PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing the relationship between near-infrared spectroscopy derived regional cerebral oxygenation and neurological dysfunction in critically ill adults: a prospective observational multi-centre protocol, on behalf of the Canadian Critical Care Trials Group
AUTHORS	Wood, Michael; Khan, Jasmine; Lee, Kevin; Maslove, David M; Muscedere, John; Hunt, Miranda; Scott, Stephen; Day, Andrew; Jacobson, Jill; Ball, Ian; Slessarev, Marat; O'Regan, Niamh; English, Shane; McCredie, Victoria; Chasse, Michaël; Griesdale, Donald; Boyd, John

VERSION 1 - REVIEW

REVIEWER	Regis Goulart Rosa Senior Critical Researcher Hospital Moinhos de Vento Brazil
REVIEW RETURNED	14-Feb-2019

GENERAL COMMENTS	In the present study protocol, the investigators describe an important and relevant prospective cohort study to evaluate the association between poor regional cerebral oxygenation and delirium among adult critically ill patients. The research question is interesting. My main comments are described bellow: 1) I might suggest the authors to emphasize throughout the abstract and text the primary and secondary outcome measures. 2) The assessment of the primary outcome (delirium) is not clear. How many times per day will patients be assessed for delirium? Who will evaluate patients? Will evaluators receive training in order to optimize CAM-ICU and bCAM accuracy? Will the investigators measure inter-rater reliability of delirium assessment? 3) Apparently there is an inconsistence between the present study protocol and the clinicaltrials.gov registry (NCT03141619) regarding the method of analysis of the primary outcome: In the clinicaltrials.gov is stated that authors will perform a correlational analysis between BtO2 and the amount of delirium days. However, in the present study protocol is stated that multivariate linear regression will be used to characterize the association between the adequate cerebral perfusion and CAM-7 delirium severity score. Please, adjust or clarify this point.

	4) The sample size is not clear. How many patients will be enrolled? 200 (in clinicaltrials.gov), 400 (in sample size calculation, manuscript), or 500 (in secondary outcomes, manuscript)? 5) Delirium is a trick outcome, given that delirium status changes over time, delirium cannot be assessed when patients are in coma, and mortality is a competing event for delirium assessment. In this context, joint models have been proposed to address these above-mentioned challenges (Lancet Respiratory 2016 Jul;4(7):534-6; PMID 27264776). Therefore, I might suggest the authors to revise the appropriateness of this kind of method of statistical analysis for this study. 6) I might suggest to include figures aimed to synthesize the study design and flow of participants, and dummy tables in the statistical analysis plan. 7)The discussion may be expanded in order to include strengths and limitations of the present study.

REVIEWER	Mona Momeni Cliniques Universitaires Saint Luc; Belgium
REVIEW RETURNED	03-Mar-2019

GENERAL COMMENTS	I would like to congratulate the authors for such an important and complete study. Delirium in critically ill patients is a major health problem and any measures to decrease its incidence should be evaluated. I have only some minor comments and questions regarding this manuscript. - Why do you include only patients that need mechanical ventilation within 24h of ICU admission? Is this because you consider these subjects being most critically ill? Do you include patients admitted to ICU after major surgery? - You mention that robot technology has indicated that ICU survivors also develop visuospatial and motor deficits. Please clarify this point as the average reader may not be familiar with this technology that has been developed. - Not any chronic cognitive dysfunction can be compared with Alzheimer's disease. Alzheimer's disease is a specific, well defined entity. However, cognitive dysfunction post surgery and post ICU may be the result of several different factors. So please omit the sentence "this population experiences chronic cognitive dysfunction similar to mild Alzheimer's disease". - Page 8: The exclusion criteria are admission to ICU > 24H. Is this a mistake? Please correct. - Page 11: Pre-existing frailty will be assessed upon enrollment. How can you assess frailty if the patient is admitted to the ICU because he's critically ill? - Page 15: Why do only participants from the Kingston region will undergo the KINARM test? By the way, this test does not provide any information about the patient's cognitive status.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment: I might suggest the authors to emphasize throughout the abstract and text the primary and secondary outcome measures.

Reply: To further illustrate our primary and secondary outcomes, we have amended the Abstract section, see page 3 lines 54-56 and 67, as well as the Introduction section, see page 8 lines148-152.

Comment: The assessment of the primary outcome (delirium) is not clear. How many times per day will patients be assessed for delirium? Who will evaluate patients? Will evaluators receive training in order to optimize CAM-ICU and bCAM accuracy? Will the investigators measure inter-rater reliability of delirium assessment?

Reply: We thank you for suggesting further clarification in this section, and we have revised the delirium screening section of the Methods accordingly, see pages 14, lines 250-255. However, due to the both the CAM-ICU (Ely, W. E., et al. 2001) and the b-CAM (Han, J. H., et al. 2013) being previously validated delirium screening tools, we did not included a measure of inter-rater reliability but we very much appreciate the suggestion.

