PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

The study protocol for the Outcomes Post Treatment - Impact on Motor Impairment of Sleep Efficiency in Spinal Cord Injury (OPTIMISE SCI): A randomized controlled trial

Authors

Furlan, Julio C; Yao, Christie; McKay, Martha; Walsh, Sandra; Boulos, Mark

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Sankari, Abdulghani**
Affiliation	**Wayne State University School of Medicine**
Date	**11-Mar-2025**
COI	**None**

This is an important feasibility study to assess the effect of early vs. late treatment of moderate to severe sleep apnea in individuals with acute traumatic SCI. The study design is sound and manuscript is well written however there are several issues need to be addressed:

1- The authors propose to use HSAT to diagnose sleep apnea and identify central and obstructive types. However including all moderate and severe OSA in the study without proper differentiation for associated hypercapnia, (hyperventilation) or sustained hypoxia and delaying their treatment is very problematic. These individuals should be excluded and treated outside the protocol to ensure safety.

- There is no assessment of adherence to CPAP , this need to be assessed as previous studies found low adherence and relationship between hours of use and clinical outcome.

- Including all moderate to severe sleep apnea regardless of type such as central with autoCPAP is contraindicated this need to be addressed

- The late group may have changes in medication or clinical condition and may require repeat of HSAt before the retreatment s launched

- Statistical analysis does not factor in adjustments to many cofounders and variables

0 the power analysis is very superficial how 22 per arm was reached based on what primary outcome? please elaborate.

- The authors omitted several studies in SCI and sleep apnea field and how this protocol was informed and build on these studies

- The introduction and discussion are long and diffuse recommend to revise to justify why this study is needed based on gap in the literature and comparison of current study

Minor, please add type of CPAP machine, what adherence cloud platform will be used, describe in details scoring criteria of sleep studies and who will do that

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Reviewer	**2**
Name	**Fleming, Melanie K.**
Affiliation	**University of Oxford**
Date	**02-Apr-2025**
COI	**None**

This is a protocol for a randomised trial of early or delayed CPAP in people with spinal cord injury. This is an important, and interesting study. I have a few suggestions to improve the clarity of the paper.

• Page 7, top – you list fatigue as being both a “medical” factor affecting therapy and a behavioural factor. It would be helpful to make clear how medical fatigue is different to behavioural fatigue.

• Page 7 – end of the first paragraph: You specify that untreated moderate to severe SRBDs can cause or aggravate pain and spasticity. It is not immediately obvious to me how these are related. Could you please either briefly explain or provide a reference that the reader could go to if they wanted to understand this relationship better.

• Study design: You mention receiving input from a person with lived experience. It would be helpful to briefly explain how their input shaped your study design, and whether you have any additional patient/public involvement planned during the study.

• The inclusion and exclusion criteria specify less than or equal to 6 weeks after injury, but figure 1 specifies 8 weeks. Please clarify why these are different

• It would be helpful if the timeline of assessments could be clearer in the text. From figure 1 it looks like there is a “close-out assessment” but it is not clear when this takes place or whether it is included in the analysis.

• The data analysis section could do with a bit more detail: For example, will you include any covariates in your analyses (such as severity of injury or age)? I presume you will use an intention to treat approach, but this isn’t specified. Will you take into account whether they

adhere to the CPAP or not, or whether their sleep efficiency is actually any better with CPAP? Given that your title implies that you are interested in how sleep efficiency impacts motor impairment it seems like this is an important consideration.

• Sample size: there could do with a bit more detail on your sample size calculation. For example, what effect size have you used to base your sample size calculation on, and what is the comparison that this is based on (e.g. is it based on detecting a difference between early vs delayed CPAP, or is the non-CPAP group included)?

• Ethical and safety considerations: Whilst I understand the need to explain the ethical considerations around the delay to CPAP, in my opinion this section is too long. I would suggest streamlining your explanation, so that you still make the point, but without going into so much detail. Additionally, it is not clear how these "cross-over cases" will be dealt with in your analyses.

• Dissemination plan: Are there any intentions to disseminate the findings to people affected by SCI (i.e. non-academic outputs)?

