PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Reduction in sympathetic tone in Obstructive sleep apnea patients: is fixed CPAP more effective than APAP? – a randomized, parallel trial protocol
AUTHORS	Treptow, Erika; Pepin, Jean Louis; Bailly, Sebastien; Levy, P; Bosc, Cecile; Destors, Marie; Woehrle, Holger; Tamisier, Renaud

VERSION 1 – REVIEW

REVIEWER	Erik Thunström Inst. Medicine dep. Molecular and Clinical Medicine, Sahlgrenska Academy, Gothenburg University, Sweden
REVIEW RETURNED	17-Jun-2018

GENERAL COMMENTS	This is an interesting study, which will add important knowledge to the field. It is well written and the authors seems to, overall, be coherent with the CONSORT statement for reporting RCT. I have only minor comments: 1. Please specify how you have defined daytime sleepiness (which is an inclusion criterion of the study). 2. Please specify who will give service to the study participants if they have problems with their CPAP (leakage etc.). Will it be the investigators responsible for the installation of the CPAP, or will it be the blinded investigators responsible for the follow-up and evaluation of the patients. 3. Which statistical methods will be used to evaluate the difference in the outcome variables: addressed (bursts/min) (independent T-test?),if so please specify. Will there be analyses of differences between base line and follow-up on individual basis (pair T-test) if so please specify this. 4. In the Sample size section: Why are you only interested in studying an "unilateral situation" which I interpret as one-sided? Would it not be of interest to see if fixed CPAP reduces burst/min less than APAP?

REVIEWER	Julia Chapman Woolcock Institute of Medical Research/University of Sydney
REVIEW RETURNED	10-Aug-2018

GENERAL COMMENTS	Treptow et al have described here a protocol for a randomized, controlled trial which will compare CPAP to APAP on the reduction in sympathetic tone in OSA. This study may be of interest to the sleep community. I have some specific questions regarding the manuscript that I think should be addressed before this protocol can be published. I have outlined them per section below. This protocol would benefit from being checked against the SPIRIT Statement checklist to ensure that all aspects are covered. Abstract: - The authors should mention that this is a blinded study in the abstract - There is no mention of sample size in the abstract, this should be included - Under “Ethics and Dissemination” the Ethics Committee should be specified as later in the manuscript as The French Regional Ethics Committee, rather than just “Ethics Committee” - The study dates listed here in the abstract should be included later in the manuscript also Introduction: - It seems incorrect to say that hypertension is a leading cause of death, but it is surely a leading intermediary factor related to cardiovascular death. This should be clarified (it is written better in the abstract) - Can the authors clarify what is meant by “late cardiovascular events”? - The introduction focusses primarily on blood pressure. The primary outcome of this protocol is vascular sympathetic tone measured by muscle sympathetic nerve activity microneurography. This technique is not explained at all in the introduction and it needs to be. There should also be an introduction to what is known about MSNA in OSA currently – e.g. how it might be different in OSA compared to controls, and some explanation of why this specific measure was chosen for this study. While there may be no RCTs, are there any observational studies that have looked at the effect of CPAP/APAP on this measurement? - The aim of the current study is to compare CPAP to APAP, but a clear hypothesis regarding direction of effect should be stated. Methods: - Similar to the point above – is this study a superiority trial or an equivalence trial? i.e. is CPAP expected to be better than APAP or are they expected to be equal? This has great implications for the sample size calculation and should be described. - In the “Population” section there should be some justification for the inclusion/exclusion criteria. Including a justification for why the participants need to suffer from daytime sleepiness in order to be included and how this will be evaluated. Are there any exclusion criteria regarding the ability to measure the primary outcome (e.g. nerve conductance disorders) - Will “consecutive patients be enrolled” or is it more correct to say that “consecutive participants will be invited to participate”? This should be clarified. - Regarding the MSNA procedure – there is no information regarding the timing of the test. Will it be done during the day/night? How long will it record for to get a bursts/minute recording? Will this be averaged over x minutes etc? - Regarding the blood pressure procedure – can the authors clarify which arm (dominant/non-dominant/always right or left) the recordings will be taken from? Can the authors provide a reference for the cutoffs for daytime and nighttime hypertension given at the top of page 9?

