PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	External Cold and Vibration for Pain Management of Children Undergoing Needle-Related Procedures in the Emergency Department: A Randomized Controlled Non-Inferiority Trial Protocol
AUTHORS	Ballard, Ariane; Khadra, Christelle; Adler, Samara; D.Trottier, Evelyne; Bailey, Benoit; Poonai, Naveen; Theroux, Jean; LeMay, Sylvie

VERSION 1 – REVIEW

REVIEWER	Barbi Egidio Institute for Maternal and Child Health, Trieste, Italy
REVIEW RETURNED	15-Apr-2018

GENERAL COMMENTS	Page 6 lines 7-9 . Authors should acknowledge that topical anaesthetic side effects are very mild and of minimal impact in real life, especially on a cost-benefit perspective. Page 6 : Line 19-20 : where is the evidence that these interventions are so time consuming? Even if “they are not tailored” they can be easily applied. Is there any evidence suggesting they are tailored only to a specific setting? (blood drawing center ? ward ?) . The authors should also address the issue of whether Buzzy is time consuming or not, in real life it also takes some time , I am not aware of any study comparing time spent applying Buzzy versus distraction. Moreover the use of Buzzy implies some distraction, at least when using the dedicated cards as suggested, and it requires 60 seconds of vibration before venipuncture. Page 6 Line 50-51 . I would not consider the fact that a study has not been performed in Canada a specific plus. Is there any evidence in this perspective? Page 8. Line 18 Exclusion of children below four is reasonable in this setting but it should be eventually acknowledged as a limit; children under four are the ones most likely in need of appropriate analgesia and most difficult to engage from a distraction point of view Page 9 methods : Are the authors going to standardise the child’s position: parents lap, sit, ? Is any kind of distraction technique used, even on an unaware basis, by nurses going to be standardised? It is hard to imagine that in real life a paediatric nurse approaching a child is not going to apply some even minimal strategy. Page 11 line 45 level of distress. Are the authors going to measure

	any level of distress before venipuncture : some children may find application of the topical anaesthesia distressing, while others may not accept the Buzzy device (e.g in our experience some children were frightened by the “bee appearance” so we chose the “lady bug “ appearance), or by the application of the ice.

REVIEWER	Marcella Montico CRO Aviano National Cancer Institute, Italy
REVIEW RETURNED	10-May-2018

GENERAL COMMENTS	Abstract Lines 15-18. This description of Non-inferiority margin should be part of methods section instead of the introduction Article Introduction Page 10, line 20-21: reference 51 should be removed from the sentence since itself cites only data coming from reference 54. Page 10, line 25-26: Please cite the original reference instead of reference 51. Page 11, line 36. There is a typo at the end of the line (“de”) Data analyses Page 16, Lines 3-14: Information given are not sufficient to replicate the sample size calculation, please provide more details Page 16, lines 23-24: Author correctly state that “Non-inferiority would be declared if the upper limit of the two sided 95% CI [...] is less than the predetermined non-inferiority margin” and this should be the main analysis. Why would they perform also a two sided T test? Page 16, Lines 24-30: In my opinion this sentence is difficult to read due to the number of parenthesis Page 16, Lines 42-46: Which of the two analysis (intention to treat or per protocol) is the primary? Discussion Page 18, Lines 49-56: In my opinion this is not a limit of the study. If randomization process is carried out properly, the influence of nurses performing will be balanced between the two groups. Moreover, it would not be the only source of this kind of variability as also the attitudes of the family and the personal experience of the child can influence the pain perception and the distress.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
Reviewer Name: Barbi Egidio
Institution and Country: Institute for Maternal and Child Health, Trieste, Italy
Competing Interests: None

Nice study, well designed.

1. Page 6 lines 7-9. Authors should acknowledge that topical anaesthetic side effects are very mild and of minimal impact in real life, especially on a cost-benefit perspective.
Following the reviewer’s comment, we added to the manuscript that the topical anesthetics had a minimal side effect profile (Introduction section, p.4). However, we did not mention the cost-benefit perspective as we did not find any literature to support this perspective. Although, the cost for one

tube of Maxlene in the province of Quebec is pretty high ($40.00CA) compared to the cost of a Buzzy ($59.95USD), considering that a Buzzy will last much longer than a tube of Maxilene.

