each specific adverse event type during the study period.

Patient Numbers

The sample size for the three-armed Opioid Trial is 105 patients per arm, for a total of 315. For the two-armed Non-Opioid Trial, a sample of 85 patients per arm, for a total of 170. Thus, the grand total for the No OUCH Study would be 485. In order to account for patients who are excluded from primary analyses due to missing data for the primary (efficacy) outcome and to adjust for loss to follow-up, the sites will recruit approximately 10% more, for a target recruitment of approximately 536 patients. However, in order to preserve the patient preference aspect of this study, which allows families to choose which trial they would like to participate in, we will over-recruit one trial in order to allow the second to achieve its sample size.

Study Timelines

Participants are enrolled, if eligible, in the ED. Once the drug is administered, patient assessments are implemented in the ED at T0, T30, T60, T90 and T120 time points. Assessments are also collected at the time of the medical examination, time of x-rays and at discharge. Two follow-ups conducted either by phone or online survey to be completed at 1-3 days post discharge and 1-2 weeks post discharge. Total study period: 14 days for all outcome data.

First Participant visit: April 2019

Last Participant visit: expected April 2021

Ethics Status

This is a Health Canada regulated clinical trial that requires REB approval at participating sites. It is required to be GCP-compliant and undertaken on a validated installation of REDCap.

Data Sources

All data entry will be performed at the sites by trained research staff, with exception of the survey data which will be entered directly by the parents. Source Documents include medical records. Some data will be collected directly from the study participants and under these circumstances REDCap is considered the source document.

Standard Operating Procedures

Data management work performed by WCHRI will be undertaken using the current version of WCHRI SOPs.

Scope of Work

WCHRI staff will perform the following tasks:

Database build, data management activities, delivery of data for analysis, preparation of DSMB reports.

Data Collection Mode

Data will be collected electronically (any transcription from paper will be performed at the study sites. WCHRI will not receive copies of paper CRFs or source documents.)

CRF Design

Data collection forms have been developed by the Principal Investigator and her staff with minimal input from WCHRI.

Data Collection System

Data will be entered into REDCap by personnel at the study sites.

Randomization and Unblinding

For Randomization and Unblinding specifics, see the protocol.

Randomization of participants will occur outside of REDCap. Should unblinding be required, this will be performed through the study unblinding project in REDCap. In addition, 1-3 days AFTER The primary outcome measures are collected, the study arm assigned to the patient will be revealed.

Study Monitoring

Monitoring will be performed by staff from the University of Alberta Quality Management in Clinical Research (QMCR) according to their monitoring plan.

Document Tracking

WCHRI will not be handling paper documents for this study.

Data Entry

The Study sites will complete electronic CRFs contained within the data collection system (REDCap) based on the contents of the patient records and other data sources.

Data Handling

Data handling practices for this study are documented in the study's data handling manual. This document will be updated throughout the study as practices are refined and as new situations arise. Specifically, this document covers issues such as data handling conventions, self-evident corrections, data query practice and will also serve to log data handling exceptions.

Data Quality

The approach to data quality is based on key points contained within ICH GCP. These are:

- Complete Minimal missing values
- Accurate Database values match original observation
- Precise Units and measurability clearly understood
- Timely Minimal time between observation and recording

- Verifiable Independent assessment or monitoring
- Traceable Actions taken are logged

The above points will be ensured as follows:

Data Validation and Queries

Electronic data collection forms will be programmed with online validation checks (also known as edit checks). Based on an understanding of the data collection forms these checks will:

- Alert data entry users to missing data
- Check that numeric variables and dates are within reasonable ranges
- Check for consistency within the data

Entered data will be subject to visual and electronic validation by data management staff according to an approved data validation plan. Issues that arise will be notified to the sites as queries, for resolution.

Data issues will be entered into the data capture system in the form of queries/discrepancies. Sites will respond to the queries, directly in the data collection system. Query responses will be reviewed by data management staff and closed once the issue has been resolved.

Source Document Verification

This will be performed by study monitors according the approved monitoring plan.

Serious Adverse Events

Serious adverse events (SAEs) are to be reported to the sponsor *(and/or PI for investigator-initiated studies)* and ethics board, by the sites, as defined in the study protocol. Periodically the sponsor (or PI) will forward copies of SAE reports to WCHRI for reconciliation with the CRF data.

