Author’s response to reviews

Title: The effect of physiotherapy including frequent changes of body position and stimulation to physical activity for infants hospitalised with acute airway infections. Study protocol for a randomised controlled trial.

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Author’s response to reviews:

General response to all reviewers:

Thank you very much for reading and commenting on this manuscript! We find that your comments have helped us improve the manuscript significantly, and are thankful for that useful feedback.

We have now changed text in the manuscript (please follow ‘track changes’), added text for clarification (please see below) and also corrected and completed the SPIRIT checklist accordingly. Our responses are listed below, with the description of actions taken. We have also prepared a table with three columns for the comments, responses, and descriptions, which we believe gives a clearer overview and is easier to follow. Unfortunately, the system did not allow pasting the table into this space. However, the corresponding author will happily forward the table or upload it in a suitable place on request!

We hope that you will now find the manuscript improved and acceptable for publication in TRIALS.

Comments from reviewer 1:

Reviewer 1 Thank you for the opportunity to read the protocol for your clinical trial on the effect of physiotherapy interventions in children with acute airway infections.

I have a couple of concerns about the planned analysis of the study, as well as the exclusion of randomised participants.

please see my comments below. I have structured them in line with the SPIRIT check list. Some of the items require further clarification in the text.
Item 3: Protocol version, item and identifier:
your section on trial status includes the following sentence: "The first version of the study protocol December 4, 2019." Please could you confirm that when you submitted your manuscript for publication, that version 1.0 of the protocol was still being used, or if there had been any updates to the protocol since version 1.0.

Authors’ response:
Thank you for the useful and detailed comments!
Thank you for pointing out the need for clarification. We agree.
Action taken:
Text changed in Trial status section:
On submission for publication, version 1.0 of the protocol was being used. April 2020.

Comment from reviewer 1:
Item 4: Funding.
You mentioned various sources of funding for the salary of SAM. Please could you clarify how other aspects of the study were funded, including, but not limited to salaries for other investigators/ staff, potential payments to sites for recruiting, financing of the physiotherapy sessions above standard care, any payments to a trial unit, pay for preparation and running of the database and randomisation system, statistician support for the planned analysis etc

Authors’ response:
Thank you, very true! We agree.
Action taken:
Elaborated text added in Funding section:
contribution to statistician support, the randomisation process, laboratory tests, for translations of information material to guardians of the participants and documents for the publication, as well as the salary for SAM.

Comment from reviewer 1:
Item 5b/ 5c: Sponsor, role of sponsor:
Your SPIRIT check-list indicates that the relevant information for the sponsor can be found on page 17 of your manuscript. I cannot find this information. Please could you reiterate who is sponsoring the study (i.e. An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.), and what exactly their role is.

Item 5d: oversight committees:
You state that since there is no one single external funding source, no data management committee is required in accordance with Swedish law.
Please could you add to the text who is taking overall responsibility of the study, who is responsible for different aspects of the ongoing study, and that no independent oversight committees are in place for this trial.

Authors’ response:
Thank you for pointing out the need for additional information. We understand and agree.
Action taken:
Text added in Funding section:
The sponsor with overall responsibility for the operability and management of this study is Region Skåne, SE-291 89 Kristianstad, Sweden. The study is performed in collaboration with Region Kronoberg, SE-351 88 Växjö, Sweden and with Lund University, Box 117, SE-221 00 Lund, Sweden, that is responsible for the design, initiation and analyses.
No independent oversight committees are in place for this trial.

Comment from reviewer 1:
Item 6b: explanation for choice of comparators.
Please could you more clearly justify the choice to include individualised and standardised physiotherapy as different arms in the trial. What are these based on?

Authors’ response:
Thank you for pointing out the need for clarification about choice of interventions. We agree.

