Author’s response to reviews

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

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Editor's comments:

Thank you for addressing the reviewers' comments. Before a decision can be made on your manuscript, I would ask that you caveat the use of statistical testing (alluded to in the comments) because, appropriately, a formal sample size calculation was not undertaken so the use and interpretation of statistical tests should be minimal. Further, estimates of effect from a pilot study should be treated with caution, due to sampling variability. Please could you provide justification for using such an estimate to calculate the sample size for a future study, as opposed to using a difference considered clinically important?

Our Response:

We are aware that there is statistical uncertainty that must be taken into consideration when the estimates are used to generalize the pilot study findings. However, providing a means to estimate these quantities enables early indicators of treatment tolerability and enrolment feasibility. A “rule of 12” for continuous variables was suggested by Julious et al. (Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharm Stat. 2005; 4: 287–291) recommending at least 12 participants for pilot studies with primary focus of estimating average values and variability for planning larger subsequent studies. We will include 30 infants per treatment arm and therefore we anticipate to obtain a plausible estimate of precision.

Clinically important differences of interest would be executive functions at five years of age rather than motor impairment. This is as we do not include preterm infants with severe abnormalities on cranial ultrasound and therefore based on previous publication we will see differences in impairments mainly in higher cognitive functions rather than in general IQ or in motor functions (Wehrle FM. Early Hum Dev. 2016 Jan;92:37-43). There is very limited quantitative MR data at term equivalent in correlation with executive functions to evaluate
clinically significant effect sizes. However, there is some data on qualitative MR in correlation with executive functions: Woodward et al. reported executive functions follow a normal distribution and mean EF will be 8.1 (standard deviation, SD = 2.5) for the preterm infants with moderate to severe brain abnormality seen on qualitative MR at term equivalent age, and mean EF will be 9.6 (SD=1.7) for the preterm infants without or with mild brain abnormality, a difference which seemed clinically important (Woodward JL. PLoS One. 2012;7(12):e51879.). With a power of 80% and a 2-sided level of significance of 5%, we would need 32 children per group. Our MR analysis is focused on quantitative MR data to evaluate the differences in global brain connectivity between the treatment groups on not on quantitative data. We have also involved a statistician which will assist in the analyses.

We hope that we could answer your question to your satisfaction and remain with kind regards