PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Brain Natriuretic Peptide to Predict Successful Liberation from Mechanical Ventilation in Critically Ill Patients: Protocol for a Systematic Review and Meta-Analysis.
AUTHORS	Deschamps, Jean; Webber, Jordan; Featherstone, Robin; Sebastianski, Meghan; Vandermeer, Ben; Senaratne, Janek; Bagshaw, Sean

VERSION 1 – REVIEW

REVIEWER	Professor Anne Greenough Kings College London, Department of Women and Children's Health, School of Life Sciences, Faculty of Life Science and Medicine
REVIEW RETURNED	21-May-2018

GENERAL COMMENTS	This is a proposal for a systematic review of studies assessing BNP as a predictor of extubation. It would be important to divide up the results according to the age of the patients.

REVIEWER	Arnaud W. Thille CHU de Poitiers
REVIEW RETURNED	25-May-2018

GENERAL COMMENTS	Review BMJ open: I read with interest the article by Jean Deschamps and colleagues who detailed a protocol for a systematic review and meta-analysis on the usefulness of natriuretic peptide to predict extubation failure in the ICU. Although in my opinion the usefulness of publication of a protocol for meta-analysis is a low interest, it might nevertheless be interesting if the protocol really provide interesting data in terms of thinking and methodology./ Unfortunately, the present protocol does not answer the different methodological limitations which will be confronted the authors. These are my main concerns: 1- The authors planned to analyze values of natriuretic peptide to weaning success. But using which peptide? BNP or NT-proBNP? Values are completely different this point is absolutely not discussed by the authors. Measured at which time? During the spontaneous breathing trial? After? The next day? Before the trial? The authors are aware that the studies that assessed this topic used sometimes BNP, sometimes NT-proBNP, sometimes at the end of SBT, sometimes before….

2- The authors absolutely not discuss the definition of weaning success. And the term successful liberation of MV is used in the objective. What are we talking about? Successful of a SBT? Successful extubation? A main problem is that the definition is different form a study to another. Extubation failure could be defined by reintubation, or sometimes the use of NIV, sometimes at 48h, sometimes at day 7.

Minor concerns
"We will perform a systematic review and meta-analysis to evaluate the value of BNP during SBT to predict extubation success in patients receiving mechanical ventilation". During? However, some studies assessed BNP values after and not during SBT (1)

"Our objective of this systematic review is to rigorously evaluate the value of BNP measurement during a SBT as a biomarker to predict extubation success among patients receiving mechanical ventilation. We hypothesize that BNP will add incremental predictive value for successful liberation from mechanical ventilation to standard clinical and biochemical parameters assessed during SBT". BNP or nt-proBNP? Which definition of successful from MV? Does it mean patient extubated or able to breathe without the ventilator? I think it is not clear

We will consider all relevant randomized and pseudo-randomized controlled trials; what does pseudo RCT mean?

All methodology detailed in the manuscript is the usual methodology for systematic review and meta-analysis and no specific data are added.

The role of BNP as an additional predictor to SBT for successful extubation is….before in the main objective you use the term liberation from MV, sorry but it is completely different.

References
1.   Grasso S, Leone A, De Michele M, Anaclerio R, Cafarelli A, Ancona G, Stripoli T, Bruno F, Pugliese P, Dambrosio M, Dalfino L, Di Serio F, Fiore T. Use of n-terminal pro-brain natriuretic peptide to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease. Critical care medicine 2007;35:96-105.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1 comments:

1.   This is a proposal for a systematic review of studies assessing BNP as a predictor of extubation. It would be important to divide up the results according to the age of the patients.

We agree with the Reviewer's comment. We are planning to perform subgroup analysis by age, as the data permits. This has been added in the manuscript (page 7, lines 238-244).

Response to Reviewer 2 comments:

1.   The authors planned to analyze values of natriuretic peptide to weaning success. But using which peptide? BNP or NT-proBNP? Values are completely different this point is absolutely not discussed by the authors. Measured at which time? During the spontaneous breathing trial? After? The next day? Before the trial? The authors are aware that the studies that assessed this topic used sometimes BNP, sometimes NT-proBNP, sometimes at the end of SBT, sometimes before….

