Author's response to reviews

Title: Glycerin Suppositories Used Prophylactically in Premature infants (SUPP) Trial: a study protocol for a pilot randomized controlled trial

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Author's response to reviews: see over
Greetings,

Many thanks for reviewing our study protocol entitled: “Glycerin Suppositories Used Prophylactically in Premature infants (SUPP) Trial: a study protocol for a pilot randomized controlled trial.”

We have carefully considered the reviewers’ comments and made changes accordingly. Our responses are indicated below in *italics*.

Sincerely,

Livingston et al.
**Reviewer:** Elizabeth Cross

**Reviewer's report:**
This is a well considered paper. Issues around unblinding, and withdrawals and exclusions, in particular, have been well thought out.

1. Minor Essential Revisions
   a. Randomisations, second paragraph: add the word 'be' to the sentence "Sequence generation will created"

   *Thanks to the reviewer for noting this. The typo has been corrected.*

   b. Discussion, first sentence: insert the word 'of' to the sentence "Previous studies on the use glycerin suppositories"

   *This typo has been corrected.*

   c. Discussion, second sentence: insert the word 'pf' to the sentence "explored the use glycerin laxatives"

   *This typo has been corrected.*

2. Discretionary Revisions
   a. How would the authors check and record if unblinding has occurred?

   *Members of the Data Safety & Monitoring Board (DSMB) can request unblinding to determine treatment allocation for certain participants. This can only occur following a treatment-related adverse event. We are not otherwise assessing the effectiveness of our blinding strategy.*
Reviewer: Munyaradzi Dimairo

Reviewer's report:
Major revisions
Background
1. The way the back the background information is structured is problematic to the reader. Did the authors conducted a systematic search of the literature on glycerin in babies? If so, can they summarise those findings to the reader in the background section. Showing scientific rigor is very important to the reader. After reading all the references given, I could see citation 9 which seem to be a systematic review. However, the findings in the review have not been made clear to the reader. I would advise the authors to be clear on: 1) How the searched the literature relating to the problem? 2) What did they found? 3) Based upon what they found, how does this research fill the gap? Some of the relevant information which is in the discussion should be in the background to set the scene.

Many thanks to the reviewer for these comments. We previously completed a systematic review on this topic and are happy to report that our manuscript was recently accepted for publication. We have added a paragraph summarizing the key findings in the background section:

“We recently conducted a systematic review on the use of glycerin suppositories and enemas in premature infants. We identified a total of 185 infants in three single-center, randomized controlled trials. These studies focused on the prophylactic use of glycerin suppositories (two trials) or enemas (one trial). Across all three trials, there were no consistent differences in terms of meconium evacuation, transition to full enteral feeding, or mortality. There were no reports of rectal bleeding or perforation, but meta-analyzed data revealed a non-significant trend towards increased risk of NEC with active treatment. We concluded that going trials should be carefully monitored and stopped if it becomes clear that this trend is a real effect and not just a spurious correlation.

The results of our systematic review were complicated by the fact that all three trials were underpowered and affected by one or more major methodological issues. As a result, the quality of evidence was low to very low. We concluded that the evidence for the use of glycerin suppositories or enemas in premature infants is inconclusive and that further research is required. As a result, we designed an external pilot study to assess the feasibility of a multicenter randomized controlled trial of prophylactic glycerin suppositories in premature infants.”

Study design
2. As a reader, I am a bit confused on whether this is an external or internal pilot trial. The statement saying “If minimal changes are needed, data from participants recruited in the pilot study will be folded into the multicentre trial” is too vague and problematic to the reader. What constitute minimal changes warranting data to be incorporated into the main trial? What are the statistical inferential rules to be used to combine the two test statistics from two different stages? Clarifying upfront on the former first is important.

Many thanks to the reviewer for this comment. This is an external pilot study that is being conducted separately and prior to a multicenter randomized trial. We have clarified this throughout the manuscript by using the word “external” explicitly. Our plan is to conduct the pilot study separately and pool results from the pilot and multicenter trial if minimal changes to the study protocol are required. If such changes are required, then we will not pool results. Since the pilot study has not been completed, we do not know if pooling is possible. If it is possible, then we will describe the statistical details in the study protocol for the multicenter study.

3. The safety outcome is unclear. What does it mean? Clarification on safety aspects is required. Of course we know that we cannot predict all safety dimension, but clinical knowledge about the treatment should enable you to anticipate most expect safety parameters. In addition, this is an intervention which has been used elsewhere which “known” safety profile, although some uncertainty always exist.

The safety outcomes in the pilot are treatment-related adverse events: anal fissure, rectal bleeding, and rectal perforation. We have changed the wording in the manuscript to make this more explicit. In our meta-analysis, there was a trend towards increased risk of necrotizing enterocolitis but the numbers were very low and likely represent a spurious correlation rather than a real effect.

4. Again, the outcome “cost” is vague. What does it mean – cost of what? In addition, in relation to treatment-related AEs, please see my above comment on safety outcome.

