PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Optimal VAsopressor TitraTION in patients 65 years and older (OVATION-65) – protocol and statistical analysis plan for a randomized clinical trial
AUTHORS	Masse, Marie-Hélène; Battista, Marie-Claude; Wilcox, M. Elizabeth; Pinto, Ruxandra; Marinoff, Nicole; D'Aragon, Frédérick; St-Arnaud, Charles; Mayette, Michael; Leclair, Marc-André; Quiroz Martinez, Hector; Grondin-Beaudoin, Brian; Poulin, Yannick; Carbonneau, Élaine; Seely, Andrew; Watpool, Irene; Porteous, Rebecca; Chassé, Michael; Lebrasseur, Martine; Lauzier, François; Turgeon, Alexis; Bellemare, David; Mehta, Sangeeta; Charbonney, Emmanuel; Belley-Cote, Emilie; Botton, Édouard; Cohen, Dian; Lamontagne, Francois; Adhikari, Neill

VERSION 1 – REVIEW

REVIEWER	Paul Young Medical Research Institute of New Zealand
REVIEW RETURNED	01-Mar-2020

GENERAL COMMENTS	Thank you for the opportunity to review the Ovation-65 study protocol manuscript. This manuscript is well thought out and well written and I do not have any substantive suggestions. Please consider the following minor points: 1. Please consider referencing the statement “Given that coronary perfusion autoregulation is maintained when MAP is at least 60 mmHg…” Also, please consider whether this statement is necessarily accurate for all patients and perhaps soften the certainty implicit in the current drafting. 2. Please revise the description of the primary end point. At present the end point is described as the high-sensitivity cardiac troponin T (hsTnT) day 3. However, as noted in the manuscript the measurement is actually taken at day 3 or before anticipated death or withdrawal of life-sustaining therapies, whichever comes first. I think that the first time that the primary end point is measured this point should be mentioned as it is important. 3. Related to point 2, one major issue is that the inconsistent time of measurement of the hsTNT creates a potential source of bias. Study treatment allocation may affect the likelihood and timing of ICU discharge and / or death. This means that the comparison being undertaken depends on post-randomisation variables and is therefore not truly a randomised comparison. 4. The issue alluded to in point number 3 cannot be solved. It is an inherent problem in all studies where such competing risks exist and I note the plans to undertake sensitivity analyses for patients who die before day 3 or are discharged before day 3. This is appropriate.

	5. I wonder if a more explicit discussion of the potential for bias to be introduced in ascertainment of the primary end point due to the competing risks could be added to the manuscript but, on the other hand, perhaps the protocol manuscript is not the place to do this. 6. hsTnT is likely to demonstrate a log normal distribution so plans to log-transform these data are appropriate.

REVIEWER	Ed Litton Fiona stanley hospital, perth, Western Australia
REVIEW RETURNED	12-Mar-2020

GENERAL COMMENTS	This randomised clinical trial protocol manuscript is clear and well considered. It is a high quality description of a pragmatic trial that would allow replication of all key components of study and conduct and will provide a valuable reference document against which to evaluate the final report of the study outcomes. It is disappointing that the trial was stopped early given that the effect estimate from the result that triggered this was not significant and that the comparator arm of OVATION-65 was usual care. Nevertheless, 159 out of a planned 200 participants still provides ample opportunity to contribute substantial new information on blood pressure management in the ICU. The punchline about stopping early comes way down in the sample size section. Might it be more helpful to the reader to announce this in the intro and then ensure the tense is consistent? Currently page 21 line 26 reports that 'no interim analysis is planned' but this seems entirely redundant, or the tense is wrong. I have one major comment and the rest are all minor. The major comment is that, as I interpret it, the primary outcome described in the trial registration (NCT03431181): Mean peak high-sensitivity cardiac troponins T (primary mechanistic outcome) [Time Frame: 7 days] …appears to be different to what is proposed in this manuscript – day three troponin. Is this the case? If so it deserves clarification. Some minor comments: Given the similarity with the 65 trial, it is worth considering whether individual patient data meta-analysis has been considered, and if so whether this is worth addressing in this current manuscript. Im curious why study participants readmitted to ICU within the same hospital episode did not resume their treatment allocation (page 14 line 33)? Is this worth clarifying? I might have missed it but I couldn't see that the specific vasopressor or combination both at baseline and during the study was being reported as described in the data collection section on page 14?

