Reviewer’s report

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

**Version:** 3  **Date:** 28 August 2014

**Reviewer:** Daniele De Luca

**Reviewer’s report:**

This is an elegant attempt to conduct formally sound research in a very difficult topic.

Probably, I would have not performed the first pilot trial since iNO is the first line treatment for PPHN in Western world (there are also some European recommendations, see ICM 2004).

The second trial is indeed useful. The need for a multi center international RCT was well known.

However, some difficulties have been pointed out by the authors and I suggest to spend a few more words on the following:

1. what is the best nebulization technique? There is a huge literature on this topic to be taken into account. Some modern nebulizers seem to provide a nice drug deposition even during HFOV, while others failed to do so with such modality. Situation is complicated because each participating center should have the same device and a kind of control measurement for the drug deposition should be provided (an in vitro study in this regard would prove useful). Anyway this should not be difficult in vitro.

2. there is some expertise about the intratracheal administration of pulmonary vasodilators. Although these are only anecdotical cases, this way seems promising and would avoid the bias due to the different nebulization technique. There are many anecdotical reports but you can refer to my review (De Luca D, et al. Eur Resp J 2011) for a comprehensive look.

3. Another potential bias to be considered for a future trial is the difference in ventilator strategy and technique. We should try to avoid as much as possible differences in ventilation (CMV vs HFOV, recruitment man oeuvres etc - recall the differences in iNO+CMV vs iNO+HFOV in the original study by Kinsella J et al., J Pediatr 1997). This is indeed possible choosing centers with same expertise level and similar ventilatory policy.

4. Again we need to reduce as much as possible intercepter variability about support therapies (surfactant, inotropes policy etc..)

5. Related to point 1, the different point where nebulizer is attached to the circuit (either in HFOV or CMV) could influence drug deposition. This must be studied in
an in vitro study prior to the trial.

6. LAST BUT NOT LEAST. PPHN is a syndrome. It may be associated to various other clinical conditions or be idiopathic. You intended to study babies with hypoxaemic respiratory failure (including perinatal aspiration syndrome, suspected/proven pneumonia/sepsis, respiratory distress syndrome, idiopathic PPHN or suspected pulmonary hypoplasia)...but how can you think that PPHN secondary to meconium aspiration syndrome is comparable to that secondary to pulmonary hypoplasia???

These are very different situations and some other examples could be provided in this regard.

I think that a trial should be much more focused on an homogeneous population (i.e: PPHN secondary to meconium aspiration or sepsis or septic shock). This is totally different and will increase significantly the value of your results.

Level of interest: An article of outstanding merit and interest 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' below