Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Noninvasive Positive–Pressure Ventilation (NPPV) for Acute Respiratory Failure*

Draft review available for public comment from January 20, 2012, to February 17, 2012.

Research Review Citation: Williams Jr JW, Cox CE, Hargett CW, Gilstrap DL, Castillo CE, Govert JA, Lugogo NL, Coeytaux RR, McCrory DC, Hasselblad V, McBroom AJ, Posey R, Gray R, Sanders GD. Noninvasive Positive–Pressure Ventilation (NPPV) for Acute Respiratory Failure. Comparative Effectiveness Review No. 68. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 12-EHC089-EF. Rockville, MD: Agency for Healthcare Research and Quality. July 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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 EHC Program 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: Quality of the report	Good	Thank you.
Peer Reviewer 2	General: Quality of the report	Good	Thank you.
Peer Reviewer 3	General: Quality of the report	Superior	Thank you.
Peer Reviewer 4	General: Quality of the report	Superior	Thank you.
Peer Reviewer 5	General: Quality of the report	Good	Thank you.
Technical Expert Panel (TEP) Member 1	General: Quality of the report	Superior	Thank you.
TEP Member 2	General: Quality of the report	Superior	Thank you.
TEP Member 3	General: Quality of the report	Superior	Thank you.
TEP Member 4	General: Quality of the report	Good	Thank you.
TEP Member 5	General: Quality of the report	Superior	Thank you.
TEP Member 6	General: Quality of the report	Superior	Thank you.
Peer Reviewer 1	General: Clarity and usability	The report is well structured and organized.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	General: Clarity and usability	Well-structured and organized, but rather long for the average reader. Although the "Key Points" answer the questions posed, and perhaps the mandate does not include recommendations, but I was looking for a "Recommendations" section to help inform policy and practice decisions.	Thank you. In the Discussion section, future research priorities are identified along with a discussion of the findings. Although the EPC program does not make explicit recommendations, it is expected that this report will be used to inform clinical guidelines.
Peer Reviewer 3	General: Clarity and usability	The structure of the report is well conceived; the divisions lend clarity to the manuscript. I would utilize bullet points for the main outcomes to highlight their importance in the text. The conclusions lend credence to the current guidelines regarding AECOPD and highlight the need for greater awareness in the guidelines for ACPE.	Thank you. The Key Points for each KQ are now summarized in bullet form in the Executive Summary and main report.
Peer Reviewer 4	General: Clarity and usability	The report is well-organized and the main points are clearly presented. The conclusions clearly identify areas where NIV should become usual area and other areas in need of definitive trials.	Thank you.
TEP Member 1	General: Clarity and usability	The report is clear and usable.	Thank you.
TEP Member 2	General: Clarity and usability	Report is well structured, organized and easily read. The conclusions do support continued efforts to assure access to as well as proper training in methods of NIPPV for a variety of causes of ARF.	Thank you.
TEP Member 3	General: Clarity and usability	The report reads well. It is logically structured and the take-home points are clear and obvious. The conclusions can be used to make clinical decisions and to inform future policy.	Thank you.
TEP Member 4	General: Clarity and usability	The report is very well structured and organized.	Thank you.
TEP Member 5	General: Clarity and usability	In summary, this is an extensive and well organized review of the use of NPPV in patients with acute respiratory failure. The benefit seems to be primarily in those with respiratory failure as a result of decompensated COPD or ACPE and these are the main conditions emphasized by their report. There needs to be further investigation into other disease conditions, as they have outlined, but their main conclusions should serve as the foundation for recommendations on the use of NPPV. The importance of provider training and experience cannot be overemphasized and probably represents the greatest challenge to universal and uniform adaptation of NPPV.	Thank you. Our discussion of issues related to provider training has been amplified in the Introduction and in the Discussion.

Commentator & Affiliation	Section	Comment	Response
TEP Member 6	General: Clarity and usability	good structure and organization	Thank you.
Peer Reviewer 1	General	The report is clinically meaningful and the key questions are appropriate.	Thank you.