	- Can the authors provide a method for the catecholamine methods they will be using? - Under “Procedures” there is a sentence stating that “A minimum of continuous pressure use for 4 hours per night will be required.” But there is no statement regarding what happens if this is not met – e.g. will the participant be withdrawn from the study? Will they be given extra time to meet this criteria? - Will the CPAP settings include a ramp? Can the authors comment on the potential for unblinding if the patients undergo 8 nights of auto-titration then move to CPAP – will they notice a difference and potentially unblind themselves? - Can the authoirs provide a reference for the choice of APAP pressure range between 6 and 16 cmH2O? - The sample size calculation should be clarified as much as possible as it is currently unclear. E.g. which program was used to make the calculation and which method/assumptions were used? How did the authors come up with their hypothesis of a reduction of 8 and 5 bursts per minute with CPAP and APAP respectively and the standard deviation of 5? Is there any background data in OSA to suggest this is likely? What are normative values of MSNA bursts? Do the authors anticipate a dropout rate and has this been taken into account in the numbers needed to enroll? - The paragraph at the start of Page 11 mentions an interim analysis. It is unclear why this is being done – there appear to be no particular safety concerns to justify this interim analysis as both groups will be receiving treatment for their OSA. There is no discussion about who will perform this analysis. An interim analysis should be conducted by a blinded data safety monitoring committee so as not to impact upon the double-blinded nature of the trial. If this interim analysis is going ahead, it should be justified and it should be made very clear who will be doing this – e.g. a blinded group who will not otherwise be involved in the study? - In the “Randomization” section there is mention of blinding, but the allocation concealment is unclear. The unblinded investigator who holds the “list” may be able to influence the order in which patients are enrolled if they know all allocations from a “list”. Better would be having the codes in opaque envelopes etc. that are opened at the time of randomization. Can the authors clarify if any attempt has been made to conceal allocation like this? - In the statistical methods section can the authors provide a reference for the multiple imputation technique that they plan to use? It is unclear what would happen if there was >20% of missing data. It is also unclear if the analysis aims to assess the difference between the groups in change from baseline, or simply at the end of treatment. This should be clarified in this section. - In the “Ethics” section there is mention of the written informed consent – the authors should refer to the appendix here. Discussion: - There are some sections here that should probably be moved/integrated with the introduction – e.g. the discussion about microneurography in the third paragraph of the discussion section. - The heading “Conclusions” may be confusing here – without it the final paragraph remains a good summary of the Discussion section. Appendix: - Should the participant information sheets that go along with the consent forms also be included here? Figures: - The legend below Figure 2 on the pdf view that I can see has

	some symbols that should not be there – this should be checked before publication.

VERSION 1 – AUTHOR RESPONSE

Revi ewer: 1
Revi ewer Na me: Erik Thunström
Instituti on and Country: Inst. Medi ci ne dep. Mol ecul ar and Cli nical Medi cine, Sahl grenska Academy, Gothenburg Uni versity, Sweden
Pl ease state any competing i nterests or state ‘ None decl ared’: None Decl ared

Pl ease l eave your comments for the authors bel ow

This is an i nteresti ng study, whi ch will add i mportant knowl edge to the fiel d. It is well written and the authors seem to, overall, be coherent with the CONSORT statement for reporti ng RCT.

I have onl y mi nor comments:

1. Pl ease specify how you have defi ned dayti me sl eepi ness (whi ch is an incl usi on criteri on of the study).
We thank the revi ewer for poi nti ng this lack of accuracy i n our protocol descri pti on. Dayti me sl eepi ness is defined by an Epworth Sl eepi ness Scal e above 10. The propensity of falli ng asl eep is eval uated i n ei ght different quoti di an situati ons. Ans wers range from 0 representi ng no chance of sl eepi ng to 3 signifyi ng hi gh chance of sleep. The fi nal score vari es from 0 to 24 and a result superior to 10 represents excessive dayti me sl eepi ness.
We i ncl uded the cut-off for dayti me sl eepi ness and reference i n Page 8.

