Reviewer's report

Title: Inhaled PGE1 in neonates with hypoxemic respiratory failure: Pilot randomized clinical trials to assess feasibility

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Reviewer: Michelle Heys

Reviewer's report:

Overview
This paper describes the protocol and outcome of babies recruited to a second a pilot study to test the efficacy of inhaled PGE1 to improve respiratory outcomes in neonates with hypoxic respiratory failure (NHRF) who had a suboptimal response to inhaled nitric oxide (iNO). The authors focus on the second pilot study but also describe the first pilot study. The title states that this is a feasibility study of ability to recruit to pilot 1 and pilot 1, however the bulk of the paper describes the study protocol and the outcome of the 7 babies recruited to the second pilot.

Some general comments:
Overall this is well written paper but I feel there is lack of clarity and consistency on whether the authors are reporting on pilot 2 alone or with pilot 1. There is very little attention paid to the recruitment itself and I do not see how this can inform the revision of a protocol to successfully recruit in the future. If indeed this is as the objective states a feasibility study for recruitment, authors need to focus more on what proportion of eligible infants were identified for screening and what recruitment strategies could be more successfully employed.

It would have been interesting to understand more about reasons for non-participation by running focus groups with professionals and parents. These are a vulnerable group of babies and parents and obtaining informed consent and involvement in clinical trials at this time point is extremely challenging. Lessons could have been learnt from the experience of these authors that could inform other similar RCTs.

Of interest the safety and feasibility study Phase I/II study was carried out by this study team 10 years ago.

I would recommend publication of this trial paper after major changes.

Major Compulsory Revisions

1. Please clarify in the abstract and paper whether this paper relates to pilot 2 only or to both pilot studies. The abstract reads more as if it relates to pilot 2 only whereas the paper suggests both (methods section of main paper relates to both pilot studies whereas results section of main paper seems to report pilot 2 only).
2. Results of abstract needs to state how long after commencement the trial for pilot 2 was terminated (~ 6 months).

3. Conclusion of abstract: did the study fail to identify eligible neonates or fail to recruit? Please clarify. Please remove statement “A longer time to recruitment” – this seems unfeasible – as for 9 months only 7 recruited. In the actual RCT – how many babies would be required? What length of study would be needed at current recruitment rate to complete the trial? I suspect that would be completely unrealistic. Increasing numbers of study sites also seems completely unrealistic. Only a significant change in protocol & time to IRB/commencement might improve recruitment.

4. In the main methods section, please define “late preterm” in list of eligibility criteria.

5. In the section on secondary outcomes please state at what time point improvement in OI relates to.

6. From the main results section please clarify how many neonates were treated with iNO in each centre? How many other babies could have been screened? Or were there only 46 potential babies invited to take part? What was the recruitment rate? Please differentiate between failure to identify eligible neonates and failure to recruit especially in the conclusions of the abstract.

7. Please include estimation of sample size that would be required to run the main RCT so that the feasibility of achieving that can be discussed. Also include an explanation of how the sample size of 50 was determined.

Minor Essential Revisions:
1. Please describe 10 sites used for study in terms of numbers of deliveries/NICU beds. Are these sites all large teaching hospital NICUs with large numbers of babies?
2. In the discussion section, please spell out DR – delivery room?

Discretionary Revisions
1. A discussion of cost of running each pilot study would have been welcome. A huge amount of work and time and effort has obviously gone into the development and running of this study.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.