## PEER REVIEW HISTORY



## ARTICLE DETAILS

| | |
|---|---|
| **TITLE (PROVISIONAL)** | Guided relaxation-based virtual reality versus distraction-based virtual reality or passive control for postoperative pain management in children and adolescents undergoing Nuss repair of pectus excavatum: protocol for a prospective, randomized, controlled trial (FOREVR Peds trial) |
| **AUTHORS** | Olbrecht, Vanessa A.; Williams, Sara; O'Conor, Keith; Boehmer, Chloe; Marchant, Gilbert; Glynn, Susan; Geisler, Kristie; Ding, Lili; Yang, Gang; King, Christopher |

## VERSION 1 – REVIEW

| | |
|---|---|
| **REVIEWER** | Emily Foxen-Craft<br>University of Michigan, United States |
| **REVIEW RETURNED** | 18-Jun-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thank you for the opportunity to review this manuscript, describing a protocol to assess the impact of guided relaxation through virtual reality, versus distraction VR and passive control, for postoperative pain management. Overall, I commend the authors for a thoughtfully designed protocol and well-written summary for presentation to a wide audience. Results from this study have the potential to yield exciting and innovative clinical implications for a high risk population. Addressing a few minor concerns may help strengthen this manuscript and implementation of this protocol:<br>Introduction:<br>The first paragraph would benefit from more strongly connecting the risk for longterm opioid use among adolescents postsurgically. The authors should explain to readers the justification for why relaxation- based VR and why distraction-based VR might help with postsurgical pain, such as the attentional model of pain or psychophysiological processes, and justify the hypothesis that relaxation-based VR will be the most effective.<br>Methodology:<br>The protocol would be strengthened by broadening the pain outcomes assessment to include some measure of pain interference or functional disability, as well as other pain dimensions, like pain quality and pain location. For instance, our results have found that despite focal location of surgery, pain can be widespread, which is associated with worse pain and emotional outcomes. The protocol may also benefit from additional resources to ensure or measure adherence or use of the techniques at home. |

| | |
|---|---|
| **REVIEWER** | Kristen Uhl, PhD<br>Dana Farber Cancer Institue<br>Boston Children's Hospital |

| | |
|---|---|
| | Harvard Medical School<br>United States |
| **REVIEW RETURNED** | 07-Jul-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | This protocol details a randomized controlled trial assessing guided relaxation-based virtual distraction versus distraction-based VR and passive control in a group of 8-18 year olds undergoing Nuss repair. The study objectives appear thoughtful and study design is sound. However, there are several small concerns related to methods and measures that are detailed below:<br>1) Consider assessing participants for pre-procedural knowledge/exposure to guided imagery as this may either make them more or less amenable to the intervention.<br>2) The rule-out of "uncontrolled psychiatric conditions" should be better operationalized. Is control psychopharmacology, therapy, functioning?<br>3) For pain intensity, will you be looking at a "snap shot" score during the day, at a certain time of day, an average daily score? Consider using a score that would be less skewed by possible medication dosage times, PT visits, etc. like a median.<br>4) Children post-pectus repair will likely experience considerably pain with breathing. How do you feel this might impact their willingness to engage in breathing-based relaxation?<br>5) Please provide additional information in relation to the 10 min daily "dose" of intervention. Will steps be taken to insure this is somewhat consistent between patients in terms of time of day (in relation to medication dosing, PT)? Also - how will differing lengths of stay (and thus differing "doses" of intervention) be dealt with? |