Peer Reviewer 1	General	I would have liked to see a key question to address implementation of a successful NIV program, training of staff (respiratory therapists and others), and selection of equipment and settings. This would have added to the practial utility of the report in my opinion.	Noted. In the Future Research section, we have identified the need for studies about the effects of training and staffing composition/ratios on NPPV effectiveness.
Peer Reviewer 2	General	Based on my read of only the Executive Summary, the report is clinically meaningful, the target population is explicitly defined, and the key questions are appropriate and explicitly stated. The audience was not explicity defined unless it is the same as the Key Informants.	Thank you.
Peer Reviewer 3	General	The report is absolutely clinically meaningful with a wealth of data regarding the use of NPPV and statements regarding effectiveness in the real world. I recommend greater clarity regarding the audience for this manuscript. The audience for this comprehensive review is primarily acute care physicians and respiratory therapy departments. I don't believe that is stated directly in the document. The key questions are very clear and address the pertinent clinical facets of NPPV.	Thank you. We have clarified the primary audience for this report in the Background section.
Peer Reviewer 4	General	In general, this is an excellent review that synthesizes a large body of randomized trials on noninvasive ventilation (NIV) for acute respiratory failure. I believe that they key questions are appropriate and explicitly stated.	Thank you.
Peer Reviewer 5	General	Overall, this is a very impressive review and reporting of the evidence in this area. The review is thorough. However, as this review reports very similar results to the existing systematic reviews and clinical practice guidelines. The strength of this report is that it has identified, explicitly, gaps in the literature and recommendations for future research.	Thank you.
Peer Reviewer 5	General	I suggest defining the target audience explicitly in the Abstract, ES, and Full Report.	We now specify the target audience in the Introduction.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	General	In my opinion, the main concern about this report is that while it is clinically relevant, it is not clinically meaningful in the way the team decided to conduct an overall analysis by combining studies across all patient populations (i.e. COPD, ACPE, post-op, etc). As the authors state, the majority of studies target patients with COPD and ACPE. Hence, the statements made in the Abstract, ES, main report, and Conclusions that NPPV is useful across all patient populations is misleading. While the authors do clarify that the findings are most relevant to patients with COPD and ACPE, the overall message still comes across as clinicians can use NPPV with the safe efficacy in all patients. This also begs the question as to the utility and meaningfulness of conducting the overall analysis across all patient populations, since the results are weighted by these 2 patient-populations, primarily.	This is an important point that we considered carefully prior to analysis and again after peer review. Although the underlying pathophysiology of acute respiratory failure differs by etiology, the studies are conceptually similar in design, intervention, and outcomes. In most instances, there was small to moderate variability in effects, even across diagnostic groups. To better address this issue of potential variability by diagnostic groups, we have modified our presentation to show forest plots by diagnostic group. Further, we have not presented summary odds ratios when variability was high. Finally, we have emphasized the paucity of data in many of the diagnostic groups.
TEP Member 1	General	The report is comprehensive. The methods and results are well described.	Thank you.
TEP Member 2	General	The report is clinically meaningful. The target population of individuals with acute respiratory failure is clearly defined. The key questions are relevant and phrased in a manner which permits logical inquiry approaches.	Thank you.
TEP Member 3	General	This report represents a great undertaking to answer key questions of concern to clinicians caring for patients with respiratory failure, impending respiratory failure and recovering from respiratory failure. It is clinically meaningful and of major value. The key questions, all 4 of them, are appropriate for the intended audiences and are explicitly outlined and answered.	Thank you.
