Author’s response to reviews

Title: Stockholm Preterm Interaction-Based Intervention (SPIBI) - Study protocol for an RCT of a 12-month parallel-group post-discharge program for extremely preterm infants and their parents

Authors:
Erika Baraldi (erika.baraldi@specped.su.se)
Mara Westling Allodi (mara.allodi@specped.su.se)
Kristina Löwing (kristina.lowing@ki.se)
Ann-Charlotte Smedler (acsr@psychology.su.se)
Björn Westrup (bjorn.westrup@ki.se)
Ulrika Ådén (ulrika.aden@ki.se)

Version: 1 Date: 22 Nov 2019

Author’s response to reviews:

Cover letter
Dear Editor of BMC pediatrics,
We hereby send you our revised study protocol for an interaction-based intervention targeting extreme premature born infants and their parents in Sweden.

We are grateful for the useful suggestions made by the reviewers and have responded point by point in the attached document. Changes in the ms have been made accordingly. We have attached one version of the revised ms with the changes highlighted in yellow and one clean version. This manuscript has not been published or submitted for publication elsewhere.

Best regards
SPIBI Research group Stockholm

Reviewer comments of the SPIBI-protocol answered in detail;

Reviewer (Rev) 1: Comment 1: “The trial endpoint is marked at 12 months CA and the EAS is the primary outcome measure. It is nice that the EAS is repeated at 24 months CA; why not again at 36 months CA?”

Answer: The idea of repeating the emotional availability scale (EAS) measurement is appealing from a scientific point of view. The measurement improves in stability as the child grows older. In our experience, families consider the video filming being one of the most intrusive part of assessment. Therefore we have only two assessments in the ethics approval. In addition, scoring of tapes by an authorized psychologist is a very time-consuming and expensive procedure. If we have funding for that procedure in the future, we might apply for ethical approval/amendment for this.
Rev 1: Comment 2. “I guess that, given the 2 follow-up moments (24 and 36 months CA), the data analyses approach described (page 21) needs to be elaborated in the sense that the design changes to a more longitudinal approach (with at least 3 measurement points) using, for example, more sophisticated methods like linear mixed models. I can see no such description (yet)? it would be good if hypothetical models can be defined at this moment already in order to avoid later 'fishing expeditions’?”

Answer: On pp. 24-25 we have changed the heading “Data analysis” to “statistical analysis plan” and included an extended section describing linear mixed models. The primary and secondary hypotheses are clearly defined on page 10 and onwards, under the heading “hypotheses”, to avoid any fishing expeditions.

We have specified the expected effects of the intervention on each instrument on pp. 19-24.

Rev 1: Comment 3. “As the authors point out themselves (page 12, first paragraph), the children / parents participating in the 'control' group are not 'true' controls in the sense that they ONLY receive the TAU but additional measurements as well. I agree with their worry. In fact, one of the suggestions to tackle this Hawthorne effect (i.e. participation in research in itself causes change in the behavior of the research participants) could be to introduce a THIRD group in the design: a post-test only group. This is a control group in which measurements are only performed at the time-point of the primary outcome, this avoiding as much interference from study participation with the results of the study as possible”

Answer: One might argue the Hawthorne effect is a possible limitation to the study, but since the control group only receives four baseline parental questionnaires and one extra physiotherapy assessment of the child, we consider the recruitment process is not likely to affect the result one year later. We have changed the text on page 14 accordingly.

To introduce a third group to compare with is a great idea from a methodological point of view, but we consider that it is not feasible. Since the amount of infants born before 28 gestational weeks is very limited (around 80 per year in our region who also lives in the region, 100 if non-residential children are included), such an approach would risk the power of the study.

Rev 1: Comment 4. “Measurements: I appreciate the use of a logbook and wonder: will any of the data reported in the logbooks be of help / use as variables to include in a (prediction)model?”

Answer: No, we don’t plan to use any data from the log book in the analysis. Our experience from previous studies have taught us that if we introduce the logbook to the parents as a research tool, the parents becomes so preoccupied with what to write to the researchers, how they describe their child and even their own handwriting skills, that they refrain from writing anything at all in the logbook. Hence, to keep the logbook as a creative part of the parental process at home, the logbook has been introduced to the families as their own document – merely as a part of their own parental development. We have added a sentence about this on page 13 in the article.

Rev 1: Comment 5. “I find the description of the TAU (for example on page 13) not clear enough. How many times are children / parents seen by a paediatrician, physiotherapist, psychologist in the 'regular' follow-up program in Sweden and what aspects of their development are screened?”

Answer: The follow-up program for high-risk infant is substantial in Sweden. We have added a paragraph with detailed information about the follow-up program in the article on page 14.
Rev 1: Comment 6. “The authors are realistic in their expectations of the number of children able to include during the recruitment period (until 2020) (page 14). But, if the targeted number of 130 is NOT reached: what will happen? Extend the recruitment period? Is there a bottom limit which the authors at least want to achieve? Moreover, the possibility of applying subgroup data analyses is mentioned (page 21): this might be jeopardized if not enough children can be recruited”.