2. Pl ease specify who will give service to the study partici pants if they have probl ems wi th their CPAP (leakage etc.). Will it be the i nvestigators responsi bl e for the installati on of the CPAP, or will it be the bli nded investigators responsi ble for the foll ow- up and eval uati on of the pati ents.
We thank the revi ewer for notici ng this i mportant poi nt that i ndeed is cruci al for the quality of CPAP treat ment. Study partici pants will have CPAP techni cal support for m their healthcare provi der (Agiradom) whi ch provide techni cal support 24h a day and 7/7 days a week, one phone or if needed directly at pati ent home. Moreover, this healthcare provi der is used to compl ete this assistance duri ng research trials. The healthcare provi der employees are trai ned i n research good cli nical practice, and how to mai ntai n the bli ndness of all ocati on to pati ents and researchers duri ng randomi zed trials.
We have added this i nformati on i n Page 11.

3. Whi ch statistical methods will be used to evaluate the difference i n the outcome vari abl es: addressed (bursts/ mi n) (i ndependent T-test?),if so pl ease specify. Will there be anal yses of differences bet ween base line and foll ow- up on i ndivi dual basis (pair T-test) if so pl ease specify this.
We thank the revi ewer to hel p us for cl arifyi ng the manuscri pt. The mai n outcome is anal yzed as the difference bet ween both groups (Fi xed vs autopil oted). To compare the evol uti on, we first compute the difference at 1 month vs baseli ne and we compare this difference val ue by usi ng a Student t-test for independent groups, accordi ng to the nor mality of the distri buti on of the difference. If not we will used a non-parametric Mann- Whitney Wilcoxon test. This poi nt has been added i nto the manuscript i n Page
12.

4. In the Sampl e size secti on: Why are you onl y interested i n studyi ng an "unilateral situati on" whi ch I interpret as one-si ded? Woul d it not be of i nterest to see if fixed CPAP reduces burst/ mi n less than APAP?
The revi ewer is absol utely right and i n our sampl e calcul ati on we have consi dered the possi bility that both treat ments may be superi or to the other one. It is the first comparison bet ween these t wo treat ment modaliti es, so we expect that there are at least equi val ent. Therefore, i nstead of the i nitial submi ssi on, the ter m unilateral has been modifi ed by bilateral.

Revi ewer: 2
Revi ewer Na me: Julia Chapman
Instituti on and Country: Wool cock Institute of Medi cal Research/Uni versity of Sydney
Pl ease state any competing i nterests or state ' None decl ared': None decl ared

Pl ease l eave your comments for the authors bel ow
Treptow et al have described here a protocol for a randomi zed, controll ed trial whi ch will compare CPAP to APAP on the reducti on i n sympathetic tone i n OSA. Thi s study may be of i nterest to the sleep community. I have some specific questi ons regardi ng the manuscri pt that I think shoul d be addressed bef ore this protocol can be published. I have outli ned them per secti on bel ow. This protocol woul d benefit from bei ng checked agai nst the SPI RIT Statement checklist to ensure that all aspects are covered.
Abstract:
- The authors shoul d menti on that this is a bli nded study i n the abstract - There is no menti on of sampl e size i n the abstract, this shoul d be i ncl uded
As suggested by the reviewer these have been added i n the abstract section.

- Under "Ethics and Dissemi nati on" the Ethics Commi ttee shoul d be specified as later in the manuscri pt as The French Regi onal Ethics Commi ttee, rather than just "Ethics Commi ttee"
The correcti on was made i n the abstract. Page 3.

