Author's response to reviews

Title: Effects of adaptive servo-ventilation therapy on cardiac function and remodeling in patients with chronic heart failure (SAVIOR-C): study protocol for a randomized controlled trial

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Author's response to reviews: see over
Professor Doug Altman  
Editor-in-Chief, Trials  

December 2, 2014  

Re: Submission of the revised manuscript (1691147314222353)  

Dear Professor Altman:  

I appreciate your e-mail dated November 7, 2014, that conveyed the valuable comments from you and two reviewers. I carefully prepared the replies to the comments on a comment-by-comment basis and the revised manuscript with colored amendments.  

I do expect that the replies be satisfactory for you and the reviewers and the revised manuscript be finally acceptable for publication in your journal.  

Sincerely,  

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Editorial requests:

1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format___________: study protocol for a randomized controlled trial.

I amended the title and subtitle formats in accordance with your kind suggestion and with the styles of the published articles in the “Study Protocol” Category of your journal.

2. Please edit your ethics statement in the Methods section to read that ethical approval 'has been obtained'.

In response to your valuable comment, I amended the wording in line 19 on page 8 of the revised manuscript as follows: “The present study has been approved by Ethical Review Board...”

3. Please move your additional file title section below the reference list.

I followed your valuable instruction.

Please also ensure that your revised manuscript conforms to the journal style (http://www.trialsjournal.com/info/instructions/). It is important that your files are correctly formatted.

In response to your valuable instructions, I made required amendments in an attempt to precisely comply with the journal style in reference to published articles in your journal. I expect that you find the revised manuscript satisfactory for the journal style.
Reviewer 1’s comments

I carefully prepared the replies to your valuable comments on a comment-by-comment basis and indicated the amendments with red characters in the revised manuscript.

Major Compulsory Revisions: no remarks

Minor Essential Revisions:

- change title. "using an innovative ventilator" is redundant.

I deleted “using an innovative ventilator” from the title as per your comment.

- Abstract: the first sentence is too long. It must be rephrased in at least two shorter parts.

As per your valuable suggestion, I divided the first sentence into two parts and duly relocated phrases to obtain better readability in lines 3 to 6 on page 3 of the revised manuscript.

- background: line 6: and not a few -->and often, patients ...

I appreciate your suggestion to use “often” in this sentence and rephrased the wording to “and are often and” in line 6 on page 5 of the revised manuscript, i.e., not using “patients” because the subject of this sentence is “patients.”

- background: line 12: beneficial not only for

The construction of “not only ... but also ...” precedes just before this wording. Therefore, I decided to replace this construction with another of “both ... and ...” in lines 12 on page 5 of the revised manuscript.

- background: line 20 and 21: to use on the long-term, due to different problems, ...

I am sorry for the misleading nature of the original wording. In consideration of your suggestion, I rephrased it to “to use for a long period” in line 2 on page 6 of the revised manuscript.
- background: 3rd paragraph: here a reference to a paper or editorial could be given describing the technical evolution in ASV devices during the last years (ASV, ASV bilevel, ASV trilevel) in line 10 on page 6 of the revised manuscript.

I added the following article as per your valuable suggestion: “Teschler H, Döhring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med* 2001, 164:614-619.” Since this article was newly inserted as reference #3 in the References Section, I correctly reordered reference numbers in the entirety of the revised manuscript.

- background: 3rd paragraph: rephrase last sentence: contractility, induces cardiac reverse remodeling, suppresses sympathetic nerve activity, improves left ventricular ejection fraction (LVEF), reduces brain ...

I fully agree with you in that prior studies have described that ASV therapy potentially improves LVEF, induces cardiac reverse remodeling, suppresses sympathetic nerve activity, and reduces BNP. However, SAVIOR-C is “confirmatory” in nature for our prior study SAVIOR-R; namely, SAVIOR-C lays emphasis on “the assessment of the effects of ASV therapy on left ventricular contractility and remodeling in patients with mild to severe CHF.” Therefore, I am willing to keep this sentence unchanged and would highly appreciate your leniency.

- Methods/Design: line 5: of an ASV group and a control group

To my knowledge, the definite article is required in describing “a” group even at its first appearance in the text. Therefore, I am willing to keep “the ASV group” and “the control group” unchanged and would highly appreciate your leniency.

- Methods/Design: line 7: at week 12 of the study, on the day of study discontinuation or on the day of ...

I amended the sentence as per your suggestion in lines 7 to 8 on page 8 of the revised manuscript.
- Methods/Design: line 9: The Steering Committee

I amended the sentence as per your suggestion in line 9 on page 8 of the revised manuscript.

- Treatment: last sentence: every night --> each night

I amended the wording as per your kind suggestion in line 3 on page 10 of the revised manuscript.

- Discussion: line 4: However, in both males and females, CHF ...

I amended the wording as per your kind suggestion in line 3 on page 14 of the revised manuscript.

- Discussion: 2nd paragraph: economic burden; mechanisms is also expected ...

