Author’s response to reviews

Title: Creative music therapy to promote brain structure, function and neurobehavioural outcomes in preterm infants: a randomized controlled pilot trial protocol

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Author’s response to reviews:

This study is described as a pilot trial, but the objectives are not clear. There is no indication of the areas of uncertainty to be investigated in preparation for a full scale trial.

• Thank you for this valid comment, we have addressed this and changed the manuscript accordingly. Description of the objectives of this pilot trial and adding indication of the areas of uncertainty to be investigated in preparation for a full scale trial.

Added on page 1:
…is conducted in preparation for a multi-centre trial … Primary objectives of this study are feasibility of protocol implementation and investigating the potential mechanism of efficacy for this new intervention.

Added on page 5/6:
…in preparation for a full scale trial. Since this is the first study to evaluate possible effects of CMT on neurobehavioural outcomes in preterm infants a pilot design is chosen to test its clinical, recruitment and outcome measurement feasibility.
The authors provide hypotheses on the effects of the CMT intervention, and state this is the first trial to examine "short- and long-term effects". However, a pilot trial is not suitable to address these hypotheses or investigate effectiveness of an intervention.

• Thanks you for this comment to which we fully agree. This pilot study if to examine the feasibility with focus on the estimation of drop-out rate, and differential drop-out rate within treatment groups. Also we are investigating the potential mechanism of efficacy for this new intervention with MRI and neurodevelopmental outcome in order to plan a multicenter full scale RCT. We have changed the manuscript accordingly.
Adapting our purpose from demonstrating effects to evaluate and discover possible effects and tendencies.

Added on page 1:
Primary objectives of this study are feasibility of protocol implementation and investigating the potential mechanism of efficacy for this new intervention. To examine the effect of this new intervention …

Changed on page 2:
This project lies at the interface of music therapy, neuroscience and medical imaging. New insights into the potential role and impact of music on brain function and development may be elucidated. If such a low-cost, low-risk intervention is demonstrated in a future multi-centre trial to be effective in supporting brain development in preterm neonates, findings could have broad clinical implications for this vulnerable patient population.

Added on page 9:
Since there is a substantial gap in present knowledge to assess the long-term impact of music therapy in preterm infants [45], and since at two years of age merely developmental milestones can be measured while more complex cognitive functions such as executive functions are only developing, secondary endpoints will also be assessed at 5 years of corrected age [61]. Along these lines, it was recently postulated that the 2-year outcome should be used as a proof for safety of neuroprotective agents rather than their efficacy [61].

The authors describe statistical analyses, including providing a level for statistical significance. A focus on significance testing is unlikely to be appropriate in a pilot trial with no sample size calculation. It would be more suitable to report results that would be useful for planning a full scale trial.

• Thanks. We have changed the statistical plan in accordance to the aims of the study.

Page 10/11:
The primary objective of this study is feasibility including the estimation of drop-out rate, and differential drop-out rate within treatment groups. Time points for the evaluation of drop-out rates will be at 38-42 weeks and at two years. Drop-out rates and their corresponding confidence intervals will be estimated using the Wilson method [66]. The success of recruitment will also be measured by summarising randomisation rates and reasons of withdrawal compared to available patients listed in the screening log. We anticipate differential protocol adherence with respect to treatment group assigned.

To test the effect of the intervention, point estimates of mean differences for efficacy will be estimated with corresponding 95% confidence interval for continuous outcomes, and differences in proportions with 95% confidence interval for the two treatment groups will be calculated for categorical outcomes. Univariate analysis of covariance (ANCOVA) will be performed to examine MRI differences between the groups. The independent variables are treatment group and gender. Resulting estimates of mean differences, and differences in proportions including variability will serve to perform the sample size calculation for the multi-center full-scale trial.
The authors also state that infants in the control (standard care) group who are exposed to music from parents will be excluded from the analysis. Although estimation of a treatment effect is not the purpose of a pilot trial, it is worth noting that this prevents an intention-to-treat analysis and could introduce bias in estimating a treatment effect.

- Thank you for this comment. We have addressed this comment. We still exclude parents who start to sing since the control group should not be exposed to music in order to function as control without music stimulation.

