Research Review Disposition of Comments Report

March 14, 2019

Research Review Title: Noninvasive Positive Pressure Ventilation in the Home

Draft review available for public comment from September 10, 2018 to October 1, 2018.

Research Review Citation: Wang Z, Wilson M, Dobler CC, Morrow AS, Beuschel B, Alsawas M, Benkhadra R, Seisa M, Mittal A, Sanchez M, Daraz L, Holets S, Murad MH. Noninvasive Positive Pressure Ventilation in the Home. Technology Assessment Program Project ID: PULT0717 (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. HHSA290201500013I.) Rockville, MD: Agency for Healthcare Research and Quality. March 2019. Available at: http://www.ahrq.gov/research/findings/ta/index.html.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality

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 PaCO2) 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 (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. Despite this, there is really a paucity of high quality data supporting the use of home NIPPV in OHS (with outcomes such as mortality, readmissions, quality of life, etc.). There is slightly more data showing that NIPPV lowers PaCO2 in OHS in both acute hypercapnic respiratory failure as well as chronic hypercapnic respiratory failure.

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			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 review's 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 review's relevant outcomes were measured). **Perez de Llano:** We have now included. **Heinemann:** We excluded this study as there was no relevant comparison group. The only relevant outcome was mortality. There were no separately measured outcomes provided for patients with OHS with different characteristics. **Budweiser:** We excluded this study as there was no relevant comparison group. The only relevant outcome was mortality. There were no separately measured outcomes provided for patients with OHS with different characteristics.
Peer Reviewer #2	General	Albeit that the relevant guidelines may be different, should you summarize as much as possible what the they recommend for each of the categories of disease, recognizing that some of their recommendations were based upon early pivotal studies demonstrating benefit?	We have added a summary of existing guidelines for each disease category to the results section of the main report.
Peer Reviewer #2	General	Before-after studies with these therapies likely do demonstrate important outcomes, yet they are excluded.	We determined at the beginning that before-after studies are not eligible for the review due to its methodological limitations (increased bias).

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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 clearly stating all of these three variables. Please see suggestions below in key aspects of the document (there may be other areas where the authors may want to pay close attention).	We thank the reviewer for the comments. We have made clarifications for the examples provided by the reviewers.
Peer Reviewer #4	General	Examples: In page ii, line 20, please consider stating, “In patients with COPD, home BPAP…”	We have revised the report accordingly.
Peer Reviewer #4	General	Page viii, Lines 45-46, please clarify by stating, “In patients with COPD, HMV (compared individually…”	We have revised the report accordingly.
Peer Reviewer #4	General	Page viii, lines 50-51, “Current comparative evidence is not available to assess the impact of many device capabilities on patient outcomes.” For clarity, suggest stating, “Current evidence is not available to assess the comparative effectiveness of many	We have revised the report accordingly.

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		devices on patient outcomes."	
Peer Reviewer #5	General	This is a work of tall order and the most comprehensive review of English language publications on Home Ventilation to date. The key questions are clinically appropriate and explicitly stated.	We thank the reviewer for the comments.
Public Reviewer #1 Phillip Porte National Association for Medical Direction of Respiratory Care	General	NAMDRC, the National Association for Medical Direction welcomes the opportunity to comment on the draft report "Home Mechanical Ventilators." We are intimately familiar with this issue and have joined with other societies to request that the Centers for Medicare and Medicaid Services revise its current National Coverage Determination for appropriate use of these devices. Unfortunately, that request was denied and current policies, albeit terribly outdated ones, continue, much to the confusion and consternation of the pulmonary medicine community.	We thank the reviewer for the comments.
Public Reviewer #1 Phillip Porte National Association for Medical Direction of Respiratory Care	General	We do have numerous specific comments: 1) Overall, the report recognizes the limited peer reviewed studies that are available to warrant more definitive observations and recommendations. One particular challenge that we raised with AHRQ staff in March is worth reiterating: many of the studies that do examine use of home mechanical ventilators are European based studies. Throughout most of Europe, there are strong support systems for home based services for ventilator dependent individuals, a support system that is tacitly understood by study authors and reviewers even though not specifically referenced. No such support systems exist in the United States.	We agree with this point. The purpose of KQ4 was to address this specific issue. Many of the studies did not explicitly mention the support systems available to patients. We have listed this in the limitations sections of the evidence summary and main document.
Public Reviewer #1 Phillip Porte National Association for Medical Direction of Respiratory Care	General	2) The report alludes to the variability in definitions used for "ventilators" but we urge clarity in this area. Specifically, the report should mention not only the variability in definitions, but also the overlap between current definitions of "ventilators" and "BPAPs. For example, in the Background and Objectives section on p ES-1, in line 10 the report indicates: "their technical features may vary considerably." We recommend adding "vary and overlap considerably". Also in the Glossary on page ES-3 re NIPPV, the definition reads: "Delivery of mechanical ventilation through a temporary interface…". We recommend changing this wording to "Delivery	Agreed. We have made revisions to clarify terms as suggested.

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		of mechanical ventilation using a BPAP or HMV device through…". Otherwise, it's not clear what mechanical ventilation" 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 "ventilators" and "RADs". This is a primary reasons why there are so few studies comparing these entities. It is more important to study the components – 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 one's feasible – 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 "We found no existing comparative evidence to support guideline recommendations of using HMV when device use approached >16 hours/day." This could be interpreted as questioning this practice that is used in some countries around the world. It would be more accurate to say "We found no existing comparative evidence to support or refute guideline recommendations of using HMV when device use approached >16 hours/day." 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, it's the alarms and not the HMV that's important	Agreed. We have made revisions to clarify terms as suggested.
Public Reviewer #1 Phillip Porte National Association for Medical Direction of Respiratory Care	General	4) Some of the "initiation criteria" do not accurately reflect what is used clinically. For example, for COPD, it is repeatedly stated that the initiation criteria "most commonly used" include Paco2 > 45 and pH > 7.35. This fails to reflect the belief in the field over the past 2 decades that PaCO2s in the 50s rather than the 40s are more predictive of success. Kohnlein et al used PaCO2s > 7.5 kPa (51.9 mm Hg) and Murphy used > 53. Only Struik et al among recent studies used PacO2 > 45 and it was a negative study. With regard to pH, most studies have not used this as a	We have revised the statements about this to reflect the range of PaCO2 cutoffs used to enroll patients, rather than stating that PaCO2>45 was commonly used. While we found no studies which directly compared the efficacy of enrolling patients with different PaCO2 levels (such as >45 versus >52), we have now performed an indirect analysis of all RCTs in COPD. Based on this post-hoc analysis, we found that a higher PaCO2

