Research Review Title:

Comments to Research Review

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	It is meaningful for COPD and lung disease patients but not for neuromuscular disease (NMD). The most important target population was completely ignored, that is, patients with advanced NMDs.	We thank the reviewer for the comments. Our literature review included available literature on adult patients with NMDs of all etiologies.
Peer Reviewer #2	General	The exclusion criteria on page 4 lists non-comparative observational and before-after studies, but why not use them to report impacts of therapies on outcomes such as ABG's? Observational studies were reported on; how do they differ from those types excluded?	We included studies that evaluated 2 or more cohorts of patients and reported pertinent outcome rates/measures in both cohorts for comparison. The cohorts could be defined by different diseases, devices, or disease characteristics, etc. We excluded studies that just reported outcome rates/measurements for just one cohort of patients, including before/after studies meeting this criteria. Regarding ABGs: We did not evaluate gas exchange (change in $PaCO_2$) as an outcome, as this was considered to be an intermediate surrogate outcome, not a patient centered clinical endpoint outcome (such as mortality, healthcare utilization, quality of life, etc.)
Peer Reviewer #2	General	After reading the review, the presumption is that the current standard of care for OHS (CPAP, BPAP) is of little benefit (the survival and QOL data as presented). Do you want to imply this for OHS or any of the other diseases?	Thank you for your thoughtful assessment. We have evaluated the 7 additional OHS studies that you noted on the last page of your PDF markup. See below for the inclusion/exclusion status of each of those studies. In total

Commentator & Affiliation	Section	Comment	Response
			Additional studies considered in your PDF markup: Salord: We excluded this study as outcomes were PaCO2, PaO2, and treatment failure with CPAP. (none of our reviewís relevant outcomes were measured). Hida: We excluded this study as there was no relevant comparison group. (The included comparison groups did not have OHS. There were no separately measured outcomes provided for patients with OHS with different characteristics.) Tsolaki: We have now included. Mokhlesi : We excluded this study as outcomes were PaCO2 and PaO2 (none of our reviewís relevant

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Peer Reviewer #2	General	There is no reporting on follow-up ABG's or oxygenation, which are frequently the reason for initiating NIPPV as per the report.	Regarding ABGs: Per our study protocol, we did not evaluate gas exchange (change in PaCO2 and/or change in PaO2) as an outcome, as we considered these outcomes as intermediate surrogate outcomes, not patient centered clinical outcomes (such as mortality, healthcare utilization, quality of life, etc.) We did comment on change in gas exchange when describing the processes used to titrate devices when initiating devices, where reported.
Peer Reviewer #2	General	Consider changing the title of the report to "NIPPV in the Home."	We agree. We have changed the title to Noninvasive Positive Pressure Ventilation in the Home.
Peer Reviewer #2	General	Please see the attached PDF for minor editorial/grammatical suggestions too.	We thank the reviewer for the comments. We have incorporated most of the suggestions in the evidence report.
Peer Reviewer #3	General	Well done	We thank the reviewer for the comments.
Peer Reviewer #4	General	This is an important and clinically meaningful report. The target population and the audience are clearly defined. The KQs are appropriate and explicitly stated with clarity. The write-up for the most part is very direct and clear. However, there are some places where there is room for greater clarity. Specifically, considering the fact that there are many conditions, device-types, and outcomes, it is important that at each sentence is capable of standing alone and clear2.65 269.45BT /F5pnsth a-6(e)-	

Commentator & Affiliation	Section	Comment	Response
		of mechanical ventilation using a BPAP or HMV device through…ò. Otherwise, itûs not clear what mechanical ventilationò is referring to. It is notable that in the recent HMV (home mechanical ventilation) HOT (home oxygen trial) published in JAMA 2016, the HMV used was actually a BPAP. The point is that the difference between the 2 terms is actually an artificial construct created by CMS definitions that force ventilator square pegs into CMS-created round holes labelled ñventilatorsò and ñRADsò. This is a primary reasons why there are so few studies comparing these entities. It is more important to study the components ï what specific technical features work best (i.e. modes like BPAP S/T vs AVAPS AE or the like? Are more sophisticated alarms more important as ventilator time/24 hours goes up? (not sure that oneûs feasible ï when pts are using vents approaching 24 hours daily, alarms are tantamount to parachutes).	
Public Reviewer #1 Phillip Porte National Association for Medical Direction of Respiratory Care	General	3) There should be more caveats that the absence of evidence for effect is not the same as absence of effect. For example, on p ES-12, the authors state ñWe found no existing comparative evidence to support guideline recommendations of using HMV when device use approached >16 hours/day.ò This could be interpreted as questioning this practice that is used in some countries around the world. It would be more accurate to say ñWe found no existing comparative evidence to support or refute guideline recommendations of using HMV when device use approached >16 hours/day.ò At some point, as suggested above, the more sophisticated alarm systems more often seen with so-called HMVs become a safety feature. In this case, itûs the alarms and not the HMV thatûs important	Agreed. We have made revisions to clarify terms as suggested.
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Commentator & Affiliation	Section	Comment	Response
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Commentator & Affiliation	Section	Comment	Response
		ALS patients.(1) 5) The goal should be to more completely rest respiratory muscles and normalize alveolar ventilation (CO2) rather than to normalize AHI, therefore, polysomnograms are expensive and unnecessary for respiratory management of NMD. Indeed, we have managed over 2000 such patients including almost 1000 by CNVS with no myopathy or lower motor neuron disease patient ever requiring a tracheotomy. This is never accomplished by sleep doctors employing ñBiPAPò on these patients. Also concerning this message: while bi-level PAP is associated with a statistical increase in survival by a matter of months, patients who are CNVS dependent cannot survive for more than minutes if disconnected from their ventilators so their survival is indisputably prolonged by CNV S, indeed by up to 64 years now for post-polio, 25 years for SMA1 CNVS dependent from as young as 4 months of age, 56 years for Duchenne CNVS dependent since 23 years of age, up to 14 years for ALS, etc.. CNVS dependence, like trach mechanical ventilation (TMV), requires the use of portable ventilators, not bi-level machines.	