	Is it worth clarifying why day three chosen for the primary outcome? Could a mean daily troponin be of greater value in interpreting cardiac damage over the entire period of exposure? Is there a risk of differential bias resulting from incomplete outcome testing as described on page 17? Was trial registration prior to enrolment of the first patient? Might be worth making that clear in the manuscript.

REVIEWER	Gerben Keijzers Gold Coast University Hospital
REVIEW RETURNED	22-Mar-2020

GENERAL COMMENTS	This is a manuscript outlining a protocol comparing two approaches to blood pressures management in patients over 65 years with vasodilatory hypotension. The comparison is between usual care (mostly vasopressor use to keep MAP>65, but could be as high as 70 or 75 as per treating clinician) and permissive hypotension (allowing a MAP of 60-65). This protocol overall is well written, although there are some areas that need clarification (see below). The recently published 65 trial leads to a few important questions about this protocol. In summary: The 65 trail study had almost 2500 patients ≥65 years who were randomized into well-matched, groups receiving usual care or permissive hypotension using a similar protocol as the proposed OVATION-65 study (lower MAP target of 60-65 mm Hg). There was no difference in 90-day mortality, which was the primary outcome: 41% permissive hypotension vs 43.8% usual care. There was a lower total dose and less time on vasopressors in the permissive hypotension group. Serious adverse events, like renal failure or SVT, were similar among the groups. In conclusion: permissive hypotension appears safe This leads to two important questions: 1- The protocol is clear that with the publication of the 65 trial the DSMC decided that recruitment for OVATION-65 needed to be halted as there was no more clinical equipoise. In essence this means that this protocol is offered for publication after these decisions were made and that the protocol will be published after recruitment has been completed. This may be an editorial decision, but am wondering to what degree a protocol publication (No matter how transparent this process has been described) adds value to the clinical trials registration which was done a priori, when recruitment is complete. 2- Due to the results of the 65 trial, it will be likely that 'ususal practice' will be converging to the intervention with clinicians being more comfortable running the MAP at 65 or 65-70 (rather than 75-80). As result the separation in MAP between the two groups will possibly be too small to detect any meaningful differences in biomarkers between the two groups. Obviously, the recruitment is nearly complete, but continuing to recruit will likely makes separation between two groups even smaller. Please address/justify

	If the editorial decision is that this protocol is eligible for publication, the following questions are worth addressing in the manuscript. 1- Abstract – the objective sentence misses an outcome. The objective is to ascertain the effect of permissive vs usual care ….. (? Add on biomarkers as outcome) 2- Adequate fluid resuscitation is mentioned in the methods of the abstract, however this needs to be explored in the methods section of the full manuscript. At the moment this is stated as per clinician judgment but were there certain minimum fluid amounts required (1L, 2L, 30ml/kg?) or are specific tools used to quantify (cardiac output monitor, point of care Ultrasound, other). I would strongly recommend to have a) the amount of fluid give prior to starting vasopressors and b) time to start of vasopressor from diagnoisis as a variables being reported 3- The primary outcome needs to have a time point added in the abstract. The manuscript suggests this is 3 days, however the clinical trials registration has 7 days as primary outcome. Please review this discordance between registered protocol and manuscript protocol 4- Page 8 – line 10-12 – the fact that the 65 trial did not collect biological samples means you cant comment on biomarkers or hypothesise on pathways. The clinical effect is well described in the 65 trial (mortality, outcomes, AEs). Please rephrase and remove the word 'clinical' 5- Page 8- line 24-25 – Along similar lines, this study cannot be to determine if the intervention compared to usual care reduces harm. This would need an appropriately powered clinical study. This study adds insights by describing biomarkers to provide data to inform new hypotheses. Please rephrase and remove 'reduces harm' 6- Lactate is a fair biomarker to measure – however there are many reasons this may be elevated and tissue dysoxia is not the only (or most important) cause of raised lactate as many aerobic adrenergic stimulation processes increase lactate. Please address 7- There is clear data that peripheral vasopressors (well monitored and needed for < 12-24 hrs) is safe and reasonable – can you comment on whether this is allowed or included (as it is part of usual care in other settings) 8- Can you clarify how MAP will be measured – is an arterial line mandated and if so, is there a particular prescribed device and timing of MAP measurement (as MAP can vary beat to beat). The MAP measurements (non-invasive vs invasive) and exact measurement techniques would benefit from more detailed description 9- The comment on consumer engagement reads as a motherhood statement. As the outcomes are primarily biomarkers I wonder to what degree ICU survivors had relevant input. Either remove the statement or add more detail (number of consumers, type of input etc)