- The study dates listed here i n the abstract shoul d be i ncl uded later i n the manuscri pt also
The study chronogram was i ncl uded i n Page 13.

Introducti on:

- It seems i ncorrect to say that hypertensi on is a leadi ng cause of death, but it is surel y a leadi ng i nter medi ary factor rel ated to cardi ovascul ar death. This shoul d be cl arified (it is written better i n the abstract)
We are thankful for this suggesti on. The revised statement was added to the introducti on Page 5 as follow: "Hypertensi on is the mai n i nter medi ary mechanis m i mplicated i n cardi ovascul ar risk".

- Can the authors clarify what is meant by "late cardi ovascul ar events"?
We acknowl edge that this ter mi nol ogy is at least not enough accurate, and we thank the revi ewer for poi nti ng this. Sl eep Apnea is associ ated with cardi ovascular activati on incl udi ng sympathetic over activity, whi ch favors vascul ar damage and hypertensi on leadi ng to peri pheral and coronary atheroscl erosis and myocardi al alterati on. These may be i nvol ved i n the pathogeni city of many cardi ovascul ar outcomes as cardi ac arrythmi as, ischemi c and non-ischemi c cardi omyopathi es at the heart level and aortic aneurys ms and cerebrovascul ar acci dents at vascul ar level. The i nci dence and progressi on of these diseases may take years to devel op and are defi ned as late cardi ovascul ar events or long-ter m cardi ovascul ar adverse events or outcomes. We substituted the ter m "l ate cardi ovascul ar events" to "l ong-ter m cardi ovascul ar outcomes" Page 5.

- The introduction focusses primarily on blood pressure. The primary outcome of this protocol is vascular sympathetic tone measured by muscle sympathetic nerve activity microneurography. This technique is not explained at all in the introduction and it needs to be. There should also be an introduction to what is known about MSNA in OSA currently – e.g. how it might be different in OSA compared to controls, and some explanation of why this specific measure was chosen for this study. While there may be no RCTs, are there any observational studies that have looked at the effect of CPAP/APAP on this measurement?

This is a very important remark made by the reviewer. We included the following paragraphs in the introduction describing the importance of the MSNA method for the understanding of the pathophysiology of systemic arterial hypertension and its sense in obstructive sleep apnea and added the adequate references:

" Muscle sympathetic nerve activity (MSNA) is one of the reference methods for measuring sympathetic activity and understanding the pathophysiology of neurogenic hypertension (18). Moreover, MSNA changes across time or after intervention are corresponding with arterial blood pressure changes in prehypertension (19).

In different models of hypertension only intermittent hypoxia, which is the main stimuli in OSA, causes neurogenesis modulation in hippocampus (20). In human, intermittent hypoxic exposure induces after 2 and 4 weeks an increase in daytime MSNA (13, 17). This increase in sympathetic tone was suggested in the early 90ies as a mechanism of hypertension in OSA (16, 21). Therefore, MSNA measurement is of particular interest in showing the effect of OSA treatment as a surrogate marker of cardiovascular outcomes. Although several studies have demonstrated the beneficial effects of OSA treatment by continuous positive airway pressure (CPAP) in sympathetic activation (14, 22-24), this measurement has never been evaluated in patients under Auto-adjusting continuous pressure (APAP). MSNA consists of a technique of microneurography minimally invasive that measures the sympathetic nerve activity of the peroneal nerve. "

- The aim of the current study is to compare CPAP to APAP, but a clear hypothesis regarding direction of effect should be stated.

As it was specified in the response to the Reviewer one, in the submitted manuscript we formulated an a priori assumption of superiority of APAP vs CPAP owing to our previous publication in Thorax journal. However, we agree with both reviewers that we do not have yet data supporting this assumption, and this has been changed throughout the manuscript. Since we based our hypothesis in a difference between the two PAP modalities on a delta change this reformulation of our hypothesis does not change the sample size calculation. Hence the assumption is bilateral and not unilateral, and therefore the aim of the study is to compare both treatment modalities without any a priori. This was modified in the document.