Action taken:
Text added in Interventions section:
The different interventions were chosen based on what is routinely carried out by physiotherapists or nursing staff in hospitals in Sweden (22), including an individualized physiotherapy treatment and a reduced non-individualized treatment. We expect that the individual intervention might be more efficient, but at the same time want to know whether the non-individualized treatment would be sufficient for these patients.

Added in section Non-individualized intervention:
The non-individualized intervention is based on what is commonly performed by the nursing-staff in Swedish hospitals, as instructed by physiotherapists

Comment from reviewer 1:
Item 7: Objectives:
Your objectives seem to indicate that each of the physiotherapy arms is to be compared to the control group. Please can you clarify in your aims section if you also wish to compare the two physiotherapy approaches to each other.

Authors’ response:
We agree, and have added information about this.

Action taken:
Text changed in Aims section:
The present study protocol describes a randomized control trial that aims to compare the effect of an individualized physiotherapy treatment, a non-individualized intervention and a control group receiving standard care.

Comment from reviewer 1:
Item 8 - Trial design:
please could you include some of the trial design key words into your "study design" section, if appropriate, such as parallel group, individually randomised, superiority, multi (two-) centre. This will help readers to have direct access to all the relevant design information straight away. Please confirm in the text that this is a superiority trial, or clarify otherwise in the text.
Authors’ response:
Thank you for these suggestions for clarifications about study design. We agree.
We want to explore the outcome in both directions, although we do not especially anticipate any adverse effect. That is also why we have chosen a two-sided test (now clarified). For that reason, we do not use the term superiority to describe the design.

Action taken:
Text in Study design section and in Abstract changed:
This is a clinical two-centre individually randomised controlled trial with three parallel groups.
Text also added in statistics section:
Two-sided two sample t-test

Comment from reviewer 1:
Item 11 - Intervention:
all study interventions should be described in sufficient detail to allow replication. You mention that all treatment arms will have access to the standard care at the ward without limitation. Was standard care identical in the two hospitals. Please could you provide more information on this, or a reference to clinical guidelines followed in these hospitals. This is particularly important for readers to assess how generalizable the results from your study would be to their practice in other countries.

You state that the individualized intervention is based on "what is routinely carried out in Sweden". Would parents be aware of these techniques, and how are you monitoring or improving adherence to the randomised treatment?

Is the individualised physiotherapy an extension of the non-individualised intervention? It might be helpful to readers to list out the differences between the interventions more clearly.

You describe that children in the control or non-individualised group, if prescribed physiotherapy, will be excluded from the trial and instead receive the individualised physiotherapy. Please can you comment in the discussion on how frequently this is expected to happen, and on the potential of this approach to dilute the study results.

Authors’ response:
We agree about the need to give more details about monitoring/adherence. New reference is also added.
Thank you for the question about the difference between the two interventions: Yes the individualized intervention may very well be described as an extension of the non-individualized intervention (or if reversed: a reduction). We have now changed the texts about the interventions significantly, in order to clarify.
We realize the confusion about the text about prescription of physiotherapy in section Inclusion of participants. The participants will not be prescribed physiotherapy, as all staff at the ward is informed of the study, which is also approved by the management at the two sites. Therefore, we do not anticipate any dilution of the study results.