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 Comments to Author:

Thank you for the opportunity to review the Ovation-65 study protocol manuscript. This manuscript is

well thought out and well written and I do not have any substantive suggestions.

Response: Thank you; we appreciate your comment.

1. Please consider referencing the statement "Given that coronary perfusion autoregulation is maintained when MAP is at least 60 mmHg…" Also, please consider whether this statement is necessarily accurate for all patients and perhaps soften the certainty implicit in the current drafting.

Response: Thank you. We have revised and softened the tone of this sentence and added a reference (page 13):

"Given that coronary blood flow is maintained over a broad range of coronary perfusion pressures under most circumstances,[37] we hypothesize that increasing vasopressors to achieve a higher MAP will have little effect on coronary perfusion but may increase the severity of demand-related myocardial ischemia via increased heart rate (i.e. reduced coronary perfusion time) and transmural pressure (i.e. afterload)."

2. Please revise the description of the primary end point. At present the end point is described as the high-sensitivity cardiac troponin T (hsTnT) day 3. However, as noted in the manuscript the measurement is actually taken at day 3 or before anticipated death or withdrawal of life-sustaining therapies, whichever comes first. I think that the first time that the primary end point is measured this point should be mentioned as it is important.

Response: We have clarified this sentence (page 13):

"The primary outcome of OVATION-65 is high-sensitivity cardiac troponin T (hsTnT) at day 3, or before anticipated death or withdrawal of life-sustaining therapies, whichever comes first."

3. Related to point 2, one major issue is that the inconsistent time of measurement of the hsTNT creates a potential source of bias. Study treatment allocation may affect the likelihood and timing of ICU discharge and / or death. This means that the comparison being undertaken depends on post-randomisation variables and is therefore not truly a randomised comparison.

4. The issue alluded to in point number 3 cannot be solved. It is an inherent problem in all studies where such competing risks exist and I note the plans to undertake sensitivity analyses for patients who die before day 3 or are discharged before day 3. This is appropriate.

5. I wonder if a more explicit discussion of the potential for bias to be introduced in ascertainment of the primary end point due to the competing risks could be added to the manuscript but, on the other hand, perhaps the protocol manuscript is not the place to do this.

Response (comments 3-5): Thank you for this observation. We agree and have added a short paragraph to the 'Risk of bias' section (formerly called 'Reducing bias'; page 16):

"A risk of bias related to the biomarker outcomes is that early death or live discharge from the ICU, which may be related to treatment allocation, are competing risks for ongoing treatment in the ICU and ascertainment of these outcomes. Our analysis plan (see Statistical analysis below) accounts for this possibility."

In the statistical analysis plan, we handle this problem by describing the sensitivity analysis pointed out in the comment and also the use of GEE models with inverse-probability weights for attrition in the primary analysis.

6. hsTnT is likely to demonstrate a log normal distribution so plans to log-transform these data are appropriate.

Response: Thank you.