Methods:

- Similar to the point above – is this study a superiority trial or an equivalence trial? i.e. is CPAP expected to be better than APAP or are they expected to be equal ? This has great implications for the sample size calculation and should be described.

The reviewer is right, we have been not enough precise in our manuscript. As stated above, the sample size calculation was based on a bilateral assumption and not an unilateral assumption.

- In the "Population" section there should be some justification for the inclusion/exclusion criteria. Including a justification for why the participants need to suffer from daytime sleepiness in order to be included and how this will be evaluated. Are there any exclusion criteria regarding the ability to measure the primary outcome (e.g. nerve conductance disorders)

We thank the reviewer for this comment, that is actually related with the French health authority rules. Indeed, patients should complain of subjective daytime sleepiness in order to be eligible for CPAP treatment.

There are i ndeed no exclusi on criteri a per se regardi ng the measurement of the pri mary outcome. The PI has i nvesti gated MSNA in more than 500 pati ents i n different popul ati ons (heart fail ure, metabolic syndrome, restl ess l eg syndrome, el derl y pati ents). These are not “excl usi on criteri a” they are onl y more techni cally difficult pati ents with a hi gher rate of techni cal fail ure. These techni cal fail ures have been taken i nto account i n our sampl e size calcul ati on.

- Will “consecutive pati ents be enrolled” or is it more correct to say that “consecuti ve partici pants will be i nvited to partici pate”? This shoul d be clarified.
Agai n, we thank the reviewer for hel pi ng us i n cl arifyi ng our manuscri pt; the sentence was changed as suggested (Page 8).

- Regardi ng the MSNA procedure – there is no i nfor mati on regardi ng the ti mi ng of the test. Will it be done duri ng the day/ni ght? How l ong will it record for to get a bursts/ mi nute recordi ng? Will this be averaged over x mi nutes etc?
We thank the revi ewer for this comment and we incl uded the foll owi ng statement concerni ng MSNA descripti on and ti mi ng:
“ We will obtai n Muscl e Sy mpathetic Nerve Activity (MSNA) from nerve recordi ngs usi ng standard tungsten mi croel ectrodes i nserted into the peroneal nerve into the popliteal area, after l ocalizati on by el ectric surface sti mul ati on (Fi gure 1). Si gnals will be filtered (700-2000 Hz), amplified (x70, 000) and full- wave rectified. The rectifi ed si gnal will be i ntegrated (0. 1 second movi ng wi ndow) for displ ay and for recordi ng (Nerve Traffic Anal yzer, Model 662c-3, Uni versity of Iowa, Bi oengi neeri ng Dept., Iowa City, I A). El ectrode position i n muscl e fascicl es will be confir med by pulse synchronous bursts of activity occurring 1. 2-1. 4 s after the ECG QRS compl ex, reproduci bl e activati on duri ng the second phase of the Valsal va maneuver, elicitati on of afferent nerve activity by mil d muscl e stretchi ng and the absence of response to startl e. Doppl er popliteal vascular fl ows (DWL500EZ) will be measured duri ng ti me peri ods concomi tant from measurement of MSNA, HR (3-lead ECG) and arteri al blood pressure. Beat-by-beat arteri al BP for vascul ar doppl er leg resistance calculati ons will be measured usi ng the CNAP® system the same time peri ods. All these signal s will be di gitalized and recorded for off-li ne anal ysis on Powerl ab system. These measurements will be perfor med before and after PAP therapy on morni ng sessi ons, fasten si nce 12 AM from foods and any beverage except water, duri ng room air breathi ng. We will average nerve activity, heart rate and arteri al bl ood pressure over 5- mi nute wi ndows of data coll ecti on at baseline and post-PAP therapy. Sympathetic bursts will be identified usi ng a specific algorithm descri bed by Ha mner and coll eagues (50) usi ng
Matl ab soft ware (The Mathworks Inc., Natick, MA USA). For purposes of quantificati on MS NA will be reported i n at least five mi nutes periods and expressed as burst frequency (bursts/ mi n and bursts/100 heart beats).”