Comment: Apparently there is an inconsistence between the present study protocol and the clinicaltrials.gov registry (NCT03141619) regarding the method of analysis of the primary outcome: In the clinicaltrials.gov is stated that authors will perform a correlational analysis between BtO2 and the amount of delirium days. However, in the present study protocol is stated that multivariate linear regression will be used to characterize the association between the adequate cerebral perfusion and CAM-7 delirium severity score. Please, adjust or clarify this point.

Reply: Thank you for noting this inconsistency, we have amended our ClinicalTrials.gov CONFOCAL2 registry to reflect our current protocol manuscript. However, the amendments take approximately 2 weeks to appear online. In addition, our original registry from May 5 2017 reflects the analysis outcome of a correlation between delirium duration (i.e., days) and regional cerebral oxygenation. However, due to our previous single-centre pilot study being unable to adjust for clinically relevant covariates in our analysis (Wood, M. D., et al 2017), we updated our analysis plan but did not modify our ClincialTrials registry. Again, we thank you for noting this discrepancy.

Comment: The sample size is not clear. How many patients will be enrolled? 200 (in clinicaltrials.gov), 400 (in sample size calculation, manuscript), or 500 (in secondary outcomes, manuscript)?

Reply: Thank you for noting this inconsistency and that this section of the Methods warrants clarification. As our pilot data suggested that approximately 20% of patients remain comatose throughout their entire ICU stay, we plan to enroll a total of 500 patients. Taking this into account, we are estimating that we will have ~400 patients that can be screened for delirium and be included in our primary outcome analysis, please see pages 21, lines 424-429. In terms of secondary outcomes (i.e.., physiological determinants of regional cerebral oxygenation during critical illness), all recruited patients (500) can be included in this analysis as we are interested in broadly assessing the determinants of cerebral oxygenation during critical illness. In addition, we anticipate (due to our pilot data mentioned above) an approximate 30% mortality rate resulting in ~350 survivors to assess long-

term neurological outcomes after ICU discharge. We have included additional clarification in the Methods section, see page 22, lines 440-447. We have also updated our ClinicalTrials.gov registry to reflect the sample size calculation, see the link above.

Comment: Delirium is a tricky outcome, given that delirium status changes over time, delirium cannot be assessed when patients are in coma, and mortality is a competing event for delirium assessment. In this context, joint models have been proposed to address these above-mentioned challenges (Lancet Respiratory 2016 Jul;4(7):534-

6; PMID 27264776). Therefore, I might suggest the authors to revise the appropriateness of this kind of method of statistical analysis for this study.

Reply: We appreciate this suggestion, as we are familiar with Dr. Colantuoni's work and her suggestion for the joint modelling approach. However, this approach is commonly recommended to evaluate the effects of an intervention on outcomes, such as ICU associated delirium. The current study is observational in nature, as there is only preliminary data at this stage suggesting that delirium is associated with poor regional cerebral oxygenation (rSO2). However, upon further study of the association between poor rSO2 and the development of delirium, as well as the physiological determinants of rSO2, we may be able to develop a targeted algorithm to optimize rSO2 during critical illness. At this hypothetical intervention stage, we fully agree that the joint modelling approach would be suitable for the analysis. Furthermore, as Dr. Colantuoni suggests, the joint modelling approach has the limitation of a single terminating event. As we have not previously assessed terminating events (e.g., mortality, ICU discharge, hospital discharge frequently occurred in our previous cohort) and outcomes, we are not sure a single end-point would encapsulate the complex heterogeneous clinical trajectories represented by critically ill patients. In addition, based on our pilot data, we have powered our primary analysis to be able exclude patients who remain comatose throughout their entire ICU stay. We have chosen to consider comatose days (i.e., RASS of -4 or -5) as a distinct syndrome. For example, a patient may be admitted with respiratory failure due to pneumonia and is mechanically ventilated with pharmacological paralysis and heavy sedation but would otherwise be neurologically intact if not for the iatrogenic coma. In contrast, a patient may have shock and remain comatose despite aggressive resuscitation and little or no sedation, which would represent very distinct pathophysiological events. We feel that including the number of days a patient spends in this highly heterogeneous state would dilute the signal and that using an average delirium severity is more appropriate in this context, while also controlling for several covariates (e.g., narcotic dosing, severity of illness, length of ICU stay) that may also affect delirium severity.

Comment: I might suggest to include figures aimed to synthesize the study design and flow of participants, and dummy tables in the statistical analysis plan.