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		criterion but rather having a “chronic stable state” or the like as a criterion. The only one to do so recently was Struik et al again – Kohnlein et al used > 7.30 and Murphy et al had a criterion for pH. The authors should reflect the ranges used and report that most more recent studies on COPD (past decade at least) have used entry criteria for PaCO2 in the 50s. This reflects the CMS criterion of ≥ 52. To not acknowledge this is misleading and would be a disservice to the field.	threshold for initiating NIPPV was associated with non-statistically significant trends in reduced mortality and reduced hospital readmissions, and a statistically significant improvement in quality of life. Of note, most of the 11 studies which used cutoff PaCO2>45 were published in the past 10 years. (1996,1998,2008,2010,2010,2011, 2011,2011,2014,2014,2014).
Public Reviewer #1 Phillip Porte National Association for Medical Direction of Respiratory Care	General	5) Along these lines, to include BMI > 30 as an “initiation criterion” for NIV is also misleading. This defines obesity and is therefore a criterion for OHS, but it is not genuinely a criterion for NIV because very few people with BMI > 30 need NIV. It’s the hypercapnia that serves as a criterion for NIV. We are certainly willing to discuss these comments with AHRQ staff/authors if they so desire.	We agree with this point. The criteria that are used to define OHS should be differentiated from the criteria used to initiate NIPPV in patients with OHS. We have revised the statements throughout the report accordingly.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	General	We appreciate the Agency’s undertaking of this research, and the EPC’s thorough review of the literature in regard to this topic. While we are in general agreement with the key findings of this draft report, we would like to offer several comments that relate to the methods and interpretation of data, particularly as it relates to the use of non-invasive positive pressure ventilation (NIPPV) in the COPD patient population.	We thank the reviewer for the comments.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Evidence Summary	The overarching goal of this initiative is to determine how best to provide this important patient population with the care they deserve, in the comfort of their home environment. While the gathering of evidence and conduct of clinical studies in this field will go on for many years, refining the best practices with which we treat these patients, there are realities to consider today. COPD alone affects tens of millions of Americans (hundreds of millions globally) and is already the third leading cause of death in the U.S., disproportionately affecting Medicare beneficiaries.1 In 2012, more than 1 million patients were admitted to U.S. hospitals suffering acute exacerbations of COPD, making it one of the leading causes of adult hospitalizations. At an average of $11,195 per admission (and upwards of $40,000 should the patient need mechanical ventilation), the estimated cost to the U.S. health care system is almost $50 billion dollars annually.2,3 Given the continued increase in the prevalence of COPD and the	We thank the reviewer for the comments. Cost effectiveness was beyond the scope of this review. We have added a sentence about cost in the background sections.

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		high cost associated with acute exacerbations, patients and payers benefit from policies that incentivize keeping them well and functioning in the home and out of the hospital.	
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Evidence Summary	These patients require a consistent level of professional service to manage their condition at home, especially when a respiratory assist device or mechanical ventilator is indicated, to minimize complications, exacerbations or escalation in care to costlier emergency or inpatient services. While much of the evidence has focused on the devices or the modes of ventilation, a holistic, real-world approach to providing therapy, services, and support is needed for these patients today. That is especially true for patients who require a full-featured, life-support ventilator to deliver non-invasive home mechanical ventilation therapy. Without considering the services and support these patients require to successfully manage their disease at home, this initiative will not fully address the scope of this issue.	We agree that respiratory support in the home is an important issue to evaluate. We have addressed this issue as was possible in the published literature in KQ4.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Evidence Summary	1 Hoyert DL and XuJQ. Deaths: Preliminary data for 2011. NatlVital Stat Rep 2012;61(6):1–65.	We thank the reviewer for the comments.
Reviewer #2 Larissa D'Andrea ResMed Corp.	Evidence Summary	2 Perera PN et al. Acute exacerbations of COPD in the United States: inpatient burden and predictors of cost and mortality. COPD 2012;9(2):131-144.	We thank the reviewer for the comments.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Evidence Summary	3 Toy EL et al. The economic impact of exacerbations of chronic obstructive pulmonary disease and exacerbation definition: a review. COPD 2010;7(3):214-228	We thank the reviewer for the comments.
Peer Reviewer #1	Introduction	Avoided the use of "NIV" for ventilatory support	Unfortunately, without additional explanation, we are unsure exactly what this comment is referring to.
Peer Reviewer #2	Introduction	Executive Summary (ES-1 to ES-20). I agree that the SAE's are probably vastly under-reported due to study design (primary outcome, etc.). This should be emphasized. I don't think that you can make the claim regarding overall SAE's on page ES-10 given the non-SAE data that you have for no treatment at all.	We agree that SAEs might be under reported but we do not have a definite conclusion on that. We also did not make direct comparisons between interventions on non-SAEs/SAEs. Our objective was to summarize all SAEs/non-SAEs reported by the studies, while recognizing the limitations of the literature. We addressed this in ES and the results sections.

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Peer Reviewer #2	Introduction	Page 1 (synthesizing the best available evidence to guide prescribing). Have you accomplished this? Based upon the current guidelines and your findings, what are your current recommendations for initiating Home NIPPV for each of these categories of disease? Are any of the guideline recommendations now refuted? Does the information in this report support them?	We have added a summary of existing guidelines for each disease category to the results section of the main report. While the purpose of this report is to summarize literature for various purposes (one of which may be to inform guideline development), in this current report, we do not develop or evaluate the validity of existing guidelines.
Peer Reviewer #3	Introduction	Appropriate	We thank the reviewer for the comments.
Peer Reviewer #4	Introduction	Excellent	We thank the reviewer for the comments.
Peer Reviewer #5	Introduction	Risk of bias assessment was robust. Category definition of chronic respiratory failure is of good quality as obesity hypoventilation is dealt with as a category separate from thoracic restrictive disease.	We thank the reviewer for the comments.
Peer Reviewer #1	Methods	EBM states that the best data available should be taken into account. When controlled studies are impossible because the intervention takes the place or function of a vital organ or bodily function, it should still be considered otherwise patients die needlessly or get invasive airway tubes.	We thank the reviewer for the comments. We completely agree.
Peer Reviewer #2	Methods	Page 2. Should ABG be one of the measurable improvements (Key Question)?	Regarding ABGs: We did not evaluate gas exchange (change in PaCO2) 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	Methods	Page 3. Table1 Comparators (Inclusion Criteria): Studies without a comparator treatment could evaluate the effect of a patient characteristic (adherence?) or laboratory criteria (ABG?) will be included, but this was not uniformly done and reported on. There are demonstrable effects of NIPPV on ABG's for many of these disease categories.	We have clarified the description of study inclusion criteria in Table1. If a study reported an outcome of interest (e.g. mortality) in 2 groups of patients based on patient or laboratory characteristics (e.g. mortality rate in patients with PaCO2>45 versus mortality rate in patients with PaCO2>52, we have included such studies in our review. We excluded studies which reported reductions in PaCO2 as the only efficacy outcome, as this was considered to be an intermediate surrogate outcome, not a patient centered clinical endpoint outcome (such as mortality, healthcare

