PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocolized Post-Extubation Respiratory Support to Prevent Reintubation: Protocol and Statistical Analysis Plan for a Clinical Trial
AUTHORS	Casey, Jonathan; Vaughan, Erin; Lloyd, Bradley; Bilas, Peter; Hall, Eric; Toporek, Alexandra; Buell, Kevin; Brown, Ryan; Richardson, Roger; Rooks, Jeffery; Wang, Li; Lindsell, Christopher; Ely, E. Wesley; Self, Wesley; Bernard, GR; Rice, TW; Semler, Matthew

VERSION 1 – REVIEW

REVIEWER	Alastair Glossop Sheffield Teaching Hospitals NHS Foundation Trust Sheffield UK Received speakers fees and honoraria from Armstrong Medical UK Ltd 2015 to current time
REVIEW RETURNED	09-Apr-2019

GENERAL COMMENTS	This is a very interesting study proposal that addresses a pressing question in contemporary critical care practice. The authors propose a pragmatic, real world comparison of a protocolised approach versus "usual care" which is a useful question to ask. There is a clear understanding of the background evidence base in this area, with statistical calculations based on results from contemporary studies. I hope that the results of this interesting study will be reported and enhance the way that we approach the management of post extubation patients in ICU.

REVIEWER	Andrea Cortegiani University of Palermo
REVIEW RETURNED	14-Apr-2019

GENERAL COMMENTS	The manuscript describes the protocol and statistical analysis plan of a single-center pragmatic cluster-crossover trial evaluating a the effect on reintubation rate at 96 hours of a protocolized post-extubation respiratory support (NIV or HFNT) or standard care in a general sample of ICU patients. The manuscript is well written, the research hypothesis is interesting and well described. I have only few comments: 1) In the INTRODUCTION, the authors failed to describe new evidence regarding the use of early NIV support following extubation in hypoxemic patients (Vaschetto et al. Intensive Care Med. 2019 Jan;45(1):62-71. doi: 10.1007/s00134-018-5478-0). I think that it may merit a bit of discussion. Citing evidence from

	strong meta-analysis may help (Yeung et al. Intensive Care Med. 2018 Dec;44(12):2192-2204. doi: 10.1007/s00134-018-5434-z). 2) Line 47 pag. 7 To improve the rational for HFNT, I suggest to add these reference (Doi: 10.1186/s12871-018-0623-4 AND doi: 10.1016/j.tacc.2019.02.001) 3) The length of the manuscript can be reduced. The primary outcome of the study is firstly cited in pag. 18. 4) Redarding the primary outcome, it is not clear to me if the criteria for reintubation are protocolized or not. Being a pragmatic trial, I suppose they are not but maybe I miss this information. If they are protocolized, they should be reported in the manuscript. If not, this should be considered a limitation of the study. 5) Line 17 Pag. 13 What does it mean "discouraged"? It means not allowed?

REVIEWER	Haibo Zhang Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Department of Anesthesia, Interdepartmental Division of Critical Care Medicine, Department of Physiology, University of Toronto, Toronto, Ontario, Canada
REVIEW RETURNED	10-May-2019

GENERAL COMMENTS	Please find attached file. - The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1

1. This is a very interesting study proposal that addresses a pressing question in contemporary critical care practice. The authors propose a pragmatic, real world comparison of a protocolized approach versus "usual care" which is a useful question to ask. There is a clear understanding of the background evidence base in this area, with statistical calculations based on results from contemporary studies. I hope that the results of this interesting study will be reported and enhance the way that we approach the management of post extubation patients in ICU.

• We appreciate the reviewer's comments.

REVIEWER 2

2. In the INTRODUCTION, the authors failed to describe new evidence regarding the use of early NIV support following extubation in hypoxemic patients (Vaschetto et al. Intensive Care Med. 2019 Jan;45(1):62-71. doi: 10.1007/s00134-018-5478-0). I think that it may merit a bit of discussion. Citing evidence from strong meta-analysis may help (Yeung et al. Intensive Care Med. 2018 Dec;44(12):2192-2204. doi: 10.1007/s00134-018-5434-z).