To my understanding, the text clearly describes “physical,” “mental,” and “economic” “burdens” “to the patient”. Therefore, I am willing to keep the sentence unchanged and would highly appreciate your leniency.

- Discussion: 3rd paragraph: ASV therapy is being accepted rapidly ... : this is a bombastic sentence and hard to read. Delete on the assumption ....

I deleted the sentences from the text as per your valuable suggestion.

- Discussion: 4th paragraph: bettering --> improving; .... and via improving the prognosis

I replaced “bettering” with “improving.” in line 9 on page 16 of the revised manuscript. However, I am willing to keep “improving” unchanged because it means “the potential of improving the prognosis and QOL of patients with CHF.”
- Table 2: wherever --> whenever

This wording means “any place where sleep study can be conducted.” Therefore, I am willing to keep “wherever” unchanged and would highly appreciate your leniency.
Reviewer 2’s comments:

I carefully prepared the replies to your valuable comments on a comment-by-comment basis and indicated the amendments with red characters in the revised manuscript.

1. ASV improves left ventricular contractility, induces cardiac reverse remodeling and suppresses sympathetic nerve activity in SDB patients, but no consistent evidences have been reported in all the CHF population. The authors should better explain the decision of testing ASV also in patients with no apneas.

Regarding the first part of your comments, I fully agree to your insightful comprehension [improvement in left ventricular contractility, induction of cardiac reverse remodeling, and suppression of sympathetic nerve activity in sleep-disordered breathing (SDB) patients; insufficient evidence about these actions of adaptive-servo ventilation (ASV) therapy in patients with chronic heart failure (CHF)]. Especially, the latter fact motivated us to conduct the present clinical study to obtain evidence about the clinical benefits of ASV therapy for patients with CHF.

Regarding the second part, please let me explain the background to plan the present clinical study in Japan. Firstly, I am willing to stress that we originally had the same comprehension as yours before planning this clinical study. Secondly, we recognized ASV—one mode of noninvasive positive pressure ventilation (NPPV)—as a therapeutic modality with potential applicability to the long-term treatment of patients with CHF because of 1) the hemodynamics-improving effect of NPPV and of 2) the simple operability and good patient adherence that the ASV device (AutoSet CS™) provides as described in our previous study currently available online [Momomura S, Seino Y, Kihara Y, Adachi H, Yasumura Y, Yokoyama H; the SAVIOR-R investigators: Adaptive servo-ventilation therapy using an innovative ventilator for patients with chronic heart failure: A real-world, multicenter, retrospective, observational study (SAVIOR-R). Heart Vessels 2014]. Thirdly, The Japanese guideline-described proportion of patients without SDB and patients with mild SDB in the CHF patient population is considerably as high as approximately 50% in real-world clinical settings. Lastly, there is a need for a novel therapeutic modality among CHF patients with and without SDB. In conclusion, we decided to include CHF patients without SDB in the present randomized clinical study is expected to provide higher level of evidence. In relation to this query of yours, furthermore, I supplemented evaluation variables for
SDB as follows in line 4 on page 11 of the revised manuscript: ...(e.g., apnea-hypopnea index), ....
2. The authors affirm to enroll patients with moderate to severe CHF, but they consider also patients in NYHA class II with mild left ventricular dysfunction (LVEF 40%). Probably these characteristics are more typical for mild (not moderate to severe) CHF. Please explain the author’s point of view.

I consider that the submitted clearly manuscript described “mild to severe” in the contexts of both the abstract and the text, where CHF patients to be enrolled in the present study were described. I would highly appreciate your reconsideration.

3. Because of the potential beneficial effect of ASV in the patient’s symptoms (both with reduced and preserved LVEF), I would consider the primary endpoint (LVEF) as secondary endpoint and further cardiac events, BNP, NYHA class as primary endpoints.

Our prior, retrospective clinical study (SAVIOR-R) suggested that ASV therapy possibly improves the cardiac function (LVEF) and symptoms (NYHA class) of patients with CHF, regardless of the severity of SDB. SAVIOR-C is a confirmatory study of SAVIOR-R. Between LVEF and NYHA class, I consider that LVEF is the only variable that is applicable to a clinical study of prospective, open-label, blinded-endpoint design. In consideration of your insightful suggestion, I added the following sentence “a variable for the evaluation of heart failure that is applicable to a randomized controlled study of prospective, open-label, blinded-endpoint design” to lines 6 to 7 on page 10 of the revised manuscript.

4. Abstract is not clear and should be better written and checked by a mother tongue reader.

I revised the abstract with the help of an experienced editor in accordance with your valuable suggestion.

Minor Essential Revisions

5. Typing errors have been found.

I revised the entire text with the help of an experienced editor in accordance with your valuable suggestion.
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

The details and technical methods of the statistical analyzes will be described. Therefore, the descriptions of statistics are necessarily limited at this time. I would highly appreciate your leniency.