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			utilization, quality of life, etc.)
Peer Reviewer #2	Methods	Page 4. See comments above regarding excluding certain types of studies.	We thank the reviewer for the comments.
Peer Reviewer #2	Methods	Page 7. You need to discuss how you developed the overall risk of bias of studies for a disease category based upon the risk of bias in individual studies.	We added the information in the revision.
Peer Reviewer #2	Methods	CPAP is the mode, unless it is C-Flex, etc.	We have corrected.
Peer Reviewer #2	Methods	For clarity in all the disease categories, when you "include" studies, I would note at the beginning of the disease category the numbers each study (RCT, observational, etc.) that were included.	We presented the information in Figure 2. We added this in this revision.
Peer Reviewer #3	Methods	Clear and well described	We thank the reviewer for the comments.
Peer Reviewer #4	Methods	The inclusion and exclusion criteria are justifiable. The search strategies are clearly stated and logical. The definitions and diagnostic criteria for condition and outcomes are appropriate. The statistical methods are appropriate	We thank the reviewer for the comments.
Peer Reviewer #5	Methods	Overall the inclusion and exclusion criteria are justifiable but it is notable that some important studies are missed (see comments in the following section "d").	We thank the reviewer for the comments. We have addressed the missing studies you identified below.
Peer Reviewer #5	Methods	The COPD section recognizes but does not distinguish between stable and Post-acute patients. There is evidence, however, to support the use of recent hospitalization as a proxy for a higher risk of recurring exacerbation. Prior hospital admission is recognized to be the biggest driver for a further exacerbation requiring admission [Mullerova H, Maselli DJ, Locantore N, et al. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. Chest. 2015;147(4):999–1007.] Also acute non-invasive ventilation use in hospital has also been recognized as a predictor of overall exacerbation rate [Yang H, Xiang P, Zhang E, et al. Predictors of exacerbation frequency in chronic obstructive pulmonary disease. Eur J Med Res. 2014;19(1):18.].	We did distinguish between stable COPD and post-acute COPD in the main report, page 19, table 8.

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Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Methods	It is clear that AHRQ has reviewed a great deal of clinical evidence, utilizing a systematic approach to weigh the strength of the evidence (SOE), in support of this report. While this approach is sound, it is also important to keep in mind that many of these respiratory conditions are accompanied by high rates of healthcare resource utilization, complications, exacerbations, hospitalizations, and readmissions, as well as confounding comorbidities. It is this complicated reality that must allow for thoughtful latitude when considering SOE. In the real world, these medically complex patients do not predictably align themselves with the strict inclusion and exclusion criteria of the typical randomized, controlled study. There are other important sources of evidence, editorials, expert opinions, and real-world experiences that may score lower on the SOE scale which could also prove very useful to consider as this work continues. It is clear that the clinical evidence is weighted and trending in favor of providing a pathway for patients with respiratory diseases to have access to the home-based ventilatory support modality most appropriate for their clinical condition.	These are important considerations and we thank the reviewer for the comments. Certainly, SOE is not the only factor to be considered in decision making.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Methods	A number of studies that were included in the report had corresponding editorials that provide additional context into interpretation of complex clinical findings from these studies (e.g. Clini, 2002. Ref. 40; McEvoy, 2009. Ref. 32; Murphy, 2017. Ref. 6). Thus we would recommend that the EPC review team and any external readers of the draft and final report to review these accompanying editorials to gain additional insight on these complex studies and the interpretation of their outcomes. For example, these editorials discuss the potential impact of ventilator settings (e.g. rate, pressure, etc.) on the results observed, which we believe will be informative to the reader of this report.	Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Methods	Likewise, a number of studies included in the assessment also reported additional secondary analyses in the form of published abstracts and conference presentation, which is expected to provide meaningful information on additional endpoints that were not included in the primary clinical study publications included in this review (presumably due to word limits in the primary study publications). For example, Murphy and colleague published results from the HOT-HMV study in JAMA 2017 (Ref 6), which included reports on Mortality and Health-related Quality of Life	Abstracts (without accompanying manuscripts) and editorials were not included in our review.

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		Outcomes in the primary publication. This was a comprehensive study that included numerous other outcomes that have subsequently been reported in abstracts, and are presumably in preparation for full publication (the abstract references are provided in our comments to the Results section).	
Peer Reviewer #1	Results	All of the key messages are inadequate, especially 1, 2, and 4.	We thank the reviewer for the comments. We provided responses for each key message-related comment".
Peer Reviewer #1	Results	Page 3, concerning Key Message 1 1) Using BiPAP (which includes inspiratory (IPAP) and expiratory positive airway pressure (EPAP) which prevents patients from comfortably fully exhaling into the atmosphere) instead of a "ventilator," can be useful early on for patients with neuromuscular disease (NMD) but eventually virtually all of the patients from noninvasive management centers (www.breatheNVS.com) become dependent on continuous noninvasive ventilatory support (CNVS), that is, noninvasive support without ever resorting to tracheotomies. Pressure preset ventilation, like BiPAP, precludes lung volume recruitment (air stacking) so it is never optimal because it precludes lung volume recruitment (LVR) as well. It is for this reason that volume preset NVS is warranted once patients become symptomatic for respiratory muscle dysfunction/hypoventilation and for the following reasons: 1) lung volume recruitment to maintain pulmonary compliance is precluded by any pressure preset mode. 2) the EPAP is always counterproductive. Although used to normalize apnea hypopnea indices (AHIs), CO2 is ignored and often remains elevated with bi-level settings that normalize AHI. This does not occur when using NVS, that is, noninvasive support at full ventilatory support settings 3) almost all optimally managed patients eventually become CNVS dependent for which volume/pressure portable ventilators must be used anyway so why begin them on bi-level devices. 4) EPAP necessitates higher IPAPs for adequate drive pressures to normalize CO2 also decreases venous return and is unnecessarily uncomfortable, that is, by impeding exhalation. 4) In 2016 Cresimanno et al. demonstrated that all sleep and ventilatory parameters are better without EPAP even for bulbar	We agree that each of these is important considerations, especially in patients with NMD. The results/scope of our review do not either support or refute these considerations. We agree that it would be unethical to do comparative studies (of device versus no device) on patients who are require 24 hours a day device use. While important, the 2016 Cresimanno et al. study you mentioned evaluated outcomes after 2 nights of device setting use, and we included studies enrolled patients with >1 month home use.

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		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 "BiPAP" 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.	
Peer Reviewer #1	Results	Page 3 Key Message 2 BiPAP cannot be used for CNVS, only portable ventilators, therefore comparative studies are unethical. They are unethical principally because CNVS can NOT be discontinued or compared with any approach that does not provide full ventilatory support. BiPAP can provide full ventilatory support but is not sanctioned as such, is rarely used as such, and is particularly impractical for daytime support.	We agree these are important considerations when planning future studies. We agree that it would be unethical to do comparative studies (of device versus no device) on patients who are require 24 hours a day device use. We have noted this in the limitations section. We have also added "where feasible" in the text of the key messages.
Peer Reviewer #1	Results	Page 3 Key Message 4 "The most commonly reported serious adverse event was acute respiratory failure (ARF)." ARF only occurs when ventilatory support is inadequate, as it never is when using NVS, and/or when airway secretions are inadequately expulsed by not using mechanical in-exsufflation or by using it at less than 50 to 60 cm H2O. This is why NONE of our SMA or myopathy/muscular dystrophy patients ever need tracheostomy tubes and NIV/NVS should never be considered without effective airway secretion management to maintain O2 sat over 94% in ambient air. The principle reason that these "key messages" are so	We thank the reviewer for the comments. We agree with the reviewer that acute respiratory failure (with its resultant costs and need for intubation/tracheostomy) may result from inadequately managed home NIPPV. In this systematic review, we evaluated all potential studies that met inclusion criteria, including those studies which evaluated NVS/CNVS. Unfortunately, the studies looking at NVS/CNVS did not meet the inclusion criteria for this review (see responses below for reasons for exclusion for the individual studies you referenced).