Action taken:
Added text about the standard care in Interventions section:
The standard care at the wards is: information to the parents about the importance of fluid intake for their infant, oxygen supplementation, nose drops and suctioning, high nasal flow, inhalations, fluid supplementation, and analgesics, according to need. Text added about not monitoring:
The randomised treatment, or indeed what will be performed in the control group, will not be monitored, so there might be differences in adherence to the interventions between parents. Our intention however, is to evaluate the current practice that includes instructions and encouragements to the parents. This attitude is in accordance with a so-called pragmatic RCT, as our intention is to apply the results to the usual care setting (39). Text added and changed in all sections about interventions regarding descriptions and dosage. Text added in section Interventions to clarify difference between interventions:
including an individualized physiotherapy treatment and a reduced non-individualized treatment. We expect that the individual intervention might be more efficient, but at the same time want to know whether the non-individualized treatment would be sufficient for these patients. Text added in section Non-individualized intervention:
The non-individualized intervention can be described as a reduced version of the individualized intervention, without using the large ball, and inhalations given typically only in the upright position, not in frequently changing positions in the arms. The intensity of the treatment will also typically be reduced, as the staff will only have to perform the intervention once, but can choose to repeat it.
Confusing text on physiotherapy prescription is removed from section Inclusion of participants. Comment from reviewer 1:
Item 12 - Outcomes:
Your primary outcome is a composite outcome of oxygen saturation, oxygen concentration, high nasal flow treatment and oral fluid intake. Please could you clarify if this outcome measure was developed for this study specifically, or if it is used more widely (in which case, please provide a reference to a paper). Has this outcome measure been validated in this patient population? How was the clinically relevant change of 2 points determined? Please provide a reference to the work determining this value.

Authors’ response:
Thank you for these questions!
We agree that it is a limitation to our study that the primary outcome is not validated, and we have now decided on making interim analyses in order to increase the knowledge about the variance of the primary outcome. Action taken:
Text added in section Primary outcome measure:
The primary outcome is a composite index that the research group constructed for this study, based on the factors that determine whether the infant needs hospitalization (28). The items in the index were chosen because of their clinical implication. They are based on objective values and are therefore not likely to differ between different assessors. The index has not been validated, but was tested in a small pilot study (unpublished material), were the clinically relevant change of two points was determined by clinical reasoning. Text also added about interim analyses:
We plan to make interim analyses of the data obtained after inclusion of 50 per cent of the estimated sample size in order to check the assumptions about the standard deviation and
recalculate the sample size. In that analysis, we will also be able to address possible safety concerns in the study, although we do not anticipate any harmful outcome.

Comment from reviewer 1:

Item 13: Participant timelines:
You outlines that data on participants will be collected at study entry, 20 minutes later and every 3 hours thereafter until discharge - during daytime only for secondary outcome measures. In the sample size section, the primary outcome time point is described as 24 hours. Please can you confirm that all participants are expected to remain in hospital for at least 24 hours.

Authors’ response:
Thank you for these comments!

Clarification: Most data will be collected every 3 hours around the clock. Exception is made for the parents’ assessment, which will be collected only during daytime. Body weight and report about inhalations and the child’s activity level will be reported once daily.

Action taken:
Time-point for assessment added at each item of Wang respiratory score in Table 2 for clarification.

Text added in section Primary outcome measure:
The oral fluid intake for analysis at hour 24 will be the collected intake during the first 24 hours in the study.

Explanations added in Statistics section:
The primary outcome is the clinical index at 24 hours, The time is chosen since our experience is that most infants will remain at hospital at that time and an effect should have been shown.

Comment from reviewer 1:

Item 14: sample size:
The standardised effect size is 2/2.8 = 0.71. This is a very large for randomised controlled trials. Please could you give additional information on the study from which the standard deviation has been obtained, including a reference.

It would be interesting to know how large this study was, how similar the study population was compared to the planned study. Many publically funded studies are encouraged to use much smaller standardised effect sizes. Please comment on how likely you think you will be able to detect such a large standardised difference between the groups.

Authors’ response:
Yes, we agree that the standardized difference of 0.71 is quite large. Since the index was developed specifically for this study and has previously not been used, the calculation of power is based on estimations. We agree that this is a weakness. However, physiotherapy interventions can have large standardize differences (Hansson EE, Jonsson-Lundgren M, Ronnheden AM, Sorensson E, Bjarnung A, Dahlberg LE. Effect of an education programme for patients with osteoarthritis in primary care--a randomized controlled trial. BMC Musculoskeletal Disorders. 2010;11:244, Delphin I, Persson G, Ekvall Hansson E. Does physical activity affect risk of revision of total hip arthroplasty? A matched pairs study. European Journal of Physiotherapy. 2017;19(3):124-30. ). A study from 2002 regarding the effect on saturation by lying prone or lying supine among infants gives and standardized effect of 0.4 (Chang YJ, Anderson GC,
Dowling D, Lin CH. Decreased activity and oxygen desaturation in prone ventilated preterm infants during the first postnatal week. Heart Lung. 2002;31(1):34-42. However, since our intervention is more extensive than this, we believe our calculation of power is reasonable. We have decided to make an interim analysis in order to recalculate the sample size, however.