| | |
|---|---|
| **REVIEWER** | Lucy Bradshaw<br>University of Nottingham, UK |
| **REVIEW RETURNED** | 15-Sep-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | This protocol describes a single centre three arm randomised controlled trial to compare guided relaxation based virtual reality to distraction VR (active control) and 360 degree video (passive control) in children undergoing Nuss repair of pectus excavatum. I note that the trial is currently recruiting, therefore my comments below relate to clarifications and providing additional details on the statistical aspects.<br><br>Outcomes and sample size<br>The protocol describes two primary outcomes of pain intensity and opioid consumption. Co-primary outcomes in RCTs are quite unusual so the rationale for this should be described in the protocol. The sample size calculation is based on pain intensity. Is the sample size also sufficient to detect an important difference in opioid consumption?<br><br>Sample size section states that “Significance (alpha) is 0.025 to control for two comparisons. “ I presume this is for the comparison of VR-GR to the two control groups? How will multiplicity from the two primary outcomes be addressed?<br><br>Statistical analysis<br>A statement needs adding on the analysis population for the primary analysis of the primary outcomes e.g. will analysis be according to allocated group regardless of adherence with allocation? |

| | |
|---|---|
| | There are quite a few analysis methods specified for comparisons between groups on page 10 and 11 so the primary analysis method for the primary outcome should be made clearer. Are all of the measurements of pain (and opioid consumption) during hospitalisation and daily up to 30 days post-op going to be included in the primary analysis model or is there one particular time point that is going to be considered primary?<br><br>Section on missing data states that "missing outcome data will be statistically imputed using last observation carried forward (LOCF) or multiple imputation". Due to the concerns of bias using LOCF, it may be better to use multiple imputation.<br><br>Randomisation<br>Please add details on who will randomise participants, how allocations are accessed and whether randomisation occurs before or after surgery. It would be useful to indicate on the flowchart (figure 1) when the surgery will take place relative to consent, baseline demographics, randomisation and beginning the intervention.<br><br>Randomisation section also says "we will consider stratification by age, if necessary, in the analysis". An adjusted analysis including age as covariate may be more appropriate? What criteria will be used to decide if an adjusted analysis is needed? Details about adjusted analyses should be in the statistical section rather than the randomisation section.<br><br>Other minor points<br>Methods on page 5 describes intervention as "a daily, 10-minute session of VR-GR, VR-D or 360 video in children" and similarly on page 7 in the interventions section. Please add details of the number of daily sessions that will take place for clarity, from figure 1 and 2 it looks like the sessions will be for up to 3 days postoperatively?<br><br>Figure 1 – Sample size of 90 for Nuss repair appears at top of flow diagram before the inclusion/exclusion and consent/assent. Should this be n = 90 for the number of participants randomised with the flow diagram starting at identification based on criteria of being scheduled to undergo Nuss repair? |

**VERSION 1 – AUTHOR RESPONSE**

Response to Reviewers:

Comments from the Editor:
Please remove the conclusion section as this is not a requirement of study protocols.
We have removed the conclusion section from our manuscript.

Response to Reviewer 1:
Thank you for the opportunity to review this manuscript, describing a protocol to assess the impact of guided relaxation through virtual reality, versus distraction VR and passive control, for postoperative pain management. Overall, I commend the authors for a thoughtfully designed protocol and well-written summary for presentation to a wide audience. Results from this study have the potential to

yield exciting and innovative clinical implications for a high-risk population. Addressing a few minor concerns may help strengthen this manuscript and implementation of this protocol:
Dr. Foxen-Craft, thank you for your kind comments. We very much appreciate your time in reviewing our study and providing us with such excellent points for improvements. We have addressed all of your comments below.

Introduction:
The first paragraph would benefit from more strongly connecting the risk for long term opioid use among adolescents postsurgically.
Thank you for this suggestion. We have added a bit more detail connecting the risk of long-term opioid use with surgery as well as elaborated on the risk of persistent opioid use in children after surgery. We have also restructured the Introduction to make it more cohesive.

The authors should explain to readers the justification for why relaxation- based VR and why distraction-based VR might help with postsurgical pain, such as the attentional model of pain or psychophysiological processes, and justify the hypothesis that relaxation-based VR will be the most effective.
We have added information regarding the mechanism of distraction-based VR as well as guided-relaxation VR, justifying our hypothesis. This will be a strong point of discussion in the manuscript that will result from this clinical trial.