Reviewer #2 Comments to Author:

1. This randomised clinical trial protocol manuscript is clear and well considered. It is a high quality description of a pragmatic trial that would allow replication of all key components of study and conduct and will provide a valuable reference document against which to evaluate the final report of the study outcomes.

Response: Thank you for this comment.

2. It is disappointing that the trial was stopped early given that the effect estimate from the result that triggered this was not significant and that the comparator arm of OVATION-65 was usual care. Nevertheless, 159 out of a planned 200 participants still provides ample opportunity to contribute substantial new information on blood pressure management in the ICU.

Response: We agree that it is disappointing that OVATION-65 will not accrue to its complete sample size. As discussed on page 18-19, the DSMC based its decision on the adjusted analysis from 65 that showed lower mortality in the intervention arm, plus results from SEPSISPAM (PMID 24635770) that showed a similar, albeit non-significant, effect on 28-day mortality.

3. The punchline about stopping early comes way down in the sample size section. Might it be more helpful to the reader to announce this in the intro and then ensure the tense is consistent? Currently page 21 line 26 reports that 'no interim analysis is planned' but this seems entirely redundant, or the tense is wrong.

Response: We have added the fact of early stopping to end of the Introduction (page 8):

"As discussed in the Statistical Analysis section, the Data and Safety Monitoring Committee (DSMC) recommended termination of enrollment in the current smaller version of OVATION-65 on 21 February 2020; patient follow-up is ongoing."

We have changed the tense to the past tense in the sentence in the Statistical Analysis section (page 19):

"Given the modest sample size and focus on biomarkers of organ injury, no interim analysis was planned."

I have one major comment and the rest are all minor.

4. The major comment is that, as I interpret it, the primary outcome described in the trial registration (NCT03431181):
Mean peak high-sensitivity cardiac troponins T (primary mechanistic outcome) [Time Frame: 7 days]
appears to be different to what is proposed in this manuscript – day three troponin. Is this the case? If so it deserves clarification.

Response: The entry on clinicaltrials.gov was an error; we did not understand that the time point listed referred to the time of the outcome, as opposed to the last time the outcome was measured. We have corrected the trial registration and have added the following to the manuscript (page 21):

"The trial was registered on www.clinicaltrials.gov on 13 February 2018 before enrolling the first patient in the study (NCT03431181). Initially, the primary outcome was listed as hsTnT at day 7; this error was subsequently corrected on 28 May 2020. Data will not be analyzed until trial follow-up is complete in August 2020."

Some minor comments:

5. Given the similarity with the 65 trial, it is worth considering whether individual patient data meta-analysis has been considered, and if so whether this is worth addressing in this current manuscript.

Response: We are considering but have not definitely planned an updated IPDMA, and have added this to the Statistical Analysis (page 21):

"An updated IPDMA[18] including data from existing trials,[16 17] the 65 trial,[22] and the current trial is under consideration."

6. I'm curious why study participants readmitted to ICU within the same hospital episode did not resume their treatment allocation (page 14 line 33)? Is this worth clarifying?

Response: We have added a sentence for justification (page 11):

"We do not mandate resumption of the permissive hypotension strategy to enhance trial feasibility, and we anticipate relatively few readmissions overall and rare readmissions before ascertainment of our primary outcome on day 3."

7. I might have missed it but I couldn't see that the specific vasopressor or combination both at baseline and during the study was being reported as described in the data collection section on page 14?

Response: Thank you for pointing out this mission. We have clarified the data collection section (page 15):

"We collect the following data: 1) Baseline data (day 1) – demographics, admitting diagnosis, etiology of hypotension, severity of illness (APACHE II score[50]), vasopressor name, dose and start time, organ dysfunction (SOFA score[23]), comorbidities (including chronic hypertension, coronary, cerebral, or peripheral vascular disease, congestive heart failure, chronic kidney disease, severe cognitive impairment, Clinical Frailty Scale[51], co-enrolment in other prospective observational studies or RCTs; 2) daily data – protocol adherence (hourly MAP while receiving vasopressors and corresponding vasopressor names, doses, and modifications) and relevant co-interventions (fluid balance, inotropes, corticosteroids, life-support interventions, sedation); and 3) primary and secondary outcomes."

