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:

To all reviewers:
Thank you for taking the time to read and reflect on the submitted files again. Thank you for your additional questions and comments to increase the clarity and understanding. Below are the responses and descriptions of the changes we made in the text. Changes in the main text can be followed by “tracked changes”. We hope that you will now find the manuscript acceptable for publication.

Best regards,
Sonja Andersson Marforio (corresponding author)

Reviewer reports:
Reviewer #1: Dear Sonja Andersson-Marforio & colleagues,

Thank you for taking on board my comments, and updating your manuscript accordingly.

I have a couple of follow-on queries:

Superiority vs. non-inferiority
You state that you do not want to use the term "superiority" to describe your trial, as you want to show that the non-individualised treatment is better than the control intervention, but also that the non-individual treatment is sufficient. It read this as you wanting to test that the non-individualised treatment is not worse than the individualised treatment. Using a two-sided (superiority test) may provide no evidence of a difference between the non-individualised and individualised treatment. This is not equivalent to evidence of no difference. If you wanted to show that the non-individualised treatment was non-inferior to the individualised
treatment, you require a different statistical test, a clearly defined non-inferiority margin, and potentially a different sample size calculation.

Please can you be more specific on how you will determine that non-individual treatment is sufficient in your patient population.

Author’s response:
Thank you for pointing out these differences. We agree.
We want to be able to detect differences between the groups. Our statistician recommends a two-sided test. We will not use a one-sided superiority test.

If a clinically relevant improvement (2 points) is found in the non-individual intervention group compared to the control group, we will interpret this as a sufficient treatment, resulting in a clinically important change. Any improvement above that will be regarded as a valuable addition.

Action taken:
Text added to Interventions section: …“, making a clinically relevant change”.

Availability of primary outcome:
You state that most (but not all?) infants will expected to remain in hospital for 24 hours, at which time the primary outcome is collected.
Please could you clarify how participants who leave hospital prior to 24 hours will be included in the analysis. Some trials may exclude those participants, although this may bias the trial results, especially if early discharge is more frequent in one arm, compared to the others. Another option may be to include these participants with their most recent measurements (likely to be taken at discharge) - assuming that these will get better with time. Please could you discuss the best option among the clinical team and add them to the protocol.

Author’s response:
Thank you for these important comments.

Action taken:
Added text in Statistical section: If an infant will be dismissed from the ward before hour 24, that participant will be excluded from this analysis and will be analysed in the same way as the other potential drop-outs.

Newly planned interim analysis:
You may not have to change anything in the text, but you may consider early on what exactly you want to look at in your interim analysis. Monitoring safety is definitely good. However, who will see the results? In my studies, I report interim safety data to an independent committee, who will treat data confidential (unless there are concerns about patient safety). If investigators and those recruiting patients and delivering the intervention were aware of interim results (which may not be representative of final results), this could change how participants are treated, and bias the results of the study. For the same reason, I sometimes consider the assumptions for the sample size for the overall population only, i.e. without revealing results for individual groups.
Pleas could you change the wording to "we plan to perform (or conduct) an interim analysis"

Author’s response: Thank you for this important comment and suggestions.

Action taken:
Changed wording in Statistical and Funding sections to “we plan to perform an interim analysis”

Added text in Statistical and Funding sections: “That {interim} analysis will be performed by a statistician independent of the study, and the result will only be presented to the research group at this stage if any harmful outcome will be detected in the intervention groups.”

Reviewer #2:
Thank you for the thorough responses. They have addressed my points appropriately. I just have two minor additional points.

They have added a sentence regarding the 'full analysis set' in the statistical and sample size calculations section which is not very clear. Could this be clarified by adding which children are included in the full analysis set i.e all children randomised?

Author’s response:
Thank you for pointing out the need for clarification. We agree.

Action taken:
Added text in Statistical section: The dataset primarily to be analysed is the full analysis set, “and with all participants who are still in the study.”

An interim analysis has been added but these are usually then reviewed by an independent data monitoring committee who would make recommendations to the trial steering committee and/or trial management group. The authors indicate there are no independent committees for this trial but it may be worth considering having one if a formal interim analysis is being carried out as they would be best placed for independent review. I would suggest calculating the clinical index and standard deviation on the controls only and use that to inform any sample size revision if that is the sole reason for an interim analysis but I also see that safety data is going to be reviewed, also something an independent committee can be useful for.

Author’s response:
Thank you for these useful suggestions!

Action taken: Text changed in funding section:
“We do not use a data management committee. However, we plan to perform an interim analysis in order to address possible safety concerns in the study. That analysis will be performed by a statistician independent of the study, and the result will only be presented to the research group at this stage if any harmful outcome will be detected in the intervention groups.”

and in statistical section:
That analysis will be performed by a statistician independent of the study, and the result will only be presented to the research group at this stage if any harmful outcome will be detected in the intervention groups.