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		inappropriate is because the reviewers do not use NVS/CNVS, that is, full noninvasive ventilatory support settings, e.g. pressure control 18-25 cm H2O and no PEEP or volume preset 800 to 1500 ml. Suboptimal management with bi-level PAP for NMD patients leads to ARF which results in intubations and tracheotomy then $400,000 per year for nursing care. The Dept. of Health and Human Services should expect better.	
Peer Reviewer #1	Results	Page 9 "Review methods. We included randomized and comparative observational studies that enrolled adults with chronic respiratory failure who used NIPPV for ≥ 1 month at home (using a home mechanical ventilator [HMV], bi-level positive airway pressure [BPAP] device, or continuous positive airway pressure [CPAP] device)." However, it is not possible to compare life sustaining interventions with anything less than life sustaining. The typically used low span bi-level PAP is not life sustaining. CNVS is life sustaining and therefore cannot be compared with low span bi-level PAP, CPAP, O2 delivery, or aspirin. DMD patients live 10 years longer (to age 40) using CNVS rather than tracheostomy mechanical ventilation (TMV) and 20 years longer than using nothing,(2) SMA1,2,3 patients can have normal life expectancies without resort to tracheotomy; polio patients over 60 years on CNVS, etc.. Many of these patients have not been hospitalized for over ½ century despite the fact that they have 0 ml of vital capacity, no ventilator-free breathing ability, and much better quality of life than if they had been forced to undergo tracheotomy by being exposed only to bi-level PAP or CPAP. Noninvasive management is far less expensive and maintains far better quality of life than invasive management so I suggest that the DHHS take an interest in it. Only historical controls are ethically possible, not randomized studies for these patients since they cannot survive without continuous support. It would be like doing a randomized study on the efficacy of parachutes for gravitational challenge.	We thank the reviewer for the comments. We have now added sections regarding this in the limitations section.
Peer Reviewer #1	Results	Page 13 – There is an ancient Chinese proverb that states that "the first step to wisdom is to call something by what it really is". "Chronic respiratory failure is a common medical condition characterized by the inability to maintain normal oxygen (PaO2 ≥	The definition we used for respiratory failure includes both hypoxemic and/or hypercapnic respiratory failure (as well as "insufficiency"). This report focuses primarily on hypercapnic respiratory failure. We agree that

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		60mmHg) and/or carbon dioxide (PaCO2 ≤ 45mmHg) levels." "Respiratory failure" implies oxygenation failure. Hypoventilation that is not fatal is "ventilatory insufficiency" 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 "While both HMV and BPAP devices provide positive pressure ventilation," 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 "volume preset" as a possibility of HMV machines.
Peer Reviewer #1	Results	Page 15 HMV: "A machine capable of delivering pressure and/or volume targeted ventilation outside of the hospital setting." 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-cycled or preset ventilation whereby patients can perform active LVR.	We thank the reviewer for the comments. We have added "volume preset" as a possibility of HMV machines.
Peer Reviewer #1	Results	Page 17 "For HMV devices, the modes utilized were pressure support ventilation and pressure controlled ventilation. " Volume preset ventilation is crucial for daytime support, that is, CNVS via mouthpiece/nasal interface. If the clinician is unfamiliar with this the patient MUST inevitably develop ARF, get intubated, then trached. www.breatheNVS.com patients are not trached.	On page 17, we were reporting the modes used by the included studies. We thank the reviewer for the comments about additional possible modes.
Peer Reviewer #1	Results	Page 3 Key Message 3 and much of the entire document concerns indications for beginning sleep ventilation. Frankly, the reason why there are so many opinions is because none are valid. Only symptoms warrant a trial or NIV/NVS. Treat patients (symptoms), not numbers.	We thank the reviewer for the comments.
Peer Reviewer #1	Results	Page 19 Obesity hypoventilation patients require positive inspiratory pressures of 30 to 55 cm H2O to normalize their O2 sat and CO2 and they tolerate these settings extremely well whether provided by pressure or volume cycling. BiPAP machines do not deliver 50 cm H2O. These patients should not	We thank the reviewer for the comments.

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		require tracheostomy tubes, but bi-level PAP won't save them.	
Peer Reviewer #1	Results	Pages 21-22 More appropriate than looking at the success or lack thereof of the mode – BiPAP, CPAP, HMV etc. is to look at the outcomes of the ventilatory support settings whether by bi-level PAP or HMV. Also, any conversation about NIV/NVS without considering MIE to clear airway debris during respiratory infections MUST result in ARF, intubation, then unnecessary resort to tracheotomies. The emphasis on the device rather than on the settings/approach is inappropriate.	We evaluated device type by device settings used as reported in the literature. We also evaluated the use of mechanical insufflation exsufflation as reported by individual studies (KQ4).
Peer Reviewer #1	Results	Page 23 "We found no major differences in the criteria considered for initiation of a HMV versus BPAP device—" Because the ventilatory support settings of NVS were not considered.	A precise definition of NVS would be useful. Assuming that you are using NVS to refer to volume preset ventilation through a noninvasive interface (mask, mouthpiece, etc.), then we have considered these equipment parameters. See Appendix, KQ3, Table F.18 and beyond where the modes of ventilation (such as volume controlled) are listed.
Peer Reviewer #1	Results	Page 23-24 "Hospitalizations for intubation were considered as primary efficacy outcomes and not serious adverse events." --- Unclear what is meant by this. These occur because of inadequate ventilator settings and suboptimal airway secretion management – using MIE at less than 50 cm H2O settings. Further, all these patients can be extubated to CNVS and MIE after the acute lung disorder is cleared.(3,4) Page 24 "For example, two European guidelines recommended an HMV device with an alternative backup power source, alarms to signal "mask off" or "low pressure" or "power failure," and a second backup ventilator for patients with any disease condition whose device use approached >16 or >18 hours/day." While this is true, 16 to 22 hours a day is not CNVS, it is sleep plus some daytime NVS. 760 NMD patients have been described who were CNVS dependent such that removal from the ventilator would cause death in minutes.(5) These patients do not need trach tubes but they do need HMVs at NVS settings and not bi-level PAP.	Death, readmission, and need for intubation were listed as primary outcomes and the impact of device use on these outcomes was reported in KQ2 analysis. We did not re-report this analysis under adverse events. We have added clarification regarding this point in the report..
Peer Reviewer #1	Results	Page 25 Limitations should also include the fact that no CNVS dependent patients were considered, only sleep and other part-time NIV users.	We did not include literature on CNVS patients as there was no literature on CNVS patients that met our inclusion criteria. We have evaluated each of the articles about CNVS patients you brought to our attention. Unfortunately (as addressed individually elsewhere in this

