Author's response to reviews

**Title:** Long-term health-related and economic consequences of short-term outcomes in evaluation of perinatal interventions

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**Author's response to reviews:** see over
Dear Miss Titmus,

Thank you for your comments. These changes are the result of your input:

1. The reason to publish this protocol is not clear. A reason I can think of could be to get suggestions from the readers of original studies for the first part. But this is not suggested. The rationale for the second part is even more unclear.

The reason for publishing our study protocol is to get in touch with researchers participating in large obstetric trials followed by long-term follow-up or researchers participating in longitudinal cohort studies. We hope to collaborate with these researchers in the future for the external validation of our multivariable prediction models.

2. The background includes previous literature only on the first part. No previous literature on modeling and its possible benefits and difficulties (in general or perinatal period particularly) is given.

We added references in our manuscript for relevant information regarding the methods used for statistical modelling.
3. Abstract is not very informative, especially the section on Methods needs more facts.

We have rewritten our abstract, and think this revised version is more informative.

4. The type of studies reviewed is not clearly stated. In abstract, the term “obstetric studies” is used. In objectives the term “interventions” is used. In Methods, “studies on interventions” is used, and only later the term RCT is given. If only trials are reviewed, that should be given early on.

The studies we reviewed for our systematic review were all RCTs with more than 350 women. We have used more uniform terms throughout the manuscript.

5. The examples before the “objectives of the study” are interesting. But they would be even more so, if the authors explained whether the original conclusions of the value of the intervention changed after long-term effects became known.

We have added a sentence in the manuscript on the alteration of the conclusions after long-term effects became known.

6. The authors do not explain why they start to look for studies on long term effects from the trials (on short term effects) from Cochrane library, searching for further studies from these trials. Why not (in addition) to search directly trials on long-term effects? There may be trials going directly to long term effects, or publishing both at the same time. Furthermore, it may be difficult to trace later papers if they are searched by the names (?) of the original authors. Different authors may be involved.

Pubmed searches did not provide us with enough relevant trials on long-term outcome, because of a lack of good MeSH terms e.g.. Therefore, we decided to search for these trials in the Cochrane library. We assumed that all important obstetric trials published will be included in one of the reviews of the Cochrane Pregnancy and Childbirth group. Because we are especially interested in the current state of affairs of follow-up after large obstetric trials, we only planned to include RCTs with more than 350 women for subsequent analysis. RCTs publishing directly about long-term effects will also be included. Furthermore, in Web of Science we will not only search for trials published by the same authors of the original RCT but we are especially interested in articles which used the (original) RCT as a reference. We assumed that, if there is something published about long-term effects of a perinatal intervention, the original RCT has been used as a reference.
7. The short term outcomes (the predictive value of which for long-term outcomes will be modeled?) includes very different types of phenomenon, e.g. caesarean delivery and periventricular leukomalacia. The rationale of selecting the short-term outcomes is not given.

We are especially interested in long-term effects of specific neonatal short-term outcomes, but we will need to adjust for potential important covariates such as caesarean section, prolonged rupture of membranes etc. We have chosen these short-term outcomes because these neonatal short-term outcomes are most often reported as outcomes in obstetric trials.

8. “Systematic review” in Methods: only trials “aimed to improve neonatal outcome” are included. Why this restriction? A perinatal intervention may have been evaluated e.g. by labor progress, and only later its long term infant effects are studied.

We will include reviews that aim to improve neonatal outcome on the short and long-term. A perinatal intervention that will be evaluated e.g. labour progress will also be included. Only reviews of perinatal interventions were there is no potential benefit for an infant whatsoever, will be excluded (for example: “antibiotics regimens for endometritis after delivery”).

9. “Systematic review” in Methods: to what does “these selected articles” refer to? Are the original Cochrane review papers read and analyzed or the new papers on long-term effects?

Characteristics of included studies (reported in every Cochrane review) will be checked to see if the study is a RCT with more than 350 women and whether long-term effects were reported. All RCTs with more than 350 will be reviewed to see if they refer to any follow-up. Thereafter, the RCT will be cross-checked with Web of Science to see which studies have referred to that RCT and reported long-term effects of this RCT.
10. The time tense in Methods section varies and it is not always clear whether some of the work has already been made.

We have changed the time sense in the methods section.

11. Description of the part 2 (modeling) is difficult to comment. Partly because it is not my field, partly because it is only superficially described. Several questions on the planned methodology remains. For example, what was POPS study design, what were the response rates in different follow-ups? The studies to be used in the validation should also be described more in detail. See also comment 2.

We have extended the description of the methods used for statistical modelling. We have described the POPS study more in detail and included follow-up rates of this study. Studies which are candidate for external validation have not been described with more detail, because we have not made a decision yet wether these studies will be used for the external validation.

12. POPS included only very pre-term infants. Can results from them be extrapolated to more term newborn? This should be commented.

At the moment, we do not know if the multivariable prediction models can be used for full-term infants. There is almost no literature of prediction models for long-term health outcomes of infants, so more research is necessary to see if these prediction models can also be generalized to full-term infants.

13. I did not understand how the second result in Discussion is achieved in the current study.

We removed the second result in the discussion.

14. At places, the meaning of the sentences is difficult to understand. The English should be checked for clarity. For example the section “Systematic review” in Methods is difficult to understand.

We think we have improved the quality of our English in the manuscript.
15. Please include a power calculation within the Methods section of your manuscript.

At the moment, we do not think it makes sense to do power calculations because we have not yet defined our long-term outcomes and the potential predictors for the specific long-term outcomes.

16. Please remove the Grant number from your Abstract.

We removed the Grant number from our Abstract

We hope that our revised manuscript will be acceptable for publication. Do not hesitate to contact me if you have any further questions on our manuscript.

With best wishes,

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