Action taken:
Text added to section Primary outcome measure:
The primary outcome is a composite index that the research group constructed for this study, based on the factors that determine whether the infant needs hospitalization (28). The items in the index were chosen because of their clinical implication. They are based on objective values and are therefore not likely to differ between different assessors. The index has not been validated, but was tested in a small pilot study (unpublished material), were the clinically relevant change of two points was determined by clinical reasoning.

Clarification added to Statistics section:
A previous pilot study (unpublished material)
Text also added in Statistics section:
We plan to make interim analyses of the data obtained after inclusion of 50 per cent of the estimated sample size in order to check the assumptions about the standard deviation and recalculate the sample size. In that analysis, we will also be able to address possible safety concerns in the study, although we do not anticipate any harmful outcome.

Comment from reviewer 1:
Item 16 - allocation:
Please provide additional information on the randomisation methods. You provide some of these details in the discussion - but they need to be included in the methods section of the text, too. Specifically, please confirm that simple randomisation will be used, or otherwise clarify if any stratification factors have been used. I suppose site was a stratification factor? Please also clarify that (if) (random) blocks used in the generation of the allocation sequence.
Please clarify where the randomisation envelopes will be kept, who will have access to them and how they are chosen. i.e. are the envelopes numbered, and are stuff instructed to use them in numerical order? Who will randomise the participants to their randomised treatment?

Item 17 - Blinding:
You state that physiotherapists are not blinded. Please clearly state that nobody, including participants, parents/carers, trial staff and statisticians are not blinded.
Are outcome assessors blinded?
Authors’ response:
Thank you for these important comments. We agree that more information about the randomisation process and blinding was needed.
Action taken:
Text added in Randomisation section:
When a child is included in the study it will be individually randomised to one of the three groups. A statistician who is independent of the study has performed randomisation in blocks, stratified by the two sites. The statistician prepared sealed paper envelopes, numbered in sequence, that are kept in in a locked safe accessible only for the researchers responsible for the study. A small number of envelopes will be brought to the study binders at the two hospital wards when needed. The staff that will include an infant in the study after parental consent is
instructed to open the envelope with the lowest number, which will be the top envelope in the binder.

Text added in Discussion section:
...and blinding of parents to participants, care providers or assessors was not possible due to the nature of the intervention. To minimize possible bias, one person will perform the intervention and another person will evaluate the result of the different interventions (make the assessment). The statistician involved in the analyses will be blinded.

Comment from reviewer 1:
Item 18 - data collection and retention
You state that participants will be excluded from the study if prescribed physiotherapy but randomised to control or non-individualised group. To understand real-life effects, it is important to collect data on all randomised participants. Please could you ensure that data are collected on all randomised participants. If there is clinical equipoise about the different approaches, which is required to defend the study design, then physiotherapy should not be prescribed to those allocated to the other trial interventions. Again, please comment on how likely this is to happen, and how trial processes could be amended to minimise this happening.
You state that your generous allowance for loss to follow-up is expected to compensate for excluding participants in the control and non-individualised group. However, if the more severely ill children are excluded, then this approach is likely to include considerable bias into the analysis. Please can you comment on this in the discussion.

