Author's response to reviews

**Title:** Long term outcome in relationship to neonatal transfusion volume in extremely premature infants: a comparative cohort study

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**Author's response to reviews:** see over
Dear Dr. Alexandersson,

We would like to thank all reviewers for critically reviewing our manuscript entitled “Long term outcome in relationship to neonatal transfusion volume in extremely premature infants: a comparative cohort study” (MS: 1677570689439381).

We have addressed the reviewers' points and, where applicable, revised the manuscript. Our reply to their comments are added to the document with their comments and highlighted in the manuscript.

We hope our revised manuscript is now acceptable for publication in your journal.

On behalf of the co-authors,
Kind regards,

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Reviewer: Robert Christensen
Reviewer's report:
Von Lindern et al report neurodevelopmental outcomes, at 18-27 months of age, of extremely preterm infants cared for in two NICUs in the Netherlands. The two NICUs differed in the volume of blood administered in each erythrocyte transfusion (15 mL/kg vs. 20 mL/kg), but they otherwise used similar transfusion guidelines.

This submission describes a longer-term follow-up of the subjects in a previous study (author’s reference #13). In the previous and present studies, no significant associations were identified between the volume of blood given and developmental outcomes. The topic is clinically important and the writing is clear. The authors are to be congratulated on continuing the observation period of their previous study subjects and reporting the new findings. They might consider the following if the submission is to be revised before publication:

Discretionary Revisions
1. The difficulty in publishing “negative findings” is well documented. Often such reports are briefer than the present report to assist readers who are at times overwhelmed with the volume of studies to read and digest. **The report was revised and shortened.**

2. Page 4. Methods. Ethics. It is unclear to what the parents were consenting, since the transfusion guidelines were preexisting and routine in each of the two NICUs. Clarification would be helpful. **The reviewer was correct to point this paragraph out. It was not stated correctly in the previous version of the manuscript. The paragraph on informed consent has been rewritten, true to the practice.**
3. Background. Perhaps readers would be better served with a shorter and more to the point introduction, with the literature review reserved for the Discussion section. Background has been shortened. The literature review was moved to the discussion paragraph.

4. Figures. (figure 1). As much as possible, previously reported data should be omitted, with references made to the figures in the previous publication (figure 1). We added Table 1 to show the data of the subcohort of infants born 24+0-27+6 included in this study. In our previous publication data on all infants (24+0-31+6) was mentioned in one table.

5. Figures. (figures 2a, 2b, 3a, 3b). Since, in the end, there were no developmental differences identified on the basis of transfusion practice, it can be questioned whether these four figures are all essential. Since space is not a strong consideration in the journal format, the authors should be at liberty to make this decision.
The figures have been looked at critically. We chose to omit them as they could be explained in the text.

Reviewer: Robin Whyte
Reviewer’s report:

A. Major Compulsory Revisions
Please:
1. Report the primary outcome as stated (composite of death, severe hearing or visual impairment, or severe neuromotor developmental delay) as odds ratio with confidence intervals in the results and in the summary. The manuscript has been rewritten to include the composite outcome as rightfully pointed out by the reviewer. Odds ratio’s (with CI) have been added.

2. Choose corrected or chronological age for your chosen outcome measurement, which should have been done a priori. Do not report both interpretations. The use of corrected age is most consistent with current literature. We restricted to reporting outcome using corrected age.

4. As, using corrected age, the finding is one of 'no effect', make that the major report in the abstract, preferably expressed as odds ration with confidence intervals.
The abstract has been changed, odds ratios and confidence intervals have been added.

B. Minor Essential Revisions
1. Please consider omitting the figures and replacing them with more detailed statistical description of results in the text.
   The figures have been deleted. A table with patient data and another one with the regression analysis are now included. Description of statistics in the manuscript itself has been expanded.

2. Please separate results from discussion with headings.
   Two separate headings have been made.

3. Please limit the discussion to mechanisms explaining your findings in terms of the intervention (i.e. limit or exclude the discussion of chronological vs corrected assessment).
   Discussion has been adapted in this respect by omitting the extensive discussion on the trigger and focussing on neuromotor developmental outcome for corrected age.

4. Although the meaning is usually clear, there are multiple small syntactical errors in writing: the whole manuscript could be reviewed by an independent writer. For example, in the first paragraph of the introduction is written: "Chen and Kirplani, on the other hand, found no statistical difference in the occurrence of (severe) intracranial pathology [8,11]."
   This suggests that Chen and Kirpalani wrote the same paper (they didn't) and spells Kirpalani wrongly. Furthermore "statistical difference" should be written "statistically significant difference" Therefore his should be written: "Neither Chen et al.[8] nor Kirpalani et al.[11], on the other hand, found a statistically significant difference in the occurrence of (severe) intracranial pathology." There are multiple other issues which will not be exhaustively described here.
   All authors have critically reviewed the manuscript and hopefully errors are corrected.

C. Answers to preformatted reviewer questions:
1. Is the question posed by the authors well defined?
   Yes
2. Are the methods appropriate and well described?
   Reasonably.
3. Are the data sound?
   Yes, but the primary outcome is missing. See methods, last paragraph, first line: "Our primary outcome was the composite of death, severe hearing or visual impairment, or severe neuromotor developmental delay at 18-27 months of uncorrected age." Death, which should be measured from admission (not discharge) has not been combined with the developmental outcomes.
   Post-natal death has been reported in the previous article on short-term outcome in relation to transfusion volume per transfusion event (i.e. 15 vs 20 ml/kg). Here we
analysed the total transfusion volume on long-term outcome, which we did not correlate to post-natal death due to bias (the earlier you die the less chance being extensively transfused.)

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

5. Are the discussion and conclusions well balanced and adequately supported by the data?

No. The discussion is confusing. Outcome should be limited to corrected gestational age only. Correlation statistics and details of regression analysis are not reported.

As responded above outcome is now limited to corrected for gestational age. We added a table with details of the regression analysis.

6. Are limitations of the work clearly stated?

They are clearly apparent (not a randomized trial, an interinstitutional comparison with multiple opportunities for confounding) but underexplored. We have expanded on the limits of our study. There is clear reference to our short-term outcome study in the same patient group where a comparison between the two hospitals is shown (see C7).

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

Yes, reference to publication in Transfusion Medicine, 2009, 19 195.

8. Do the title and abstract accurately convey what has been found?

No. Title is fine and clear, but abstract lacks numeric or statistical summary of findings. The findings are of no difference; the writing suggests otherwise. We have included numeric findings in the abstract and omitted incompatibility between abstract and results/discussion.

9. Is the writing acceptable?

Not quite. A small amount of tidying up of punctuation and syntax is required but essential. If the authors really want to report 'correlation' then they need to report the whole of the regression analysis.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published