PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	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)
AUTHORS	Ali, Samina; Rajagopal, Manasi; Klassen, Terry; Richer, Lawrence; McCabe, Christopher; Willan, Andy; Yaskina, Maryna; Heath, Anna; Drendel, Amy; Offringa, Martin; Gouin, Serge; Stang, Antonia; Sawyer, Scott; Bhatt, Maala; Hickes, Serena; Poonai, Naveen

VERSION 1 – REVIEW

REVIEWER	Sergey Motov Maimonides Medical Center, USA
REVIEW RETURNED	14-Dec-2019

GENERAL COMMENTS	I have read with great interest your manuscript. I applaud your pursuit for safe ans effective analgesic options in Pediatric ED. The only comment i have is the choice of oral hydromorphone. Hydromorphone is highly euphoric opioid with prominent addictive properties. In equianalgesic dosing regimens, hydromorphone does not provide superior analgesia in comparison to morphine.Futhermore, hydromorphone use is associated with much more frequent respiratory depression and cns depression requiring naloxone reversal. Hydromorphone should not be used as a first-line opioid analgesic in the ED in managing acute MSK pain in pediatric ED. Acetaminophen, Ibuprofen, Nitrous oxide, IN Fentanyl, IN Ketamine and even oral morphine are better options. Please expand in your rationale on the reasons you have chosen hydromorphone.

REVIEWER	Akihito Hagihara National Cerebral and Cardiovascular Center, Kyushu University, Japan
REVIEW RETURNED	27-Jan-2020

GENERAL COMMENTS	(Major comment) I think this is a carefully prepared study protocol. My only concern is validity of assent made by a little child with severe pain. It might be difficult for little children to correctly understand medical effect and toxicity of analgesic under severe conditions. When a child's opinion differs with his/her parent/caregiver's, which opinion is prioritized? If enrollment is made according to a child's opinion, is this ethically correct? If enrollment is made according to a parent/caregiver's opinion, is this ethically correct? Since age range of children is wide (i.e., 6-17 years of age), there is a big

	difference in the ability to understand. How does the role of a parent/caregiver vary depending upon the age of a child in deciding intervention type? For clarification of details relating to these problems, I think more explanations are necessary. (Minor comments) 1. (p7, line 12; p7, line 50) It seems that “the family” and “parent/caregiver and/or child” are used interchangeably. Other than these, these two types of expressions were used interchangeably many other places. Since caregiver and/or child is not family, “the family” may not be adequate. Please revise the expressions throughout a manuscript. 2. (p8, lines 48-49) More explanations are required to clearly show “the rare occurrence where a treating physician needs to know what the child has received.” What is the rare occurrence? 3. (p9, lines 23-24) When the family does not voice a preference, they might refuse to participate in the study. Why did you exclude this possibility? 4. (p10, line 8) What is REB? Please add the full spelling of REB. 5. (Others) Many scales to evaluate a child’s physical and mental condition were used in the study. If these scales are included in the appendix, please indicate relevant parts in the main text.

VERSION 1 – AUTHOR RESPONSE

Reviewer	Comment	Original Text	Response to Comment
Editorial Requests	Please revise the Strengths and Limitations section of your manuscript (after the Abstract). This section should contain five short bullet points, no longer than one sentence each, that relate specifically to the methods.	“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,	We have removed the first bullet point, as it was not directly related to methods. We have added a new point, and abbreviated the others, further. New text: “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