2. Page 6 : Line 19-20 : where is the evidence that these interventions are so time consuming? Even if “they are not tailored” they can be easily applied. Is there any evidence suggesting they are tailored only to a specific setting? (blood drawing center ? ward ?) . The authors should also address the issue of whether Buzzy is time consuming or not, in real life it also takes some time , I am not aware of any study comparing time spent applying Buzzy versus distraction. Moreover the use of Buzzy implies some distraction, at least when using the dedicated cards as suggested, and it requires 60 seconds of vibration before venipuncture.
We are aware of the efficacy of many pharmacological and non-pharmacological interventions, such as sweet tasting solutions, needle-free injection systems, and distraction. As such, it is important to note that we never stated that all these interventions were time consuming. We stated that “most of these interventions involved delays in treatment, OR require a lot of time, specific training, OR additional staff”. Consequently, we modified the sentence for clarity and to avoid confusion (Introduction section, p.5).
However, even if these interventions are scientifically proven and seem “easy to apply”, they are not necessarily implemented in clinical practice or used by healthcare professionals. As stated in the manuscript, some clinical settings, such as the emergency departments, had different barriers which rendered difficult the implementation of these interventions (e.g. time constraints, busy and rapid environment, etc.). For example, the efficacy of anesthetic cream for needle-related procedure is very well demonstrated. However, a study demonstrated that less than 1% of nurses applied topical anesthetic in children undergoing needle-related procedure in the emergency departments, mainly due to the application time (McLean, Obispo, & Young, 2012). Consequently, this intervention may be more implementable in an external clinic, for example, where time is less trivial. So, there is a difference between an intervention which can be “easily applied” and an intervention which is “more adaptable” to the context of a specific clinical setting. As stated by Chambers et al. (2009) some distraction interventions required training and a minimum of 15 minutes to be applied, which is not optimal for an emergency department context. In this setting, it is demonstrated that healthcare professionals think it is easier and faster to restrain the child without using any pain management intervention (Ramponi, 2009). For this reason, we need to offer alternative intervention adapted to the clinical setting (e.g. fast and easy-to-use intervention, such as the Buzzy device). However, some interventions are more implantable than other, depending on the context. Maybe the wording “they are not tailored” is not quite appropriate and we modified the sentence accordingly.
Secondly, we never stated that the Buzzy device was not time-consuming at all. We only stated that the Buzzy device is a fast and easy-to-use non-pharmacological method, which is adapted for an emergency department context were time is trivial. We are aware that the use of any pain management intervention would necessarily take a minimum of time. Finally, we want to clarify the fact that we are not using the distracting cards in this study.

3. Page 6 Line 50-51 . I would not consider the fact that a study has not been performed in Canada a specific plus. Is there any evidence in this perspective?
We agree with the reviewer on this comment. However, we think it is a specific plus for our study for different reasons. First, most RCTs on the efficacy of the Buzzy device were performed in Turkey and results cannot be necessarily generalized to Canadian settings. Second, the Buzzy device is not yet approved for a general use by Health Canada and we hope that the results of our study will provide evidence-based data to support its eventual approbation. Third, there is an interest from the Canadian hospital decision makers to obtain data regarding the efficacy of the Buzzy device with a Canadian population before to proceed to its implementation in clinical settings. For all these reasons, we believe that the fact that it is the first study in Canada to assess the efficacy of the Buzzy device represents one of the strengths of our study.

4. Page 8. Line 18 Exclusion of children below four is reasonable in this setting but it should be eventually acknowledged as a limit; children under four are the ones most likely in need of appropriate analgesia and most difficult to engage from a distraction point of view
Following the reviewer's recommendation, we acknowledged this limit in the Limits section (p.17).

5. Page 9 methods: Are the authors going to standardise the child's position: parents lap, sit, ?
Is any kind of distraction technique used, even on an unaware basis, by nurses going to be standardised? It is hard to imagine that in real life a paediatric nurse approaching a child is not going to apply some even minimal strategy.
The child's position during the needle-related procedure will not be standardized, considering that forcing a child to adopt a specific position could increase his distress. However, it was already planned to consider the child's position (sitting position, one a parent's lap, dorsal decubitus, dorsal decubitus against his will) as a potential covariate (see Covariates section, p.13).
The use of other non-pharmacological interventions during the needle-related procedure, such as distraction, was also a potential covariate that will be documented by the research nurse (see Covariate section, p.13). As pointed out by the reviewer, it is a natural reflex by nurses and/or parents to use non-pharmacological interventions to distract children from a painful procedure and it would be non-ethical to prevent them to do it.
The potential covariates, including the child's position and the use of non-pharmacological interventions, will be included in a covariate model (ANCOVA) in an attempt to determine predictors of pain scores reduction (see Statistical methods section). The other potential covariates that will be considered in the data collection and analyses are described in the Covariates section (p.13).