8. Is it worth clarifying why day three chosen for the primary outcome? Could a mean daily troponin be of greater value in interpreting cardiac damage over the entire period of exposure?

Response: It is conceivable that a daily troponin (either mean or area under the curve) would be more associated with cardiac damage, but we selected day 3 for a couple of reasons:

- Concern that a longer period of measurement would leave this outcome more vulnerable to the effect of competing risk of death or live discharge from the ICU (see response to Reviewer 1, comments 3-5)
- Concern that daily blood sampling would decrease feasibility by making consent less likely and by increasing trials cost

9. Is there a risk of differential bias resulting from incomplete outcome testing as described on page 17?

Response: Thank you for giving us the opportunity to clarify this point; we have moved it to the outcomes section (page 14):

“We had originally planned to measure additional secondary outcomes but lack resources to do so for each participant. We have described these as planned ancillary studies in online supplementary file S3.”

The outcomes listed in the current protocol will be measured on every participant.

10. Was trial registration prior to enrolment of the first patient? Might be worth making that clear in the manuscript.

Response: We did register the trial before enrolment of the first patient and now make this point explicitly (page 21):

“The trial was registered on www.clinicaltrials.gov on 13 February 2018 before enrolling the first patient in the study (NCT03431181).”

Reviewer #3 Comments to Author:

This is a manuscript outlining a protocol comparing two approaches to blood pressures management in patients over 65 years with vasodilatory hypotension. The comparison is between usual care (mostly vasopressor use to keep MAP>65, but could be as high as 70 or 75 as per treating clinician) and permissive hypotension (allowing a MAP of 60-65).

This protocol overall is well written, although there are some areas that need clarification (see below).

The recently published 65 trial leads to a few important questions about this protocol.
In summary: The 65 trail study had almost 2500 patients ≥65 years who were randomized into well-matched, groups receiving usual care or permissive hypotension using a similar protocol as the proposed OVATION-65 study (lower MAP target of 60-65 mm Hg). There was no difference in 90-day mortality, which was the primary outcome: 41% permissive hypotension vs 43.8% usual care. There was a lower total dose and less time on vasopressors in the permissive hypotension group. Serious adverse events, like renal failure or SVT, were similar among the groups. In conclusion: permissive hypotension appears safe

Response: Thank you for your comment regarding the protocol as well-written.

This leads to two important questions:

1. The protocol is clear that with the publication of the 65 trial the DSMC decided that recruitment for OVATION-65 needed to be halted as there was no more clinical equipoise. In essence this means that this protocol is offered for publication after these decisions were made and that the protocol will

be published after recruitment has been completed. This may be an editorial decision, but am wondering to what degree a protocol publication (No matter how transparent this process has been described) adds value to the clinical trials registration which was done a priori, when recruitment is complete.

Response: We understand your point and we would have preferred to publish the protocol before the end of recruitment. Although recruitment is complete, patient follow-up is ongoing, and no analyses have been performed.

As we wrote in our original cover letter:

"This protocol is for a randomized trial of permissive hypotension (target mean arterial pressure 60-65 mmHg) vs. usual care in critically ill patients receiving vasopressors for a vasodilatory cause of hypotension. Our original plan was to enroll 200 patients (likely to take until July 2020), but today the Data Safety Monitoring Committee advised termination of enrollment due to completion of a similar trial (PMID 32049269) that showed reduced mortality in the permissive hypotension arm in an adjusted analysis. Data collection will be complete for our trial in August 2020, and we therefore believe that the timing of our protocol submission remains consistent with BMJ Open policies."

Moreover, as noted by reviewer 2 in his comments, the publication of the full protocol, as opposed to the limited information registered on clinicaltrials.gov, "would allow replication of all key components of study and conduct and will provide a valuable reference document against which to evaluate the final report of the study outcomes."