TEP Member 4	General	I find the information to be both relevant and useful to the clinician. This report will provide the clinician with objective data when determining whether to use NPPV or not for the population addressed in this report.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 5	General	Noninvasive positive pressure ventilation (NPPV) in acute respiratory failure has become a widely accepted mode of ventilatory support, yet continues to suffer from inconsistent adaptation and use. It does require significant training and more attention than its invasive ventilation counterpart which may explain its spotty adaptation. This requirement for its use may also explain its limited use in conditions other than in patients with chronic obstructive pulmonary disease (COPD) and acute cardiogenic pulmonary edema (ACPE). This comparative effective review provides a balanced and detailed evaluation of the data available and generally addresses the primary aim of their analysis which is to determine whether these research results would be expected to be realized in general use outside the research setting. While they do touch on training and provider experience in NPPV (page 3,4), there is not much emphasis on this aspect in the executive summary. This is especially important since this treatment cannot be effectively blinded in these randomized trials, since intubation which tempered by a subjective component is a key outcome variable and training and experience are the moderating factors most likely to influence the use of NPPV in the non-research setting. The authors otherwise do provide a clinically meaningful report with well formed questions and a thorough review of the literature.	The Introduction has been revised to emphasize the need for training. We have also added a comment in the Discussion about the potential for harm if NPPV is employed by clinicians without adequate training.
TEP Member 6	General	Excellent document. Strong review of the evidence, conclusion is based on the evidence.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 7	General	The document is well-researched and written. The methodology for systematic analysis and drawing inferences appear to be apt. The main concern is that the document doesn't add much to what has already been established in the medical literature and suffers from a lack of input from content experts. Multiple systemic reviews have already been performed on the topic areas reviewed by the Duke group and although there are some differences between the findings in the present document and prior reviews (for example, less evidence for benefit of NPPV in extubation failure setting in the present document than in prior review by Burns et al), for the most part the conclusions are the same. Also, the vetting process for the questions could have been more thorough. Some of the questions, such as 2 comparing CPAP and BPAP have been addressed repeatedly in previous literature (mainly for cardiogenic pulmonary edema (CPE)) and the clinical importance of the question is debatable considering that the 2 modes can be delivered by the same device by flipping a switch. None of the previous reviews has detected any important difference between the modes, and with the exception of CPE, there are virtually no studies comparing the 2. Thus, the findings related to this question were entirely predictable and effort was wasted in trying to address it. My concern here is mainly that substantial resources and time were invested in this product which doesn't seem to benefit the field. Clinicians familiar with the field could have predicted the findings. It seems that a proper needs assessment for such a review wasn't fully executed before the project was approved, and although there was clinician input on formation of questions, the project might have proved more valuable had content experts been included on the team that formulated questions and participated in document writing and development. Alternatively, one wonders whether an umbrella review that could have been done more expeditiously might have sufficed.	We agree that previous systematic reviews have addressed many of the questions included in this report. However, topic nominators and key informants (during a formal topic development process) strongly encouraged a comprehensive update. In addition, we conducted analyses—including mixed treatment effects analyses and analyses by effectiveness rating—that have not been done previously. We also formally rate the strength of evidence and prioritize future research needs, key contributions that are missing from prior reports.

Commentator & Affiliation	Section	Comment	Response
Davila, David Davila (Baptist Health Sleep Clinic)	General	I am attempting for Dr. Sidney Hayes in Little Rock and AHRQ to write comments on NPPV CER review but had difficulty with navigation of the site. I am a practicing sleep physician and deal mostly with patients with chronic respiratory failure and sleep apnea in Sleep Clinic. I do, however, interact with patients in acute respiratory failure in our hospital setting. My overall experience is that NPPV usefulness is significantly limited by the clinicians experience with PAP in terms of adjusting settings empirically and troubleshooting common interface issues. In addition having respiratory and sleep technologist readily available with deep experience in trouble shooting these issues. Seems almost as important to me as the difficult patient sub group types. I would say, however, that if any of the patient sub groups have underlying sleep apnea this might predict a bit more success with NPPV, although this is just from personal experience. Alternatively, those with obstructive lung disease tend to have more end expiratory pressure resistance or intolerance. If more systematic comments are desired please let me know.	We have revised the Introduction to note the need for training to use these technologies well. Regarding sleep apnea, our report focused on acute respiratory failure, not treatment of sleep apnea. Studies typically described the etiology of acute respiratory failure but did not systematically describe whether participants also had sleep apnea. For some studies, patients with sleep apnea were specifically excluded.
