Author's response to reviews

Title: Rationale and study design of PROVHILO - a worldwide multicenter randomized controlled trial on protective ventilation during general anesthesia for open abdominal surgery

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Author's response to reviews: see over
Dear dr Doig,

Thank you for your kind words and valuable suggestions to improve our manuscript. We have revised the paper on the under mentioned issues and marked the adapted text in red colour in the manuscript.

1. Page 7, "Randomization is performed using a dedicated website. Randomization is balanced per center.". I assume you meant 'stratified' by center, not 'balanced'. Please also provide details regarding how the randomization sequence was generated (blocked, variable size blocks or minimization).

   **We agree and modified the text accordingly:**
   
   Randomization sequence is generated using random blocks and is stratified per center. (page 7; line 2)

2. Was blocking applied to any other trial factors?

   **We added the following to the manuscript:**
   
   No blocking is applied to other trial factors. (page 7; line 3)

3. Please also report whether the study website is password protected and encrypted. Please report the level of encryption.

   **We added the following to the manuscript:**
   
   Randomization is performed using a dedicated, password protected, SSL-encrypted website. (page 7; line 1)

4. Provide methodological references to support your thresholds for interim analysis. It is very interesting that you have a strict p-value for your primary outcome (0.0005) yet you allow consideration for stopping early due to other 'complications' which may not be as clinically important as your primary outcome at the first interim analysis with a lax p-value (0.022). You need to resolve this issue by explicitly defining your primary outcomes and these other 'complications' or reconsidering your stopping rules. Please address this issue and justify your decisions in your Discussion.

   **We are not able to support this approach with references. The steering committee has discussed the safety issue with the statistician and agreed on being stricter with possible beneficial and less strict with possible harmful effects of the intervention on PPC (post-operative pulmonary complications). We aimed at: 1) protecting patients; 2) having a lower chance of achieving positive effects of the intervention on PPC if they were not really present. The other mentioned complications refer also to PPC. Definitions of the primary outcomes are to be found earlier in the text (page 11; line 17 to page 12; line 16).**

   We modified the statistical considerations of the interim analysis as follows:
If the intervention has a strong trend for improving post-operative pulmonary complications (as defined in the text above) with a p–value < 0.0005 is found at 300 patients or p-value < 0.014 at 600 patients, termination of the study is considered. The third and final analysis is performed at 900 patients with a p–value of 0.045 for significance. When post-operative pulmonary complications occur significantly more frequent in the intervention group, terminating the study due to harm will be considered when p ≤ 0.022 for each interim analysis. (page 14; line 14-21)

We discussed our reasons in the Discussion section as follows:
The main concern in the statistical interim analysis is not to withhold positive effects of the treatment to the control group. However, to achieve maximal protection for the patients and to have a lower chance of achieving positive effects of the intervention on post-operative pulmonary complications if they were not really present, different stopping rules are defined for a strong beneficial effect on post-operative pulmonary complications of the intervention versus a worse effect on post-operative pulmonary complications. (page 20; line 4-9)

5. Please expand your statistical analysis section. Please explicitly state the analytical model that will be used to assess your primary outcome.

We agreed and added the following section to the Statistical analysis:
Primary outcome is the total occurrence of pulmonary complications within the first 5 days presented as a percentage. The percentage will be analyzed as continue data. If the data is normally distributed, Student’s t–test will be used or when not normally distributed the Mann–Whitney U test will be used. (page 15; line 7-10)

6. Report the key variables that will be assessed for baseline imbalance, how imbalance will be defined and what will be done in the presence of imbalance.

We added the variables that will be assessed for baseline imbalance in Statistical analysis:
The following variables are collected: gender, age, height, weight, functional status (independent, partially dependent or totally dependent), physical status (according to the American Society of Anesthesiologists (ASA), cardiac status (heart failure, according to the New York Heart Association (NYHA), acute coronary syndrome, or persistent ventricular tachyarrhythmia’s), COPD if inhalation therapy and/or steroids are used, respiratory infection in the last month, smoking status, alcohol status in the past 2 weeks, history of active cancer, weight loss ≥ 10% in the last 6 months, history of diabetes mellitus, use of oral anti–diabetics, use of antibiotics in the last 3 months, use of statins, type of scheduled surgery (emergency or non–emergency and surgical procedure), transfusion of blood products in the preceding 6 hours, vital parameters (tympanic temperature, respiratory rate, SpO2 (%), blood pressure, heart rate), airway secretion score (the patient is required to cough and the presence of secretion will be
subjectively evaluated; if yes: purulent or not), VAS–scores for dyspnea and pain, blood samples (glycemia, uremia, creatinine, AST, ALT, bilirubin, Hb, WBC count, platelet count, PT, PTT, and biomarkers [see below]) and a chest X–ray (assessed on mono- and bilateral infiltrate, pleural effusion, atelectasis, pneumothorax, cardiopulmonary edema).

We expect the baseline to be balanced, as this trial is randomized and sufficiently powered. In accordance to this suggestion, we added a definition of baseline imbalance and the analytical model in case of imbalance to our statistical analysis section:

As this is a randomized controlled trial, we expect that randomization in this large study population will sufficiently balance the baseline characteristics. Baseline balance is tested and imbalance compensated in all pre-operative variables (as mentioned above) and on ARISCAT scores. However if imbalance occurs, the confounding factor will be corrected using a multiple logistic regression model. For this we will treat the proportion as a binary response (complications occur during day one to day 5 post operative).

7. You report your intention to use a Proportional Hazards model to assess 'time dependent' variables. I believe you meant 'time to event' variables. Please list all variables you intend to assess as 'time to event' variables.

We agree and modified the text according to this suggestion.

Time to event variables (primary and secondary outcomes) are analyzed using a proportional hazard model adjusted for possible imbalances of patients' baseline characteristics.

We added a definition for ‘time course variables’ and described a statistical model for these variables as well.

Time course variables (e.g. repeated measures of vital parameters, blood values, VAS-scores, actual mobility) are analyzed by a linear mixed model. The linear mixed models procedure expands the GLM so that the data are permitted to exhibit correlated and nonconstant variability. The model includes two factors: 1) study group (fixed factor, intervention or control group), each level of the study group factor can have a different linear effect on the value of the dependent variable; 2) time as a covariate, time is considered to be a random sample from a larger population of values, the effect is not limited to the chosen times.

8. We added a section on the reporting of (serious) adverse events. This issue arose after submission of the manuscript.

All serious adverse, unexpected and related or possibly related adverse events will be reported blinded to the appointed international SAE-manager, who assesses the events and reports this information to the DSMB within 24 hours of that event in the case of a serious adverse event or within one week in the case of an adverse event.