Author's response to reviews

Title: The VICI-trial: High frequency oscillation versus conventional mechanical ventilation in newborns with congenital diaphragmatic hernia: An international multicenter randomized controlled trial

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Author's response to reviews:

Regarding: Manuscript No.: MS: 1783299324526732

Title: The VICI-trial: High frequency oscillation versus conventional mechanical ventilation in newborns with congenital diaphragmatic hernia: An international multicenter randomized controlled trial

Dear Sir/Madam,

We are pleased to hear that our manuscript, in a revised version, may be resubmitted for publication in BMC Pediatrics. We have considered the reviewers’ comments and made emendations accordingly, which we discuss below.

Yours sincerely,

Lieke van den Hout, MD, MSc, PhD

Editorial requests:

1) Please include a 'Competing interests' section between the Conclusions and Authors' contributions.

We included this section between the conclusions and authors contributions (see text, page 16, line 20-21).

2) Please include an Authors' contributions section before the
Acknowledgements and Reference list.

We included this section before the Acknowledgements and reference list (see text, page 17, line 1-9)

Report reviewer 1:

Despite significant advances in the treatment of CDH during the last years, CDH remains a rare but severe congenital anomaly with a high rate of mortality and morbidity. The optimal mechanical ventilation of such patients is controversially discussed and there is a lack of evidence-based ventilation strategies. A large randomized clinical trial is urgent necessary. High frequency oscillation ventilation (HFO) and conventional ventilation (CV) are currently widely used strategies. However some small studies have suggested that HFO may improve survival and pulmonary outcome in infants with CDH. The planned multicenter randomized controlled clinical trial in CDH infants aims to compare initial HFO and CV. This will provide in the future an optimization of ventilatory treatment strategies and a reduction of mortality and morbidity. The planned study is well designed to test the hypothesis and the protocol is well written. The planned statistical analysis is appropriate.

Minor points

1. Please explain the abbreviation VICI.

The acronym VICI is deducted from: HFO versus conventional Ventilation in Infants with Congenital diaphragmatic hernia: an International randomised clinical trial. In Latin vici means 'I have conquered’ which refers to our patients with CDH which are very vulnerable and ill and sometimes have to struggle to survive. We added the meaning of our acronym

In the text (see page 5, line 8-12).

2. The planned begin and the duration of the study is not specified.

The study begun in October 2008, when the medical ethics committee of the Erasmus Medical Center gave approval. It is difficult for us to specify an exact end date, since congenital diaphragmatic hernia is a rare disease. However, we will continue recruiting patients for our trial until we reached the number of 400 participants. Our goal is to have this amount of patients included by the first of October 2013 (see text, page15, line 2 and page 15, line 8-10).

3. There is no information about the used ventilators and ventilation modes. This was in the past an important problem of several HFO studies.

We added the ventilation goals and settings and the type of ventilators used in this trial (see text, page 9, line 10- page 10, line 19). Indeed, the use of different ventilators and treatment protocols is an important problem in studies on ventilatory treatment in CDH patients. Therefore, we aimed to treat all patients
according to the same protocol with predefined ventilation settings for both HFO and conventional ventilation.

4. Laboratory parameters are sampled only in combination with routine measurements or if a catheter is already present. This can lead to essential drop outs which hamper the planned use of the ANOVA for repeated measurements.

All participants in the VICI-trial are severely ill newborns in whom an arterial line and a urinary catheter is placed as a part of routine measurement. Therefore, we are able to take nearly all laboratory measurements at the first day of life and day 3, 7, 14 and 28. Also, in all these patients laboratory measurements and routine tracheal suctioning take place on a daily base. We take the laboratory samples for the purpose of the VICI-trial at the same moment the routine daily laboratory measurements or routine suctioning is performed. In this way, no extra stressful and possibly painful procedures are undertaken for the purpose of the VICI-trial.

On the other hand, collecting laboratory samples in this way may indeed account for a small number of missing values. This happens especially in those patients who are doing very well and in whom the arterial line and urinary catheter were removed before day 28. However, we will still be able to collect samples in these patients at the time points before removal of the line and/or catheter. These data will still be included in the analysis, whereas the data that could not be collected are regarded as missing.

We chose to perform a repeated measurements ANOVA analysis for the following well-concerned reasons. First, the data we aim to sample are composed of repeated measurements obtained in different individuals at five different time points. Repeated measurements ANOVA allows for missing data at different time points and is considered as the optimal way for evaluation of longitudinal data (Fitzmaurice G et al. Applied Longitudinal Analysis. 1st ed John Wiley & Sons, 2004) (See text, page 8, line 5-7).

5. LCI can not be measured by bodyplethysmography (page 11) and lung volumes measured by SF6 washout and bodyplethysmography are difficult to compare. One of the most interesting lung function parameter in CDH-infants is the respiratory compliance (see Roehr CC et al. J Pediatr Surg. 2009; 44(7):1309-14).

We agree with the reviewer and rewrote this paragraph (see text, page 13, line 11- page 14, line 3). Lung function tests are only performed in two of our study centres, since only these centres have the expertise and equipment to perform these measurements. These two centres are already measuring lung function in children below the age of one who were diagnosed with CDH as a part of their routine follow-up. At one centre, FRC (functional residual capacity) and LCI (lung clearance index) are measured by using helium gas dilution. At the other centre, the FRC is determined by plethysmographic measurements and the LCI is defined by SF6 measurements. These measurements will be analysed
separately, since the method of measuring lung function differs for both centres.

We are very well aware of the fact that there are several ways to express lung function and several ways to measure lung function in these young children. Moreover, reference values are lacking in this field. However, since these are the methods we currently use to measure lung function in these centres, we believe this is the best way to evaluate if the initial mode of ventilation has an effect on lung function during the first year of life at this moment. We evaluate lung function by determining the FRC for the following reasons. A recent publication of our group revealed that FRC measurements in ml/kg were elevated in CDH patients, especially in patients who were ventilated for a longer time or underwent an ECMO procedure. However, we were not able to measure the FRC in controls in this paper (Ref: Lung function during the first year of life after repair of congenital diaphragmatic hernia: a longitudinal follow-up study’ L. van den Hout, M. Spoel, I. Reiss, C. Meeussen, S. Gischler, J.C. de Jongste, D. Tibboel, H. IJsselstijn. Pediatric Critical Care Medicine, 9 June). Indeed, the respiratory compliance could also be of great value in measuring lung function. Unfortunately, we had some technical difficulties measuring respiratory compliance, which led to the choice of the FRC as an outcome parameter in this study.

6. Table 1: Explain the abbreviations (PMA, DC). Is there an intention to classify the BPD (mild, moderate, severe) according Table 1?

PMA means post-menstrual age and DC means discharge. The meaning of these abbreviations are added to the table (see text table 1).

The severity of BPD is a secondary outcome measure. The severity of BPD in our patients will be classified according to table 1 (see text, page 6, line 10).

7. Is there an external funding of the study?

Solely departmental funding supported this study (see text, page 16, line 24-25).

Furthermore, we added H. te Beest as an author on this paper. She assisted in writing the research protocol and currently monitors the data collection of this trial (see text, page 1, line 8 and for authors contribution see text, page 1, line 8-9.)