Maitland, Jeff (American College of Chest Physicians, Quality Improvement Committee	General	Approve with comments. On behalf of the American College of Chest Physicians (ACCP) the ACCP Quality Improvement Committee (QIC) appreciates the opportunity to comment on this report. Overall the QIC felt that this report was very thorough and well written. The QIC notes that the use of NPPV for end-of-life patients is not mentioned. It is not uncommon to have patients who made the decision to forgo CPR and intubation but are placed on NPPV, without prior consent. The QIC warns that the misuse of NPPV may be a larger problem than not using it when indicated. The QIC also mentioned that there was no discussion of NPPV for patients with acute respiratory distress syndrome (ARDS). The QIC notes that many physicians are tempted to use NPPV in this situation, regardless of the underlying cause of the ARDS.	In our updated literature search, we identified one study that specifically evaluated NPPV in patients with ARDS. These results are now included in the report. In addition, one study specifically included a large proportion of patients with “do not intubate” orders, and this study is singled out for special mention. In the Discussion, we have added a comment on the need for studies to evaluate the appropriate role of NPPV in end-of-life patients.
Peer Reviewer 5	Abstract	Overall, the abstract summarizes the main points well. I have the following suggestions to consider: Please identify the patient populations more clearly in the objectives	Because of word count limitations, we were unable to describe explicitly the broad range of populations. However, we have added a comment that we address populations with a broad range of acute respiratory etiologies.
Peer Reviewer 5	Abstract	Indicate the total number of patients included overall and for each subgroup analyzed	We have added the number of subjects analyzed for each KQ.
Peer Reviewer 5	Abstract	The Conclusions do not follow from the Results as the results do not present any data for the patient populations, while the Conclusions discusses use for different patient populations	The revised Results describe the populations contributing to the results and findings for some subgroups. We think the Conclusions are now better supported by the Results.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	Executive Summary	The ES is well written. Overall, the inclusion and exclusion criteria are justifiable and the search strategy is logical and clearly stated. Again, my main issue about the analysis is stated in the General Comments above, regarding the decision to combine all patient populations when the weight of the studies represent patients with COPD and ACPE.	As described above, we considered this issue carefully and give summary estimates by subgroups when there is substantial heterogeneity in effects overall. Important subgroup findings are also reflected in the strength of evidence tables included in the Executive Summary and main report.
Peer Reviewer 5	Executive Summary	The detail presented in the ES is reasonable as an ES and provides the important Methods and Results for the readers. The practical value of the ES could be improved with the addition of a section that provides the Key Recommendations in a bullet format (as in the main Report). Such a section would be of added value, as many clinicians will not have time to ever read more than the ES.	Summary, bulleted findings have been added to the ES.
Peer Reviewer 5	Executive Summary	Please note the following to consider: Background: Suggest you define acute respiratory failure in the Background for readers who will only have time to read the ES	Acute respiratory failure is defined in the first paragraph of the Background section.
Peer Reviewer 5	Executive Summary	Please correct the following: Reference 23 is a systematic review of NIV for weaning specifically (line 49, page 10 [ES-2]). Reference 24 is a clinical practice guideline that is not limited to COPD patients (line 52, page 10 [ES-2]). Reference 25 [p. ES-2] is a guideline, but does not represent a professional society.	Reference 23 on line 49 is the correct citation. Reference 24 does cover multiple conditions and has been deleted. Reference 25 has been deleted.
Peer Reviewer 5	Executive Summary	There are other professional society guidelines (Indian Society, German, BTS) that would be important for the authors to include in this ES and in the main Report. It will also be important for the authors to specify how this report differs from these other guidelines and how this report should be used by readers/clinicians [compared to existing guidelines and systematic reviews of the same evidence]	In the main report, we have added a citation to the British Thoracic Society guidelines. The current report is a systematic review of the evidence, not a clinical guideline.