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			report , none of these studies met our inclusion criteria. We have listed this in our limitation section.
Peer Reviewer #1	Results	Page 25 760 CNVS users became CNVS dependent without bi-level titrations(4) so is it true that "There is a need to determine the optimal targets and process of device titration"? www.breatheNVS.com centers have reported over 700 such CNVS dependent ventilator users alone and none should ever require tracheotomies. Maybe an entirely different treatment paradigm should be considered for the sake of the patient's quality of life as well as the treasury	We thank the reviewer for the comments.
Peer Reviewer #1	Results	This review considers only "NIV." NIV has come to mean CPAP and low spans of bi-level PAP used to treat sleep disordered breathing. This makes respiratory failure inevitable and subjects these patients to invasive airway tubes and preventable morbidity and mortality. Noninvasive ventilatory support (NVS) is completely ignored in this review. Not a single CNVS dependent ventilator user is mentioned. Why does our government continue to promote a paradigm of inadequate ventilatory assistance/support, inadequate airway secretion management, inevitable resort to hospitalizations, bronchoscopies, intubations, and tracheostomies, and long-term nursing care at enormous expense in quality of life and money and provide financial incentives for all these invasive procedures but no incentives for long-term CNVS nor extubation and tube decannulation to CNVS and MIE to save money and lives?(4,5) I'll tell you why. Because physicians profit, hospitals profit, nursing agencies profit, all profit except patients and taxpayers. Compensate outcomes, not devices and unnecessary invasive interventions. Physicians of www.breatheNVS.com have many ALS, SMA, and DMD patients who have become CNVS dependent without ever going to a hospital or developing respiratory failure. They simple stay home and cost only the price of HMV rental or about $10,000 per year. Why continue to pay $400,000/year for nursing management of tracheostomy tubes and TMV when the tubes could have been avoided in the first place? Why compensate physicians with 11.75 RVUs for placing a tracheostomy tube in 15 minutes whereas education for multiple hours to avoid them is good for 1 RVU? Why should any physicians take notice of the more humane noninvasive management when NIV reviews	We used the term NIV to include all ventilation through a noninvasive interface (mask/mouthpiece), and excluded "invasive" interfaces (tracheostomy and endotracheal intubation). This covers CPAP, BPAP, as well as other modes of mechanical ventilation such as volume controlled ventilation, pressure controlled ventilation, etc. This would include "volume preset." CNVS (or patients who require 24 hour ventilation with a mechanical ventilator device through a noninvasive interface) was not included in this report because we did not find a single comparative study on CNVS that met our inclusion criteria. We do appreciate you reviewing several articles about CNVS patients. Unfortunately (as addressed individually elsewhere in this report , none of these studies met our inclusion criteria. We have listed this in our limitation section. .

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		sponsored by the DHHS do not even consider it because there can be no “controlled studies”? Please address each one of my points.	
Peer Reviewer #2	Results	Page 23 and 24 (TRD, written material and table regarding reference 53); the patient numbers are different.	We have corrected. Thank you.
Peer Reviewer #2	Results	Page 27 has some out of order sections; see the marked up PDF.	We have reformatted the report.
Peer Reviewer #2	Results	Page 28 (NMD, line 20, observational study evaluating BPAP patients correctly ventilated, reference 54); higher survival does not add up to a lower odds ratio (0.25). This needs to be reworded. Verify that this error is not repeated elsewhere.	We corrected this. Thank you.
Peer Reviewer #2	Results	Page 33 (OHS) Nearly every RCT quoted here is able to demonstrate a reduction in PaCO2 (frequently associated with increased PaO2) with use of NIPPV as major outcome of the study. This is not included in Table 13 as a major effectiveness outcome. Considering the role of ABG findings when initiating Home NIVVP, when they are available, changes in ABG should be included as an outcome measure for OHS as well as other disease categories.	We did not evaluate gas exchange (change in PaCO2) as an outcome, as this was considered to be an intermediate surrogate outcome, not a patient centered clinical outcome (such as mortality, healthcare utilization, quality of life, etc.)
Peer Reviewer #2	Results	Page 42 (Key Points-KQ1) You need to finish the second to the last sentence in the paragraph ("and one study".....).	We have corrected.
Peer Reviewer #2	Results	Page 43. Top paragraph on Stable disease versus.... You have 5 studies, but only describe 4.	One study did not report this information. We have clarified this.
Peer Reviewer #2	Results	Page 47. Same concerns as above about adverse event under-reporting.	One study did not report this information. We have clarified this.
Peer Reviewer #2	Results	Page 48. Table 19. Reference numbers are wrong.	We have revised the report accordingly.
Peer Reviewer #2	Results	Page 52. Table 21. No SOE for shorter hospital stay for HMV in other respiratory diseases.	For SOE rating, with the inputs from Key Informants, we identified and chose the outcomes most relevant to patients. Therefore, we rated the strength of evidence for 4 outcomes (mortality, need for intubation, quality of life and all-cause hospital admissions). Length of hospital stay, although an important outcome, it was deemed not critical (please see GRADE guidance on important vs

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			critical outcomes).
Peer Reviewer #3	Results	Clear	We thank the reviewer for the comments.
Peer Reviewer #4	Results	For CPAP devices, modes were not specified. This needs some clarification. Specifically, there are no modes for CPAP. There are flow modifications such as expiratory pressure relief that can be stated to not being available.	We agree and have clarified this.
Peer Reviewer #4	Results	In page viii, lines 22-24, "In COPD (34 studies), common criteria for NIPPV initiation were FEV1<50% normal, PaCO2 >45mmHg, pH>7.35, and/or hypoxia." I am uncertain if this threshold of 45 mmHg for PaCO2 was the most common. It is my understanding that 52 mmHg for PaCO2 is a more commonly used threshold. Is it possible to summarize the proportion of studies that used the 45 mmHg in the executive summary? On second thoughts, perhaps the authors mean to state that the thresholds for initiation were all greater than 45 mmHg, but then the sentence is a bit misleading. There is greater clarity in page 12, lines 16-20. Perhaps this should be included in the executive summary. The PaCO2 threshold is a common barrier for implementation barrier as it defines the presence of chronic respiratory failure.	We have revised the statements about this to reflect the range of PaCO2 cutoffs used to enroll patients, rather than stating that PaCO2>45 was commonly used. While we found no studies which directly compared the efficacy of enrolling patients with different PaCO2 levels (such as >45 versus >52), we have now performed an indirect analysis of all RCTs in COPD. Based on this post-hoc analysis, we found that a higher PaCO2 threshold for initiating NIPPV was associated with non-statistically significant trends in reduced mortality and reduced hospital readmissions, and a statistically significant improvement in quality of life.
Peer Reviewer #4	Results	Page 15, "After a follow-up of 12 months, 7 out of 23 patients in the BPAP group developed severe COPD exacerbation with AHRF while 14 out of 26 patients in the COPD group had severe exacerbation with AHRF." Should be corrected to state, "After a follow-up of 12 months, 7 out of 23 patients in the BPAP group developed severe COPD exacerbation with AHRF while 14 out of 26 patients in the CPAP group had severe exacerbation with AHRF."	Thank you. We have corrected.
Peer Reviewer #5	Results	d. Results: 1)The COPD excludes the following important works in the period covered by the literature synthesis: a.Oscroft NS et al. The effects of withdrawing long-term nocturnal non-invasive ventilation in COPD patients. COPD. 2010; 7(2):111–116.	. We have now included this study.