Methodology:
The protocol would be strengthened by broadening the pain outcomes assessment to include some measure of pain interference or functional disability, as well as other pain dimensions, like pain quality and pain location. For instance, our results have found that despite focal location of surgery, pain can be widespread, which is associated with worse pain and emotional outcomes. The protocol may also benefit from additional resources to ensure or measure adherence or use of the techniques at home.
Unfortunately, we have already begun recruiting for this trial. As such, we are currently unable to make any changes to the protocol. However, this information is very valuable, and we will take this into consideration for subsequent trials.

Response to Reviewer 2:
This protocol details a randomized controlled trial assessing guided relaxation-based virtual distraction versus distraction-based VR and passive control in a group of 8-18 year olds undergoing Nuss repair. The study objectives appear thoughtful and study design is sound. However, there are several small concerns related to methods and measures that are detailed below:
Dr. Uhl, thank you for your thoughtful comments and insights. We have responded to each of your comments below.
1) Consider assessing participants for pre-procedural knowledge/exposure to guided imagery as this may either make them more or less amenable to the intervention.
Thank you for this suggestion. At the end of the trial, patients are asked to fill out a satisfaction survey. We ask them specifically about their knowledge/exposure to VR as part of that survey. We do not ask explicitly about the guided imagery. Because we have already started recruitment, we cannot modify this but will certainly take this into consideration for subsequent trial design.

2) The rule-out of "uncontrolled psychiatric conditions" should be better operationalized. Is control psychopharmacology, therapy, functioning?
We have clarified this exclusion criteria and updated our manuscript to state “underlying psychiatric disease associated with hallucinations or delusions.” It has not impacted recruitment thus far as we have not recruited any patient with underlying psychiatric disease.

3) For pain intensity, will you be looking at a "snap shot" score during the day, at a certain time of day, an average daily score? Consider using a score that would be less skewed by possible medication dosage times, PT visits, etc. like a median.
We will be collecting all pain scores from the EPIC record as well as those associated with the study visit. We will also be collecting all analgesic medication consumption (both opioid and non-opioid) and will work with our statistician to analyze the data in the best way.

4) Children post-pectus repair will likely experience considerably pain with breathing. How do you feel this might impact their willingness to engage in breathing-based relaxation?
Although pectus repair is associated with significant chest discomfort, deep breathing is part of their recovery process. They are asked to participate in deep breathing for pulmonary toilet ten times per hour. Our therapy would assist with this goal.

5) Please provide additional information in relation to the 10 min daily "dose" of intervention. Will steps be taken to insure this is somewhat consistent between patients in terms of time of day (in relation to medication dosing, PT)? Also - how will differing lengths of stay (and thus differing "doses" of intervention) be dealt with?
We have added this information to the protocol. We will attempt to standardize this dose as much as possible with a daily visit. The postoperative management of these patients is protocolized and thus virtually all patients are discharged home on postoperative day 3 or 4. As such, we will do sessions for 3 days postoperatively. If children receive fewer sessions, we will work with our statistician as necessary.

Response to Reviewer 3:
This protocol describes a single center three arm randomized controlled trial to compare guided relaxation based virtual reality to distraction VR (active control) and 360-degree video (passive control) in children undergoing Nuss repair of pectus excavatum. I note that the trial is currently recruiting, therefore my comments below relate to clarifications and providing additional details on the statistical aspects.
Dr. Bradshaw, thank you for your thoughtful comments. Please see our response to each below.