Peer Reviewer 5	Executive Summary	Page 12 [ES-4]: Fig ES 1 - is a poor reproduction and difficult to read	We have provided what we hope will be a clearer image of this figure.
Peer Reviewer 5	Executive Summary	Methods: Please define or describe the panel members' expertise and experience.	The Key Informants' and Technical Expert Panel members' backgrounds/expertise are summarized in Executive Summary Methods, opening section (Input from Stakeholders). These contributors' names, degrees, and affiliations have been added to the front matter of the final report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	Executive Summary	Suggest you define the domains (risk of bias, consistency, directness, precision) pertaining to the SOE either in the text in the Methods or in footnote of Table ES2 for readers who will only have time to read the ES	The GRADE domains are described in the data extraction and quality assessment section of the ES.
Peer Reviewer 5	Executive Summary	Page 13 [ES-5], lines 53-53 – the authors searched key citations but no do specifically mention whether they searched the references of other guidelines (such as ref 24 and 25) and recent BTS, Indian Society, and German guidelines	The second paragraph of the data sources and selection section describes and cites the review articles and clinical guidelines used to search for references.
Peer Reviewer 5	Executive Summary	Page 14 [ES-6], line 3 – change descried to described	This has been corrected.
Peer Reviewer 5	Executive Summary	Results: Page 18 [ES-10] – suggest shortening the first paragraph as is it has redundancies with Figure ES2.	Thank you for the suggestion. The paragraph has been shortened.
Peer Reviewer 5	Executive Summary	Figure ES2 – including 'articles' is potentially confusing. These look like duplicated papers. Please define in the first paragraph of the Results or Legend of the figure or delete.	We present the literature flow diagram using a standard EPC format.
Peer Reviewer 5	Executive Summary	Please change 'subjects' to 'patients' throughout the paper and especially all of the Tables	Although these individuals were certainly patients, they are all also subjects in research studies. We have retained the subject designation.
Peer Reviewer 5	Executive Summary	Key Question 2 (starts on page 21 [ES-13]) – BPAP vs CPAP – In my opinion, the problem of combining all patient populations is more prominent in this section. Here, all but 1 study refers to patients with ACPE. Hence, KS2 is really about the use of BPAP vs CPAP in this population only. The results here really only refer to patients with ACPE. Although the authors do mention this limitation on lines 39 and 40, I strongly suggest a re-phrasing. It is misleading to suggest that this 'limits the applicability…'. One simply cannot apply these findings to any population except patients with ACPE.	We have added bulleted summary key points to the ES. One bullet point specifically describes the lack of evidence in conditions other than ACPE and describes the findings as having uncertain applicability to other conditions.
Peer Reviewer 5	Executive Summary	Discussion: Please change subjects to patients throughout.	Although these individuals were certainly patients, they are all subjects in research studies. We have retained the subject designation.
Peer Reviewer 5	Executive Summary	Page 26 [ES-18], lines 21-22 – This is not entirely accurate. Several professional society guidelines (not reviews) include multiple patient populations. It would be important to mention this here for the readers and reference these guidelines for readers to refer to. It would also be important to clarify that the overall results really represent the benefit of NPPV in patients with COPD and ACPE.	We revised our description in the ES to more clearly cite the reviews. In the main report, we have added additional citations for reviews and guidelines separately.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	Executive Summary	Page 26 [ES-18], line 38 – "Because of the small number of available RCTs, we combined trials examining NPPV for both the prevention and treatment of extubation failure." In my opinion, this is not a valid analysis. While the authors have indicated that this is a limitation, I would suggest that there are no clinical grounds to combine these populations as the results have little to no clinical meaning.	The analyses have been revised to analyze these groups separately.
Peer Reviewer 5	Executive Summary	Page 26 [ES-18], lines 41-44 – mentions that most of the data represent studies of patients with COPD and CHF. This begs the question as to why the authors conducted a primary analysis where they combined the data across all patient populations	The analyses have been revised to analyze separately NPPV used to prevent and NPPV used to treat acute respiratory failure postextubation.
