Author's response to reviews

Title: The OPERA trial - Comparison of early nasal high flow oxygen therapy with standard care for prevention of postoperative hypoxemia after abdominal surgery: rationale and study protocol for a multicenter randomized controlled trial.

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Author's response to reviews: see over
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**Responses to Reviewers’ comments** on manuscript MS 6788248731050384: «The OPERA trial - Comparison of early nasal high flow oxygen therapy with standard care for prevention of postoperative hypoxemia after abdominal surgery: rationale and study protocol for a multicenter randomized controlled trial.»

Dear Editor-in-chief,

We would like to thank you and the Reviewer for the excellent feedback and the opportunity to clarify and further improve our manuscript. We have integrated these points into the enclosed revision of the manuscript, which we are delighted to resubmit for your consideration and, separately, a point-by-point response to all concerns.

We have also modified the title as requested to better conform to the journal style.

Please, do not hesitate to contact me if you need further information.

Yours faithfully,

**Emmanuel Futier, M.D., Ph.D. (Corresponding author)**
**Bruno Pereira, Ph.D. (Biostatistician)**
Responses to Reviewer's report:

1. Major Compulsory Revisions
None.

2. Minor Essential Revisions
Somewhere in the Methods please state the number of centres if this is known, or the number of anticipated centres if not yet finalised.

The information was added in the Methods section (Page 14, line 7).

Statistics methods, paragraph 2, it is good practice to pre-specify covariates that will be used in adjusted analyses for RCTs, not to select these based on screening based on statistical tests. See the CONSORT statement for guidance on this. This sentence needs to be amended, or, if screening variables is to be the primary method of variable selection for the adjusted analysis then it should be relegated to an exploratory analysis.

We have modified the Statistics methods in order 1) to better clarify the use of covariates in the adjusted analysis and 2) to consider within and between centers variability (Page 11, lines 12-16).

3. Discretionary Revisions
Section on Study population:
- Might it worthwhile explaining why BMI > 35, emergency surgery, patients with sleep apnea are to be excluded?

We deliberately restricted study entry to non-obese patients, patients without sleep apnoea and non-emergent surgery to provide a relatively homogeneous group of patients and avoid potential confounding in the interpretation of data. Indeed, obese patients with known sleep apnoea usually receive chronic application of continuous positive end-expiratory pressure (CPAP), which is to be introduced early after tracheal extubation thus rendering not possible the use of high-flow nasal cannula oxygen therapy. Patients with emergency surgery may not be able to be extubated at the end of surgery, thus rendering application of high-flow nasal cannula oxygen therapy also not possible.
We have added a comment in the Methods section (Page 7, lines 3-4).

Statistics
- provide a reference from Stata's mi procedure (the Stata manual will do)

Please apologize for the lack of precision. We have added a reference as requested (Royston P. Multiple imputations of missing values. Stata Journal 2004, 4:227-41).

- final sentence in final paragraph. There is move away from summarising evidence in terms of statistical significance towards presenting effect sizes and confidence intervals, I suggest you edit that sentence to read something like "All effect sizes will be presented with 95% confidence intervals", or at least make an additional statement about CIs.
We have modified the final paragraph accordingly.

- Throughout the investigators acknowledge that routine care may vary across centres and that only management of intra operative mechanical ventilation is to be protocolised. Is centre to be considered, for example as a random effect in the proposed Poisson regression?

We fully agree that centre should be considered and have modified the Statistics methods (Page 11, lines 12-16).

4. Minor issues not for publication
Section on Study population, second paragraph, in the brackets should read "for an unplanned...", "as" is missing.

We have modified accordingly.

Section on Randomisation, second sentence is missing "The" as the first word.

We have modified accordingly.

Statistics
- The end of the second sentence in the first paragraph, is this a reference to software, or a reference that has not been formatted properly?

An interim analysis is planned using the Lan and DeMets method ((East software, Cytel Inc., Cambridge, MA).
We have modified the section accordingly (Page 11, lines 8-9).

- Stata should not be STATA

We have modified accordingly (Page 12, line 4).

- the correct citation for Stata is given at:
www.stata.com/support/faqs/resources/citing-software-documentation-faqs/

We have modified accordingly (Page 12, line 4).