We appreciate the reviewer's comments. Additionally, we are planning to assess all variations of BNP assays used in the studies selected for inclusion. We will perform pooled analyses of BNP assays of all types initially to increase statistical power given the likely limited number of studies for each type. We acknowledge that a major determinant of BNP rise will be generation, which is dependent on release and DNA mediated production, as well elimination, which is known to vary depending on assays (20-22 min for BNP, 120 min for NT-proBNP). As such, we have decided to limit time to drawing of BNP to within 2 hours from SBT, which corresponds to 5 half-lives of the shortest BNP assay (110 min, rounded to 120 min). This will limit the risk of significant decrease of levels of BNP assays that could give a false negative. Generation of NT-proBNP, being a precursor to BNP which is then cleaved, should not lead to significant change in rate of elevation for the purpose of this study, and would not affect the determination of our time limits. We will perform subgroup analysis of each subtype of BNP if there are sufficient data from studies of each to perform pooled meta-analyses, to assess if one of the assays has better predictive value. We have included comment on this on page 5, lines 164-169 and page 6, lines 170-172.

As well, we acknowledge the variation in techniques used in regards to timing of BNP assays measurements between studies. We propose to initially include all studies that measure BNP assays of all types as long as performed within 120 minutes of the SBT, even if only a pre or a post assay was performed. However, we recognize the complexity of these variations. As such, one of the objectives of our review will be to further described knowledge gaps and set priorities for future work in this area.

2.   The authors absolutely not discuss the definition of weaning success. And the term successful liberation of MV is used in the objective. What are we talking about? Successful of a SBT? Successful extubation? A main problem is that the definition is different form a study to another. Extubation failure could be defined by reintubation, or sometimes the use of NIV, sometimes at 48h, sometimes at day 7.

We appreciate the Reviewer's comments. The primary outcome of interest for our review is success in liberation of a patient from mechanical ventilation. The focus of our review is not on "weaning success" per se or determination of the success of a SBT. We recognize the literature (and CPGs) may use the terms inter-changeably; and as such, we have now defined and included specific mention of capture of data related to "weaning" and "SBT", as provided by each study evaluated (page 6; lines 216-219). We will perform subgroup analyses of the different methods of SBP if there is sufficient data across included studies.

"The primary endpoint will be liberation of MV, as defined in each study. We will consider successful liberation of MV not requiring reintubation or application of new non-invasive ventilation in the 48 hours following initial extubation, but will analyze any additional data after 48 hours as available in studies. SBT success will be as defined in each study, and data on criteria used to define it will be analyzed as available."

With respect to the Reviewer's comment the two different terms (liberation of mechanical ventilation and successful extubation), we recognize these have not been well-defined and may be used inter-changeably at times. We have clarified our use of terminology in the document to better define

liberation from MV, and have corrected any potentially confusing statements to streamline the goals of the study. We have decided to use the definition of the American College of Physician/American Thoracic Society Clinical Practice Guidelines for successful liberation of mechanical ventilation: a patient not requiring reintubation or application of new non-invasive ventilation in the 48 hours following initial extubation.

3.   "We will perform a systematic review and meta-analysis to evaluate the value of BNP during SBT to predict extubation success in patients receiving mechanical ventilation". During? However, some studies assessed BNP values after and not during SBT (1)

We have now clarified this statement to reflect use of BNP concomitant with SBT (recognizing it may be measure before, during or after) (page 4; line 123-126 and page 5; line 166-169).

4.   "Our objective of this systematic review is to rigorously evaluate the value of BNP measurement during a SBT as a biomarker to predict extubation success among patients receiving mechanical ventilation. We hypothesize that BNP will add incremental predictive value for successful liberation from mechanical ventilation to standard clinical and biochemical parameters assessed during SBT". BNP or nt-proBNP? Which definition of successful from MV? Does it mean patient extubated or able to breathe without the ventilator? I think it is not clear

Please see responses to Comments 1-3.

5.   We will consider all relevant randomized and pseudo-randomized controlled trials; what does pseudo RCT mean?

To clarify, we use the term pseudo-randomized controlled trials to refer to studies in which patients are randomized according to methods other than random allocation sequences, such as patient characteristics or other measures (i.e., by date of inclusion in study, alternate days inclusion, date of birth, etc.). This leads to each patient not having the same chance as others to be included in each of the study groups. We have clarified this on page page 5, lines 155-159.

6.   All methodology detailed in the manuscript is the usual methodology for systematic review and meta-analysis and no specific data are added.

We appreciate the reviewer's comments. Given that this is a protocol for a systematic review, there is no available baseline data that was acquired in the process and can be reported in this submission.

7.   The role of BNP as an additional predictor to SBT for successful extubation is….before in the main objective you use the term liberation from MV, sorry but it is completely different.

The Reviewer's comment is correct. We have now tried to clarify that our primary outcome of interest is successful liberation from MV and not "successful extubation" per se. We have corrected this throughout the manuscript.