Authors’ response:
We realize that text about prescription of physiotherapy is confusing. The infants will not be prescribed physiotherapy as all staff at the ward is informed of the study which is also approved by the management at the two sites. Please also see response to Item 20 and 11.
Action taken:
Confusing text in section Inclusion of participants removed.

Text added in Statistics section:
The drop-outs will be analyzed according to age, possible viral infection, gender, allocation group, and severity of illness at admission to the ward (saturation, respiratory rate and heart rate or more data if collected).

Text added in Discussion section:
We have, however, calculated generously on the drop-out rate to compensate for this, and the drop-outs will be closely analyzed as described earlier.

Comment from reviewer 1:
Item 19 - data management
Please describe who will enter the data onto the database, what steps are in place to ensure the accuracy of the data. Please also give more details on the data storage, and its security. Will be external hard drive be encrypted? How will the data be backed-up, to ensure data are not lost?

Authors’ response:
Thank you for pointing out these uncertainties that are now clarified.
Action taken:
Details added in section Data management:
The data from the paper protocols will be manually entered onto the database by the primary investigator (SAM). The accuracy of the data in randomly chosen protocols will be double-checked by two other researchers in the group. During the period of entering data, the hard drive will be regularly backed-up to a USB-memory, which will also be kept in a safe.

Comment from reviewer 1:
Item 20 - statistical methods
Your planned analysis refers to data collected at 20 minutes and 24 hours. Data are collected at multiple other time points. Please describe how these data will be presented, and how their collection is justified.
In your sample size, you describe two primary tests, i.e. individualised intervention vs. control, and non-individualised intervention vs. control. Your planned analysis is an ANCOVA model - with additional t-tests or similar being performed if the overall test is significant.
Please can you give more details on this testing structure, i.e. will you first perform a global test to assess if there is any treatment effect. What significance level does this test have to show before you proceed to the pairwise tests?
Are there no circumstances under which you may wish to compare the two physiotherapy interventions directly? Currently, your multiplicity adjustment does not account for this - and you will not be able to recommend one physiotherapy approach over the other if at least one is shown to perform better than the control.
Your pairwise tests seem to be limited to t-tests. Why would you not also use an ANCOVA or similar to adjust for baseline characteristics, in line with the overall test?
You are planning subgroup analyses by gender. Your analysis is not formally powered for this. Please clarify if this will be a formal analysis, or exploratory in nature.
You plan to use the intention to treat analysis, which commonly includes all those randomised into the trial. Please clarify how you will include those participants who will be excluded from the trial due to physiotherapy being prescribed to them.

Authors’ response:
Thank you for these useful comments!
The reason we want to collect data at different times is that we want to know more about time to recovery. We have now clarified that in text.
We agree about the need for clarification, and also want to compare all groups. We have now corrected for comparisons between all groups, and given more details about the analyzing process.
We have also decided on an interim analysis were we intend to analyze the variance of the primary outcome in order to re-calculate the sample size.
Thank you for this clarification about gender analysis not powered. We agree.
Physiotherapy treatment will not be prescribed to any participant in the study (please see also answer to item 11 and item 18 above).

Action taken:
Significant changes made in Statistics section. Examples below.
Text added:
To increase the knowledge about what time the infants will recover, data are collected every 3 hours. We will analyse the time the infants recover by means of Fisher’ Exact test and Kaplan-Meier analysis.
Sample-size recalculated in order to compare all groups.
Numbers changed in Study design section and in Figure 1:
We plan to include 162 infants who will be randomised to either the individualized physiotherapy intervention group, the non-individualized intervention group, or the control group, 54 in each group.
Text added in statistical section:
The effect of the individualized physiotherapy intervention, the non-individualized intervention and a control group receiving standard care on clinical index at 24 hours will be assessed by an ANCOVA model with adjustment for baseline clinical index and post hoc test for the different group combinations will be performed.
Text added about planned interim analyses.
Clarifications made about tests.
Text added: Explorative subgroup analyses by gender will be performed.
The misleading text about prescription of physiotherapy treatment to study participants is removed.
The wording intention-to-treat removed.
Comment from reviewer 1:
Item 21 - data monitoring
You state that no data management committee is required for your study under Swedish law. Would it be reassuring to have an independent committee look at the accumulating data and assess where there are any safety concerns? Please confirm in the text that there will only be one single final analysis, and no planned interim analyses for this trial.

