Author's response to reviews

Title: Osteopathic manipulative treatment and pain in preterms: study protocol for a randomized controlled trial.

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Author's response to reviews: see over
Review of the manuscript

Manuscript number: 1870865153133926 entitled 'Osteopathic manipulative treatment and pain in preterms: study protocol for a randomized controlled trial.'

Dear Editor,

thank you very much indeed for your comments and the possibility to review the paper. A detailed description of all changes have been provided below. For any further information, please do not hesitate to contact me.

Sincerely

Francesco Cerritelli

Answer to reviewers

Editor
1. Please ensure that the authors' initials in the Authors' Contributions section are consistent.
   A: OK, done

2. When uploading your revised manuscript, please remove the attached documentation as your manuscript cannot proceed with these attached.
   A: OK, done

Reviewer #1:

Comment [1]: Sample size difference
   Different numbers in study groups. Why only 20 students and 20 professional? Perhaps only do professionals in same sample size as sham and control so as not to affect results. Sample types may be different and need to be accounted for in results
   A: Thank you for the comment, however I possibly misunderstood what the reviewer is suggesting as in the manuscript I cannot find the details she referred to.

Comment [2]: Mean costs will be different based on the acuteness of the illness that has them in NICU?
   A: Yes they are and are based on DRG (as specified in the manuscript).

Comment [3]
   Are the babies selected and then randomized based on level of illness or age of preterm? More unwell and preterm babies seeing a less experienced practitioner might affect the results. More unwell children will potentially have more pain or take longer to improve in health scores.
   A: Again thank you, however both age and severity of illness (measured by the DRG type) will be included in the regression model. Then as this is the first trial looking at pain in preterms, findings will be used for further trials, which could possibly be stratified by level of illness.

Comment [4]: A "per protocol analysis" envisages determining the biological effect of OMT, but this restriction of analysis to the selected patient population may not show the practical application of OMT across all populations.
A: Based on previous studies, we are confident that 'pre-protocol analysis' is practically applicable in the context of NICU. However an 'intention-to-treat' analysis has been added.

Comment [5]: Last observation carried forward LOCF to handle missing data may bias result in under reporting of side effects or over reporting of benefit of OMT and may over estimate precision and reliability and the power of the trial to assess treatment because the sample size on which estimates are based is lowered and there is a tendency to underestimate the variability of the results. To minimise bias perhaps collect information on reason for drop outs and include methods that provide type 1 error rates.

A: Well, I might be agree however we planned a monitoring board, which will be dealing with drop-outs using in addition the Lan–DeMets generalisation of the O’Brien–Fleming boundary sequential method for type I error.