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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): 486–488.	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): 538–544.	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; 127:2132–8. 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;127:450–3. 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 patients with acute respiratory failure. It used domiciliary CPAP/NIV use as an outcome rather than an exposure. Outcome data (mortality, hospital admission, quality of life, etc.) was not reported for those who used domiciliary CPAP/NIV versus those who did not.

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Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Results	We recommend that the EPC review team and any external readers of the draft and final report to review accompanying editorials (e.g. Clini, 2002. Ref. 40; McEvoy, 2009. Ref. 32; Murphy, 2017. Ref. 6) to gain additional insight on these complex studies and the interpretation of their outcomes.	We have reviewed these studies. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Results	In addition, we recommend that the EPC review team and any external readers of the draft and final report to review the accompanying abstracts noted below and perform updated literature searches to identify additional publications that were not available at the time the original search was completed. The HOT-HMV study in JAMA 2017 (Ref 6) was a comprehensive study that included numerous other outcomes that have subsequently been reported in abstracts, and are presumably in preparation for full publication including the following:	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Results	Murphy P, Arbane G, Bourke S, et al. Improving admission free survival with home mechanical ventilation (HMV) and home oxygen therapy (HOT) following life threatening COPD exacerbations: HoT-HMV UK Trial NCT00990132. European Respiratory Journal. Conference: European Respiratory Society Annual Congress. 2016;48(no pagination). PMID: 614779787. [Abstract/ conference proceeding]	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Results	Murphy P, Moxham J, Polkey M, et al. HOT HMV UK: An investigation into mechanisms of action of home mechanical ventilation (HMV) following acute hypercapnic exacerbations of COPD. European Respiratory Journal. Conference: European Respiratory Society Annual Congress. 2011;38(no pagination). PMID: 72116497. [Abstract/ conference proceeding]	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Results	Murphy PB, Arbane G, Bisquera A, et al. Home mechanical ventilation (HMV) and home oxygen therapy (HOT) following an acute exacerbation of COPD in patients with persistent hypercapnia: Predicting 1 year admission-free survival in the hot-HMV UK trial. Thorax. 2017 December;72 (Supplement 3):A26-A7. PMID: 619739045. [Abstract/ conference proceeding]	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Results	Murphy PB, Arbane G, Bourke S, et al. Hot-HMV UK trial secondary outcome analysis: early readmission is reduced by the addition of home mechanical ventilation to home oxygen therapy in COPD patients with chronic respiratory failure following a life-threatening exacerbation. Thorax. 2016 December;71:A68-A9. PMID: 615030762. [Abstract/ conference proceeding]	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.

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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.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Results	Murphy PB, Moxham J, Polkey MI, et al. UK hot-HMV trial: Acceptability and tolerability of high pressure domiciliary non-invasive ventilation (NIV) in COPD. Thorax. 2011 December;66:A55. PMID: 70627758. [Abstract/ conference proceeding]	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Results	Criner GJ, GU Q, Murphy PB, et al. Cost-effectiveness of home oxygen therapy-home mechanical ventilation (HOT-HMV) for treatment of chronic obstructive pulmonary disease (COPD) with chronic hypercapnic respiratory failure following an acute exacerbation of COPD in the United States. Presented at the American Thoracic Society 2018 International Conference; May 18-23, 2018; San Diego, California. Abstract A2518.	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	Results	Lastly, we note that the report excluded any discussion of the economic impact of home ventilation in patients with COPD. The cost-effectiveness and budget impact of novel therapies remain important considerations to patients, clinicians, payers, and policymakers. In addition to the Criner abstract noted above, we identified four additional studies that address the economics of home ventilation in the COPD patient population (Dretzke 2015, Tuggey 2003, Clini 2007, Becker 2015) that would be relevant to the EPC review team and external readers of the draft and final report	We agree that cost effectiveness is important. Nevertheless cost effectiveness is outside the scope of this review.
Peer Reviewer #2	Discussion/ Conclusion	There is no discussion of reversal of chronic respiratory failure in any of the disease categories as this analysis was not performed. I would consider this to be a flaw in the design, specifically in the evaluation of the effectiveness of NIPPV. Is this not an opportunity to assess a target level measurable improvement?	We did not evaluate improvement in PaCO2 as an outcome, as we considered it as an intermediate surrogate outcome, not a patient centered clinical outcome (such as mortality, healthcare utilization, quality of life, etc.).
Peer Reviewer #2	Discussion/ Conclusion	Page 53 (Findings in Relation to What is Known) misses the opportunity to state what is known about using NPPV for each of these diseases. It reiterates the findings of the report. What are the current standards, and what literature supports them?	Unfortunately, outlining the current standards of care (in the United States or other countries) is beyond the scope of this review. Even in the United States alone, there is substantial variability in practices and guideline recommendations regarding device use.

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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 limitations identified. I do not believe that any important literature was omitted. The authors have clearly identified future research needs in this area. They are very insightful and appropriate.	We thank the reviewer for the comments.
Peer Reviewer #5	Discussion/ Conclusion	The authors demonstrate sufficient scientific equipoise and are aware of the limitations of the study relating to the common limitations in the field, particularly those of heterogeneity and the inconsistency of reporting of device type (i.e., difficulty in differentiating HMV from BPAP), device used (e.g., manufacturer and model), key device characteristics (e.g., mode used), and device titration protocol and targets.	We thank the reviewer for the comments.
Peer Reviewer #5	Discussion/ Conclusion	However, the authors do not recognize the limitation due to confining the search to English language only. In a systematic review on domiciliary non-invasive ventilation in COPD alone, we noted that abolishing language restrictions meant that 19% of the included studies were non-English, a substantial proportion of the overall evidence base omitted by reviews prior to our review [Health technology assessment 2015; 19(81):1-246; DOI: 10.3310/hta19810]. Therefore it would be fair to state the language limitation and its attendant risk of bias.	This is an important consideration. We have added this to our limitations.

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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 affected by amyotrophic lateral sclerosis (ALS). We explored consequences of positive end-expiratory pressure (PEEP) application on effectiveness of ventilation, sleep architecture and heart rate variability (HRV) in patients with ALS naïve to ventilatory treatment. Methods: In two consecutive nights, 25 patients received in random order 0 or 4cmH20 of PEEP during nocturnal NIV administration (Idea Ultra ResMed) with the same level of total positive inspiratory pressure. Polysomnographies were performed to evaluate sleep and NIV quality, as well as HRV. HRV was analyzed on 4-h periods and on 5-min segments of stable NREM sleep. Results: We did not observe differences in gas exchanges during NIV with and without PEEP. Conversely, during PEEP application increases in leaks (41.4 ± 29.3% vs 31.0 ± 25.7%, P= 0.0007) and in autotriggerings (4.2 (IQR 1.3–10.0) vs 0.9 (IQR 0.0–3.0) events/h, P<0.001, PEEP vs no PEEP, respectively occurred. Besides, N3 sleep stage duration decreased (2.5% (IQR 0.0–18.0) vs 0.0% (IQR0.0–12.1), P= 0.001) and arousal/awakening index increased (16.9 ± 7.4 vs 13.4± 5.0 events/h, P= 0.01). Data on HRV were available in 15 patients. A higher low/high frequency ratio, either in the 4-h (3.8 ± 2.6 vs 2.9 ± 1.7, P= 0.04, PEEP vs no PEEP, respectively) or in the 5-min segments (2.6± 1.8 vs 1.45 ±0.9 P= 0.01) was found during	We excluded this study, as the intervention comparisons were only administered for 2 nights (not 1 month or more as defined in our protocol).

