Author's response to reviews

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

Authors:

Beena Sood (bsood@med.wayne.edu)
Martin Keszler (mkeszler@wihri.org)
Meena Garg (mgarg@mednet.ucla.edu)
Jonathan M Klein (jonathan-klein@uiowa.edu)
Robin Ohls (rohls@salud.unm.edu)
Namasivayam Ambalavanan (nambalavanan@peds.uab.edu)
C. Michael Cotton (cotte010@mc.duke.edu)
Monica Malian (mmalian@dmc.org)
Pablo Sanchez (Pablo.Sanchez@nationwidechildrens.org)
Satyan Lakshminrusimha (slakshmi@buffalo.edu)
Leif D Nelin (Leif.Nelin@nationwidechildrens.org)
Krisa P Van Muers (vanmeurs@stanford.edu)
Rebecca Bara (rbara@med.wayne.edu)
Shampa Saha (saha@rti.org)
Abhik Das (Adas@rti.org)
Dennis Wallace (dwallace@rti.org)
Rosemary D Higgins (higginsr@mail.nih.gov)
Seetha Shankaran (sshankar@med.wayne.edu)

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

Dear Drs. Altman, Furberg, and Grimshaw,

Thank you for the thorough and constructive review of our manuscript. We have responded specifically to each of the comments by the reviewers and to Editorial Requests. We are including a detailed cover letter that delineates all changes to the manuscript and identifies the site in the revised manuscript with changes appropriately marked. The responses have been numbered to correspond to the reviewers’ or editor’s comments. In the manuscript, we have highlighted responses with a line in the left margin, underlining of edited text in red and strikethrough of deleted text in blue.

We hope that the revisions made have addressed the reviewers’ concerns about the manuscript. We believe that these revisions have greatly enhanced our manuscript. We are grateful for the opportunity to resubmit the manuscript. Please feel free to contact me should you have any further questions.

Sincerely,

Beena G. Sood, MD, MS
Associate Professor, Department of Pediatrics
Wayne State University
Associate Neonatologist
Children's Hospital of Michigan
Hutzel Women's Hospital
Tel: 313-745-5091
e-mail: bsood@med.wayne.edu
I) EDITORIAL REQUESTS:

1) Please attach the additional file containing the list of approving ethical committees, and include an additional file title and legend section after the figure legend section in the main manuscript document.

This has been done.

II) REFEREE 2:
MAJOR COMPULSORY REVISIONS:

1. As I understand it when you conducted baseline screening of the neonatal units and identified 775 infants who received INO for NHRF – with around a third experiencing a suboptimal response – suggests 250 infants. Can you comment on why in 6 months only 46 were screened?

The reviewer has rightly pointed out that the number of infants screened (n=46) over the 6 month period was lower than expected based on historical data and survey. Improvement in perinatal care has markedly reduced the incidence of PPHN refractory to INO. Reduction of post-term births and meconium aspiration syndrome has decreased the number of infants with moderate to severe PPHN. As pointed out in references # 31-33 and outlined on page 19, lines 8-16, early use of surfactant and INO has reduced the ECMO/death rate to less than 10% in this population. In addition, American Congress of Obstetricians and Gynecologists (ACOG) revised its guidelines restricting elective induction of labor / cesarean section at less than 39 weeks of gestation in 2009. This recommendation has led to a significant decrease in late-preterm and early-term infants and reduced the incidence of PPHN. These factors might have contributed to the difference in the incidence of PPHN during the survey (2009-10 - when the ACOG guidelines were gradually being implemented) and during the pilot trial.

2. What power does the sample size of 149 per arm give you to detect what % difference in your need for ECMO or death outcome at what p-value?

We have clarified the effect size, α and β in the Methods Section on Page 8, lines 5-7. In addition we present here in greater detail the basis of our sample size calculations for the main trial taken from the study protocol.

Sample size for the main IPGE$_{1}$ trial:

The main trial will test the null hypothesis that, in patients with NHRF with sub-optimal response to INO, there would be no difference between the IPGE$_{1}$ and control groups in the primary outcome of ECMO /death $<$120 days of age. The rate of ECMO and or death prior to 120 was obtained from the results of RCTs of INO in term and near-term infants with NHRF and a survey of all NICHD Neonatal Research Network sites.

