PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

INhaled Sedation vs. Propofol in REspiratory failure in the Intensive Care Unit (INSPiRE-ICU1): protocol for a randomised, controlled trial.

Authors

Boncyk, Christina; Devlin, John W; Faisal, Hina; girard, Timothy D; Hsu, Steven H; Jabaley, Craig S; Sverud, Ida; Falkenhav, Magnus; Kress, John; Sheppard, Karen; Sackey, Peter V; Hughes, Christopher

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Wang, Tianlong**
Affiliation	**Xuanwu Hospital, Capital Medical University, Beijing, China**
Date	**08-Apr-2024**
COI	**No.**

This is an innovative study designed to discover the effect of inhalational anesthetic agents on ICU long-term sedation patients. The idea is full of innovation.

My only problem is:

1）Isoflurane has also been shown to be cause l long-term cognitive decline (J Neuroinflammation 2022, 19: 64) in elderly central nerve system and may cause side effects in developing neural system (Front Cell Neurosci 2017, 11: 119). Do you have any safe properties ?

Reviewer	**2**
Name	**Khan, Saad**
Affiliation	**Ottawa Hospital Research Institute, Regenerative Medicine**
Date	**08-May-2024**

COI	**None**

The protocol is well written, detailed and clearly defines inclusion and exclusion criteria as well as relevant primary and secondary outcomes.

Reviewer	**3**
Name	**Rubulotta, Francesca**
Affiliation	**McGill University, Critical Care Medicine**
Date	**28-Jul-2024**
COI	**None**

Recommendation for Publication of INSPiRE-ICU1 Protocol

I has been a pleasure reviewing this manuscript and detailing the protocol for the INSPiRE-ICU1 trial, which evaluates the efficacy and safety of inhaled isoflurane compared to intravenous propofol for sedation in mechanically ventilated ICU patients.

I would like to express my appreciation for the thoroughness and clarity provided in your work. The study design is robust and adheres to the Standard Protocol Items for Randomised Trials (SPIRIT) statement, ensuring that the methodology aligns with established standards.

While I noted a few minor editorial suggestions that could enhance the clarity and flow of the manuscript, I believe these adjustments are manageable and do not detract from the overall quality of the research. Therefore, I recommend that the paper be accepted for publication with minor revisions.

VERSION 1 - AUTHOR RESPONSE

We thank the Reviewer for this comment. While comments on the neurologic implications of inhaled anesthetics have been demonstrated to have both harmful and beneficial effects in animal models, there is more uncertainty among human studies, with suggestion of neuroprotective effects following trauma or acute ischemia (PMID: 33080307, 28480032). These questions are important and we hope to shed light on their potential impact among critical illness survivors as part of this study that includes cognitive assessments of survivors as part of our secondary outcomes. We hope to be able to expand on these comments within our study findings and within the results manuscript.

September 12, 2024

Christine Ferguson

Associate Editor

BMJ Open

Re: **INhaled Sedation vs. Propofol in REspiratory failure in the Intensive Care Unit (INSPiRE-ICU1): protocol for a randomized, controlled trial**

Dear Ms. Ferguson:

We thank you for the opportunity to revise and resubmit our protocol for publication in the *BMJ Open.* We thank the Editor and Reviewers for their thoughtful reviews and suggestions that have improved the quality and message of our submission. We have been able to adequately address all concerns from the Editor and Reviewers and are excited for the opportunity to be able to disseminate our manuscript. **To address the revisions, we will now outline the revisions in a point-by-point response to the comments of the Editor and Reviewers**. For each point, we will include the query/comment in ***bold italics*** followed by our response. Any text modified in the manuscript is shown in "red font."

POINT-BY-POINT RESPONSES:

REVIEWER 1:

1. ***Isoflurane has also been shown to be cause I long-term cognitive decline (J Neuroinflammation 2022, 19: 64) in elderly central nerve system and may cause side effects in developing neural system (Front Cell Neurosci 2017, 11: 119). Do you have any safe properties ?***
   We thank the Reviewer for this comment. While comments on the neurologic implications of inhaled anesthetics have been demonstrated to have both harmful and beneficial effects in animal models, there is more uncertainty among human studies, with suggestion of neuroprotective effects following trauma or acute ischemia (PMID: 33080307, 28480032). These questions are important and we hope to shed light on their potential impact among critical illness survivors as part of this study that includes cognitive assessments of survivors as part of our secondary outcomes. We hope to be able to expand on these comments within our study findings and within the results manuscript.

REVIEWER 2:

We thank the Reviewer for their comments on our protocol submission.

REVIEWER 3:

We thank the Reviewer for their comments on our submission. We ask the Editor if there are additional minor revision comments that are not present within the Decision Letter to please let us know.