Authors’ response:
Thank you for these comments! We now intend to make interim analyses.
Action taken:
Text added to Funding section:
However, we plan to do interim analyses in order to address possible safety concerns in the study.
Text also added in Statistics section:
We plan to make interim analyses of the data obtained after inclusion of 50 per cent of the estimated sample size in order to check the assumptions about the standard deviation and recalculate the sample size. In that analysis, we will also be able to address possible safety concerns in the study, although we do not anticipate any harmful outcome.

Comment from reviewer 1:
Item 25 - protocol amendments:
Please could you provide more detail how important protocol changes will be communicated.

Authors’ response:
Thank you clarifying the need for this information. We agree.
Action taken:
Text added to section Study design:
Any significant changes of the protocol will be registered at ClinicalTrials.gov and communicated to the staff involved through the contact-staff on the both sites.
Comment from reviewer 1:
Minor comments:
Item 6a: Background: for non-expert readers, please could you explain the term "prone position". Similarly, in the section on the intervention, you mention the "supine" position. Please could you also explain this.

Authors’ response:
We understand, and want the text to be as clear as possible.
Action taken:
Text added at the end of the Background section and in section Individualized intervention:
prone position (lying on their stomach)
Text added in Interventions section:
The position for all infants at baseline is supine on the bed, that is, lying on their backs.

Comment from reviewer 1:
Last sentence page 10: "stimulate to active arm or leg movement". Should this read "activate"?

Authors’ response:
Thank you for this comment!
We hope the meaning is more clear (and correct) now. The term ‘stimulate to motor activity’ is often used in paediatric physiotherapy, but maybe not so much in other domains.
Action taken:
Wording changed in section Individualized intervention:
stimulate the infant to actively move their arms or legs.

Comment from reviewer 2:
Reviewer #2: This study is a small randomised control trial looking to evaluate two procedures already in place in hospitals in Sweden to improve clinical outcomes of children with acute airway infection. It is important to add evidence to clinical procedures and good to see clinical trials like this being run. I have a few comments to help with clarification.
The analysis is described as intention to treat but under the inclusion of participants paragraph, children in the control group or non-individualised group who later are prescribed physiotherapy will be excluded. If they are excluded from the study (and thus the analysis) then I would suggest the analysis is per-protocol and that this later possible exclusion of certain children be made clear in Figure 1. It would also be helpful to indicate whether children in the individualised group who do not receive their intervention, as a physiotherapist was not available, will have their data included or not. It is mentioned as part of possible 'drop out' in the discussion section that they will be excluded but these children should be included in the analysis if it is intention to treat.
I would suggest adding when some of the secondary outcomes will be measured i.e respiratory rate, wheezing sound, retractions/nasal flaring, general condition in Table 1. I would also suggest indicating how the oral intake at each feeding session fits into the specific time points when the clinical index is calculated. I.e would they use the nearest feeding session fluid intake or just the feeding session prior to when everything else is measured?

Authors’ response:
Thank you for the positive acknowledgement about need for this type of clinical trial!
We highly agree about confusing text under Inclusion of participants. The participants will not be prescribed physiotherapy, as all staff at the ward is informed of the study, which is also approved by the management at the two sites. Agree about need for clarification about time for assessment of oral fluid intake.

Action taken:
Confusing text on PT treatment deleted from section Inclusion of participants.