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Commentator & Affiliation	Section	Comment	Response
		60mmHg) and/or carbon dioxide (PaCO2 ≤ 45mmHg) levels.ò ñRespiratory failureò implies oxygenation failure. Hypoventilation that is not fatal is ñventilatory insufficiencyò not failure. Since this is inappropriately termed, there is a tendency to treat ventilatory insufficiency/failure with O2 rather and CPAP/BiPAP than with NVS to correct CO2. Low span bi-level will not correct CO2 with more advanced muscle dysfunction so NVS should be used.	assessment of hypoxia (and subsequent oxygen administration) should be done in the context of any underlying hypercapnia.
Peer Reviewer #1	Results	Page 13 ñWhile both HMV and BPAP devices provide positive pressure ventilation,ò HMVs also provide volume preset ventilation. Volume targeted pressure cycled ventilation results in loss of pulmonary compliance by preventing lung filling (lung volume recruitment (LVR)). Volume preset ventilation permits active LVR to maintain compliance and to satisfy Herring-Breuer reflex and eliminate dyspnea. www.breatheNVS.com centers preferentially use volume preset ventilation on HMVs for all NMD patients and, often, COPD patients as well. It must be used for daytime support anyway.	We thank the reviewer for the comments. We have added ñvolume presetò as a possibility of HMV machines.
Peer Reviewer #1	Results	Page 15 HMV: ñA machine capable of delivering pressure and/or volume targeted ventilation outside of the hospital setting.ò This is confusing. Volume targeted ventilation is bi-level PAP like AVAPs or IVAPs with pressures varying to target a tidal volume. HMVs also can provide volume	

Commentator & Affiliation	Section	Comment	Response
		require tracheostomy tubes, but bi-level PAP won't save them.	
Peer Reviewer #1	Results	Pages 21-	

Commentator & Affiliation	Section	Comment	

Commentator & Affiliation	Section	Comment	Response
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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Results	b. Zhou X, Yang J, Shen C. Effect of non-invasive positive pressure ventilation and long-term oxygen therapy in patients with stable COPD. Clin Med J China. 2008; 15(4): 486ï488.	We could not locate this study (and neither could our library network).
Peer Reviewer #5	Results	c. Meecham-Jones DJ et al. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. Am J Respir Crit Care Med. 1995;152(2): 538ï544.	We excluded this study as outcomes were not presented separately per device usage group, but rather combined from both groups.
Peer Reviewer #5	Results	The neuromuscular section excludes the following important works in the period covered by the literature synthesis Farrero E et al. Survival in amyotrophic lateral sclerosis with home mechanical ventilation: the impact of systematic respiratory assessment and bulbar involvement. Chest 2005; 127:2132ï8. doi:10.1378/chest.127.6.2132	We have now included this study.
Peer Reviewer #5	Results	Aboussouan LS et al. Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. Ann Intern Med 1997;127:450ï3. doi:10.7326/0003-4819-127-6-199709150-00006.	We have now included this study.
Peer Reviewer #5	Results	Gruis KL et al. The cost-effectiveness of early noninvasive ventilation for ALS patients. BMC Health Services Research. 2005; 5:58.	We excluded this study as outcome measured was cost-effectiveness (not one of the outcomes included in our study)
Peer Reviewer #5	Results	Ward S et al. Randomized controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. Thorax. 2005; 60(12):1019-24.	We excluded this study as this included several pediatric patients with congenital myopathies.
Peer Reviewer #5	Results	3) The Obesity section excludes the following important works in the period covered by the literature synthesis: Masa JF et al. Non-invasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnea. Thorax. 2016; 71(10):899-906. doi: 10.1136/thoraxjnl-2016-208501.	We have now included this study.
Peer Reviewer #5	Results	Carrillo A et al. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012; 186(12):1279-85.	We excluded this study as this study enrolled hospitalized

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Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Results	Murphy PB, Arbane G, Phillips R, et al. Home mechanical ventilation (HMV) and home oxygen therapy (HOT) following an acute exacerbation of COPD in patients with persistent hypercapnia: Results of the per protocol analysis from the hot-HMV UK trial. Thorax. 2017 December;72 (Supplement 3):A25-A6. PMID: 619739041. [Abstract/ conference proceeding]	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.