We have changed the wording to indicate that “cost” refers to the explicit costs of conducting a randomized trial (i.e., database design, data storage, printed materials, and salary for research assistants).
5. The statement “The pilot study will allow us to perform a more accurate sample size calculation for the multicenter study” is unclear given that researchers haven’t stated the objective related to estimating sample size related parameters of interest. They need to be more specific. Is this related to the standard deviation or something else? In addition, which one would you trust: parameters based on previous; 3 referenced studies (as given on the sample size section) or this pilot trial of 30 participants? It seems you have all the information you need to conduct an accurate sample size with the information you gave.

Many thanks to reviewer for this comment and our apologies for the confusion. The purpose of this study is first and foremost to assess feasibility. We have removed the section on sample size calculation.

6. Although the researchers gave good justification for their sample size of 30 (15 per group) based on “selected” extant literature, we have shown in recent studies that this is inefficient to answer pilot and feasibility objectives [1, 2]. A minimum of 25 to 35 per group may be required depending on the feasibility or pilot parameters of interest. This ties in with my comment above.

Many thanks to the reviewer for providing those references. We would humbly suggest that the number of participants required for a pilot study has not been definitively established and that there is ongoing debate in this area. We also think it is important to consider the clinical context when determining how many to participants to include in a pilot study. One of the difficulties of conducting clinical trials in children is that there are far fewer patients compared to the adult environment. Thus, we would argue that it is not reasonable to insist on large numbers (and more resources) for a pilot study when there are competing studies and other research priorities for the same group of patients. While we fully agree that larger numbers would be ideal from a statistical standpoint, we cannot justify this approach on ethical or clinical grounds.

We should also note that many pilot studies, including one published in the most recent issue of this journal, use sample sizes much smaller than 30 to assess feasibility:

NOURISH, Nutritional OUtcomes from a Randomised Investigation of Intradialytic oral nutritional Supplements in patients receiving Haemodialysis: a pilot randomised controlled trial Louise Jackson, Judith Cohen, Benjamin Sully, Steven Julious. Pilot and Feasibility Studies 2015, 1:11
7. Given the feasibility objectives stated by the researchers, what’s the point of conducting a randomised pilot trial? It’s not clear what they will benefit from randomisation when their stated feasibility objectives can be answered without randomisation. The case for randomisation has not been explained. Of course, feasibility objectives are often part of the pilot trial, but the case for a pilot should be well explained within its objectives. The researchers may find this reference useful regarding the differences between pilot and feasibility objectives [3].

We would suggest that it would be difficult to conclude that a randomized trial is “feasible” if the pilot study doesn’t actually involve randomizing participants. We agree that it would be possible to conduct a single-arm study to assess the intervention and estimate sample size… but such an approach would only establish the feasibility of a multicenter single-arm cohort study, not a randomized trial with a parallel design. Furthermore, one of the challenges of conducting this study is that the participants are premature infants who are extremely fragile and at risk for poor outcomes. As a result, parents may be hesitant to participate in a randomized trial, especially within the first few days of life when their infant’s clinical course is still uncertain. Thus, we feel it is important to conduct a pilot study that includes randomization.

8. I am not sure the sample size estimation based on hypothesis testing for a future definitive RCT is helpful here unless this is an internal pilot trial. Again, this ties in with my previous comment on lack of clarity on what this pilot trial is (internal or external)? I am a bit confused here.

We apologize again for the confusion. The purpose of this study is to assess feasibility and we have removed the details on sample size calculation.

9. Expected drop-out rate has not been factored into the sample size calculation although it could be an outcome as well.

These details are discussed under “Outcomes” and “Potential Pitfalls” in terms of post-randomization exclusions and number of participants reaching primary endpoint. When we have a better sense of what these values are, we will incorporate these factors into a sample size calculation for the multicenter trial (which will appear in the study protocol for that subsequent study).

10. Descriptive approach to statistical analysis is fine. However, the statistical analysis is not detailed enough for the reader. For instance, given the small sample size, what method will be used to calculate those 95% CI wound proportions – normal approximation or else?

We are planning on using normal approximation for estimating 95% confidence intervals for dichotomous outcomes (1.96 × squareroot(p(1-p)/sample size). We have no specific preferences though and we are open to whatever approach the reviewer feels is most appropriate.
In addition, the cost variable is always “extremely” skewed to the right if you ask a health economist. So I am not sure mean and standard deviation will give you the useful information about the distribution of the costs.

*Thanks to the reviewer for this comment. We are simply planning to get a sense of the mean cost per infant randomized (i.e., total explicit costs divided by the number of participants). This will give us a better sense of the feasibility of a multicenter trial and will be used to justify the amount of funding required. We have modified the wording in the manuscript accordingly.*

In addition, you vaguely stated that this pilot trial will help you to accurately calculate the sample size. However, there is not section on statistical analysis to help you achieve this since there are many ways to estimate parameters from pilot trials to inform the sample size. For instance, you could use confidence interval or bayesian approach or just use the point estimate of the parameter of interest. I would advise authors to careful think about all study objectives and outcomes and how the analysis will address all of these. The details are not enough at the moment.

*We apologize again for this and have removed the sample size calculation for the multicenter trial.*

Minor comments
Provide the study ethics approval number

*The approval numbers from the Research Ethics Board and Health Canada have been provided.*