Answer: In our experience of similar studies in the same population and region, we will include the postulated number of participating families. If the target is not reached, we plan to extend the inclusion time and expand the study into other regions of Sweden. We have changed the sentence about this on page 16.

Rev. 1: Comment 7. “(page 27): Availability of data and materials. The authors mark this as 'not applicable'. However, in this (new) day and age of Open Science I would strongly suggest to look at the possibilities for sharing data and materials (in the Swedish context of course)”

Answer: We share the interest and positive attitude towards open access data. However, in our ethical vetting and when we ask for parental consent we have stated that the data we collect will only be used by the current group of researchers for the current study. If we plan a follow-up study in the future, we ask for consent to share data.

On an aggregated level, the SPIBI research-team may share aggregated data upon reasonable request.

Importantly, our manual for the intervention is free to use for any other research team after some initial information/education from the SPIBI research team.

Rev 1: Minor comment 8. “Abstract: penultimate sentence it is stated that the trial will give valuable information for all children in Sweden. I suggest to change this to all children born in the Stockholm region since I can imagine that the possibilities to provide an intensive type of care like SPIBI is (more) difficult to realize in all regions of Sweden (?)”

Answer: The care and follow up for extremely preterm infants in Sweden is regarded as highly specialized and successfully centralized to eight regional hospitals. The information from the trial should be applicable to infants in all these regions, although we acknowledge a minority of children may reside in rural areas and for practical reasons may not get the same support. Changes have been made in the abstract to “the trial will give valuable information about extremely preterm children and their parents during infant and toddler age after regional hospital care in Sweden” (page 4).

Rev 1: Minor Comment 9. “English needs some language corrections. For example, in the abstract (background section) it should be run (instead of runs) and (discussion section) the word parental is misspelled (= parnetal). Likewise, on page 6 it should be “Since parental sensitivity seems to be ... (instead of seem to be). And so there are many more examples throughout the text. Please check carefully”.

Answer: Thank you for this valuable information, we have sent the article for language check and made all the suggested changes in the text.

Rev 1: Minor comment 10. “I suggest to add the words 'emotional availability' to the keywords for this paper (as it is the main outcome measure)”
Answer: Yes, an excellent idea, we have corrected this in the list of keyword, see yellow-marked text (page 4).

Rev 1: Minor Comment 11. “The text describing the measurements and the information in Table 2 do not match. For example, the BRIEF is also administered at 3 years CA (and missing from the Table). And so are the PSE, RES, HADS and STAI at term age? “

Answer: Thank you for bringing this to our attention, we have checked this up and ensured that the information matches (changes in table 2 and page 21 in the protocol).

---------------

Rev 2: Comment 1. “Is it an already ongoing study?”

Answer: Yes, the study is ongoing.

Rev 2: Comment 2. “In contrast, a pharmaco-economic assessment based on the main outcome variables (parents and child) may be a valuable add on”

Answer: This is a great suggestion and we will make an amendment in the ethical vetting for this in the future. As we have no parental consent of this right now, and medical information about the parents is a sensitive issue from an ethical point of view, we cannot change the protocol at this point. In the future, we will ask for permission to add;
- Number of days on sick leave over the first two years for mother and father. Data from National social insurance agency (Swedish Försäkringskassan).
- Number of visits to emergency units and other care givers for the child over the first two years. Data from medical journals.
- Drug prescription for child, mother and father over the child’s first two years. Data from Drug registry.

Rev 2: Comment 3. “Power calculation: I miss the number in the abstract”

Answer: The strict word count of the abstract do not allow us to add the power calculation in the abstract. However, an extended statistical section is added under the heading “statistical analysis plan” on page 24-25, and the power analysis can be found on page 16-17.

Rev 2: Comment 4. “I suggest that the authors should also consider subgroup randomization, since this reviewer assumes that the % outcome will display a gestational age-dependent variability”

Answer: Thanks for this valid suggestion. For the primary outcome, we estimate that GA will not be a covariate, since maternal EAS-scale sensitivity was not shown to be altered with differential severity of neurodevelopmental impairment (Biringen et al., 2014)."

We acknowledge our secondary outcomes cognition and motor development are related to GA in the range 22-40 weeks, but possibly less so in the narrow range of 22-27 weeks included in the present study.

Therefore we consider the risks of altered main results due to unbalanced recruitment small. Furthermore, considering the limited number of eligible infants we have we don’t think subgroup randomization is feasible in the current study.
Best regards
The SPIBI Research group Stockholm
Authors: Erika Baraldi, Psychologist and PhD student; Mara Westling Allodi, Professor of Special Education; Kristina Löwing, Physiotherapist, PhD; Ann-Charlotte Smedler, Psychologist, professor emerita of Psychology; Björn Westrup, Neonatologist, PhD; Ulrika Ådén, Neonatologist, professor of neonatology