• We appreciate the reviewer's comment. We have attempted to draw a distinction between the interventions in the studies referenced by the reviewer, extubation to NIV vs. continued invasive mechanical ventilation after a failed breathing trial, and the interventions of the PROPER trial, extubation to NIV or conventional oxygen after a successful breathing trial. However, we agree with the reviewer that this body of literature highlights the potential benefits of NIV, more generally, and we have added these referenced to the introduction section (page 6)

3. Line 47 pag. 7 To improve the rational for HFNT, I suggest to add these reference (Doi: 10.1186/s12871-018-0623-4 AND doi: 10.1016/j.tacc.2019.02.001)

- We have added the suggested references to the section of the introduction referencing the physiological and clinical benefits of HFNC (page 7)

4. The length of the manuscript can be reduced. The primary outcome of the study is firstly cited in pag. 18.

- As suggested by the reviewer, we have added a description of the primary outcome to the last sentence of the introduction. We have attempted to include only the required study details in the manuscript and move extraneous details to the supplement. If the editor has specific suggestions on sections to remove or word limits, we would be happy to make efforts to further reduce the length.

5. Regarding the primary outcome, it is not clear to me if the criteria for reintubation are protocolized or not. Being a pragmatic trial, I suppose they are not but maybe I miss this information. If they are protocolized, they should be reported in the manuscript. If not, this should be considered a limitation of the study.

- The reviewer highlights an important decision in the design of the PROPER trial. The decision to reintubate is made by the clinical team (not protocolized). The justification for this approach is described on pages 18-19:
  - "Any decision to reintubate will be made by the clinical team. Prior studies have attempted to protocolize the decision to reintubate [34,36,37][32,34,35]. Because the goal of the PROPER study is to evaluate the performance of protocolized support when applied to a broad population of critically ill adults in "real-world" practice, we deliberately deferred all decisions regarding management of post-extubation respiratory failure and reintubation to the clinical team with no involvement or guidance from the research team."
- As suggested by the reviewer, this is now explained in the "strengths and limitations" section on page 4:
  - "Decisions regarding management of post-extubation respiratory failure and reintubation to the clinical team

6. Line 17 Pag. 13 What does it mean "discouraged"? It means not allowed?

- This paragraph describes the manner in which non-invasive ventilation was applied in the trial. The study protocol used by the respiratory therapist during the trial made several directives regarding "best practices" for non-invasive ventilation, including that sedatives not be used to increase tolerance of NIV. We have added a reference in this section to figure 3 (the study protocol) to clarify that these "best-practices" were listed on the study protocol

REVIEWER 3

7. Single-center study. Even if the results are positive using the protocolized support in this single-center study, there is still a long way to suggest a generalized application to other centers nationally and internationally due to a number of factors including different practice of usual care, weaning criteria, qualifications of respiratory therapists, just name a few. Multicenter trials are required to confirm the findings.

- We agree with the reviewer. Although the PROPER trial is expected to be one of the largest trials of post-extubation respiratory support, its conduct at a single center is an important limitation that affects the generalizability of the results. This limitation is highlighted in the strengths and limitations section on page 5, and we have added a section to the discussion further highlighting this point and specifying that we will provide extensive data on the use of NIV and HFNC in the usual care arm to help interpret the results of PROPER in the appropriate context:
  - "The provision of post-extubation support in the usual care group of this single center trial may not match the experience at other centers so we will provide data on the use of NIV and HFNC in the usual care arm of PROPER to assist in the interpretation of the results."

8. Non-selection of patients. This lack of selected patients to participate in the study maybe redundant and consumes a lot of medical resources. Prophylactic use of NIV has been extensively examined in

patients considered to be at a high risk of post-extubation respiratory failure, and has significantly reduced reintubation rates. There is a general consensus that justify prophylactic post-extubation NIV, based on several factors including history of smoking, age, respiratory or cardiovascular disease, poor cough and etc.

- We agree with the reviewer that previous trials have suggested benefits of post-extubation respiratory support for specific patient populations. Some experts have postulated that the summation of previous data, showing benefit in hypercarbic patients, non-hypercarbic high-risk patients, and non-hypercarbic low risk patients, suggests that ALL patients would benefit from post-extubation support. The PROPER trial compares protocolized support, provided to all patients, to usual care in which post-extubation support is provided only to patients with specific risk factors (the approach suggested by the author). We agree that protocolized post-extubation support is resource intensive. Some centers are already providing post-extubation support to all patients, and the goal of the PROPER trial is to evaluate whether this approach provides added clinical benefit.

9. Lack of blinding. The two study arms do not allow blinding making it difficult to begin the intervention approaches at similar baseline level post-extubation. For instance, physicians may intentionally delay extubation in high-risk patients while may perform early extubation to exercise NIV or HFNC in low-risk patients. On the other hand, there is no clear criteria of indication for reintubation that is subjectively up to a decision by physicians. These issues need to be addressed.