Outcomes and sample size:
The protocol describes two primary outcomes of pain intensity and opioid consumption. Co-primary outcomes in RCTs are quite unusual so the rationale for this should be described in the protocol. The sample size calculation is based on pain intensity. Is the sample size also sufficient to detect an important difference in opioid consumption?
We apologize for the confusion. It was our intention to have the primary outcome be pain intensity only, with opioid consumption as a secondary outcome. Our statistical analysis plan is based on pain intensity as this was our intention. We do not yet have any preliminary data on opioid consumption and, as such, we have not run a sample size calculation to detect this difference. Our intention is to then use data derived from this study to better understand how to power a larger clinical trial in the future.

Sample size section states that “Significance (alpha) is 0.025 to control for two comparisons. “I presume this is for the comparison of VR-GR to the two control groups? How will multiplicity from the two primary outcomes be addressed?
It is correct that significance level (alpha) 0.025 is to control for the comparison of VR-GR to the two control groups. We again apologize for the confusion on the primary outcome. We have clarified that our primary outcome is pain intensity, which is consistent with our statistical approach

Statistical analysis:

A statement needs adding on the analysis population for the primary analysis of the primary outcomes e.g. will analysis be according to allocated group regardless of adherence with allocation?
We apologize for the lack of description on the analysis population. We have added the following to the manuscript: Intent to treat: all patients who were randomized and received any intervention. Subjects will be analyzed according to their randomized intervention assignment regardless of the intervention actually received.

There are quite a few analysis methods specified for comparisons between groups on page 10 and 11 so the primary analysis method for the primary outcome should be made clearer. Are all of the measurements of pain (and opioid consumption) during hospitalization and daily up to 30 days post-op going to be included in the primary analysis model or is there one particular time point that is going to be considered primary?
The primary outcome is changes in pain intensity during hospitalization. We have made changes in the manuscript to reflect this and modified the description of our analysis for the primary outcome to be clearer.

Section on missing data states that “missing outcome data will be statistically imputed using last observation carried forward (LOCF) or multiple imputation”. Due to the concerns of bias using LOCF, it may be better to use multiple imputation.
We have made this change.

Randomization:
Please add details on who will randomize participants, how allocations are accessed and whether randomization occurs before or after surgery. It would be useful to indicate on the flowchart (figure 1) when the surgery will take place relative to consent, baseline demographics, randomization and beginning the intervention.
We have added more specific detail about the randomization process. Randomization will occur before surgery. We have also added when surgery will take place on the flowchart (Figure 1).

Randomization section also says, “we will consider stratification by age, if necessary, in the analysis”. An adjusted analysis including age as covariate may be more appropriate? What criteria will be used to decide if an adjusted analysis is needed? Details about adjusted analyses should be in the statistical section rather than the randomization section.
We agree with the reviewer that analysis with adjustment for covariates is more appropriate and should be in the statistical section. We have made the changes in the manuscript.

Other minor points:
Methods on page 5 describes intervention as “a daily, 10-minute session of VR-GR, VR-D or 360 video in children” and similarly on page 7 in the interventions section. Please add details of the number of daily sessions that will take place for clarity, from figure 1 and 2 it looks like the sessions will be for up to 3 days postoperatively?
We have added for “up to 3 days” on pages 5 and 7 for clarity.

Figure 1 – Sample size of 90 for Nuss repair appears at top of flow diagram before the inclusion/exclusion and consent/assent. Should this be n = 90 for the number of participants randomized with the flow diagram starting at identification based on criteria of being scheduled to undergo Nuss repair?
Thank you. We have removed the (n=90) from the top of the diagram.