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Peer Reviewer #2	Discussion/ Conclusion	Figure 3 (page 51) and Tables 21-26 (page 51-52) demonstrate a paucity of studies included in the report except for COPD. Based upon this, only two findings have better than a low SOE. Obviously this limits the conclusions that one can make from this report, but are we left to conclude that NIPPV is of no benefit in OHS?	Regarding OHS (discussed above as well). Based on all reviewer comments, we have added 7 studies to our review (1 study on COPD, 2 studies on NMD, 3 studies on OHS, and 1 mixed study). Based on this, our conclusions and key points regarding OHS have changed to the following: HMV/BPAP mix (compared to no device) was associated with lower mortality. BPAP (compared to no device) was associated with improved sleep quality. Of note, the key points for the other disease states did not change.
Peer Reviewer #2	Discussion/ Conclusion	The future research section is appropriate. It seems to recognize that there is utility in using NIPPV for these diseases and focuses on fine tuning the process.	We thank the reviewer for the comments.
Peer Reviewer #3	Discussion/ Conclusion	Good summation	We thank the reviewer for the comments.
Peer Reviewer #4	Discussion/ Conclusion	This discussion is excellent. The authors have honed in on the key findings well. The major findings are clearly stated and the	

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Peer Reviewer #5	Discussion/ Conclusion	The future research section clearly identifies all important research areas in relation to the technical value of home mechanical ventilation. However it seems to be non-committal about the urgent need for research in the two other dimensions of value in healthcare interventions, namely, the allocative value (cost-effectiveness, reduction in unscheduled resource utilization, etc.) and the personalized value (Quality of Life). It may be a good idea to consider including those dimensions in the future research section.	While important, we did not assess cost effectiveness in this report and cannot comment on the need for additional research in this area. We have added a statement about quality of life in this section.
Peer Reviewer #1	References and notes	1) GRAZIA CRESCIMANNO, FRANCESCA GRECO, SALVO ARRISICATO, NOEMI MORANA AND ORESTE MARRONE: Effects of positive end expiratory pressure administration during noninvasive ventilation in patients affected by amyotrophic lateral sclerosis: A randomized crossover study5) ABSTRACT Background and objective: No studies have evaluated the impact of different settings of non-invasive ventilation (NIV) in patients	

Commentator & Affiliation	Section	Comment	Response
		PEEP administration. Conclusion: In ALS patients, PEEP application during NIV was associated with worse NIV and sleep quality and with higher sympathetic activity.	

Peer Reviewer #1

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 6	Background	Post hoc subgroup analyses are most suspect when the investigators themselves choose which ones to do. When a *reviewer* suggests a post hoc analysis, the risk for bias is lower, but still exists. The investigatorsû omission of the proposed analysis from the protocol could reflect either 1) investigator bias, that is, they left it out because they are biased or 2) oversight, that is, they didnût think of it or didnût think it was important, whereas the reviewer, who has better knowledge of the topic area, thinks it is. In either case the post hoc analysis should be included in the publication if it is conducted and reported adequately.	Thank you for your review/feedback. We will include the post hoc analysis in the main report.
Peer Reviewer # 6	Background	As the protocol doesnût protect against bias in this situation, other measures to protect against bias should be considered. Here are some scenarios: 1) Reviewers suggested several post hoc analyses, but the investigators chose to do this one. 2) The reviewers who suggested the analysis are biased and chose this analysis over others because they believe it would support their position. investigators detect bias in the reviewersû suggestions, they should consider whether other post hoc analyses should be done in addition to the one they performed.	We ag

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Peer Reviewer # 6	Background	One of these comments suggests stratifying studies by the PaCO2 thresholds 45-	

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 6	Writeup	P103 Results *"The post-hoc subgroup analysis was only possible for studies comparing BPAP use with no device use in COPD patients."* State how many studies you started with (22 RCTs, 6 observational) and how many were excluded and why, eg ñn studies did not report the paCO2 criterion, and x used a paCO2 threshold during an episode of acute respiratory failureò, or put this information into the last sentence of the methods on p102. Also, if there is anything salient about the subset of included studies, e.g.	