Words removed in Statistical section:
intention-to-treat
Text added to Statistical section:
Incomplete observations and drop-outs are expected to amount to about 20%. Thus a total of 162 patients are needed to be included in the study. The drop-outs will be analyzed according to age, possible viral infection, gender, allocation group, and severity of illness at admission to the ward (saturation, respiratory rate and heart rate or more data if collected). Also clarified in the Discussion section: We have, however, calculated generously on the drop-out rate to compensate for this, and the drop-outs will be closely analyzed as described earlier. Time-point for assessment added at each item of Wang respiratory score in Table 2 as suggested.

Text added in section Primary outcome measure:
The oral fluid intake for analysis at hour 24 will be the collected intake during the first 24 hours in the study.

Comment from reviewer 2:
I was interested that the authors have assumed in the sample size calculations that the individualised and non-individualised interventions will have the same effect on the children and their primary outcomes compared to control. It may be worth saying something about this in the discussion as I guess the study will not be powered to compare those two arms directly.

Authors’ response:
Thank you for these comments.
We want to be able to detect the same clinically relevant change of at least 2 points in the primary outcome, irrelevant of the allocation group.
We have now recalculated the sample-size in order to compare all groups.

Action taken:
Text significantly changed in section Statistical and sample size calculations.

Comment from reviewer 3:
Reviewer #3: This a review by the SPIRIT protocol editor for Trials. This is a well written comprehensive protocol for a randomised controlled trial assessing the effect of individualized physiotherapy treatment and a non-individualized intervention programme involving frequent changes of body position and stimulation to physical activity for infants hospitalized with acute airway infections. You taught me a new word "praxis" - thank you!
Few general comments
1. Consider adding Randomised controlled trial to the keywords.
2. Table 2 consider adding (28) after Wang score for people reading quickly who missed earlier reference.

SPIRIT checklist - It is not acceptable for Trials journal for the authors to leave any items blank, with N/A or miss out in the SPIRIT checklist. Further information giving rationale and why an item is not applicable is required. Please either edit the protocol and insert page numbers in the checklist or insert relevant information in the SPIRIT checklist.

I will use the SPIRIT checklist to structure further comments on the manuscript.

Authors’ response:
Thank you for general positive and useful comments!
Thank you for this advice. We agree.
Action taken:
1. randomised controlled trial added to keywords.
2. Reference (31) added in Table 2.
(same reference, although with a new number now after addition of more references)

Comment from reviewer 3:
Item 2b. All items from the World Health Organization Trial Registration Data Set. Please state: Please refer to Item 2a and registration in the ClinicalTrials.gov NCT03575091.

Authors’ response:
Thank you for this useful suggestion!
Action taken:
Added to the SPIRIT checklist 2b:
Please refer to Item 2a and registration in the ClinicalTrials.gov NCT03575091.

Comment from reviewer 3:
Item 5b: I was not clear on the information on page 17 who was the sponsor. Please also give the contact details for the sponsor. It is the role of sponsor(s) to ensure that proper arrangements are in place to initiate, manage and report on a study. Sponsors must also ensure that appropriate indemnity is in place before research begins. A sponsor does not usually conduct the investigation.

Authors’ response:
Thank you for pointing out the need for additional information. We understand and agree.
Action taken:
Text added in Funding section:
The sponsor with overall responsibility for the operability and management of this study is Region Skåne, SE-291 89 Kristianstad, Sweden. The study is performed in collaboration with Region Kronoberg, SE-351 88 Växjö, Sweden and with Lund University, Box 117, SE-221 00 Lund, Sweden, that is responsible for the design, initiation and analyses.
No independent oversight committees are in place for this trial.

Comment from reviewer 3:
Item 5c: I could not find information on page 17 on the role of sponsors etc so information needs to be inserted into the protocol. An example of what has been written is: "The sponsor played no
Authors’ response: Thank you for pointing this out and for the useful suggestion! We understand.