## VERSION 2 – REVIEW

| | |
|---|---|
| **REVIEWER** | Emily Foxen-Craft<br>University of Michigan |
| **REVIEW RETURNED** | 04-Nov-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | Again, I commend the authors for the efforts in developing and disseminating information about this exciting clinical trial. As long as the authors include a description of the limitations of their work, I strongly recommend publication. |

| | |
|---|---|
| **REVIEWER** | Kristen Uhl, PhD<br>Dana Farber Cancer Institute/Boston Children's Hospital<br>United States |
| **REVIEW RETURNED** | 08-Oct-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | This article details a protocol for a randomized controlled trial of guided relaxation-based virtual reality vs. distraction-based virtual reality or passive control for postoperative pain management in children and adolescents undergoing nuss procedures. Overall, the study appears well constructed and researched, however it would benefit from additional explanation around methodology. Specific suggestions include:<br><br>1. Please provide more detailed explanation, rationale, or data to support hypothesis that 10 min daily sessions over 3-4 days will result in quantifiable changes in initial outcome variables and that these changes could still be observed post-hospitalization<br>2. Please discuss whether results will be examined within different age stratifications. It could be hypothesized that certain interventions may be more or less acceptable/effective in younger vs. older patients in this cohort.<br>3. Please provide additional details around timing and consistency of 10 min sessions. Will each patient be visited at the same time of day? How will you control for acute pain exacerbating (like physical therapy) or alleviating (medication taking) that may occur either before or after sessions?<br>4. Clarify if the total opiate outcome variable will be corrected for patient weight/size. |

| | |
|---|---|
| **REVIEWER** | Lucy Bradshaw<br>University of Nottingham, UK |
| **REVIEW RETURNED** | 07-Oct-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thank you for responding to my statistical queries on the protocol. Please find some further comments below.<br><br>• Thank you for clarifying the primary outcome for the study. I notice on the trial registration at clinicaltrials.gov that there are many primary outcomes listed. Please consider updating the trial registration so that description of outcomes measures are consistent with the protocol paper.<br><br>• Thank you for adding text on the analysis population. This currently states that “Intent to treat: all patients who were randomized and received any intervention. Subjects will be analyzed according to their randomized intervention assignment regardless of the intervention actually received.” Does this mean |

| | |
|---|---|
| | that participants who do not receive either VR-GR, VR-D or 360 video will be excluded from the analysis? If so, this is not true intention to treat which should include all randomised participants in the analysis so the sentence either needs to remove the reference to intention to treat or be updated.<br><br>• Randomisation/patient recruitment. Thank you for adding further details. Please add further details on who will enrol patients in the study and who will assign patients to the interventions as per Item 16c of the Spirit checklist e.g. will different individuals be responsible for enrolling and randomising participants to the individuals who are involved in implementing the allocated intervention?<br><br>Minor comments:<br>• Sentence in page 6 of the protocol needs updating "Patient recruitment has not yet begun, and we anticipate a total study duration of two years. Patient recruitment began in July 2020."<br><br>• Page 7 – secondary outcome sentence "during hospitalization" is repeated twice |

**VERSION 2 – AUTHOR RESPONSE**

***Response to Reviewer 1*:**
Again, I commend the authors for the efforts in developing and disseminating information about this exciting clinical trial. As long as the authors include a description of the limitations of their work, I strongly recommend publication.

Dr. Foxen-Craft, thank you for your kind comments. We have a list of the limitations of the study in the "Article summary" section per the guidelines of submission to *BMJ Open*. Also given the publication guidelines, we do not have a discussion included in this protocol paper. However, we wholeheartedly agree that a discussion of limitations will be necessary and will be included in the paper presenting our results/findings from the trial.

***Response to Reviewer 2*:**
This article details a protocol for a randomized controlled trial of guided relaxation -based virtual reality vs. distraction-based virtual reality or passive control for postoperative pain management in children and adolescents undergoing nuss repair procedures. Overall, the study appears well constructed and researched, however it would benefit from additional explanation around methodology. Specific suggestions include:

Dr. Uhl, thank you for your thoughtful comments and insights. We have responded to each of your comments below.

1) Please provide more detailed explanation, rationale, or data to support hypothesis that 10 min daily sessions over 3-4 days will result in quantifiable changes in initial outcome variables and that these changes could still be observed post-hospitalization.