It would be useful to have more specific descriptions of the outcomes listed in manuscript. The authors could include the exact measurement or scales as well as the method of collection (e.g. what will be measured in the "Visual and hearing exam").

- We have added more details in the outcome section, on page 9:
- Assessments of visual problems such as corrective glasses, strabism, severe visual impairment or blindness [64]
- Assessment of hearing problems such as moderate hearing impairment not requiring hearing aids, hearing aids or cochlear implant [64]

The outcomes should also match what is provided in the ClinicalTrials.gov registration record.

- Thank you. We adapted the measurements on the website of ClinicalTrials.gov

Follow-up for the trial extends to 5 years of corrected age for the participants. It is not clear why long term follow-up is required for this pilot trial.

- Thank you for this. We have clarified this in the manuscript as follows:
  Specification of reasons why also long-term follow-up is warranted and required on p.9:

Since there is a substantial gap in present knowledge to assess the long-term impact of music therapy in preterm infants [45], and since at two years of age merely developmental milestones can be measured while more complex cognitive functions such as executive functions are only developing, secondary endpoints will also be assessed at 5 years of corrected age [61]. Along these lines, it was recently postulated that the 2-year outcome should be used as a proof for safety of neuroprotective agents rather than their efficacy [61]. Hence following secondary endpoints will be assessed at 5 years of corrected age relating….

The authors provide a good description of the CMT intervention. A minimum of 10 sessions of CMT are to be delivered, but it might be useful to record the number and length of the sessions received. This would be useful, when reporting the trial, to provide detail on the extent of the intervention delivered.

- Thank you for this comment to which we fully agree.
  Specification of the documentation of the length and duration of sessions on p.7 and adding Appendix3:
The exact number, time and duration of sessions is documented in the individual session protocol and final report (Appendix 3). The authors should provide some justification for the sample size of 60 (30 per treatment group), related to the objectives of this pilot study.

- Thanks, we have clarified this point. We added the justification for our sample size on page 5:

… since a minimum of 30 participants for each arm in pilot studies is recommended in order to estimate parameters for future sample size calculations [50].

The title of the manuscript should indicate that this is a protocol for a pilot trial.
- Adding “pilot” trial to title on p.1:
randomized controlled pilot trial protocol

In Table 1 it would be helpful to label the rows, to clarify what is show in each row.
- Labelling the rows in table 1 (compare table 1)

Further minor suggestions:
In the 'Background' section of the abstract, the end of last sentence should be: "… will have developmental benefits in short- and long-term brain function."

In sub-section "Neurobiology of music during early life", sentence 3 should start: "This is particularly important following preterm birth …"

In the second paragraph of the sub-section "Neurobiology of music during early life", the end of the first sentence should be: "… into the newborn period and through early neonatal life" or "… into the newborn period and during early neonatal life."

In the sub-section "Potential benefits of creative music therapy (CMT)", the fifth sentence should read: "… tailored to the infant's needs …"

In the sub-section "The intervention", the second sentence appears to have a missing reference "(REF)".

In the sub-section "Outcomes", the sentences after the lists of secondary endpoints should start: "Additionally a parental questionnaire …"
- Changed all minor editing suggestions as recommended

Reviewer 2
Sample size: I understand that a sample size calculation is not appropriate for a pilot study but I am left wondering why you have chosen a sample size of 30 in each group? You can justify that using the literature on pilot studies (see reference 32 and 34 in a study by Pincus T., Anwar S., McCracken L., McGregor A., Graham L., Collinson M. & Farrin A.J. (2013) Testing the credibility, feasibility and acceptability of an optimised behavioural intervention (OBI) for avoidant chronic low back pain patients: protocol for a randomised feasibility study. Trials 14(1), 172-176).

- Thanks you for this comment. We have clarified this point in the manuscript. We added the justification for our sample size on p. 5:
  … since a minimum of 30 participants for each arm in pilot studies is recommended in order to estimate parameters for future sample size calculations [50]

Statistical analysis: In line with best practice you need to be clear on the purpose of the statistical analysis and what results will be generated and reported

- Thank you for this comment. We have changed the paragraph statistical analysis accordingly (see above) as above
  Page 6 line23 - REF - what does this mean? As this is not blind peer reviewed it is appropriate to include the reference even if it identifies the authors RER correcting to real reference on page 5 line 23
  Page 6 - is the music therapist the primary author. If the music therapist (the interventionist) is part of the research team how will the risk of bias be minimised, especially if that person is the one recording the data in relation to parental involvement and environmental influences. Page 7 line 8 and 9 - will you use a standardised form to record this data and who will record it?