Peer Reviewer 5	Executive Summary	Conclusions: Page 28 [ES-20], line 39 – Please clarify that most of these studies refer to patients with ACPE and therefore these findings are limited to this patient population and cannot be generalized beyond	The text has been revised to state that these findings are derived from ACPE populations.
Peer Reviewer 5	Executive Summary	Overall, I have a concern about a blanket statement to use NPPV in post-operative patients and weaning patients without being explicit about the important limitations regarding few studies (only 2 studies for post-operative patients) and that the use of NPPV in weaning and post-extubation respiratory failure studies were conducted in centers with significant expertise. Other reviews and guidelines on this topic have noted these important issues and it would be important for the authors to provide some words of caution for the readers. Many readers are inexperienced in the use of NPPV, in general, and I would be concerned that they may not have the experience or expertise at their institutions to use NPPV with similar success rates in patients who are weaning from mechanical ventilation and its use in post-extubation respiratory failure.	We appreciate the caution. Our statement describes "potential benefit" and limited evidence for these findings.
Peer Reviewer 1	Introduction	The Introduction is adequate.	Thank you.
Peer Reviewer 2	Introduction	clear and logical	Thank you.
Peer Reviewer 3	Introduction	I recommend adding that NPPV does not require moderate sedation (instead of only "deep" sedation) Page ES-2, line 26: add "moderate and/or" just prior to "…deep sedation" Page 3, line 39: add "moderate and/or" just prior to "…deep sedation"	The text has been modified to specify "moderate and/or deep sedation."
Peer Reviewer 4	Introduction	No specific comments.	Noted.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	Introduction	Please refer to my General Comments at the beginning of this review. Some of my comments for the ES are applicable to the Main Report. Please see those comments in the sections above and include those suggestions for the Main Report. In the following, I will address the specific issues for the authors to consider.	See responses to specific comments below.
Peer Reviewer 5	Introduction	Introduction, Figures, and Tables: The Introduction is well written and sufficiently detailed.	Thank you.
Peer Reviewer 5	Introduction	Figure 1, page 37 [6] – difficult to read, please provide a more clear rendition	We have provided what we hope will be a clearer image of this figure.
Peer Reviewer 5	Introduction	Suggest adding the patient populations in a column in your forest plot figures (e.g., COPD, CPE, etc) so readers can identify which studies refer to which patient population	We revised the forest plots to group studies by patient population/diagnosis.
Peer Reviewer 5	Introduction	Table 5 – please define the Diagnosis 'Mixed' in the footnote of the table	We have added a footnote indicating that "mixed" refers to any patient sample where < 70% have a single etiology for acute respiratory failure.
TEP Member 1	Introduction	No comments.	Noted.
TEP Member 2	Introduction	Introduction is clear and thorough.	Thank you.
TEP Member 3	Introduction	Good overall review of the clinical problem and its magnitude as well as the options clinicians need to choose from.	Thank you.
TEP Member 4	Introduction	The introduction clearly states the objective of this report as well as the patient population in which the key questions are addressed	Thank you.
TEP Member 5	Introduction	As outlined above, training and provider experience are crucial elements for successful NPPV. This is a difficult area to characterize in review of research investigations since appropriate trained and experience staff are implied and fall outside the realm of study design. The authors highlight this in their "Barriers.." section, and also include this in Figure 1.	We have modified the Introduction to note that training is important to the successful implementation of NPPV treatments.

Commentator & Affiliation	Section	Comment	Response
TEP Member 5	Introduction	Patient selection and locale of treatment are important components of NPPV that are not well appreciated. The authors do touch on this with KQ 4 and further investigate these factors by comparing results based on whether the study was a North American country or Europe. Comparing results by country also indirectly addresses the possibility of influence on outcome based on training and experience. Severity of illness is also mentioned, but not otherwise analyzed in this report.	Noted.
TEP Member 6	Introduction	clearly stated	Thank you.