2. Due to the results of the 65 trial, it will be likely that 'ususal practice' will be converging to the intervention with clinicians being more comfortable running the MAP at 65 or 65-70 (rather than 75-80). As result the separation in MAP between the two groups will possibly be too small to detect any meaningful differences in biomarkers between the two groups. Obviously, the recruitment is nearly complete, but continuing to recruit will likely makes separation between two groups even smaller. Please address/justify

Response: The concern that clinicians would lack equipoise for higher MAP values following publication of the 65 trial was one of the reasons the DSMC recommended stopping enrolment. Given that recruitment in OVATION-65 stopped 8 days after the publication of the 65 trial, we do not think that our results will be influenced by the results of 65. The question of whether usual care has evolved over time, both before the commencement of OVATION-65 and in the same period for patients not enrolled in the trial is being investigated in a separate study.

If the editorial decision is that this protocol is eligible for publication, the following questions are worth addressing in the manuscript.

3. Abstract – the objective sentence misses an outcome. The objective is to ascertain the effect of permissive vs usual care ….. (? Add on biomarkers as outcome)

Response: Thank you. We have revised this sentence (page 3):

"The objective of OVATION-65 (**O**ptimal **VA**sopressor Titra**TION**-**65**) is to ascertain the effect of permissive hypotension (vasopressor titration to achieve MAP 60-65 mmHg) vs. usual care on biomarkers of organ injury in hypotensive patients ≥65 years old."

4. Adequate fluid resuscitation is mentioned in the methods of the abstract, however this needs to be explored in the methods section of the full manuscript. At the moment this is stated as per clinician judgment but were there certain minimum fluid amounts required (1L, 2L, 30ml/kg?) or are specific tools used to quantify (cardiac output monitor, point of care Ultrasound, other). I would strongly recommend to have a) the amount of fluid give prior to starting vasopressors and b) time to start of vasopressor from diagnoisis as a variables being reported

Response: We did not specify a minimum amount of fluid or tools to assess volume status, and have added this point to page 9:

"Aligned with the 65 trial,[22] we do not specify a minimum volume of fluid or specific examinations for volume status prior to the clinical (pre-randomization) decision to commence a vasopressor."

5. The primary outcome needs to have a time point added in the abstract. The manuscript suggests this is 3 days, however the clinical trials registration has 7 days as primary outcome. Please review this discordance between registered protocol and manuscript protocol

Response: We have added the time point of the primary outcome to the abstract (page 3):

"The primary outcome is high-sensitivity troponin T, a biomarker of cardiac injury, on day 3."

Thank you for pointing of the discordance between the protocol registration and this manuscript. See our response to reviewer 2, comment 4, reproduced here.

The entry on clinicaltrials.gov was an error; we did not understand that the time point listed referred to the time of the outcome, as opposed to the last time the outcome was measured. We have corrected the trial registration and have added the following to the manuscript (page 21):

"The trial was registered on www.clinicaltrials.gov on 13 February 2018 before enrolling the first patient in the study (NCT03431181). Initially, the primary outcome was listed as hsTnT at day 7; this error was subsequently corrected on 28 May 2020. Data will not be analyzed until trial follow-up is complete in August 2020."

6. Page 8 – line 10-12 – the fact that the 65 trial did not collect biological samples means you can't comment on biomarkers or hypothesise on pathways. The clinical effect is well described in the 65 trial (mortality, outcomes, AEs). Please rephrase and remove the word 'clinical'

Response: We have revised this sentence (page 8) as follows:

"The 65 trial collected no biological samples, precluding exploration of mechanisms underlying the effect of vasopressor dosing in that trial."

7. Page 8- line 24-25 – Along similar lines, this study cannot be to determine if the intervention compared to usual care reduces harm. This would need an appropriately powered clinical study. This study adds insights by describing biomarkers to provide data to inform new hypotheses. Please rephrase and remove 'reduces harm'

Response: We have revised this sentence (page 8):

"The main objective of OVATION-65 is to determine whether permissive hypotension (MAP 60-65 mmHg) in patients ≥65 years old with a vasodilatory cause of hypotension and receiving vasopressors, compared to usual MAP targets, reduces organ injury as measured by biomarkers."