- Regardi ng the bl ood pressure procedure – can the authors clarify whi ch ar m (domi nant/non- domi nant/al ways right or left) the recordi ngs will be taken from? Can the authors provi de a reference for the cutoffs for dayti me and ni ghtti me hypertensi on given at the top of page 9?
We thank the revi ewer for aski ng precisi on about these poi nts.
Regardi ng the reference of the cutoffs, this is written i n our manuscri pt: Dayti me hypertensi on is defi ned as dayti me SBP > 135 mmHg and/or DBP > 85 mmHg, and ni ghtti me hypertensi on as SBP > 120 mmHg and/or DBP > 70 mmHg.
The l ast reference of the 2018 ESC/ESH gui deli nes has been added i n our manuscri pt.
Regardi ng the method for ambul atory bl ood pressure measurement the followi ng sentence has been added: “Ambul atory bl ood pressure will be measured in the domi nant ar m over 24 hours at 15 mi n i ntervals duri ng dayti me and every 30 mi nutes ni ghtti me (ABP monitor 90207, Spacel abs Healthcare, Issaquah WA). Bl ood pressure acquisiti on began at a morni ng sessi on and ended 24 hours later.”

- Can the authors provi de a method for the catechol ami ne methods they will be usi ng?

The method used to measure cathecol ami nes will be hi gh-perfor mance li qui d chromatography with electrochemi cal detecti on as descri bed as foll owi ng in the paper:
Catechol ami nes (epi nephri ne, norepi nephri ne, and dopami ne) will be measured by hi gh-perfor mance li quid chromatography with el ectrochemi cal detecti on (Coul array Detector, ESA Di onex, Chel msford, USA).

- Under “Procedures” there is a sentence stati ng that “A mi ni mum of conti nuous pressure use for 4 hours per night will be required.” But there is no statement regardi ng what happens if this is not met – e.g. will the partici pant be withdrawn from the study? Will they be given extra ti me to meet this criteria?

Partici pants with l ower usage hours than 4 hours per ni ght duri ng titrati on phase will not be i ncl uded i n randomi zati on. A statement concerni ng this criteri on was added i n Page 11.

- Will the CPAP setti ngs incl ude a ramp? Can the authors comment on the potenti al for unbli ndi ng if the patients undergo 8 ni ghts of auto-titrati on then move to CPAP – will they notice a difference and potenti ally unblind themsel ves?

The revi ewer is right that the pati ent even with a ramp may experi ence a difference bet ween CPAP and the 8 ni ghts of auto-titrati on usi ng APAP duri ng the runni ng peri od. This is why we will sel ect pati ent who are naï ve from PAP treat ment and duri ng protocol presentati on to the pati ent, it will be said that we will test t wo different treat ment modaliti es without sayi ng any superi ority from one to the other one. To all pati ents it will be sai d that after a runni ng peri od, their PAP therapy will be set owi ng the ar m they will be randomi zed i n and this will change the experi ence on PAP compared to the runni ng peri od. We will pay attenti on not to say i n one arm conti nuous and one ar m auto-adj usted. Moreover, we have trai ned the healthcare provi der techni ci ans who will be i n charge of setting the PAP therapy not to say anythi ng regardi ng the setti ng to the pati ent. Even though we acknowl edge that pati ent will experi ence differences on the different ar ms, we beli eve that our procedures will mai ntai n suffici entl y bli ndness from the pati ents i n order not to alter their response to treat ment comparabl e.

- Can the authors provi de a reference for the choice of APAP pressure range bet ween 6 and 16 c mH2O?