		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."	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."
	Please reformat the main text so that it follows the structure recommended in the journal's instructions for authors for study protocols, for example the main text of your manuscript should contain an Ethics and Dissemination section.		Thank you. We have reviewed the recommended structure guidelines and matched our headings to the same. https://bmjopenrespres.bmj.com/pages/authors/#submission_guidelines
Sergey Motov	I have read with great interest your manuscript. I applaud your pursuit for safe and effective analgesic options in Pediatric ED.		Thank you for your kind and positive feedback. Our team aspires to positively impact the care of injured children.
	The only comment I have is the choice of oral hydromorphone. Hydromorphone is highly euphoric opioid with prominent addictive properties. In equianalgesic dosing regimens, hydromorphone does	"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	Thank you for this question. Our team spent quite a large amount of time reviewing the literature prior to choosing oral hydromorphone as our oral opioid for this trial. Your comments regarding equianalgesia and adverse events between morphine and hydromorphone are very

	not provide superior analgesia in comparison to morphine. Furthermore, hydromorphone use is associated with much more frequent respiratory depression and cns depression requiring naloxone reversal. Hydromorphone should not be used as a first-line opioid analgesic in the ED in managing acute MSK pain in pediatric ED. Acetaminophen, Ibuprofen, Nitrous oxide, IN Fentanyl, IN Ketamine and even oral morphine are better options. Please expand in your rationale on the reasons you have chosen hydromorphone.	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]"	much true and established for intravenous administration of both, but not as clear for oral administration. Our team, having recently completed a systematic review regarding short-term opioid use and opioid use disorder, did not identify any articles that specifically pointed to one opioid as more dangerous for this risk than any other, for children (manuscript being prepared). You have suggested acetaminophen and ibuprofen as alternatives, both of which I am happy to report are included within this trial. As this is a study of oral medications (with a view to inform at-home management of pain, as well), intranasal fentanyl, inhaled nitrous oxide, and intranasal ketamine were not feasible, although good choices for non-orally administered analgesia. Our team has previously published three clinical trials for this same condition (musculoskeletal injury in children) and have shown that oral morphine offers no better analgesia than ibuprofen (Poonai 2014 CMAJ, LeMay 2017 Pediatrics, Poonai CMAJ 2017). This is precisely why we have chosen a potentially more potent oral opioid. Of note, this study has been approved by six ethics boards across Canada, as well Health Canada, our highest authority in Canada for matters that pertain to drug safety. We did not choose codeine, tramadol, or hydrocodone, due to both

			Canadian and American FDA warnings regarding their use in children. Further we have studied oxycodone in a 300-patient prospective cohort (manuscript being prepared) and determined that it was no more effective than ibuprofen. Lastly, to address any remaining fears re: serious adverse events, we assure you that this clinical trial is federally regulated and highly monitored (every 3-month visits), and to date, we have recruited 200 patients with no reported serious adverse events. We have added the following additional information to the protocol Introduction, to address this: "Two clinical trials of oral morphine versus ibuprofen have shown that oral morphine was not superior to ibuprofen alone. (....) Further, tramadol, hydrocodone, and codeine are not recommended for widespread use in children due to safety concerns."
Akihito Hagihara	I think this is a carefully prepared study protocol. My only concern is validity of assent made by a little child with severe pain. It might be difficult for little children to correctly understand medical effect and toxicity of analgesic under severe conditions.		Thank you. We wholly agree that a younger child would be unable to fully comprehend the risks and benefits of participating in research. Please note that it is an ethical requirement of all Canadian institutions to assent children from approximately 7 years of age and older. Please also note that the assent forms are simplified and that assent, alone, does not give the research team permission to

