Reviewer's report

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

Version: 2
Date: 2 April 2015

Reviewer: Munyaradzi Dimairo

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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.

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 warrants 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.

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.

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.

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.

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.

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].

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.

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

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? 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. 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.

Minor comments

Provide the study ethics approval number


2. Sim J, Lewis M: The size of a pilot study for a clinical trial should be calculated


**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

No conflict of interest declared