Data Coding

Adverse events will be coded with MedDRA by WCHRI staff. A formal coding review will be undertaken by an authorized individual prior to database lock or delivery for interim analysis.

Data Extract and Delivery

Data will be extracted into SAS data sets for delivery to the study statistician.

Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB). The DMSB will operate under the rules of an approved charter which will outline all terms of reference, as well as the frequency of meetings, that will be reviewed at the organizational meeting of the DSMB. Prior to each DSMB meeting, the study statistician shall prepare reports with interim data for presentation to the DSMB.

The following timelines will need to be met in order to have enough time to prepare and submit the report to the DSMB.

- Data quality review will be performed 6-8 weeks prior to the data of the planned DSMB meeting and any necessary queries raised.
- Study sites will be asked to review and respond to queries within 1-2 weeks

- 4-5 weeks before the DSMB meeting data will be exported and provided to the statistician for preparation of the DSMB reports.

Archiving and Destruction

After study completion all study materials will be returned to the Principal Investigator / Sponsor for archiving.

Electronic data will be retained in WCHRI secure systems until such time as these systems are decommissioned or until the Principal Investigator requests their deletion.

Tasks and Responsibilities

These are summarized in the following table:

Task	Responsibility	Notes
CRF design	PI	
Database configuration	WCHRI	
Database documentation	WCHRI	
Database acceptance testing	WCHRI / PI	
Monitoring	CRU	
Document flow and tracking	N/A	
Data entry	Study sites	
Data validation	WCHRI	
Discrepancy resolution	Study sites	
Data extract	WCHRI	
Analysis database creation	WCHRI	
DSMB Reports	WCHRI	
Study materials archiving	Study sites / PI	
Data archiving	PI	

Authorization:

Author: (Signature) Pamela Marples **Date:** 12 Apr 2019

Authorized by: (PI or Sponsor) Dr. Samina Ali **Date:** 15 April 2019

Reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6-8 (Table 1)
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	20
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	21
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or	13-14

		groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	11-12
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7 (Table 1)
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-11 and Figure 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11-12
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-11 And Appendix 2 for Case Report Form
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10

Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14 And Appendix 3 for data management plan
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12-13
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14 and Appendix 4 for DSMB charter
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12-13
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14-15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10, 15, and Appendix 1
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15, 21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8 (Table 1)
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in	15

		results databases, or other data sharing arrangements), including any publication restrictions	
3Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15 and 8 (Table 1)
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Reporting checklist for protocol of a clinical trial (SPIRIT-PRO Elaborations only).

		SPIRIT-PRO Elaboration	Page Number
Roles and responsibilities: contributorship	#5a	Specify the individual(s) responsible for the PRO content of the trial protocol.	20
Background and rationale	#6a	Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.	11-12
Background and rationale	#7	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	11-12
Trial Design	#10	Specify any PRO-specific eligibility criteria (eg, language/reading requirements or prerandomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.	7 (Table 1)
Interventions: adherence	#12	Identify the PRO endpoint as the primary, secondary (and if so - whether a key/important secondary), or an exploratory endpoint. Specify the PRO concepts/ domains used to evaluate the intervention (eg, overall health- related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.	11-12
Interventions: concomitant care	#13	Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not pre-randomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple	10-11, Figure 2

		questionnaires, whether order of administration will be standardized.	
Outcomes	#14	When a PRO is the primary end point, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses.	12
Methods	#18a(i)	Justify the PRO instrument to be used and describe domains, number of items, recall period, instrument scaling and scoring (eg, range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.	11
Data collection	#18a(ii)	Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other).	8, 13-14
Data collection	#18a(iii)	Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.	11
Data collection	#18a(iv)	When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available.	N/A
Data collection	#18b(i)	Specify PRO data collection and management strategies for minimizing avoidable missing data.	10-11

Data Collection	#18b(ii)	Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.	10
Statistics	#20a	State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error.	12-13
Statistics	#20c	State how missing data will be described and outline the methods for handling missing items or entire assessments (eg, approach to imputation and sensitivity analyses).	12-13
Data monitoring	#22	State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; eg, in the participant information sheet and consent form.	N/A as single dose administration study