Our study is the first to apply VR therapy in perioperative care, therefore no defined treatment protocols exist for the use of VR in this scenario. Our pilot data supports the association of a single, 10-minute session with transient reductions in pain and anxiety. The 10-minute daily session over 3-4 days is based upon the standard duration of a guided relaxation/mind-body therapy session. The 3-4 days is limited by the duration of hospital stay of these patients. Up until now, most VR studies use VR to help manage acute, procedural pain. We hope that results from this study will help further inform the appropriate treatment protocol and we are also planning on studying this in greater detail in subsequent studies. We will discuss this rationale as well as the limitations of this approach in our manuscript presenting the results and findings of this trial. We have added the rationale for the 10-minute daily sessions to the "Interventions" in the Methods section.

2) Please discuss whether results will be examined within different age stratifications. It could be hypothesized that certain interventions may be more or less acceptable/effective in younger vs. older patients in this cohort.

We do not anticipate that age will play a role in our findings. However, we will stratify by age in the analysis, if necessary (age 8-13 and 14-18 years old). We have added this information to the Methods.

3) Please provide additional details around timing and consistency of 10-minute sessions. Will each patient be visited at the same time of day? How will you control for acute pain exacerbating (like physical therapy) or alleviating (medication taking) that may occur either before or after sessions?

We will coordinate our visits around daily care for the patients. It will likely be impossible to have all patients visited at the same time each day. We will do our best to accomplish this. However, we will collect all pain scores and all medication consumption for each patient. This information is described in the protocol. We have also added that we will make every effort to visit patients at the same time each day. The timing of study visits will be documented and collected in our case report forms.

4) Clarify if the total opiate outcome variable will be corrected for patient weight/size.

We will calculate the total opiate outcome in morphine equivalents mg/kg/day – this adjusts for patient weight. This information was added to the manuscript in multiple areas.

***Response to Reviewer 3*:**

Thank you for responding to my statistical queries on the protocol. Please find some further comments below.

Dr. Bradshaw, thank you. Please see our response to each below.

1) Thank you for clarifying the primary outcome for the study. I notice on the trial registration at clinicaltrials.gov that there are many primary outcomes listed. Please consider updating the trial registration so that description of outcomes measures is consistent with the protocol paper.

We will absolutely update the ClinicalTrials.gov registration for the trial to ensure consistency with the protocol paper.

2) Thank you for adding text on the analysis population. This currently states that “Intent to treat: all patients who were randomized and received any intervention. Subjects will be analyzed according to their randomized intervention assignment regardless of the intervention actually received.” Does this mean that participants who do not receive either VR-GR, VR-D or 360 video will be excluded from the analysis? If so, this is not true intention to treat which should include all randomised participants in the analysis so the sentence either needs to remove the reference to intention to treat or be updated.

I have updated the sentence to read as follows: “All patients who were randomized will be included in the analysis and analyzed according to the group to which they were originally assigned, regardless of the treatment (if any) they received.” This was always our intention, but the wording was confusing.

3) Randomisation/patient recruitment. Thank you for adding further details. Please add further details on who will enroll patients in the study and who will assign patients to the interventions as per Item 16c of the Spirit checklist e.g. will different individuals be responsible for enrolling and randomising participants to the individuals who are involved in implementing the allocated intervention?

Our clinical research coordinator is responsible for enrolling and randomizing participants. We have added this to the methodology in the paper.

4) Minor comments:

a) Sentence in page 6 of the protocol needs updating “Patient recruitment has not yet begun, and we anticipate a total study duration of two years. Patient recruitment began in July 2020.”

We have deleted the first portion of the first sentence to clarify that recruitment began in July 2020.

b) Page 7 – secondary outcome sentence “during hospitalization” is repeated twice

We have deleted the “during hospitalization” duplication.