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		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	References and notes	2) Ishikawa Y, Miura T, Ishikawa Y, Aoyagi T, Ogata H, Hamada S, Minami R. Duchenne muscular dystrophy: survival by cardio-respiratory interventions. Neuromuscular Disorders 2011; 21:47–51	We excluded this study as it included pediatric patients.
Peer Reviewer #1	References and notes	3) Bach JR, Gonçalves MR, Hamdani I, Winck JC. Extubation of unweanable patients with neuromuscular weakness: a new management paradigm. Chest 2010;137(5):1033-1039.3	We excluded this study as this study did not report relevant outcomes after 1 month or more of home NIPPV.
Peer Reviewer #1	References and notes	4) Bach JR, Sinquee D, Saporito LR, Botticello AL. Efficacy of mechanical insufflation-exsufflation in extubating unweanable subjects with restrictive pulmonary disorders. Respir Care 2015;60(4):477–483.	We excluded this study as this study did not report relevant outcomes after 1 month or more of home NIPPV.
Peer Reviewer #1	References and notes	5) Gonçalves MR, Bach JR, Ishikawa Y, Saporito, Winck JC. Continuous noninvasive ventilatory support outcomes for neuromuscular disease: a multicenter collaboration and literature review. Pulmonology 2018;24 [Epub ahead of print].	Unfortunately, we were unable to locate the text of this manuscript, even after a comprehensive search Pulmonology's website.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	References and notes	We recommend that the EPC review team and any external readers of the draft and final report to review: Accompanying editorials (e.g. Clini, 2002. Ref. 40; McEvoy, 2009. Ref. 32; Murphy, 2017. Ref. 6).	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	References and notes	HOT-HMV study in JAMA 2017 (Ref 6) accompanying abstracts: o Murphy P, Arbane G, Bourke S, et al. Improving admission free survival with home mechanical ventilation (HMV) and home oxygen therapy (HOT) following life threatening COPD exacerbations: HoT-HMV UK Trial NCT00990132. European Respiratory Journal. Conference: European Respiratory Society Annual Congress. 2016;48(no pagination). PMID: 614779787. [Abstract/ conference proceeding]	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	References and notes	Murphy P, Moxham J, Polkey M, et al. HOT HMV UK: An investigation into mechanisms of action of home mechanical ventilation (HMV) following acute hypercapnic exacerbations of COPD. European Respiratory Journal. Conference: European Respiratory Society Annual Congress. 2011;38(no pagination). PMID: 72116497. [Abstract/ conference proceeding]	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea	References and notes	Murphy PB, Arbane G, Bisquera A, et al. Home mechanical ventilation (HMV) and home oxygen therapy (HOT) following an acute exacerbation of COPD in patients with persistent	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.

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ResMed Corp.		hypercapnia: Predicting 1 year admission-free survival in the hot-HMV UK trial. Thorax. 2017 December;72 (Supplement 3):A26-A7. PMID: 619739045. [Abstract/ conference proceeding]	
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	References and notes	Murphy PB, Arbane G, Bourke S, et al. Hot-HMV UK trial secondary outcome analysis: early readmission is reduced by the addition of home mechanical ventilation to home oxygen therapy in COPD patients with chronic respiratory failure following a life-threatening exacerbation. Thorax. 2016 December;71:A68-A9. PMID: 615030762. [Abstract/ conference proceeding]	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	References and notes	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.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	References and notes	Murphy PB, Moxham J, Polkey MI, et al. UK hot-HMV trial: Acceptability and tolerability of high pressure domiciliary non-invasive ventilation (NIV) in COPD. Thorax. 2011 December;66:A55. PMID: 70627758. [Abstract/ conference proceeding]	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	References and notes	Criner GJ, GU Q, Murphy PB, et al. Cost-effectiveness of home oxygen therapy-home mechanical ventilation (HOT-HMV) for treatment of chronic obstructive pulmonary disease (COPD) with chronic hypercapnic respiratory failure following an acute exacerbation of COPD in the United States. Presented at the American Thoracic Society 2018 International Conference; May 18-23, 2018; San Diego, California. Abstract A2518.	We have reviewed this study. Abstracts (without accompanying manuscripts) and editorials were not included in our review.
Public Reviewer #2 Larissa D'Andrea ResMed Corp.	References and notes	Additional studies that address the economics of home ventilation in the COPD patient population (Dretzke 2015, Tuggey 2003, Clini 2007, Becker 2015).	Thank you for these references. We have reviewed these references. While important, cost effectiveness was not part of this review.
Peer Reviewer #1	Discussion/ Conclusion	The Discussion promotes expensive and needlessly invasive management rather than more humane noninvasive management	We thank the reviewer for the comments.
Peer Reviewer #1	Clarity and Usability	The manuscript is well-written. The conclusion foster the premise that devices and invasive interventions should be compensated rather than outcomes and more humane options.	We thank the reviewer for the comments.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Clarity and Usability	Overall well organized, with the limitations as described above. The findings are, in general, not applicable to practice decisions, as they are somewhat disparate with current (and generally appropriate) standards of care, particularly in OHS. They contribute limited new information regarding practice decisions. Current standards of care are not well outlined in the report. Are the findings of this report supportive of them or are they refuted?	Regarding OHS, 3 new studies were added which have modified our key points, providing limited evidence for improved outcomes in OHS. Unfortunately, outlining the current standards of care (in the United States or other countries) is beyond the scope of this review. Even in the United States alone, there is substantial variability in practices and guideline recommendations regarding device use.
Peer Reviewer #3	Clarity and Usability	Very useful though nothing drastically new to experienced clinicians	We thank the reviewer for the comments.
Peer Reviewer #4	Clarity and Usability	Clarity and Usability: The review is well structured and organized. The conclusions are highly relevant to practice. With regards to heath policy there needs to be greater clarity for PaCO2 threshold for patients with COPD considering that this may affect the target population significantly. Any ability to stratify or categorize studies by PaCO2 thresholds 45 – 52 and > 52 mmHg could have significant impact on health policy.	While we found no studies which directly compared the efficacy of enrolling patients with different PaCO2 levels (such as >45 versus >52), we have now performed an indirect analysis of all RCTs in COPD. Based on this post-hoc analysis, we found that a higher PaCO2 threshold for initiating NIPPV was associated with non-statistically significant trends in reduced mortality and reduced hospital readmissions, and a statistically significant improvement in quality of life.
Peer Reviewer #5	Clarity and Usability	The report is generally well structured and usable, although providing a list of abbreviations immediately after the Contents section could make it more usable. The overall conclusions are in keeping with what is known on the subject and the evidence review robustly summarizes the available English language literature. However, in the final summary conclusions (page 55), it does not make a statement on obesity hypoventilation. Authors may consider inserting a final statement on the effect of HMV/BPAP on obesity hypoventilation on page 55.	We have added conclusions about OHV in the key messages, abstract, and conclusions.
Peer Reviewer #5	Clarity and Usability	There has not been a review of this scale which has firmly and reasonably concluded that in COPD, home BPAP (compared to no device) was associated with lower mortality, intubations, hospital admissions, and dyspnea, which is certainly an addition to the current knowledge base although it does not distinguish between the stable and post-acute populations. This evidence review also significantly firms up our existing knowledge of the effect of HMV/BPAP on thoracic restrictive diseases and neuromuscular diseases, which is practically useful and relevant to policy decisions.	We thank the reviewer for the comments.

