Author's response to reviews

Title: Elective high-frequency oscillatory ventilation in preterm infants with respiratory distress syndrome: an individual patient data meta-analysis.

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Author's response to reviews: see over
Thank you for Reviewing our paper \textit{Elective high-frequency oscillatory ventilation in preterm infants with respiratory distress syndrome: an individual patient data meta-analysis.}

We have revised the manuscript, gratefully using the reviewer’s comments and suggestions. We are happy that we could answer all queries. Please find below our response to the reviewer, per question and comment.

Thank you,

Filip Cools, Lisa Askie, Martin Offringa, for the Prevention of Ventilator Induced Lung Injury collaborative study Group (PreVILIG Collaboration).

\textbf{Major points.}

1. The main question of this study is the outcome of HFOV compared to CV and the risk for adverse effect. This will mainly depend on the controls used in the studies. The inclusion criteria of the randomized trials regarding the CV used should be better defined.

   We include all types of “conventional”, i.e. tidal, time-cycled ventilations: pressure- or volume controlled, synchronized or not, with or without pressure-support, with or without volume-guarantee. \textbf{We have now clarified this on page 8.}

2. The ventilation strategies including the non-invasive ventilation has been distinctly improved during the last 20 years. Was this considered in the inclusion criteria of the studies? Is it useful for the planned comparisons to include studies in which no lung protective ventilation strategy was used (see page 12)?

   The ventilation strategy per se is not included as one of the inclusion criteria for studies. However, the effect of changes of ventilation strategies over time will be assessed in the pre-specified protocolized subgroup analyses and in the secondary ‘one-stage’ analyses. The usefulness of including studies in which no ‘lung protective ventilation strategy’ was used, is evaluated by looking at the differences in effect of those trials as compared with trials where such a strategy was used. Further details of the analyses will depend on the data that can be acquired regarding ventilation strategy. \textbf{We have added a sentence regarding the one-stage approach on page 15.}

3. A difficult problem may be the aggregation of the individual data. In this point is the protocol sparse. Does a standardized case report form (CRF) exist for each patient?

   We indeed use a new set of pre-specified and clearly defined variables (both for patient-level and trial-level factors as well as for outcomes), and a new coding system which is specifically designed for this project. We describe this in the protocol. An Excell spreadsheet which was specifically designed for the data collection. Trialists are allowed to provide the individual patient data in any format. Data transformation to the new format and coding system can be done by the trialists themself or by the PreVILIG investigators’ team. \textbf{We have now clarified this on page 8.}

4. The interpretation of outcome measures and adverse effects may be difficult if
different methods of ventilatory support are used in the same patient (e.g. CV, HFOV, CPAP,...). Are these patients excluded from the study or how they will be considered?
This is always the problem in pragmatic clinical trials. The accepted approach to this problem is to use the intention to treat analysis. This is mentioned on page 12. In addition, sensitivity analyses will be done to explore the importance of factors such as “cross over due to treatment failure” on the outcome of the patients. This is described on page 16.

5. The individual data will be de-identified. Who performs the anonymization and in which way? Is a later identification of any patient for reevaluation possible? (page 8)
The original data will be de-identified by the original investigators by replacing the patient identifier by a “patient number in the trial” (i.e. 001, 002, 003, etc.) before it is sent to the PreVILIG Data Management Team. The PreVILIG Data Management Team will then merge the received data files into a common individual patient database of all included trials. Analyses of the common IPD Database will only be done by members of the PreVILIG Secretariat and Data Management Team, and not by any of the original investigators. Thus, only the original investigator is able to link the “patient number” to the original patient identifier. We have clarified this on page 8-9.

Minor points
Page 1: Mr. Thome-U is meanwhile in Leipzig, Germany: Thank you. Corrected.
Page 2: Sentence before last: Individual Patient Data (IPD) meta-analysis is a well known technique for a meta-analysis. (Unfortunately, application seldom possible). At least from the Perinatology IPD studies are know. (e.g. Jorgensen AL et al. BJOG. 2008): We have now written that “in the field of neonatology, it has not been used previously” (page 2).