**VERSION 3 – REVIEW**

| | |
|---|---|
| **REVIEWER** | Emily Foxen-Craft<br>University of Michigan, Michigan Medicine, USA |
| **REVIEW RETURNED** | 24-Nov-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | Congratulations on launching this study and the well written protocol. The only critical feedback I have at this point of review is to ensure that the verb tense in the method section is accurate at the time of final submission/proofs (e.g. if the recruitment is ongoing, is the future tense applicable for the rest of the procedures). |

| | |
|---|---|
| **REVIEWER** | Kristen Uhl<br>Dana Farber Cancer Institute/Boston Children's Hospital<br>United States |
| **REVIEW RETURNED** | 27-Nov-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thank you for addressing suggested comments from the prior revision! |

| | |
|---|---|
| **REVIEWER** | Lucy Bradshaw<br>University of Nottingham, UK |
| **REVIEW RETURNED** | 25-Nov-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thank you for responding to indicate that the trial registration on clinicaltrials.gov will be updated so that the description of the outcomes and labelling as primary/secondary is consistent with protocol paper. The trial registration should be updated as soon as possible so that there is consistency between the two sources before the protocol paper is published.<br><br>Thank you for responding to my query on the intention to treat population. The first sentence in the paragraph describing the analysis populations in the statistical analysis section requires updating to remove “and received any intervention” for consistency with the revised second sentence in the paragraph.<br><br>The following has been added to the statistical methods section in response to another reviewers comment about possible impact of age on the effect of the interventions “We do not anticipate that age will have an impact on our findings. However, we will stratify by age, if necessary, in the analysis (age 8-13 years, 14-18 years).” Please clarify if this means that a subgroup analysis for age will be conducted to explore whether there is any evidence of an interaction between the effect of the intervention and age of the child? It should be noted that since the trial is powered to detect overall differences between the groups, this sort of subgroup analysis related to age would be regarded as exploratory. |

## VERSION 3 – AUTHOR RESPONSE

**Response to Reviewers:**

*Comments from the Editor*:

We appreciate the opportunity to publish our work. We have responded to the final comments from the reviewers and have uploaded a marked copy as well as a clean version.

***Response to Reviewer 1*:**

Congratulations on launching this study and the well written protocol. The only critical feedback I have at this point is to ensure that the verb tense in the method section is accurate at the time of final submission/proofs.

Dr. Foxen-Craft, thank you for your kind comments. We have gone through the entire manuscript and updated the verb tense of the protocol to indicate ongoing patient recruitment. Due to COVID, we are a bit behind in recruitment and, as such, recruitment will still be ongoing at the time of publication.

***Response to Reviewer 2*:**

Thank you for addressing suggested comments from your prior revision!

Dr. Uhl, thank you for the time and effort you placed in reviewing and strengthening our work.

***Response to Reviewer 3*:**

Thank you for responding to indicate that the trial registration on clinicaltrials.gov will be updated so that the description of the outcomes and labelling as primary/secondary is consistent with the protocol paper.

Dr. Bradshaw, thank you. We have submitted these changes to ClinicalTrials.gov and anticipate that these changes will be public by next week.

1) Thank you for responding to my query on the intention to treat population. The first sentence in the paragraph describing the analysis populations in the statistical analysis section requires updating to remove “and received any intervention” for consistency with the revised second sentence in the paragraph.

We have made this change.

2) The following has been added to the statistical methods section in response to another reviewer’s comment about possible impact of age of the interventions “We do not anticipate that age will have an impact on our findings. However, we will stratify by age, if necessary, in the analysis (age 8-13 years, 14-18 years).” Please clarify if this means that a subgroup analysis for age will be conducted to explore whether there is any evidence of an interaction between the effect of the intervention and age of the child? It should be noted that since the trial is powered to detect overall differences between the groups, this sort of subgroup analysis related to age would be regarded as exploratory.

We have updated the sentence to read as follows: “Although the trial is not powered to detect overall differences between groups by age, we will perform an exploratory analysis in which we will stratify by age (age 8-13 years, 14-18 years) to explore a possible influence of age.”