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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 investigators' 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 didn't think of it or didn't 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 doesn't 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. The first scenario doesn't apply here. For the second one, if the investigators detect bias in the reviewers' suggestions, they should consider whether other post hoc analyses should be done in addition to the one they performed.	We agree with the reviewers' suggestion to conduct this post hoc analysis. We do not detect significant bias in this suggestion (by two reviewers). After review with our clinical team, we did not find any additional post hoc analyses to perform.
Peer Reviewer #6	Background	I read the reviewers' comments that led to the post hoc analyses. Overall I find the rationale for the paCO2 subgroup analysis reasonable even though it is a bit circular. Their point—their hypothesis—was that studies that used a higher pCO2 as a criterion would have larger effect sizes and that current thinking reflects this. However, the reviewer who suggested specific categories may have been picked a cutoff level (52) because it looked like it would separate a group of positive studies from a group of negative ones. Their other rationale for the post hoc analysis is a strong one—an estimate of the effect for a threshold of 52 or greater would be relevant to the practice of units that use that threshold. An estimate combining all thresholds would not.	We agree with the AE comment and therefore we chose this specific subgroup analysis.

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Peer Reviewer #6	Background	One of these comments suggests stratifying studies by the PaCO2 thresholds 45-52 and >52. The authors used three levels—45-49, 50 to 51, and 52 or greater. It is not clear why the authors did it this way, and it created categories with only one study in 2 of the 3 analyses. As changing criterion for categories can introduce bias, the authors should say why they didn't use the ones the reviewer suggested.	The PaCO2 cutoffs used were chosen, as these cutoffs are commonly used in clinical practice/guidelines for approval. For example, in the United States, CMS currently approves RADs for patients with COPD based on CO2 of 52 or greater. In addition, we wished to see if there was a dose response (higher cutoffs associated with increasingly better outcomes)
Peer Reviewer #6	Analysis	This was an analysis of mortality, readmission, and quality of life. Because no studies directly evaluated the relationship between pCO2 and these outcomes, the investigators grouped and then combined studies by the level of hypercapnia required to initiate NIPPV.	We agree, correct.
Peer Reviewer #6	Writeup	Overall, too little information is provided in the writeup of the post hoc analyses. These analyses may be less important and valid, but that does not mean they should not be described in sufficient detail to interpret them.	We agree with AE about the limitations of these types of analyses. We have added additional information in the methods of the final report to explain the analyses as requested.
Peer Reviewer #6	Writeup	P8 (pdf 42) line 51 "*We were unable to assess publication bias because the number of studies included in the analysis was small (n<20).*" The idea here is not well-formed and the sentence is unusable in its current form. I think the authors mean that because there were fewer than 20 studies they couldn't use certain graphical or statistical tests for publication bias (there are no citations so I don't know which ones they mean), and I can't tell whether or not the authors are referring to studies that were done but not published (traditional publication bias) or differences between the published studies that were and were not eligible for the post hoc analysis. At any rate not being able to perform these tests doesn't mean there was no way to assess publication bias. One could compare the effect sizes for all the BPAP vs no device studies with those for the subset that were eligible for the post hoc analysis. As noted below, it would also be helpful to give the total number of subgroup studies (11, but this is given only in the rebuttal table) and the total for all studies of BPAP for no device (22 RCTs and 6 observational studies) as well as the reasons why many of them weren't eligible. This information can help inform the reader's judgment of the representativeness of the subgroup studies and also of its usefulness.	There is increasing consensus in statisticians and systematic review methodologists that traditional statistical methods (funnel plots, Egger's regression test, etc.) are not reliable in detecting potential publication bias especially when the number of studies is small and/or heterogeneity is large. We revised the sentence to clarify this and added a citation. We agree that other qualitative approaches can be useful in evaluating reporting bias or publication bias. We added the analyses in the report per suggestion. We also added the reasons for those studies not eligible for the post hoc analyses.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Writeup	P20 (pdf 54) line 16ff, "*The post-hoc subgroup analyses of the levels of hypercapnia (PaCO2) used as an initiation criterion for initiation of NIPPV suggested that higher PaCO2 levels (e.g. PaCO2 ≥52 mmHg compared to PaCO2 ≥50 compared to PaCO2 ≥45) were associated with statistically significant improved quality of life (p=0.01) and non-statistically significant trends in reduced mortality (p=0.54), and reduced hospital readmissions (p=0.41) (Appendix Figures H.11-13.).*" This is confusing and the term "trend" should be avoided in this context. I think it would be better to say "The other post-hoc subgroup analysis indicated that BPAP was associated with improved quality of life (a v b, p=0.01). Differences in mortality and hospital readmissions favored BPAP but were not statistically significant (-----) .41) (Appendix Figures H.11-13.)." Don't just give p values, give effect sizes. It would also be helpful to compare these effects (that is the effect sizes, regardless of statistical significance) to those for the whole sample of studies of BPPV vs. no device.	We agree and made the recommended changes in the report.
Peer Reviewer #6	Writeup	P68(pdf 102) lines 8-9 *"…does initiating NIPPV in patients with baseline PaCO2 ≥ 45mmHg versus PaCO2 ≥50mmHg impact clinical outcomes?"* It is puzzling that the question is phrased as a "for example" and that one category is missing. The background should relay information from the reviewers that describe the rationale for the subgroup analysis—that is, current concepts emphasize a higher initiation threshold than that used in some studies. (More precisely, they want an effect size estimate that is pertinent to centers that use a threshold of 52 or greater.)	We have modified the background section of the analysis.
Peer Reviewer #6	Writeup	P68 (pdf 102) lines 14-18. The Methods section here reports study selection criteria but not much else. Could be worthwhile to say the methods were otherwise identical to those of the original analysis and refer the reader to the pertinent section of the main report.	We agree and made the changes.

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 "n studies did not report the paCO2 criterion, and x used a paCO2 threshold during an episode of acute respiratory failure", 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. if they were on the high or low side of ROB ratings for the overall sample, mention it.	We added in the document.
Peer Reviewer #6	Writeup	P106 Conclusions. This section reports the effect sizes in Figures 1-3 but doesn't say anything about the validity or usefulness of the findings. If the investigators don't think the findings are valid, say so, and explain why. If you do think they are, say that. It is not necessary to conduct an elaborate strength of evidence assessment, but not very helpful to say nothing about it. (Based on what I read, I think it is probable that higher paCO2 criteria are associated with bigger effect sizes, and possible that lower paCO2 criteria are associated with no effect, but the estimates of effect are imprecise and uncertain, but the authors might be aware of other limitations.)	We agree and changed the sentences