			proceed with study procedures. Rather, the parent/caregiver must also consent, after reading a comprehensive and detailed consent form. Only if the parent/caregiver has consented will the child's assent be considered valid. We hope this addresses your concerns.
	When a child's opinion differs with his/her parent/caregiver's, which opinion is prioritized? If enrollment is made according to a child's opinion, is this ethically correct? If enrollment is made according to a parent/caregiver's opinion, is this ethically correct?		I appreciate your advocacy and concern for children. Both the parent/caregiver must consent and the child must assent for the study to proceed. If the child does not assent, the study will not proceed, even if their parent/caregiver has consented, as we would consider it unethical to force a child to participate in a study and receive medications against their will. If the parent/caregiver does not consent, the study will not proceed and the child will not be asked for assent. We have added the following to the Methods section: "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."
	Since age range of children is wide (i.e., 6-17 years of age), there is a big difference in the ability to understand. How does the role of a parent/caregiver vary depending upon the age of a child in deciding intervention type? For clarification of details relating to these problems, I think more explanations are necessary.		Within most Canadian institutions, we have consent forms for parent/caregivers, assent forms for young children (generally 6-12 years), and mature minor consent forms for accompanied or unaccompanied minors. All these forms are written in a manner to reflect the reading and comprehension capacity of the target group. This should address your concerns regarding the ability to understand, at different developmental stages. We have added the following to the Methods section, to address both this concern and your concern re family discordance in consent/assent: "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."
	It seems that "the family" and "parent/caregiver and/or child" are used interchangeably. Other		Thank you. For consistence and clarity, we have removed the term 'family' from the manuscript, wherever we were specifically referring to

	than these, these two types of expressions were used interchangeably many other places. Since caregiver and/or child is not family, “the family” may not be adequate. Please revise the expressions throughout a manuscript. (p7, line 12; p7, line 50)		the caregiver/parent and child duo.
	More explanations are required to clearly show “the rare occurrence where a treating physician needs to know what the child has received.” What is the rare occurrence? (p8, lines 48-49)	“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.”	Thank you. We have reworded this, for clarity, to: “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.”
	When the family does not voice a preference, they might refuse to participate in the study. Why did you exclude this possibility? (p9, lines 23-24)	“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.”	The consent/assent process precedes the choosing of study trial by the caregiver/parent and child. So, they will already be consented at the time that they are choosing their study trial. In the consent form that they have signed, it explicitly states that we will assign them to the Opioid trial if they do not have a preference, so they know to expect this. If they change their mind at the point that they are choosing a trial, they can, of course, withdraw their consent at any time, as is the understanding for all trials that are conducted in Canada. We have added the following to the Methods section:

			"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."
	What is REB? Please add the full spelling of REB. (p10, line 8)		REB is "Research Ethics Board", and it is defined at its first occurrence, in the Recruitment and Data Collection Section.
	Many scales to evaluate a child's physical and mental condition were used in the study. If these scales are included in the appendix, please indicate relevant parts in the main text.		We elected not to present all scales in the protocol appendices, as they are all validated, widely used in children's pain research, and previously reported in the literature. We have provided the references to each of these commonly used scales in the protocol, at their first mention. Included references: 1. LeMay S, Ballard A, Khadra C, et al. Comparison of the psychometric properties of 3 pain scales used in the pediatric emergency department: Visual Analogue Scale, Faces Pain Scale-Revised, and Colour Analogue Scale, *Pain* 2018;159:1508-17 doi:10.1097/j.pain.0000000000001236. 2. Tsze DS, von Baeyer CL, Pahalyants V, et al. Validity and Reliability of the Verbal Numerical Rating Scale for Children Aged 4 to 17 Years With Acute Pain, *Annals of Emergency Medicine* 2018;71:69,702.e3 doi:10.1016/j.annemergmed.2017.09.009.

Formatting Amendments	Table/s should be embedded: Kindly embed your table (should be editable and in table tools format). Tables should be placed in the main text where the table is first cited.		Thank you. This has been done.
	Required figure/s format: Figures can be supplied in TIFF, JPG or PDF format (figures in document, excel or PowerPoint format will not be accepted), we also request that they have a resolution of at least 300 dpi and 90mm x 90mm of width.		Thank you. These have been changed to PDF.

VERSION 2 – REVIEW

REVIEWER	Sergey Motov Maimonides Medical Center, USA
REVIEW RETURNED	19-Mar-2020

GENERAL COMMENTS	very well deigned study.

REVIEWER	Akihito Hagihara National Cerebral and Cardiovascular Center, Japan
REVIEW RETURNED	25-Mar-2020

GENERAL COMMENTS	All points raised were adequately addressed in the updated version of manuscript.