Action taken: Text added in Section Funding:
The funders played no part in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Comment from reviewer 3: Item 14: Sample size - could you insert a reference for the pilot study please "A previous pilot study has shown that the standard deviation is approximately 2.8"

Authors’ response: Unfortunately we do not have a reference, as the calculations build on a small unpublished pilot study.

In the planned interim analysis, however, we will recalculate the sample size based on the data collected so far. Please also see response and text added in Item 21b below.

Action taken: Text added in Statistics section: (unpublished material)
Text also added in section Primary outcome measures:
The index has not been validated, but was tested in a small pilot study (unpublished material), were the clinically relevant change of two points was determined by clinical reasoning.

Comment from reviewer 3: Item 21b: Leaving this blank is not acceptable. Please insert information into the protocol on interim analyses and formal stopping rules for the trial. For instance, perhaps there are no anticipated problems that are detrimental to the participant but please include in the protocol.

Authors’ response: We now plan to perform interim analyses of possible harm.

Action taken: Text added in Funding section: However, we plan to do interim analyses in order to address possible safety concerns in the study.
Text added in Statistics section: We plan to make interim analyses of the data obtained after inclusion of 50 per cent of the estimated sample size in order to check the assumptions about the standard deviation and recalculate the sample size. In that analysis, we will also be able to address possible safety concerns in the study, although we do not anticipate any harmful outcome.
We now also refer to the passage in Ethics section about close monitoring of the participants.

Comment from reviewer 3: Item 26b: Can suggest something like this "On the consent form, participants will be asked if they agree to use of their data should they choose to withdraw from the trial. Participants will also be asked for permission for the research team to share relevant data with people from the
Universities taking part in the research or from regulatory authorities, where relevant. This trial does not involve collecting biological specimens for storage."

Authors’ response:
Thank you for this advice.
No sharing of the data will be done, except un-personalized, which we have now clarified.

Action taken:
Text added in Ethics section:
On the consent form, parents to participants will be informed that no unauthorized person can access personal data. The data will be un-personalized and coded with a trial ID number before analysis. No published material will contain identifiable participant information. This trial does not involve collecting biological specimens for storage.

Comment from reviewer 3:
Item 30: Provisions for post-trial care - you could state "There is no anticipated harm and compensation for trial participation" and it would be helpful to know if there will be any provision for post-trial care.
* Item 31 c: I note information on page 13 for access to data. Also, page 17 "Availability of data and materials - Not applicable." Consider stating "The datasets analysed during the current study are available from the corresponding author on reasonable request."

Authors’ response:
Thank you for these valuable suggestions. We agree about the need for clarification.
Action taken:
Text added in Ethics Section:
There is no anticipated harm and compensation for trial participation.
Ordinary patient injury insurance applies as with all health care in the hospital.
If the infants will need continued care post-trial, the standard care at the hospital will be available.
Text on Availability of data and material changed to
The datasets analyzed during the current study are available from the corresponding author on reasonable request.
Comment from reviewer 3:
Item 33: See above 26b there will be no biological specimens collected.
Authors’ response:
Thank you for this suggestion.
Action taken:
Text added in Ethics section:
This trial does not involve collecting biological specimens for storage.
Comment from reviewer 3:
References: There were nine articles that could not be checked, please ensure information as in guidelines below. One article was not validated.
Authors’ response:
We do not know why the references was not checked or validated, as we think that the guidelines were followed closely on submission. The article that was not validated, Chin HJ (former ref 29, new 32) is indexed in Scopus (both article and journal), but not in Medline.
Reference 6 is a dissertation. Four of the references not checked are books (ref 1, 23, 24, (25) and 30 – former 27).
References 28, 29, 41 (former 37, 26, 38) are web-sites.

Action taken:
We have double-checked the availability in databases and on the Internet.
Link to ref 6 is provided in list.
Specified section and page number now added to book references, which makes an additional reference 24.
English clarification/translation provided in list to the two Swedish web-sites 29, 41.
Two new articles are also added (27, 39).