• Figure 1: I'm not really clear what the difference is between randomisation and allocation. I'm also not really sure I understand what the x in the 3/6/9 month columns is for (having a x in each column implies to me that they are receiving or doing something but I'm not sure what). Finally when is "close out" ?

Minor comments

• Recruitment and Randomisation: Who will do the randomisation?

• Blinding: The first sentence is worded a bit strangely, I'm not sure what you mean by "blinded for the participants". I suggest rewording to "blinded to group allocation"

• Has recruitment started already? It would be helpful to specify when it opened to recruitment (or when it is planned to open if not already).

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Dr. Abdulghani Sankari, Wayne State University School of Medicine

Comments to the Author:

This is an important feasibility study to assess the effect of early vs. late treatment of moderate to severe sleep apnea in individuals with acute traumatic SCI. The study design is sound and manuscript is well written however there are several issues need to be addressed:

1- The authors propose to use HSAT to diagnose sleep apnea and identify central and obstructive types. However including all moderate and severe OSA in the study without proper differentiation for associated hypercapnia, (hyperventilation) or sustained hypoxia and delaying their treatment is very problematic. These individuals should be excluded and treated outside the protocol to ensure safety.

Answer: The current standard of care does not typically involve any sleep testing or treatment in most centres for this patient population; therefore, there is clinical equipoise and it is ethically justifiable to delay treatment in the context of this important clinical trial. This commentary was added in the subsection on "ethical and safety considerations".

There is a board certified sleep neurologist reviewing all HSATs to ensure clinical standards are met. The HSAT can differentiate central from obstructive sleep apnea, as well as assess for hypoxia. This additional information was added in methods.

- There is no assessment of adherence to CPAP, this need to be assessed as previous studies found low adherence and relationship between hours of use and clinical outcome.

Answer: This information is mentioned in the last paragraph of the subsection "Intervention" in the Methods. Additional information was also added in the revised version of the manuscript.

- Including all moderate to severe sleep apnea regardless of type such as central with autoCPAP is contraindicated this need to be addressed.

Answer: CPAP can treat central apnea in many cases; in the course of their clinical care, patients may also complete an in-lab titration study and get started on BiPAP or ASV, if clinically indicated.

- The late group may have changes in medication or clinical condition and may require repeat of HSAt before the retreatment s launched.

Answer: The delay is unlikely to significantly change the results of their in-hospital unattended sleep screening testing; if there is concern that the patient's clinical picture or medications has substantially changed, a repeated in-hospital unattended sleep screening testing will be considered. This additional information was added to the revised version of the manuscript.

- Statistical analysis does not factor in adjustments to many cofounders and variables

0 the power analysis is very superficial how 22 per arm was reached based on what primary outcome? please elaborate.

Answer: We revised the subsections on "Data Analysis" and "Sample Size Estimation".

- The authors omitted several studies in SCI and sleep apnea field and how this protocol was informed and build on these studies.

Answer: This manuscript is focused on the description of a RCT protocol that, in our opinion, included the most pertinent papers related to the topic of the RCT. We are performing a

systematic review on this topic that will capture most (if not all) papers on sleep apnea and SCI.

- The introduction and discussion are long and diffuse recommend to revise to justify why this study is needed based on gap in the literature and comparison of current study.

Answer: We revised the manuscript as suggested.

Minor, please add type of CPAP machine, what adherence cloud platform will be used, describe in details scoring criteria of sleep studies and who will do that

Answer: We revised the manuscript as suggested.

Reviewer: 2

Dr. Melanie K. Fleming, University of Oxford

Comments to the Author:

This is a protocol for a randomised trial of early or delayed CPAP in people with spinal cord injury. This is an important, and interesting study. I have a few suggestions to improve the clarity of the paper.

• Page 7, top – you list fatigue as being both a "medical" factor affecting therapy and a behavioural factor. It would be helpful to make clear how medical fatigue is different to behavioural fatigue.

Answer: The paragraph that mentioned them was removed because the other reviewer suggested to reduce the Introduction section and that paragraph was less relevant than the other ones.