- The reviewer astutely highlights two important design considerations in our trial. Given the nature of the interventions, blinding is not possible in this (or any) trial of post-extubation support. Therefore, there is a risk that knowledge of group assignment could lead to imbalances in co-interventions. We highlight this concern in the limitations section and on page 31 we specify our plan to address this problem:
  - "Treating clinicians are aware of study group assignment and so clinicians may alter the timing of extubation or management of post-extubation respiratory failure based on group assignment. To assess for such bias, we will present characteristics of the two study groups at extubation, including duration of mechanical ventilation prior to extubation, and information about use of rescue respiratory support in the two groups. We will also perform analyses that adjust for these factors or conduct prespecified sensitivity analyses."
- As described in our response to reviewer 2, we explain our rationale for not protocolizing reintubation on pages 18-19, and we have added a statement to the limitations section (page 4), noting that reintubation was not protocolized:
  - "Decisions regarding management of post-extubation respiratory failure and reintubation to the clinical team."

10. Randomization. It is unclear whether patients will be randomly assigned into the two clusters, and if patients (i.e., AECOPD, hypercapnia and cardiac failure) who need to be transferred from usual care group to NIV or HFNC group based on physician's assessment would be excluded from the data analysis.

- We appreciate the reviewer's comment requesting clarification on whether the unblinded, cluster cross-over design might allow selection bias. We have clarified in the "Randomization and Treatment Allocation" section on page 11 that patients are assigned to bed locations based on bed availability, without selection based on patient characteristics. This section now reads:
  - "All beds in the study unit care of patients of the same acuity, and patients are assigned to bed location based on availability without selection by patient characteristics. Patients admitted to the ICU remain in the same bed until death or ICU discharge. Among patients in the study ICU in the year prior to the trial who would have met criteria for enrollment, there was no difference in the incidence of reintubation in patients admitted to the beds in each of the two clusters."
- Additionally, on page 22, we explain that the analysis will be intent-to-treat. Patients will be analyzed with their assigned cluster, regardless of their receipt of post-extubation respiratory support.

We expect that some patients in the protocolized group will not receive support and that some patients in the usual group will receive support as part of usual care.

11. Timing of intervention. It suggests that the duration of NIV or HFNC support would be no less than five hours with a median of 17 hours prior to being evaluated for weaning. It is unknown, although it sounds a very short period of time, whether 5 hours of protocolized respiratory support would have significant impact on reintubation rate at 96 hours post-extubation.

- We agree with the reviewer. Decisions regarding duration of therapy require balancing potential benefits of longer support duration with potential harms on ICU length of stay (by requiring patients who are at low risk of reintubation to stay in the ICU for longer periods of support). We gave considerable thought to this particular trial choice, and we describe the rationale in the discussion section to the potential impact of this decision (copied below) and as a limitation. This decision may make it harder to show a benefit of post-extubation support (bias towards the null), but it will increase the likelihood of showing benefit in ICU-free days (the sole pre-specified secondary outcome). Importantly, structuring the intervention in this way will also allow analysis evaluating the dose-response of post-extubation respiratory support, something that has never been evaluated in previous trials. As noted, the expected MEDIAN duration of support will be 17 hours with half of patients receiving more than 17 hours and many patients receiving more than the 24 hours provided in previous trials. We have attempted to note that extubation at 23:59, could allow a protocol compliant patient to receive as little as 5 hours of support, but this is expected to apply to only a very small number of patients.
  - "Previous trials have provided 24 to 48 hours of support [5,25,26,36,37][5,24,25,33,34]. We elected a lower minimum duration because this support can only be provided in an ICU setting at many centers, and in a population with a low baseline reintubation rate the intervention could potentially lead to longer ICU lengths of stay than necessary. The design of the PROPER trial specifies the provision of post-extubation respiratory support from extubation until at least 5AM the following day, at which point the patient's readiness to wean from post-extubation respiratory support is assessed. This strategy involves a minimum of 5 hours of respiratory support, and our preliminary data suggest a median of 17 hours of support. While shorter than other studies, our approach allows removal of support and transfer from the ICU on the day following extubation, if clinically appropriate, or continuation of respiratory support when clinically indicated."
  - "In our design, we have made choices to bias towards the null. This means there are several threats to observing a difference between study groups. Foremost, the anticipated median duration of post-extubation respiratory support of 17 hours is shorter than the 24-48 hours delivered in some prior trials."