We reviewed the eligibility criteria of our current trial and the numbers reported in the INO trials [1, 2] (Table 4). We considered the following:

i). The infants eligible for our study would represent a smaller proportion of infants in the study arm of the INO trials – the ones with a less favorable response – they are likely to have a composite outcome of death/ECMO somewhere between the estimates for the control and study groups reported in the INO trials.
ii). We did not consider the Early INO (EINO) study numbers as these were less sick babies than in our revised Pilot (in fact they were of similar severity of illness as our previous Pilot where we enrolled infants at OI>15 before qualifying for INO) [3]

iii). Based on the Phase I Pilot published in 2004[4], 30% of infants who had met criteria for INO had a response to IPGE1 without subsequent need for INO or ECMO – however this was after short term administration of IPGE1 in a dose response study. The proportion of responders is likely to be the same as or higher when IPGE1 is administered for a longer period as in the proposed Phase I trial.

iv). The population of infants with NHRF today is very different from the population in the INO trials that led to its FDA approval for use in NHRF. Currently, infants with NHRF are less likely to have meconium aspiration and sepsis as underlying pathologies and are more complicated. However, there are no recent studies that provide current estimates of causes and outcomes of NHRF.

**Table 4:** Published data for the composite outcome of ECMO/death:

<table>
<thead>
<tr>
<th></th>
<th>Control arm (%)</th>
<th>Study arm (%)</th>
<th>Absolute risk reduction (%)</th>
<th>Relative risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark 2000</td>
<td>66</td>
<td>40</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>NINOS 1997</td>
<td>63.6</td>
<td>45.6</td>
<td>18</td>
<td>28</td>
</tr>
</tbody>
</table>

Based on various sample size calculations (Table 5), we propose a sample size of 149 per group for the MAIN TRIAL.

**Table 5:** Sample Size for different scenarios for the Pilot IPGE1 RCT using composite outcome of ECMO/Death with $\alpha$ of 0.05, power 80%, 2-tailed test:

<table>
<thead>
<tr>
<th>Control arm (%)</th>
<th>Study arm (%)</th>
<th>Absolute risk reduction (%)</th>
<th>Relative risk reduction (%)</th>
<th>Sample size per group (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>24</td>
<td>16</td>
<td>40</td>
<td>133</td>
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<tr>
<td>40</td>
<td>22</td>
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<td>18</td>
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<td>32</td>
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<tr>
<td>50</td>
<td>32</td>
<td>18</td>
<td>36</td>
<td>117</td>
</tr>
<tr>
<td>50</td>
<td>30</td>
<td>20</td>
<td>40</td>
<td>93</td>
</tr>
</tbody>
</table>

The Pilot trial will allow us to determine the safe dose – therefore only 1 dose will be used in the Main RCT. The Pilot RCT will also give us an idea of the current rate for ECMO/death in the control and study groups.
3. How does this vary with the pilot size of 50 per arm? It needs to be really clear to the reader what the probability of a false positive or negative would be with these sample sizes.

Given that this pilot study with the main goal of establishing feasibility was halted far short of the total projected enrollment, power of the study for efficacy is no longer meaningful. We have nevertheless responded to the reviewer’s concern and clarified in the revised paper the power of the Pilot RCTs (Page 13, lines 9-13 under Sample Size): “Comparison of the combined IPGE₁ groups (n=100) with the control group (n=50) would have a power of 76.9% to detect a 16% absolute risk reduction in the composite outcome of ECMO/Death from 50% in the control arm to 34% in the study arm with α of 0.25, 2-tailed test. The higher Type I error rate could erroneously lead to a conclusion of efficacy of IPGE₁ but would not increase the risk of missing an efficacious treatment [5-7].”

4. Please also comment on the power of your pilot (n=50) to detect your secondary outcomes – including correction for multiple testing. I suspect you are significantly underpowered and it is again important to be clear on this.

RCTs are not powered to detect differences in secondary outcomes, only in the primary outcome. If any of the secondary outcomes had achieved statistical significance, reliance would be placed on the observed effect size rather than on statistical significance testing with correction for multiple testing as a basis for decision making [8]. Furthermore, this information would be considered hypothesis-generating and would be incorporated into determining the sample size for the main study.

III) Minor Investigator initiated revisions:
   a. Page 3, line 1: “effects” changed to “events”
   b. Page 6, line 1: “an” changed to “a”
   c. Page 8, line 4: “future” inserted
   d. Page 8, line 5: deleted “in the main trial”

REFERENCES:


