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)	Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review
AUTHORS	Bernardes Neto, Saint Clair; Torres, Rodrigo; Lima, Íllia; Resqueti, Vanessa; Fregonezi, Guilherme

VERSION 1 – REVIEW

REVIEWER	Orlikowski David APHP INSERM France
REVIEW RETURNED	09-Apr-2019

GENERAL COMMENTS	Really interesting and practical protocol that will be helpful to boult recommandations fro these population. I have few comments: page 3, line 39, the sentence Intensive care unit admission may be a cause of neuromuscular disorders. Do the authors mean neuromuscular weakness; There is an ambiguity because neuromuscular disease are defined as progressive disease that could be different than ICU acquired weakness. Line 59 please if Guillain bArré syndrome and myasthenia gravis are considered add this reference for weaning:Chevrolet JC(1), Deléamont P. Repeated vital capacity measurements as predictive parameters for mechanical ventilation need and weaning success in the Guillain-Barré syndrome.Rev Respir Dis. 1991 Oct;144(4):814-8. `page 4 the problem of bulbar impairment and cough weakness are not discuss. The problems are ver y important and may impact weaning and eventually decanulation. Please add a paragraph about.

REVIEWER	Erika MacIntyre University of Alberta
REVIEW RETURNED	14-Apr-2019

GENERAL COMMENTS	I have the following concerns Page 3 Line 17. strength (2) is not a strength. Most studies are undertaken by experts in the field. One could argue that this may introduce bias Line 25. First sentence is confusing. Please clarify Line 37. Second sentence is confusing and repetitive Line 45. First sentence is repetitive Page 4

	Second paragraph. Why are we talking about the elderly now? Confusing Third paragraph. Confusing. Do you mean 3 separate attempts at extubation with re-intubation. That would end up being longer than 7 days. I don't know that this is a widely known or accepted definition of "difficulty weaning" What also is not clearly discussed is that many of these patients would extubate to non-invasive ventilation. This would be considered a success in this population as many of these individuals would be non-invasively ventilated prior to admission or will eventually progress to NIV later in the stages of disease. The last paragraph of the introduction (page 5) is confusing. What are the authors trying to say? Once again, it is unclear if the use of Non-invasive ventilation post extubation is considered a success. Page 5 Interventions The authors describe the use of SBT to determine readiness for extubation however many patients with NMD will fail SBT but may still be ready to extubate to NIV. How with this be addressed? I don't believe that SBT the most appropriate tool in this case to determine readiness for extubation. It should likely be that this initial reason for intubation (pneumonia, sepsis, etc…) has resolved Comparators I am not entirely clear what the authors are getting at here. Also they categorize outcomes as simple (which makes sense), difficult (3 attempts in 1 week would suggest that the patient is extubated and re-intubated almost daily which I don't think is realistic) and prolonged (other definitions have considered prolonged to be >14 days or >21 days, not >7day) Language. I am unclear. Are non-English language articles actually being included? Page 6 line 50 is a double negative The search strategy does seem adequate and thorough. Can this section be condensed (seems a bit long) Page 7 line 49. I am not clear about the translation aspect. Will all languages be included? I don't see how that will be possible? Who is translating? Page 8 I don't think it is necessary to list all of the domains and go into detail about bias. (line 6-25) "Dealing with missing data". Is this section necessary? This should

	be captured in how the studies are scored. Page 9 Assessment of reporting bias. Should this not be captured in the "Risks of Bias individual studies section"? "Data synthesis". The authors are once again discussing heterogeneity. They already talked about heterogeneity in the "assessment of heterogeneity" section Page 10 I don't think the authors will have enough studies to perform subgroup analysis and I am uncertain what they are trying to look at when performing subgroup analysis. Overall the authors really seem to go on and on about the methodological quality assessment. This should be evaluated using a scoring system (like Ottawa Newcastle, or Downs and Black. There are others as well) I think most of the paper should be more concise. I do think work is needed in this area. There really are no clear guidelines and weak evidence to guide clinicians in this are so a it is a study that is worthwhile undertaking.

REVIEWER	Yuki Kataoka Hyogo Prefectural Amagasaki General Medical Center
REVIEW RETURNED	16-May-2019

GENERAL COMMENTS	Overall Evaluation: Thanks for giving me to review this manuscript. Neto et al. wrote a protocol for a systematic review. They will investigate "the effects of different weaning protocols in individuals with NMD receiving invasive MV in weaning success, duration of weaning, duration of stay in the ICU, duration of hospital stay and ICU mortality." This is a well-written manuscript. However, there are several methodological aspects the warrant further clarification may be indicated. Major Authors should refer to PRISMA-P and attach the checklist as a supplemental table. Authors should include Conclusion section. p3 line 10 Ethics and dissemination This statement should include the ethical consideration of this protocol itself. p3 line 17 (2) the interaction of several professionals with experience in mechanical ventilation, in NMD and in systematic reviews Authors did not refer to this point in the method section. In Introduction section, authors explained the general statements of

weaning, however, authors did not mention the NMD specific weaning strategy, which is the "intervention" of this review.

p 5 line 8
quasi-RCTs (studies with different methods for allocation). Other study types, such as non-randomised trials
Authors should explain the detailed difference between quasi-RCTs and non-randomized trials.

p5 line 17
adults (above sixteen years old)
Authors should clarify the reason for this cut-off point.

p 5 line 52
The protocols will also be compared in relation to the classification of weaning outcomes, in order to identify the wich protocols develop better outcomes. Simple – successful after first attempt; Difficult – require up to three attempts (or less than 7 days to reach success); Prolonged – require more than 7 days to reach success).
Why authors refer for the outcome in Comparators section?

p 6 line 37
We will search all databases from their inception to the present,
Authors should give specific names to clarify the appropriateness of information sources.

p 8 line 49 Unit of analysis issues
I think researchers will be able to conduct cluster randomized trials for weaning protocols. Authors should clarify this point.

Assessment of reporting biases
Why authors search trial registries? They also will be able to assess the information of unpublished trials.

p9 line 38
We will perform a sensitivity analysis with a fixed-effect model.
If they conduct this sensitivity analysis, the confidence interval would be narrower. What is the purpose of this analysis?

p10 line 16
Subgroup analysis and investigation of heterogeneity
Subgroup analysis should be done based on the participants or intervention. Why they refer to the outcome?

p10 line 31
1. Repeat the analysis by excluding any unpublished studies.
This analysis would lead to the "publication bias".

Minor
p7 line 22, 40, 47,59 RCT=>RTC?

p10 line 46
In the present protocol of systematic review and in the subsequent systematic review there was no and there will be no involvement of patients or public.

The sentence would be broken.

REVIEWER	Helen Morgan Cardiff University UK
REVIEW RETURNED	23-May-2019

GENERAL COMMENTS	This is a well structured review protocol incorporating the key methodological requirements for conducting a systematic review and meta-analysis. There are some methodological amendments that I suggest the authors consider, some of which will help limit publication bias. It is not clear that the search strategy will be effective at identifying all the literature. I would suggest that the authors include a librarian or information specialist in this review to ensure that the searches are adequately conducted. The authors should refer to the PRESS Peer Review of Electronic Search Strategies checklist which provides detail on designing an effective search strategy e.g. including Medical Subject Headings. I would expect to see a comprehensive search strategy for one database, preferably Medline, documented in the protocol possibly as supplementary information. Will the Medline search incorporate the segments: 'Epub Ahead of Print and In-Process' to ensure recently published studies are identified? Consider, if authors have access, one other database such as Web of Science (segments: Science citation Index and Conference Proceedings Citation Index- Science) or Scopus. Citation tracking, using Scopus or Web of Science or Google Scholar) is also a very useful supplementary search method to identify other studies. When the authors write the final systematic review publication please can they ensure that they are explicit in listing all information sources to ensure reproducibility and transparency.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 - Orlikowski David
Dear Reviewer, thanks a lot for your comments. After the review the following adjustments were made:
Reviewer 1: I have few comments: page 3, line 39, the sentence Intensive care unit admission may be a cause of neuromuscular disorders. Do the authors mean neuromuscular weakness; There is an ambiguity because neuromuscular disease are defined as progressive disease that could be different than ICU acquired weakness.
Authors: The difference between acquired ICU muscle weakness and the progressive weakness of the neuromuscular disease was enhanced on page 3 (line 39).
Reviewer 1: Line 59 please if Guillain bArré syndrome and myasthenia gravis are considered add this reference for weaning:Chevrolet JC(1), Deléamont P. Repeated vital capacity measurements as predictive parameters for mechanical ventilation need and weaning success in the Guillain-Barré syndrome.Rev Respir Dis. 1991 Oct;144(4):814-8.
Authors: The reference of CHEVROLET JC (1991) on weaning in Guillain Barre and Myasthenia Gravis in line 59 was included.

Reviewer 1: page 4 the problem of bulbar impairment and cough weakness are not discuss. The problems are ver y important and may impact weaning and eventually decanulation. Please add a paragraph about.
Authors: A paragraph was created on page 4 on bulbar impairment and cough weakness, with its impact on weaning and decannulation.

Reviewer 2 - Erika MacIntyre
Dear Reviewer, thanks a lot for your comments. After the review the following adjustments were made:
Reviewer 2: Page 3 Line 17. strength (2) is not a strength. Most studies are undertaken by experts in the field. One could argue that this may introduce bias.
Authors: Strength (2) in page 3 (line 17) was withdraw from the text.
Reviewer 2: Line 25. First sentence is confusing. Please clarify.
Authors: The sentence in Page 3 (line 25) was written again.
Reviewer 2: Line 37. Second sentence is confusing and repetitive and Line 45. First sentence is repetitive.
Authors: The sentences in Page 3 (line 37 and line 45) were written again and organized.
Reviewer 2: Page 4. Second paragraph. Why are we talking about the elderly now? What also is not clearly discussed is that many of these patients would extubate to non-invasive ventilation. This would be considered a success in this population as many of these individuals would be non-invasively ventilated prior to admission or will eventually progress to NIV later in the stages of disease.
Authors: The second paragraph of Page 4 brings the elderly just as an example of difficult weaning populations, such as chronic diseases ones. The paragraph was written again to clarify this.
Reviewer 2: Third paragraph. Confusing. Do you mean 3 separate attempts at extubation with re-intubation. That would end up being longer than 7 days. I don't know that this is a widely known or accepted definition of "difficulty weaning".
Authors: The third paragraph definition of difficult weaning is related to three spontaneous breathing tests with failure or even with success but with necessity to re-intubation within 48 hours after extubation. If that takes longer than 7 days it would be considered as prolonged weaning. This definition is commonly used in the ICU.
Reviewer 2: The last paragraph of the introduction (page 5) is confusing. What are the authors trying to say? Once again, it is unclear if the use of Non-invasive ventilation post extubation is considered a success.
Authors: The patients that are extubated to non-invasive ventilation are not included in this protocol since they are not able to be weaning from mechanical ventilation. This was corrected in the last paragraph on Introduction.
Reviewer 2: Interventions. The authors describe the use of SBT to determine readiness for extubation however many patients with NMD will fail SBT but may still be ready to extubate to NIV. How with this be addressed? I don't believe that SBT the most appropriate tool in this case to determine readiness for extubation. It should likely be that this initial reason for intubation (pneumonia, sepsis, etc…) has resolved.
Authors: The interventions (in page 5) will be considered just the use of SBT as an indicator of readiness for extubation in this protocol. The patients that do not tolerate the SBT and are addressed to NIV will not be included in this review. The resolution of initial reason for intubation is one of the clinical parameters to be considered to perform the SBT.
Reviewer 2: I am not entirely clear what the authors are getting at here. Also they categorize outcomes as simple (which makes sense), difficult (3 attempts in 1 week would suggest that the patient is extubated and re-intubated almost daily which I don't think is realistic) and prolonged (other definitions have considered prolonged to be >14 days or >21 days, not >7day)
Authors: The comparators will be performed among the 4 described protocols, regarding the success or failure of weaning. Afterwards, an analysis will be made of the retrospective results of weaning type (simple, difficult or prolonged) according to the proposed classification used in the study.

Reviewer 2: Language. I am unclear. Are non-English language articles actually being included?
Authors: There will be no restrictions on language of publications.
Reviewer 2: Page 6, line 50 is a double negative.
Authors: Line 50 (Page 6) was corrected.
Reviewer 2: The search strategy does seem adequate and thorough. Can this section be condensed (seems a bit long).
Authors: The search strategy was relatively extensive due to the large number of NMDs that will be used as synonyms to identify the maximum number of papers on the subject, even if they deal with a single specific condition.
Reviewer 2: Page 7, line 49. I am not clear about the translation aspect. Will all languages be included? I don't see how that will be possible? Who is translating?
Authors: In the authors group we have people that can translate studies from English, Portuguese, Spanish, Italian and French. If there are studies in other language, official translators will be contacted to translate the articles.
Reviewer 2: I don't think it is necessary to list all of the domains and go into detail about bias. (line 6-25)
Authors: The subgroup analysis was included in the expectation that we can find some studies that, due to the profile of the patients proposed for the study, evaluate specific conditions of difficult or prolonged weaning, or between adults and children.
Reviewer 2: "Dealing with missing data". Is this section necessary? This should be captured in how the studies are scored.
Authors: The "Dealing with missing data" section has been withdrawn and the missing data will be considered within how the studies are scored.
Reviewer 2: Page 9. Assessment of reporting bias. Should this not be captured in the "Risks of Bias individual studies section"?
Authors: The "Assessment of reporting biases" was transferred to the "Risk of Bias individual studies" section.
Reviewer 2: "Data synthesis". The authors are once again discussing heterogeneity. They already talked about heterogeneity in the "assessment of heterogeneity" section.
Authors: The first paragraph of "Data synthesis" section has been withdrawn.

Reviewer 3 - Yuki Kataoka

Dear Reviewer, thanks a lot for your comments. After the review the following adjustments were made:
Reviewer 3: Authors should refer to PRISMA-P and attach the checklist as a supplemental table.
Authors: The PRISMA-P checklist has been included with the corresponding pages.
Reviewer 3: Authors should include Conclusion section.
Authors: a Conclusion section was added at the end of the protocol.
Reviewer 3: Ethics and dissemination: This statement should include the ethical consideration of this protocol itself.
Authors: Formal ethical approval will not be required as it will be a systematic review, but the authors emphasized this and highlighted that included studies require ethical approval.
Reviewer 3: In Introduction section, authors explained the general statements of weaning, however, authors did not mention the NMD specific weaning strategy, which is the "intervention" of this review.
Authors: In the Introduction section the protocols elected to be studied in this protocol are described in page 4 (lines 16 – 26). In NMD another kind of weaning strategy is extubating the patient to NIV (described in the last paragraph of Introduction) but it was not included as an intervention for this protocol.
Reviewer 3: p 5 line 8 - quasi-RCTs (studies with different methods for allocation). Other study types, such as non-randomised trials. Authors should explain the detailed difference between quasi-RCTs and non-randomized trials.
Authors: The page 5 (line 8) was written again.

Reviewer 3: p5 line 17 - adults (above sixteen years old). Authors should clarify the reason for this cut-off point.
Authors: The age of sixteen years old or above was determined for classifying adult patients as similar to several articles, because this is one of the decisions taken in many ICUs due to the high and weight of these patients.
Reviewer 3: p 5 line 52 - The protocols will also be compared in relation to the classification of weaning outcomes, in order to identify the wich protocols develop better outcomes. • Simple – successful after first attempt; • Difficult – require up to three attempts (or less than 7 days to reach success); • Prolonged – require more than 7 days to reach success). Why authors refer for the outcome in Comparators section?
Authors: The outcomes used in page 5 (line 52) will not be studied as an outcome of this review, but rather will be identified so that a comparison can be made between these types of weaning.
Reviewer 3: p 6 line 37 - We will search all databases from their inception to the present. Authors should give specific names to clarify the appropriateness of information sources.
Authors: Page 6 (line 37) was written again with specific dates
Reviewer 3: p8 line 49 Unit of analysis issues - I think researchers will be able to conduct cluster randomized trials for weaning protocols. Authors should clarify this point.
Authors: Page 8 (line 49): this subsection was included to reinforce that the intervention chosen for this protocol is not addressed in crossover studies, where several interventions are done in sequence and then compared.
Reviewer 3: Assessment of reporting biases - Why authors search trial registries? They also will be able to assess the information of unpublished trials.
Authors: Page 9 (line 30): the databases of Trials Registration will be searched to identify trials that were held, carried out and have been published in full.
Reviewer 3: p9 line 38 - We will perform a sensitivity analysis with a fixed-effect model. If they conduct this sensitivity analysis, the confidence interval would be narrower. What is the purpose of this analysis?
Authors: Page 9 (line 38): the purpose of this analysis was to verify the possibility of an accurate meta-analysis, and if it were not possible to direct to a narrative synthesis without the meta-analysis.
Reviewer 3: p10 line 16 - Subgroup analysis and investigation of heterogeneity. Subgroup analysis should be done based on the participants or intervention. Why they refer to the outcome?
Authors: Page 10 (line 16): the populations will be also analyzed in subgroups, if possible, according to the kind of weaning not as an outcome, but as a classification of subgroup. The same will be carried out for the age. And in each subgroup analysis the primary and secondary outcomes will be compared.
Reviewer 3: p10 line 31 - 1. Repeat the analysis by excluding any unpublished studies. This analysis would lead to the "publication bias".
Authors: Page 10 (line 31): the (1) sensitivity analysis was withdraw.
Reviewer 3: p7 line 22, 40, 47,59 RCT=>RTC?
Authors: Page 7 (line 22): the author initials (RTC) was corrected in the whole text.
Reviewer 3: p10 line 46 - In the present protocol of systematic review and in the subsequent systematic review there was no and there will be no involvement of patients or public. The sentence would be broken.
Authors: Page 10 (line 46): the sentence was written again.

Reviewer 4 – Helen Morgan

Dear Reviewer, thanks a lot for your comments. After the review the following adjustments were made:
Reviewer 4: It is not clear that the search strategy will be effective at identifying all the literature. I would suggest that the authors include a librarian or information specialist in this review to ensure that the searches are adequately conducted.

Authors: The author Dr. Illia NDF Lima is a specialist in systematic reviews, with experience in search strategies, having conducted the search in different reviews.
Reviewer 4: Will the Medline search incorporate the segments: 'Epub Ahead of Print and In-Process' to ensure recently published studies are identified?
Authors: Search will incorporate the segment “Epub Ahead of Pring and In-Process” in the Medline.
Reviewer 4: When the authors write the final systematic review publication please can they ensure that they are explicit in listing all information sources to ensure reproducibility and transparency.
Authors: At the time of publication all the information sources will be listed.
Reviewer 4: Consider, if authors have access, one other database such as Web of Science (segments: Science citation Index and Conference Proceedings Citation Index- Science) or Scopus. Citation tracking, using Scopus or Web of Science or Google Scholar) is also a very useful supplementary search method to identify other studies.
Authors: Web of Science and Scopus have been added to the protocol.

VERSION 2 – REVIEW

REVIEWER	Erika MacIntyre University of Alberta, Canada
REVIEW RETURNED	23-Jul-2019

GENERAL COMMENTS	I have reviewed the updated manuscript with a focus on the issues that I previously raised. I have included my original comments, the authors reply and then a new set of comments/suggestions. Reviewer 2: Line 25. First sentence is confusing. Please clarify. Authors: The sentence in Page 3 (line 25) was written again. Reviewer 2: This is fine. One grammatical error. Might I suggestion “populations” instead of “kind of patient” Reviewer 2: Line 37. Second sentence is confusing and repetitive and Line 45. First sentence is repetitive. Authors: The sentences in Page 3 (line 37 and line 45) were written again and organized. Reviewer 2:This is better. Still some grammatical errors (sentence is too long) Reviewer 2: Third paragraph. Confusing. Do you mean 3 separate attempts at extubation with re-intubation. That would end up being longer than 7 days. I don’t know that this is a widely known or accepted definition of “difficulty weaning”. Authors: The third paragraph definition of difficult weaning is related to three spontaneous breathing tests with failure or even with success but with necessity to re-intubation within 48 hours after extubation. If that takes longer than 7 days it would be considered as prolonged weaning. This definition is commonly used in the ICU. Reviewer 2: “failure of initial weaning” is confusing. Is this then failure of SBT or extubation failure (re-intubation within 48 hours). I agree with the definition but still needs a bit of clarity Reviewer 2: The last paragraph of the introduction (page 5) is confusing. What are the authors trying to say? Once again, it is unclear if the use of Non-invasive ventilation post extubation is considered a success. Authors: The patients that are extubated to non-invasive ventilation are not included in this protocol since they are not able to be weaning from mechanical ventilation. This was corrected in the last

	paragraph on Introduction. Reviewer 2:I still find this paragraph confusion. Perhaps you should just cut it and make sure the role of NIV is clearly defined in your outcomes. Is extubation to NIV in a neuromuscular population considered success or failure? Reviewer 2: The conclusion is new and highly problematic. You are already introducing bias by saying “probably pressure support”. You cant’s state that in you conclusion as you do not know that yet. Is it common to have a conclusion in a protocol?

REVIEWER	Yuki KATAOKA Hyogo Prefectural Amagasaki General Medical Center
REVIEW RETURNED	09-Jul-2019

GENERAL COMMENTS	The authors generally respond to my concerns, but some concerns remain. Reviewer 3: p8 line 49 Unit of analysis issues - I think researchers will be able to conduct cluster randomized trials for weaning protocols. Authors should clarify this point. Authors: Page 8 (line 49): this subsection was included to reinforce that the intervention chosen for this protocol is not addressed in crossover studies, where several interventions are done in sequence and then compared. I can show an example of a cluster randomized trial to investigate the protocolized weaning. https://clinicaltrials.gov/ct2/show/NCT00157287 Authors should reconsider this point. Reviewer 3: p9 line 38 - We will perform a sensitivity analysis with a fixed-effect model. If they conduct this sensitivity analysis, the confidence interval would be narrower. What is the purpose of this analysis? Authors: Page 9 (line 38): the purpose of this analysis was to verify the possibility of an accurate meta-analysis, and if it were not possible to direct to a narrative synthesis without the meta-analysis. My question was the reason to choose fixed-effect model as sensitivity analysis. For example, if authors observe precise results from the main analysis using random effects model, authors would observe narrower confidence intervals from sensitivity analysis. Is that meaningful? If authors observe imprecise results from the main analysis and precise results from sensitivity analysis, how they explain it?

REVIEWER	Dr Helen E Morgan Cardiff University Wales UK
REVIEW RETURNED	02-Aug-2019

GENERAL COMMENTS	I believe that the authors have addressed reviewers comments and this protocol should be accepted.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2 - Erika MacIntyre

Dear Reviewer, thanks a lot for your comments. After the review the following adjustments were made:

Reviewer 2.1: This is fine. One grammatical error. Might I suggestion “populations” instead of “kind of patient”

- Reviewe 2: Line 25. First sentence is confusing. Please clarify.
- Authors: The sentence in Page 3 (line 25) was written again.

Authors: It was changed “kind of patient” for “population.

Reviewer 2.1: This is better. Still some grammatical errors (sentence is too long).

- Reviewer 2: Line 37. Second sentence is confusing and repetitive and Line 45. First sentence is repetitive.
- Authors: The sentences in Page 3 (line 37 and line 45) were written again and organized.

Authors: The sentence was reviewed and divided in smaller sentences.

Reviewer 2.1: “failure of initial weaning” is confusing. Is this then failure of SBT or extubation failure (re-intubation within 48 hours). I agree with the definition but still needs a bit of clarity.

- Reviewer 2: Third paragraph. Confusing. Do you mean 3 separate attempts at extubation with re-intubation. That would end up being longer than 7 days. I don’t know that this is a widely known or accepted definition of “difficulty weaning”.
- Authors: The third paragraph definition of difficult weaning is related to three spontaneous breathing tests with failure or even with success but with necessity to re-intubation within 48 hours after extubation. If that takes longer than 7 days it would be considered as prolonged weaning. This definition is commonly used in the ICU.

Authors: The sentence was reviewed and rewritten to clarity the definition.

Reviewer 2.1: still find this paragraph confusion. Perhaps you should just cut it and make sure the role of NIV is clearly defined in your outcomes. Is extubation to NIV in a neuromuscular population considered success or failure?

- Reviewer 2: The last paragraph of the introduction (page 5) is confusing. What are the authors trying to say? Once again, it is unclear if the use of Non-invasive ventilation post extubation is considered a success.
- Authors: The patients that are extubated to non-invasive ventilation are not included in this protocol since they are not able to be weaning from mechanical ventilation. This was corrected in the last paragraph on Introduction.

Authors: Extubation to NIV is not considered success. It is a protocol that can be used for some NMD as a weaning procedure. But in this article it will not be considered as a weaning strategy, because we are using the SBT as a decision point for the extubation. The last paragraph of introduction was rewritten.

Reviewer 2.1: The conclusion is new and highly problematic. You are already introducing bias by saying “probably pressure support”. You cant’s state that in you conclusion as you do not know that yet.

Is it common to have a conclusion in a protocol?

Authors: The conclusion was not part of the article at the first version, but it was a section asked for by the other reviewers.

But it was rewritten taking out the bias of deducing that a particular protocol (Pressure Support) will be superior.

Reviewer 3 - Yuki Kataoka

Dear Reviewer, thanks a lot for your comments. After the review the following adjustments were made:

Reviewer 3.1: I can show an example of a cluster randomized trial to investigate the protocolized weaning.

https://clinicaltrials.gov/ct2/show/NCT00157287

Authors should reconsider this point.

- Reviewer 3: p8 line 49 Unit of analysis issues - I think researchers will be able to conduct cluster randomized trials for weaning protocols. Authors should clarify this point.

- Authors: Page 8 (line 49): this subsection was included to reinforce that the intervention chosen for this protocol is not addressed in crossover studies, where several interventions are done in sequence and then compared.

Authors: We have considered this point and decided to follow the orientation to include cluster randomized trials if we are able to find it.

Reviewer 3.1: My question was the reason to choose fixed-effect model as sensitivity analysis.

For example, if authors observe precise results from the main analysis using random effects model, authors would observe narrower confidence intervals from sensitivity analysis. Is that meaningful? If authors observe imprecise results from the main analysis and precise results from sensitivity analysis, how they explain it?

- Reviewer 3: p9 line 38 - We will perform a sensitivity analysis with a fixed-effect model. If they conduct this sensitivity analysis, the confidence interval would be narrower. What is the purpose of this analysis?

- Authors: Page 9 (line 38): the purpose of this analysis was to verify the possibility of an accurate meta-analysis, and if it were not possible to direct to a narrative synthesis without the meta-analysis.

Authors: We have considered this point and decided to perform just randomized effect for sensitivity analysis, especially since we will probably find groups with few individuals.

Reviewer 4 – Helen Morgan

Dear Reviewer, thanks a lot for your comments and suggestions.

Reviewer 4: I believe that the authors have addressed reviewers comments and this protocol should be accepted.

VERSION 3 – REVIEW

REVIEWER	Yuki KATAOKA Hyogo Prefectural Amagasaki General Medical Center
REVIEW RETURNED	10-Sep-2019

GENERAL COMMENTS	Authors responded to my questions appropriately.