TEP Member 7	Introduction	In the first few paragraphs of the introduction, some terminology needs clarification. For example, the word “continuous” should be removed from end expiratory pressure. When expiratory pressure is combined with higher inspiratory pressure in bilevel modes, it is not continuous.	While the comment is technically correct, the distinction is clinically unimportant. There are in fact two pressures: a continuous level that is periodically augmented by additional inspiratory pressure.
Peer Reviewer 1	Methods	The inclusion and exclusion criteria are reasonable. The search strategies and definitions are reasonable. The statistical methods are appropriate.	Noted.
Peer Reviewer 2	Methods	inclusion/exclusion criteria are justifiable. The exclusion of non-English papers is a limitation. Definitions of outcomes and statistical methods are appropriate. Suggest showing similarities and differences between methods used here and the GRADE methodology.	Noted. We described the limitation related to English-language only studies in the Discussion. The GRADE and AHRQ approach to grading are similar.
Peer Reviewer 3	Methods	The methodology is well constructed and clearly explained. The outcome measures are logical and well presented. The statistical methods are appropriate for this analysis.	Thank you.
Peer Reviewer 4	Methods	1) I don't think the exclusion of non-English literature is well-justified, especially since differences between conclusions of this review and the Canadian guidelines may at least in part be explained due to exclusion of Chinese-language literature in this review (with the exception of 16438899 which I believe is a Chinese-language paper translated into English by the journal for their English edition).	We made the a priori decision to exclude non-English language studies based on: a) the large body of English language studies and b) wanting to include studies from countries with systems of care that would be most applicable to the settings in the United States. This rationale has been clarified in the Methods section.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Methods	2) Rather than excluding studies published before 1990, I'd consider including them but performing a sensitivity analysis to explore whether treatment effect differs with year of study. The relevant question is whether changes in other aspects of care (as summarized by the year of study publication) modify the effect(s) of NIV. As an example, cumulative meta-analyses of thrombolysis for MI have shown a consistent benefit over time despite evolution in the care of these patients.	At this point in the project, it is not possible to include studies prior to 1990 as this would require a new search. However, other reviews have included only 1-2 of these earlier studies, and their inclusion would not change our conclusions. Based on the included studies, we conducted an exploratory analyses and found smaller effects for more recent studies. We have included these results in the revised report.
Peer Reviewer 4	Methods	3) I would strongly encourage the authors to present the results of all binary outcomes as risk ratios rather than odds ratios. Clinicians do not understand odds ratios as well, and often misinterpret these as risk ratios. This point is important because odds ratios are more extreme (further from 1) than corresponding risk ratios.	Because of the relatively high event rates, we use OR as a preferred summary estimate of effect. However, we translate the OR into risk differences in the summary strength of evidence tables.
Peer Reviewer 4	Methods	4) The diagnosis of pneumonia is potentially subject to ascertainment bias in studies of noninvasive vs. invasive ventilation because it may be easier to obtain specimens in the invasively ventilated patients. Please comment.	Most studies reported hospital-acquired pneumonia, which is typically defined as pneumonia developing at least 48 hours after admission. The diagnosis is based on clinical, radiographic, and—less frequently— sputum samples. We considered this issue but do not think it is an important source of bias for this outcome.