8. Lactate is a fair biomarker to measure – however there are many reasons this may be elevated and tissue dysoxia is not the only (or most important) cause of raised lactate as many aerobic adrenergic stimulation processes increase lactate. Please address

Response: We have added a sentence to the Secondary outcomes section to address this limitation (page 14):

"We selected lactate as a reasonable measure of tissue hypoxia in critically ill patients but recognize that hyperlactatemia may result from other factors, including aerobic glycolysis, reduced oxidative phosphorylation, and decreased clearance.[46]"

9. There is clear data that peripheral vasopressors (well monitored and needed for < 12-24 hrs) is safe and reasonable – can you comment on whether this is allowed or included (as it is part of usual care in other settings)

Response: We did not mandate vasopressor delivery through a central line and have clarified that on page 12 (see response to question 10).

10. Can you clarify how MAP will be measured – is an arterial line mandated and if so, is there a particular prescribed device and timing of MAP measurement (as MAP can vary beat to beat). The MAP measurements (non-invasive vs invasive) and exact measurement techniques would benefit from more detailed description

Response: MAP values were taken from the nursing vital signs flowsheet and measured by an arterial line (if present) or non-invasive blood pressure cuff otherwise, consistent with usual practice. We have clarified this on page 12-13:

"As per usual care of patients receiving vasopressors, we expect central venous catheters (to avoid extravasation) and arterial catheters (for close MAP monitoring) to be in place for most patients. MAP is measured by an arterial line if present or by a non-invasive blood pressure cuff otherwise; values are taken from the nursing vital signs flowsheet. Peripheral venous lines to deliver vasopressors or non-invasive blood pressure measurements do not constitute protocol deviations, consistent with a pragmatic study design."

11. The comment on consumer engagement reads as a motherhood statement. As the outcomes are primarily biomarkers I wonder to what degree ICU survivors had relevant input. Either remove the statement or add more detail (number of consumers, type of input etc)

Response: We have clarified this section as follows (page 18):

"The protocol was developed with input from 2 ICU survivors (EB and DC), who participated in protocol development meetings, contributed to the selection of 6-month cognitive function as a secondary outcome, and are co-authors of this manuscript."

VERSION 2 – REVIEW

REVIEWER	Paul Young Medical Research Institute of New Zealand
REVIEW RETURNED	01-Jun-2020

GENERAL COMMENTS	I have no further suggestions.

REVIEWER	Gerben Keijzers Gold Coast University Hospital Bond University Griffith Uni
REVIEW RETURNED	01-Jun-2020

GENERAL COMMENTS	I would like to commend the authors for systematically addressing and/or rebutting all comments. My comments have been addressed satisfactorily.

	One minor issue that was not specifically addressed was my recommendation to list a) the amount of fluid given prior to starting vasopressors and b) time to start of vasopressor from diagnoisis as variables being reported. My assumption is that you may not have access to this data , but if you do have this data it would provide additional useful inormation on this topic.

REVIEWER	Ed Litton Fiona Stanley Hospital Perth Western Australia
REVIEW RETURNED	03-Jun-2020

GENERAL COMMENTS	The authors have fully addressed my comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer #3 Comments to Author:

One minor issue that was not specifically addressed was my recommendation to list a) the amount of fluid given prior to starting vasopressors and b) time to start vasopressor from diagnosis as variables being reported. My assumption is that you may not have access to this data, but if you do have access to this data, it would provide additional useful information on this topic.

Response: Thank you for your comment. We do not collect data on the amount of fluid administered prior to starting vasopressors. We do collect data on the time from hospital admission and from ICU admission to the initiation of vasopressors. We have clarified this on paged 15 and 16.

Reviewer #1 Comments to Author:

I have no further suggestion.

Response: Thank you.

Reviewer #2 Comments to Author:

The authors have fully addressed my comments.

Response: Thank you.