6. Page 11 line 45 level of distress. Are the authors going to measure any level of distress before venipuncture: some children may find application of the topical anaesthesia distressing, while others may not accept the Buzzy device (e.g in our experience some children were frightened by the "bee appearance" so we chose the "lady bug" appearance), or by the application of the ice.
The level of distress/anxiety will be assessed before the needle-related procedure using both Children's Fear Scale (self-report scale) and Procedure Behavioral Check List (observational scale). This information was already reported in the Covariates section (p. 13).

Reviewer #2
Reviewer Name: Marcella Montico
Institution and Country: CRO Aviano National Cancer Institute, Italy
Competing Interests: None declared

This is a well written and interesting protocol. I only have few comments about the statistical section and some suggestion for the text.

Abstract
1. Lines 15-18. This description of Non-inferiority margin should be part of methods section instead of the introduction
As recommended by the reviewer, we moved the description of the non-inferiority margin in the Methods section of the Abstract.

Article
Introduction
2. Page 10, line 20-21: reference 51 should be removed from the sentence since itself cites only data coming from reference 54.
We removed the reference 51 from the sentence (p.9).

3. Page 10, line 25-26: Please cite the original reference instead of reference 51.

We made the correction to the manuscript and cited the original reference instead of reference 51 (p.9).

4. Page 11, line 36. There is a typo at the end of the line (“de”)
We made the correction to the manuscript (p.10)

Data analyses
5. Page 16, Lines 3-14: Information given are not sufficient to replicate the sample size calculation, please provide more details
We are not sure to understand which supplemental details the reviewer would like to obtain. We think that all the required parameters are well described, allowing replication of the sample size calculation. The following parameters are reported:
-Primary outcome
-Non-inferiority margin (the method used to determine the non-inferiority margin is extensively described)
-Power (90%)
-Alpha (0.025)
-Software (G* Power software, version 3.0.10)
However, if the reviewer still believes that the information provided is not sufficient to replicate the sample size calculation, we would appreciate if she can specify which information is missing and we will add it to the manuscript.

6. Page 16, lines 23-24: Author correctly state that “Non-inferiority would be declared if the upper limit of the two sided 95% CI [...] is less than the predetermined non-inferiority margin” and this should be the main analysis. Why would they perform also a two sided T test?
The sentence was modified according to the reviewer comment for more clarity (Statistical methods section, p.15).

7. Page 16, Lines 24-30: In my opinion this sentence is difficult to read due to the number of parenthesis
Following the reviewer recommendation, we removed some parentheses from the sentence.

8. Page 16, Lines 42-46: Which of the two analysis (intention to treat or per protocol) is the primary?
The primary analysis will be performed according to the intention-to-treat principle. We added this specification to the Statistical methods section of the manuscript (p.15).

Discussion
9. Page 18, Lines 49-56: In my opinion, this is not a limit of the study. If randomization process is carried out properly, the influence of nurses performing will be balanced between the two groups. Moreover, it would not be the only source of this kind of variability as also the attitudes of the family and the personal experience of the child can influence the pain perception and the distress.
We agree with the reviewer and recognized that it should not be considered as a limit of the study since the randomization process will be performed adequately by an independent statistician. The influence of nurses performing the needle-related procedure is supposed to be balanced between groups (as the other potential source of variability). Consequently, we rephrased the sentence to recognize the potential variability of all covariates and removed this statement from the limit section (p.18). We also recognized that other sources of variability may influence the pain perception and distress of the child, and they were consequently added as covariates (see Covariates section, p.13).

VERSION 2 – REVIEW

REVIEWER	Marcella Montico IRCCS CRO Aviano-National Cancer Institute Italy
REVIEW RETURNED	17-Jul-2018

GENERAL COMMENTS	The authors have addressed quite all the issues raised. Only one comment is pending: I'm not familiar with G*Power software, however to replicate the calculation of sample size authors should provide either standard deviation or effect size (which takes into account standard deviation). Comment on the revised version: Page 15, last sentence - page 16, first sentence. Authors have correctly distinguished the primary and secondary analysis but "secondary analysis" is cited also in the next sentence with a different meaning. I suggest to rephrase one of the two sentences, i.e. specifying only which is the primary analysis in the first sentence.