**Author’s response to reviews**

**Title:** Cluster randomised comparison of the effectiveness of 100% oxygen versus titrated oxygen in patients with a sustained return of spontaneous circulation following out of hospital cardiac arrest: a feasibility study. PROXY: Post ROSC OXYgenation Study

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**Author’s response to reviews:**

Dear Editor,

Thank you for the opportunity to rewrite and resubmit the manuscript. I have detailed the changes as recommended below.

Editor Comments:

1. Title page should
   * list institutional addresses and email addresses for all authors
   * indicate the corresponding author

   This has been altered and now reads as above

2. Trial Registration, "retrospectively registered on DD/MM/YYYY".

   This has now been altered and now is as above
3. "Aim" should be merged into "Background" section.

This has been performed

4. Declarations section

*Before "Ethics committee approval was obtained", please add a subtitle "Ethics approval and consent to participate", please also make clear here if written informed consent was obtained from each participant before enrolled.

*"No individual patient data held" should be "Not applicable".

*"All authors were involved in the set up and delivery of the trial." please make clear the contribution of each author.

This has been altered

5. Tables should not be embedded as figures or spreadsheet files, but should be formatted using ‘Table object’ function in your word processing program.

Tables are as table objects in Word

6. Figures should be provided as separate files, not embedded in the main manuscript file. Tables should NOT be submitted as figures but should be included in the main manuscript file. Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript in Figure legends section, not in the graphic file.

Reviewer reports:

Clifton W Callaway (Reviewer 1): The authors have addressed the prior reviews well. A few grammatical or structural suggestions may improve the final version:

- In the abstract and methods, "...paramedics were consented..." is a common usage but "consent" is not a transitive verb. Usually, authors write "...paramedics provided consent..."
This has been performed

- In Results, Section 4.5, the text states that clinical outcomes are not examined, but the clinical outcomes are in Table 2. It would be better to write that "clinical outcomes are in Table 2, but we made no comparison between groups because of the feasibility design and small sample size."

This has been adjusted using the wording suggested

- In Results, Section 4.4, the ABG results appear to be averages: include also a SD or some measure of spread.

This has been added

- Table 5, first data cell has "1 (6) (1) (10l)" which probably means "1 subject (6%) with a flow at 10 l/min". It is great and informative to have the actual flow rates in the table, but clarify the notation somehow.

This has been adjusted to improve clarity

Patrick Sulzgruber (Reviewer 3): I would like to thank the authors for their effort to revise this manuscript. The authors adequately addressed all comments raised and the quality of the manuscript has been clearly improved. The manuscript now describes a technically sound piece of scientific research with data that supports the conclusions. I feel that this manuscript is now acceptable for publication.

Thank you for your comments

Markus B Skrifvars (Reviewer 4): Comments regarding the paper "Cluster randomised comparison of the effectiveness of 100% oxygen versus titrated oxygen in patients with a sustained return of spontaneous circulation following out of hospital cardiac arrest: a feasibility study. PROXY: Post ROSC OXYgenation Study"
I have read with interest this revised version. The paper has been changed, and improved to some extent. However, I am still very much concerned about the conclusion given the results. My impression are that this study shows:

1. It is appears very difficult to titrate oxygenation using peripheral oxygen saturation in the pre-hospital setting. If one combines the "missing data" and "unable to measure" in Table on ends up with almost 40% of the patients. I think would be a huge problem for a future trial.

Our conclusion states “However, the relatively few eligible patients and incomplete initiation of the allocated intervention are challenges to future research. More feasibility work is required to explore the best way of addressing this important research question.” This has been substantially changed from the original following reviewers concerns . This work highlights issues future trials may face

2. I am surprised with the ABG results on admission to the hospital, there appear to be very little difference between the 100% group and the titrated oxygen group. The patients on 100% appear to have a very severe oxygenation problem with a P/F ratio less than 100. This is also a worry and will make it very difficult to achieve separation between groups.

Thank you for your comments, we have changed our conclusions significantly to prevent overestimating the outcome

3. I am puzzled by the comment that the authors wish to cite a small trial suggesting harm from hyperoxia, and that they do not want to cite a much larger trial suggesting that there is no harm. We have included this reference to cite the possibility that hyperoxia may be harmful. We have stated that oxygen is a mainstay of current treatment of cardiac arrest in the background section. There is apparent equipoise in the literature with a recent UK guidance also concerned regarding hyperoxia in all medical patients. https://doi.org/10.1136/bmj.k4169

4. A number of patients in the titrated arm are according to Table 5 being treated with mechanical ventilation with an FiO2 of 100%. This will dilute any difference between the interventions.

We are aware of this an have downplayed the success of this feasibility trial as a result of these findings
All in all this pilot study provides some interesting data. However, I would not consider it feasible to do a large randomized controlled trial based on these results, but rather the contrary. The way oxygen is delivered and monitored would need to completely changed.

We agree and have stated in our conclusion that More feasibility work is required to explore the best way of addressing this important research question.