We will used the same methodol ogy as previ ous tri al i n our research see Pepi n et al [Pepi n Thorax 2016]

- The sampl e size calcul ati on shoul d be cl arified as much as possi bl e as it is currently uncl ear. E.g. which program was used to make the calcul ati on and whi ch met hod/assumpti ons were used? How di d the authors come up with their hypothesis of a reducti on of 8 and 5 bursts per mi nute with CPAP and APAP respectivel y and the standard devi ati on of 5? Is there any background data i n OSA to suggest this is likel y? What are nor mati ve val ues of MSNA bursts? Do the authors antici pate a dropout rate and has this been taken i nto account i n the numbers needed to enroll?

We thank the revi ewer to mai ntai n our attenti on in provi di ng as much as possi bl e a good readi ness of the methodol ogy. For all statistical anal ysis, we are using the program: Proc Power of SAS v9. 4.
In order to i mprove cl arity, a new for mul ati on of the assumpti ons are specified i n the text as foll ow Page 11: “We hypothesized the i mpact of PAP therapy to be 8±5 bursts/ mi n i n one ar m group and 5±5 bursts/ mi n in the other ar m with no a pri ori assumpti on group. Assumi ng an al pha error of 5%, a statistical power of 80%, i n bil ateral situati on, 34 patients per ar m will need to be enrolled i n the study.”
The foll owi ng sentence has been added i nto the manuscri pt :”In the sampl e size, we antici pate that 10 % will not meet the criteri a of compli ance to pressure support after 1 week, and 10% more will drop out before ter mi nati on of the study.”

Regardi ng the change i n MS NA as we previ ousl y menti on, there is no data on effect of different PAP modaliti es on MSNA change across ti me. Herei n, we used the change that has been demonstrated by Narki ewi cz et al [Narki ewi cz et al Nocturnal Conti nuous Positive Air way Pressure Decreases Dayti me Sympathetic Traffic i n Obstructive Sl eep Apnea Circul ati on 1999], and that we have found usi ng the same met hodol ogy i n a previ ous set of pati ents published i n 2015 [Tami si er Sl eep 2015]. It is i mportant to note that i n this paper we reported MS NA usi ng a different met hodol ogy. Usi ng the burst count MSNA went from 40. 49 ± 5.63 to 35. 47 ± 4. 06 burst/ mi n after 6 months of CPAP.
We i ndeed antici pate a drop-out rate of 20% due to the i nability to obtai n MS NA recordi ng i n the t wo measurements, drop out and do not meet the compl iance criteri a after one week runni ng peri od. The foll owi ng sentence has been added in the
met hodol ogy secti on page 11: “In the sampl e size, we antici pate that 10 % will not meet the criteri a of compli ance to pressure support after 1 week, and 10% more will drop out before ter mi nation of the study.”

- The paragraph at the start of Page 11 menti ons an i nteri m anal ysis. It is uncl ear why this is bei ng done – there appear to be no particul ar safety concerns to justify this interi m anal ysis as both groups will be recei vi ng treat ment for their OSA. There is no discussi on about who will perfor m this anal ysis. An i nteri m anal ysis should be conducted by a bli nded data safety monitori ng commi ttee so as not to impact upon the doubl e-bli nded nature of the trial. If this interi m anal ysis is goi ng ahead, it shoul d be j ustified and it should be made very cl ear who will be doi ng this – e.g. a bli nded group who will not other wise be i nvol ved i n the study?
The revi ewer is right there are no safety concerns and herei n the i nteri m anal ysis is not about safety concern but rather about the feasi bility of the study. As we previ ousl y menti on i n the present manuscri pt, although if present a difference i n sympathetic inhi biti on bet ween PAP modaliti es is a very i mportant fact for cli nici an and researcher, there is no previ ous data on this. Hence, we set our study to serve as prelimi nary data and if at i nteri m anal ysis we confir m difference trend then it will argue for compl eti ng the whol e sampl e size. The sentence was modifi ed as foll ow: “Because it is a pil ot study, we will perfor m…”
The i nteri m anal ysis will be perfor med by an i ndependent statistician who has no connecti on with the study. The i nteri m anal ysis does not need to be perfor med by a data safety monitori ng commi ttee si nce there is not safety issue. The statistician will have not been i nvol ved in the study and is part of an i ndependent data center i n our uni versity hospital. The foll owi ng sentence has been added i n the method: “This interi m anal ysis will be perfor med by a bli nded statistical whi ch have no regard on the randomi zati on list neither contacts with the i nvestigator nor i nvol vement in the study.”