- Thanks. We have changed the manuscript accordingly and clarified these points.

Adding information to minimize bias since the first author is recording data on page 7:
  The music therapy process is documented by the music therapist in a standardized form (Appendix 3) …
  An independent study nurse randomly monitors this process to minimize bias.
  Adding Appendix 3: the standardized session protocol of the study

Page 7 line 19- I think it is important for transparency to state what 'third party' will do the central randomisation. As the study is ongoing this information is available

- This has been adapted in the manuscript. Thanks Clarification of third party for transparency on p.7:
  Central randomization was performed by the Clinical Trial Center Zurich on the basis of randomisation lists.

Page 7 - line 53 and 54 - Is it necessary to repeat the hypothesis here in this section on data analysis. If you wish to do so it might be useful to link it more e.g. In order to test the null
hypothesis that ........................................ the following statistical analysis tests will be conducted: and then outline the tests.

• Thank you for this remark. We have changed the manuscript accordingly.

Titles and legends for table and figure: I note a title for both at the end of the reference list. To me the title does not reflect the content. The table is more than the course of the music trial as it also includes outcome measures and the Figure is not the formulation of the hypothesis - perhaps it is more correctly 'Factors leading to the development of the hypothesis'
  • Adapted titles of the table and figure as suggested

Table 1, needs a legend to explain the abbreviations. I note a list of abbreviations but for the reader a legend with the relevant abbreviations makes it easier to read.
  • We have deleted the list of abbreviations to the table since they are listed already at the end of the article.

Just an observation: I note that the study has been recruiting since Jan 2015 and it is now 2017. The protocol is written in the future tense which is as expected in a protocol but it feels a little strange to read what you will do when you are actually doing it.
  • Thanks for this valuable remark. We changed the protocol to the present tense (all pages).

know more about the study site. How many pre-term births are in the unit (on average) every year? What is the expected duration of this study? Has feasibility work been done prior to the pilot study? If it takes so long to recruit why haven't the authors considered extending the study to other sites?
  • We have added more details thanks. Explanation why recruitment takes much longer than expected on p.11:

Although approximately 120 preterm infants under 32 SSW are treated in the unit every year, recruiting time is much longer as expected since approximately 60% of the patients treated in our unit are from other countries and cultures and study participation is often limited because of language and ethnical barriers [67]. Culturally congruent study information available in other languages may reduce some of these barriers in future investigations and a multi-centre study is warranted to recruit enough participants for a full scale trial in an appropriate time span.

I note that you state that preterm babies who are not stable enough are excluded as they may be over stimulated but what about the study participants? Are you collecting data on possible adverse events in the study group? How do you know that some of them will not be over stimulated? I note you will monitor for safety of all participants but what will be considered an adverse event of this intervention as opposed to a preterm's reaction to something else in the environment??
  • Thanks for this comment towards safety. We have clarified this point in the manuscript

More detailed explanation how the risk of participations` overstimulation is avoided on p.6:
To ensure the safety of the infants the chosen study music therapist is a well-trained and experienced music therapist with specialized competencies, sensitivity and responsiveness in neonatal music therapy [52]. CMT with premature infants is based upon the premise that infants should be neither overwhelmed nor over-stimulated [41]. However, in the case, the infants would show adverse reactions (e.g. unexpected strong apnea, bradycardia, hypoxia) during the music therapy intervention, the music therapist would adapt or stop the treatment immediately. Moreover, the nurse in charge continuously monitors the therapy process to additionally guarantee the safety of the participants.

Is there a particular time of day for the delivery of the intervention e.g. morning, afternoon or evening

• We have added this detail Specification of the time of day for the delivery of intervention (p.7, Appendix 3):

The exact number, time and duration of sessions is documented in the individual session protocol and final report (Appendix 3).