PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical examination, critical care ultrasonography and outcomes in the critically ill: cohort profile of the Simple Intensive Care Studies-I
AUTHORS	Hiemstra, Bart; Eck, Ruben; Koster, Geert; Wetterslev, Jorn; Perner, Anders; Pettilä, Ville; Snieder, Harold; Hummel, Yoran; Wiersema, Renske; De Smet, Anne Marie; Keus, Frederik; van der Horst, Iwan; Study Group, SICS

VERSION 1 - REVIEW

REVIEWER	Bernd Saugel Department of Anesthesiology Center of Anesthesiology and Intensive Care Medicine University Medical Center Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg, Germany
REVIEW RETURNED	25-Apr-2017

GENERAL COMMENTS	Thank you very much for the opportunity to review your manuscript " Cohort profile: clinical examination, critical care ultrasonography and outcomes in the critically ill: the Simple Intensive Care Studies-I" (bmjopen-2017-017170). In this manuscript, you report the protocol and cohort profile of a large observational clinical study (including 791 patients so far) aiming at evaluating the diagnostic and predictive value of clinical and haemodynamic variables obtained by physical examination and critical care ultrasound (CCUS). You state to measure both clinical and hemodynamic variables without interfering in patient care, train novices in obtaining values for advanced variables based on CCUS in the intensive care unit, and create an infrastructure for a registry with the flexibility of temporarily incorporating specific (hemodynamic) research questions and variables. You collect the data prospectively in a single university institution after approval by the appropriate review board and registration at clinicaltrials.gov. Overall, the manuscript is very well written. The introduction precisely describes the medical problem and is clearly arranged. The methods are clearly described. Statistical analyses have been adequately applied and the results are clearly described and presented (although this is only a description of the study population). The main conclusions are substantiated by the preliminary results of the study and you adequately discuss weaknesses and strengths of the study. Data presentation in the figures and tables is of acceptable quality. You should, however, more clearly describe the purpose of the paper. You basically report the study protocol and the characteristics of the patients included in your database so far. The paper, therefore, reads like a study protocol ("trials" paper) rather than an

	original research paper. This might be confusing for the reader. You might consider stating the purpose and aim of this paper explicitly at the end of the introduction, at the beginning of the discussion, and in the conclusion section. This can help to structure the paper more clearly and make the message more straightforward.

REVIEWER	Otavio T. Ranzani University of São Paulo, Brazil / University of Barcelona, Spain
REVIEW RETURNED	27-Apr-2017

GENERAL COMMENTS	Hiemstra B, Eck RJ and coworkers described a cohort profile aimed to implement a prospective registry with several aims and potential dynamic inclusion and exclusion of different research questions. The manuscript is well written and the cohort aims are very important to clinical practice. I have some comments below. Thank you to the opportunity to revise your work. 1 - Abstract: the abstract needs a revision to better reflect the manuscript content. For instance, at the end of the abstract, it appears an aim that was not previously reported: “With the included variables, we aim to continuously improve the prediction model for 90-day mortality”. I suggest to the authors specify before the objective to create a prediction model or rephrase this sentence. 2 – Strengths/Limitations: Please, rephrase or expand this sentence “Critical care ultrasound measurements are not obtainable in each patient” 3 - Introduction: the introduction is focused on the additional prognostic contribution of CCUS to other measurements, although several aims/studies described are aiming to investigate agreement between the measures. 4 - The authors obtained Ethical approval, informed consent and etc. However, the authors should better define and discuss which definition their used about the “no interference on patient care”, a term repeatedly over the manuscript. When we do a bedside exam like this (CCUS, in this case), it prompt provides information for the clinical practice. Do the authors mean that this is not an interventional study in the sense that there is not a protocol to be followed after some diagnosis from CCUS? Or CCUS is already a daily practice for all patients in the four units, and so, the no interference refers to spend time on the CCUS that would interfere in the routine practice? One of the items from Table-1 requires a “PEEP-challenge”, which in my opinion could be without any clinical implication, by it may characterize an intervention (as stated in page 14, lines 10-14). 5 - Following the same issue, please discuss the management/feasability and ethics of obtaining an important exam at the bedside and blinding the ICU physicians: “The ICU physicians were blinded for our CCUS measurements”. Are the novices doing clinical assistance too, in the moment of exams were performed? Please, comment. 6 – The authors discussed well the problem with multiplicity. I would suggest to also discuss how the power/sample size will be managed for every ongoing and dynamic research questions.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Bernd Saugel
Institution and Country: Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Competing Interests: None declared

Thank you very much for the opportunity to review your manuscript " Cohort profile: clinical examination, critical care ultrasonography and outcomes in the critically ill: the Simple Intensive Care Studies-I" (bmjopen-2017-017170).

In this manuscript, you report the protocol and cohort profile of a large observational clinical study (including 791 patients so far) aiming at evaluating the diagnostic and predictive value of clinical and haemodynamic variables obtained by physical examination and critical care ultrasound (CCUS). You state to measure both clinical and hemodynamic variables without interfering in patient care, train novices in obtaining values for advanced variables based on CCUS in the intensive care unit, and create an infrastructure for a registry with the flexibility of temporarily incorporating specific (hemodynamic) research questions and variables.
You collect the data prospectively in a single university institution after approval by the appropriate review board and registration at clinicaltrials.gov.