12. Training. It is much appreciated that all respiratory therapists received training and ongoing education on the delivery of post-extubation respiratory support prior to caring for patients assigned to the protocolized support group. Would physicians, especially those junior physicians, assigned to the usual care arm receive training or be provided with any sort of guidelines to follow?

- Additional education was provided to the critical care fellows who cared for patients in the study units, in the form of a structured 60-minute lecture reviewing existing literature on post-extubation respiratory support and describing the rationale for the trial. We have added a description of this process to the "Training" section on page 16:
  - "Additional education was provided to the critical care fellows who cared for patients in the study units, in the form of a structured 60-minute lecture reviewing existing literature on post-extubation respiratory support and describing the rationale and protocol for the trial."

13. It states in Page 6 that "The only post-extubation therapy suggested to potentially reduce the rate of reintubation is respiratory support …". However, there is a large body of evidence suggesting that administration of prophylactic corticosteroids before elective extubation was associated with significant reductions in the incidence of reintubation [i.e., Crit Care Med, 2006;34(5):1345-1350; Chest 2017;151(5):1002-1010]. This issue needs to be discussed.

- We agree with the author on the role for corticosteroids in patients at high risk of post-extubation stridor. We were drawing a distinction between therapies given prior to extubation (like steroids) and post-extubation therapies like NIV and HFNC. We have rephrased as:
  - "One of the few therapies suggested to potentially reduce the rate of reintubation is post-extubation respiratory support with either non-invasive ventilation (NIV) or high flow nasal cannula (HFNC)."

14. Please elaborate the description "A single randomization was performed to determine which cluster would receive protocolized support during the first block."
- We have clarified this section which now reads:
  - "A single randomization was performed which determined that the cluster associated with back hallway would receive protocolized support during the first block. The front hallway received usual care during the first block, and the blocks have alternated every three months (Fig. 2)."

15. Please elaborate the description "Protocol recommendations may be altered at the discretion of the respiratory therapist or the clinical team."
- This has been clarified as:
  - "Device settings may be altered at the discretion of the respiratory therapist or the clinical team."

16. As per the protocol, "In the event that any patient in the trial dies in the 96 hours following enrollment without experiencing reintubation, they will be classified in the primary analysis as having met the primary outcome. Patients who are discharged from the hospital before 96 hours following enrollment without having experienced reintubation will be classified as not meeting the primary outcome." This sounds a bit of misleading in the relationship between reintubation and outcome at 96 hours following enrollment. Would the number of ICU-free days in both 96 hours and 28 days be considered for secondary outcome?
- We appreciate the reviewers' comment about the complexity of accounting for competing risk of mortality in any analysis of reintubation. If a patient is extubated and experiences respiratory failure in the first 24 hours but experiences a cardiac arrest before intubation, or changes their goals of care to DNR/DNI and dies without intubation, classifying them as "not reintubated" could introduce significant bias. Therefore, these patients will be classified as "reintubated" in the primary analysis. We will also conduct a sensitivity analysis examining the effect of classifying these patients as "not reintubated" as described in the "Sensitivity analyses" section on page 24:
  - "To assess the impact of design considerations on the outcomes, we will conduct several sensitivity analyses. First, we assumed all patients who died within 96 hours to have required reintubation. We will repeat the analysis of the primary and secondary outcome classifying patients who died within 96 hours without experiencing reintubation as not meeting the primary outcome."
- ICU-free days are a method of adjusting for the competing risk of mortality on ICU stay by giving all patients who die "0" ICU-free days. Unobserved days following discharge are counted as ICU-free days. ICU-free days in the 96 hours following extubation would deal with the competing risk of mortality in the same fashion as ICU free days to day 28, without providing clear analytical benefit. Using ICU-free day to 96 hours would also make the value judgement that a 4-day ICU stay (which would provide 0 ICU-free days in 96 hours) is as bad as death (which also provides 0 ICU-free days in 96 hours).

VERSION 2 – REVIEW

REVIEWER	Andrea Cortegiani Policlinico Paolo Giaccone, University of Palermo, Italy
REVIEW RETURNED	10-Jun-2019

GENERAL COMMENTS	I have no further comments

REVIEWER	Haibo Zhang St. Michael's Hospital, University of Toronto, Ontario, Canada
REVIEW RETURNED	07-Jun-2019

GENERAL COMMENTS	The authors have addressed all my comments. Thanks.