Reviewer's report

Title: PROtective Ventilation with a low versus high Inspiratory Oxygen fraction(PROVIO) and its effects on postoperative pulmonary complications: protocol for a randomized controlled trial

Version: 0 Date: 11 May 2019

Reviewer: Sabrine N.T. Hemmes

Reviewer's report:

Xue-Fei Li et al plan to perform a RCT comparing the effect of 30% versus 80% FiO2 during lung-protective ventilation on PPCs. This trial will hopefully give answers to this unclarified point of discussion. My main concern is that the sample size is relatively small (see comment 14). Also, the English language of this manuscript needs to be improved. Please find my minor comments below:

1. Trial Registration
   As the authors aim to publish in an international journal, I would to also register their trial on an international site (such as ClinicalTrials.gov or other)

2. Throughout the manuscript sentences are written in the past tense. However, as this is the protocol of a trial that has not been finished yet, it is more logical to use present or even future tense. Please adjust. Some examples, but there are more in the text:
   - Abstract: 'Postoperative pulmonary complications (PPCs) have been the most common peri-operative complication following surgical site infection'
   - p.8 L1: '…and ventilation settings were permitted to alter until acquiring the satisfied oxygenation…' settings are permitted to alter.

3. The manuscript (especially abstract, introduction, methods) needs to be revised by a native English speaker. Some examples:
   - p. 3 L.8 - 14: 'About 2.0% to 5.6% [patients?] developed postoperative pulmonary complications (PPCs) in more than 234 million patients accepting [undergoing] surgery. Up to 40% [of PPC's?] [can occur after] general and vascular surgery, which [making] these the most common perioperative complications following surgical site infection (SSI)'
   - p.3 L.18 - 20: 'Preventing the PPCs has been a major indicator to evaluate the safety and quality of healthcare' What do the authors mean here?
   - p.3 L.20 - 22: 'A possible explanation for increasing morbidity [in patients that develop?] PPCs is that mechanical ventilation'
   - p.9 L.28 - 31: 'Vasoactive agent therapy is permitted when the hemodynamics get instability with the discretion of the attending anesthetist'
1. p.11 L47: 'Any ventilatory settings play a critical role...' Any or many?

4. p.4 L.2 - 5: 'Evidence is lacking for a regular application of a high FiO2 in abdominal surgery suggested by a Cochrane review [20]'
   Please add the most recent evidence on hyperoxia, published in BJA 2019

5. p.4 L.20 - 24: 'Higher FiO2 seems to be associated with pulmonary complications and adverse clinical outcomes, but the existing evidence is insufficient to warrant its effect to promote PPCs'
   Please add references here.

6. p.6 L. 50: '…perioperatively (from intubation to extubation).'
   Change for intra-operatively, otherwise you suggest that the patients also receive the intervention before and/or after surgery, e.g. peri-operatively.

7. p.5 L57: 'Emergency unblinding is permissible if hypoxemia occurs.' How is hypoxemia defined? Which SpO2 and for what duration?

8. p.6 L2-6: 'There will be an evaluation of risk according to the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score [22] before the randomization'
   What will the ARISCAT score be used for? Is a high ARISCAT score one of the inclusion criteria? If so, please state this in the chapter 'Study Population' and in the Abstract

9. p.7 L5: 'Other settings are shown in table 1.' Or do the authors mean Table 2?

10. p.7 L43-45: 'In general, surgery patients rarely require adjustment of the FiO2 in 30% FiO2 group according to the previous trials and clinical practice.' Please provide references.

11. p.5 L57: 'Emergency unblinding is permissible if hypoxemia occurs.' How is hypoxemia defined? Which SpO2 and for what duration?

12. p.9 L10 - 15: 'After extubation, patients will be sent to the PACU or ward where they will be oxygenated with 2L/min, pure oxygen via a nasal tube in 24 hours. At the same time, they will accept standard monitoring'
   Did the authors define a minimal SpO2? If patients are hypoxic, will they receive higher flows of oxygen?

13. p.10 L8: Will the DSMB remain blinded to the study intervention?

14. p.13 L12-13: 'The PROXI trial demonstrates that the incidence of PPCs, PONV, and SSI after abdominal surgery were not significantly different in patients receiving 80% or 30% FiO2'
   If in the PROXI trial, which included 1400 patients, there was no difference in PPCs, how do the authors expect to find a significant effect on PPCs in their study sample of 252 patients? Shouldn't the authors consider to increase their sample size?

15. 'Emergency surgery population were not excluded in PROXI trial, which is an independent risk factor of pulmonary complications' But the PROVIO trial aims to include only elective surgery.

16. p.13 L50-52: 'The iPROVE-O2 trial is an ongoing randomized controlled trial (clinicaltrials.gov
identifier: NCT02776046)…
The iPROVE trial has been published in 2018, please alter your Discussion.

**Level of interest**
Please indicate how interesting you found the manuscript:

An article of importance in its field

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Not suitable for publication unless extensively edited

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Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

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