- In the “Randomi zati on” secti on there is menti on of bli ndi ng, but the allocati on conceal ment is uncl ear. The unbli nded i nvestigator who hol ds the “list” may be abl e to i nfl uence the order i n which pati ents are enrolled if they know all all ocati ons from a “list”. Better woul d be havi ng the codes i n opaque envel opes etc. that are opened at the ti me of randomi zati on. Can the authors clarify if any attempt has been made to conceal all ocati on like this?
The revi ewer is right the peopl e hol di ng the randomi zati on list shoul d not be an investi gator and actually they are not si nce t wo i ndependent persons are hol di ng the randomi zati on list (i n case of absence). The randomi zati on list was issue from the Cli nical Research Direction from our uni versity hospital whi ch is not i nvolved i n the conducti on of the trial. To this extent we do not need to use codes i n opaque envel opes. This procedure was set by the research depart ment of Grenoble Al pes Uni versity hospital i n order to provi de randomi zation quality to i nvesti gators. The foll owi ng sentence has been added i n page 12: “Randomi zati on list was provi ded by the cli nical research depart ment of Grenobl e Al pes uni versity hospital and the randomi zati on list is hel d and foll owed by t wo i ndependent persons from the study. These persons provi de allocati on directly to the healthcare provi der mai ntaini ng bli ndness of the pati ent and the i nvesti gators.”

- In the statistical methods secti on can the authors provi de a reference for the multi pl e i mputati on techni que that they pl an to use? It is uncl ear what woul d happen if there was >20% of missi ng data. It is also uncl ear if the anal ysis ai ms to assess the difference bet ween the groups i n change from baseli ne, or simpl y at the end of treat ment. This shoul d be clarified i n this secti on.
The foll owi ng sentences have been added i nto the manuscri pt:
- by usi ng MC M chai ns for qualitative vari abl es or full conditi onal specification for quantitative vari abl es.
- “Vari abl es with more than 20% of mi ssi ng val ues will not be taken i nto account.

- In the “Ethics” secti on there is menti on of the written i nfor med consent – the authors shoul d refer to the appendi x here.
A reference to the supplementary file was added in the Ethics secti on Page13.

Di scussi on:

- There are some secti ons here that shoul d probabl y be moved/i ntegrated with the introducti on – e.g. the discussi on about mi croneurography i n the third paragraph of the discussi on secti on.
We thank the revi ewer for this suggesti on, however si nce we added a compl etel y new secti on on MSNA techni c and si gnificati on i n the introducti on, we beli eve that this secti on may stay i n the discussi on. However, if this secti on remai ns an issue for the revi ewer, we may remove it from the discussi on.

- The headi ng “Concl usions” may be confusi ng here – without it the fi nal paragraph remai ns a good summary of the Discussi on section.
The headi ng Concl usi ons was removed as suggested.

Appendi x:
- Shoul d the partici pant infor mati on sheets that go al ong with the consent for ms also be i ncl uded here?
We beli eve that the consent for m provi des the necessary i nfor mati on for the suppl ementary file.

Fi gures:
- The l egend bel ow Fi gure 2 on the pdf vi ew that I can see has some symbol s that shoul d not be there – this shoul d be checked before publicati on.
We checked the l egend bel ow Fi gure 2 and made the necessary correcti ons.

VERSION 2 – REVIEW

REVIEWER	Erik Thunström Inst. of Medicine, Sahlgenska Academy, Gothenburg University
REVIEW RETURNED	17-Nov-2018

GENERAL COMMENTS	It is an interesting study, looking forward to reading the results.