Reply: Again, we thank you for the suggestion and we have substantially amended our infographic to more accurately reflect our study design. Please see the update version of Figure 1. Due to the sheer volume of information collected (e.g., medication dosing, delirium screening, admitting diagnosis, comorbidities) resulting in >100 columns of data, we have decided not to have include a dummy table, however, we appreciate the suggestion. As this collection process is recorded in an electronic case report form, the data collection process, and subsequent data analysis, is streamlined across sites.

Comment: The discussion may be expanded in order to include strengths and limitations of the present study.

Reply: As per the BMJ Open guidelines, we have included a Strengths and Limitations section after the Abstract. However, this section has been substantially re-written as the Editor raised similar concerns, please see pages 5-6, lines 83-107.

Reviewer: 2

Comment: Why do you include only patients that need mechanical ventilation within 24h of ICU admission? Is this because you consider these subjects being most critically ill? Do you include patients admitted to ICU after major surgery?

Reply: We have mirrored our inclusion and exclusion criteria from the BRAIN-ICU study, as well as our prior study, to facilitate future meta-analysis across critical care studies. Furthermore, patients admitted after elective surgery are generally excluded, as their duration of mechanical ventilation is <24h, one of the main exclusion criteria.

Comment: You mention that robot technology has indicated that ICU survivors also develop visuospatial and motor deficits. Please clarify this point as the average reader may not be familiar with this technology that has been developed.

Reply: We have included additional information to clarify that this robotic technology (i.e., the KINARM) is the same robot that will be used at follow up in the current protocol, see page 7 lines 121-122.

Comment: Not any chronic cognitive dysfunction can be compared with Alzheimer's disease. Alzheimer's disease is a specific, well defined entity. However, cognitive dysfunction post surgery and post ICU may be the result of several different factors. So please omit the sentence "this population experiences chronic cognitive dysfunction similar to mild Alzheimer's disease".

Reply: We appreciate this suggestion and we have amended this phrase to more accurately illustrate that ICU survivor’s performance scores were similar to patient’s with Alzheimer’s disease, see page 7, lines 123-125.

Comment: Page 8: The exclusion criteria are admission to ICU > 24H. Is this a mistake? Please correct.

Reply: Enrolling patients as close to ICU admission as possible is central to our research program. We believe that during the resuscitative phase of critical illness patients experience an ischemic/hypoxic event, indicated by low levels of regional cerebral oxygenation, that leads to acute and chronic neurological dysfunction. Our pilot study has shown that poor regional cerebral

oxygenation during the first 24-hours of critical care is an independent predictor of the subsequent development of delirium (Wood, M. D., et al 2017). Therefore, this is not a typographical error but we appreciate the suggestion and attention to detail.

Comment: Page 11: Pre-existing frailty will be assessed upon enrollment. How can you assess frailty if the patient is admitted to the ICU because he's critically ill?

Reply: The Clinical Frailty Scale is a 9-point scale, which takes less than 5 minutes to administer and does not require specialized medical equipment and is a well validated and reliable measure to assess frailty. Each point on its scale corresponds with a written description of frailty and possesses a pictograph to assist with frailty classification (i.e., score ≥5 is considered to be frail). Therefore, trained research staff will approach whomever consented for the study (i.e., the Substitute Decision Maker or the patient) to ascertain the patient's pre-existing frailty status. We have revised the Methods section to clarify this concern, see page 13, lines 241-244.

Comment: Page 15: Why do only participants from the Kingston region undergo the KINARM test? By the way, this test does not provide any information about the patient's cognitive status.

Reply: Kingston is the only region to undergo the KINARM assessment as none of the other sites currently possess this robotic technology, which at present, is not mobile to transfer across sites. As this limitation will increase the selection bias of our sample of participants who can return for robotic testing, we will only use descriptive statistics on this dataset until we can conduct a multicentre study where the KINARM robot can be used to collect performance data across multiple sites. We have clarified this section of the Methods, see page 21, lines 414-417. In addition, your comment about the KINARM not providing information about a patient's cognitive status raised the important point that this section warranted further clarification. Revising this section, we realized that we did not include Trail Making A/B and we have substantially retooled Figure 3 and created a task description table to further illustrate each domain (e.g., cognitive, motor, sensory) that the various KINARM tasks assess. Please see Table 1 for the task descriptions and page 15-16 lines 291-296 for the KINARM Method revisions.

VERSION 2 – REVIEW

REVIEWER	Regis G Rosa Critical Care Department, Hospital Moinhos de Vento.
REVIEW RETURNED	04-Apr-2019

GENERAL COMMENTS	I would like to commend the authors for their efforts in improving the present study protocol. I recommend publication.

REVIEWER	Mona MOMENI Cliniques Universitaires Saint Luc; Université Catholique de Louvain
REVIEW RETURNED	04-Apr-2019

GENERAL COMMENTS	Thank you for this nice revision of your manuscript. My concerns and questions have been adequately addressed.