• Page 7 – end of the first paragraph: You specify that untreated moderate to severe SRBDs can cause or aggravate pain and spasticity. It is not immediately obvious to me how these are related. Could you please either briefly explain or provide a reference that the reader could go to if they wanted to understand this relationship better.

Answer: The paragraph that mentioned them was removed because the other reviewer suggested to reduce the Introduction section and that paragraph was less relevant than the other ones. Of note, this information was obtained from our preliminary data analysis from our recent studies, but the data were not published yet.

• Study design: You mention receiving input from a person with lived experience. It would be helpful to briefly explain how their input shaped your study design, and whether you have any additional patient/public involvement planned during the study.

Answer: Additional information on their input was included in the revised version of the manuscript in the subsection on "Patient and Public Involvement".

• The inclusion and exclusion criteria specify less than or equal to 6 weeks after injury, but figure 1 specifies 8 weeks. Please clarify why these are different.

Answer: The correct timeline is 8 weeks after injury. We corrected the text. Thank you for flagging this.

• It would be helpful if the timeline of assessments could be clearer in the text. From figure 1 it looks like there is a "close-out assessment" but it is not clear when this takes place or whether it is included in the analysis.

Answer: We revised the text and Figure 1.

• The data analysis section could do with a bit more detail: For example, will you include any covariates in your analyses (such as severity of injury or age)? I presume you will use an intention to treat approach, but this isn't specified. Will you take into account whether they adhere to the CPAP or not, or whether their sleep efficiency is actually any better with CPAP? Given that your title implies that you are interested in how sleep efficiency impacts motor impairment it seems like this is an important consideration.

Answer: We revised the manuscript as suggested.

• Sample size: there could do with a bit more detail on your sample size calculation. For example, what effect size have you used to base your sample size calculation on, and what is the comparison that this is based on (e.g. is it based on detecting a difference between early vs delayed CPAP, or is the non-CPAP group included)?

Answer: We revised the manuscript as suggested.

• Ethical and safety considerations: Whilst I understand the need to explain the ethical considerations around the delay to CPAP, in my opinion this section is too long. I would suggest streamlining your explanation, so that you still make the point, but without going into so much detail. Additionally, it is not clear how these "cross-over cases" will be dealt with in your analyses.

Answer: We revised the manuscript as suggested.

• Dissemination plan: Are there any intentions to disseminate the findings to people affected by SCI (i.e. non-academic outputs)?

Answer: As previously planned, we added the following in the revised version of the manuscript - "As above mentioned every participant will eventually receive a "white paper" in English, where the main findings of the clinical trial will be summarized in lay language."

• Figure 1: I'm not really clear what the difference is between randomisation and allocation. I'm also not really sure I understand what the x in the 3/6/9 month columns is for (having a x in each column implies to me that they are receiving or doing something but I'm not sure what). Finally when is "close out" ?

Answer: There are three trial groups in the allocation. However, only the participants with moderate-to-severe sleep-related breathing disorders were randomized into the early-CPAP therapy group or the delayed-CPAP therapy group. Figure 1 was revised accordingly.

Minor comments

• Recruitment and Randomisation: Who will do the randomisation?

Answer: We revised the manuscript as suggested. Randomisation has been performed by a research assistant using an online randomization system (Research Randomizer by the Social Psychology Network, Wesleyan University).

• Blinding: The first sentence is worded a bit strangely, I'm not sure what you mean by "blinded for the participants". I suggest rewording to "blinded to group allocation"

Answer: We revised the manuscript as suggested.

• Has recruitment started already? It would be helpful to specify when it opened to recruitment (or when it is planned to open if not already).

Answer: We revised the manuscript as suggested. Of note, recruitment was initiated in August 2022.

Reviewer: 1

If you have selected 'Yes' above, please provide details of any competing interests.: NA

Reviewer: 2

If you have selected 'Yes' above, please provide details of any competing interests.: Not applicable

VERSION 2 - REVIEW

Reviewer	**2**
Name	**Fleming, Melanie K.**
Affiliation	**University of Oxford**
Date	**07-May-2025**
COI	

Thank you for making the changes. I have nothing further