Reviewer's report

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.

Version: 0 Date: 16 Jan 2020

Reviewer: Ines Rombach

Reviewer's report:

Dear Sonja Andersson-Marforio,

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.

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.

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.

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?

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.

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.

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.

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.
Item 13: Participant timelines:
You outline 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.

Item 14: sample size:
The standardised effect size is $2/2.8 = \text{>0.71}$. 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.

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 staff 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/careers, trial staff and statisticians are not blinded.
Are outcome assessors blinded?

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.

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?

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.

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.

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

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.

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

Level of interest
Please indicate how interesting you found the manuscript:
An article of limited interest

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Quality of figures**
All images and figures within the manuscript should be genuine i.e. without evidence of manipulation. No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. If you have concerns about the veracity of the figures you should choose the first option below.

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Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

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