Overall, the manuscript is very well written. The introduction precisely describes the medical problem and is clearly arranged. The methods are clearly described. Statistical analyses have been adequately applied and the results are clearly described and presented (although this is only a description of the study population). The main conclusions are substantiated by the preliminary results of the study and you adequately discuss weaknesses and strengths of the study. Data presentation in the figures and tables is of acceptable quality.

Reply:
We sincerely appreciate these positive comments.

You should, however, more clearly describe the purpose of the paper. You basically report the study protocol and the characteristics of the patients included in your database so far. The paper, therefore, reads like a study protocol ("trials" paper) rather than an original research paper. This might be confusing for the reader. You might consider stating the purpose and aim of this paper explicitly at the end of the introduction, at the beginning of the discussion, and in the conclusion section. This can help to structure the paper more clearly and make the message more straightforward.

Reply:
Thank you for this suggestion. We have now made the purpose of our study clearer.

Reviewer: 2
Reviewer Name: Otavio T. Ranzani
Institution and Country: University of São Paulo, Brazil / University of Barcelona, Spain
Competing Interests: None declared.

Hiemstra B, Eck RJ and coworkers described a cohort profile aimed to implement a prospective registry with several aims and potential dynamic inclusion and exclusion of different research questions. The manuscript is well written and the cohort aims are very important to clinical practice. I have some comments below. Thank you to the opportunity to revise your work.

Reply:

Thank you for acknowledging the importance of this work for clinical practise.

1 - Abstract: the abstract needs a revision to better reflect the manuscript content. For instance, at the end of the abstract, it appears an aim that was not previously reported: “With the included variables, we aim to continuously improve the prediction model for 90-day mortality”. I suggest to the authors specify before the objective to create a prediction model or rephrase this sentence.

Reply:
Thank you for this comment. We have now rephrased the aim of the study and amended this sentence.

2 – Strengths/Limitations: Please, rephrase or expand this sentence “Critical care ultrasound measurements are not obtainable in each patient”

Reply:
Thank you for this comment. We have rephrased and expanded this limitation.

3 - Introduction: the introduction is focused on the additional prognostic contribution of CCUS to other measurements, although several aims/studies described are aiming to investigate agreement between the measures.

Reply:
Thank you for highlighting this ambiguity. In the introduction, we have tried to summarise what is currently known from literature regarding the research question of the basic study and highlighted several shortcomings in previous studies. All sub-studies were listed in this paper to illustrate the study structure. It was never our intention to fully elaborate on the rationale, research questions and study designs of all sub-studies. We have now made this clear at the end of the introduction.

4 - The authors obtained Ethical approval, informed consent and etc. However, the authors should better define and discuss which definition their used about the “no interference on patient care”, a term repeatedly over the manuscript. When we do a bedside exam like this (CCUS, in this case), it prompt provides information for the clinical practice.
Do the authors mean that this is not an interventional study in the sense that there is not a protocol to be followed after some diagnosis from CCUS? Or CCUS is already a daily practice for all patients in the four units, and so, the no interference refers to spend time on the CCUS that would interfere in the routine practice?

Reply:
Thank you for pointing out this unclarity. CCUS is on indication part of routine practice in our department. It is not standard performed in all patients each day. We have now made this clearer in the cohort description section. We have also highlighted the observational nature of our study and that no intervention was used.
We agree that “no interference on patient care” was used repeatedly. We have now deleted or edited several phrases to reduce its repetition.

One of the items from Table-1 requires a “PEEP-challenge”, which in my opinion could be without any clinical implication, by it may characterize an intervention (as stated in page 14, lines 10-14).

Reply:
In our ICU some intensivists use the “PEEP-challenge” as a diagnostic test to assess fluid responsiveness, so that it is routine practice. The “PEEP-challenge” was a sub-study and evaluated as a diagnostic test and is not an (experimental) intervention.

5 - Following the same issue, please discuss the management/feasability and ethics of obtaining an important exam at the bedside and blinding the ICU physicians: “The ICU physicians were blinded for our CCUS measurements”. Are the novices doing clinical assistance too, in the moment of exams were performed? Please, comment.

Reply:
Thank you for this comment. As explained in our reply to comment 4, ICU physicians could use CCUS on indication independent from this study. We therefore consider it ethical not to reveal the measurements obtained for the study purposes. If any possible abnormality was observed by CCUS, an independent qualified intensivist was contacted for judgement of informing the attending intensivist. We have now made this clearer.
The novices who collected the data for the study were involved in routine practice. This has been clarified as well.

6 – The authors discussed well the problem with multiplicity. I would suggest to also discuss how the power/sample size will be managed for every ongoing and dynamic research questions.

Reply:
The aim of this paper was to highlight the design of the entire study structure. All sub-studies need separate detailed descriptions, including sample size considerations, rather than one overall solution or perspective.
The combination of the multiplicity and sample size issues are difficult. We acknowledge that, as a rule of thumb, at least 10 events are necessary for each variable included in the final model. However, it is more important that findings observed in an initial cohort will be validated in a preferably independent, separate cohort. We have added these considerations in the strengths and limitations section.

VERSION 2 – REVIEW

REVIEWER	Otavio T. Ranzani University of São Paulo, Brazil / University of Barcelona, Spain
REVIEW RETURNED	26-May-2017

GENERAL COMMENTS	The authors clarified all points from my previous review. In my opinion, these minor changes improved the readability, importance and clarified the applicability of the SICS Study Group studies. Thank you for the opportunity.