Peer Reviewer 4	Methods	5) I don't think the various potential indications for NIV (COPD, pulmonary edema, etc) should be merged into one summary for each key question, regardless of the degree of statistical heterogeneity, because of pathophysiological differences among these clinical indications. I would report the clinical populations separately in the primary analysis.	This is an important point that we considered carefully prior to analysis and again after peer review. Although the underlying pathophysiology of acute respiratory failure differs by etiology, the studies are conceptually similar in design, intervention and outcomes. In most instances, there was small to moderate variability in effects, even across diagnostic groups. To better address this issue of potential variability by diagnostic groups, we have modified our presentation to show forest plots by diagnostic group. Further, we have not presented summary odds ratios when variability was high. Finally, we have emphasized the paucity of data in many of the diagnostic groups.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Methods	6) The authors have not pooled length of stay because of concerns about the suitability of using weighted mean difference (WMD) when the underlying distribution is skewed. However, simulation suggests that the statistical properties of WMD are acceptable when the underlying distribution is skewed (see BMC Medical Research Methodology 2008, 8:32). A more important problem is created by the difference in mortality between the NIV and invasive groups. Ideally outcomes like length of stay and duration of mechanical ventilation should be analysed separately in survivors and non-survivors. I'd suggest that the authors consider pooling length of stay outcomes or provide a more compelling justification for not doing so.	Thank you for the citation. While we agree that there may be useful statistical approaches to generating summary estimates from skewed data, the problem with survivorship bias remains. Therefore, we have not pooled data for length of stay.
Peer Reviewer 4	Methods	7) Please clarify whether the duration of mechanical ventilation outcome includes the period of both non-invasive and invasive ventilation. (For a fair comparison, it should.)	We reported the duration of mechanical ventilation as reported by the authors. In most instances, the details of how this outcome was calculated were not reported.
Peer Reviewer 4	Methods	8) Did the authors quantify the extent of agreement between reviewers for selection of articles for inclusion and quality (overall rating of good, fair, or poor quality in the risk of bias section) of the included studies?	No, we did not compute a kappa or other measure of agreement for decisions on article selection.
Peer Reviewer 4	Methods	9) I think the whole division of setting into US and non-US settings is flawed. This framework underestimated the variation in practice within the US (which is substantial in virtually every aspect of medical practice examined) and overestimates variation between the US and Canada (an example with which I am most familiar).	The analysis compares US/Canada versus European versus other geographical regions. Regions are used as proxy for experience with NPPV. Although geographical region is a crude proxy for experience, we think the analysis gives the reader some useful information on variation in effects.
Peer Reviewer 4	Methods	10) In the quality rating section, comparability of groups at baseline is difficult to judge in practice, since (1) statistical testing is meaningless for 'Table 1' differences as any significant differences arise by chance by definition in a RCT, (2) not all the potentially important prognostic factors may be reported or even known, (3) clinically important differences may be concealed by small sample sizes, (4) few trials will typically report analyses adjusted by pre-selected prognostic variables, and (5) any within trial baseline differences are even less important in a meta-analysis where results are combined with other trials.	Evaluating comparability of patient characteristics at baseline is a standard component of quality ratings as described in the AHRQ Methods Guide.
Peer Reviewer 4	Methods	11) Having adequate power for the main trial outcome is not relevant to risk of bias, as defined as focusing on the internal validity of the trial (see BMJ 2011;343:d5928). I'd consider dropping this.	Depending on the quality rating system, power is sometimes included, and we elected to include this criterion in our evaluation.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Methods	12) Did the authors consider exploring subgroup effects for the variables for which sufficient studies existed (i.e. efficacy-effective score and setting, taking into account the patient population (i.e. COPD, pulmonary edema, etc) either in a trial-level meta-regression or a stratified analysis?	In KQ4, we present subgroup analyses by efficacy-effectiveness score and setting.
Peer Reviewer 4	Methods	13) I don't think it's reasonable to combine studies of NIV to prevent post-extubation respiratory failure in patients at high risk (i.e. in patients who pass a spontaneous breathing trial but who have high-risk features for intubation) and those of NIV to treat patients with respiratory failure post-extubation. The authors discuss this point in the Discussion, but I would suggest reconsidering the decision to combine these two populations, which I think are clinically quite dissimilar.	Thank you for this comment. We have revised KQ3 to analyze 3 separated groups: NPPV used to wean from invasive ventilation, NPPV used to prevent acute respiratory failure following extubation and NPPV used to treat acute respiratory failure following extubation.
Peer Reviewer 5	Methods	The Methods section is well written and provides adequate details of the rigorous methods used to conduct this review. Both the inclusion and exclusion criteria are justifiable. The search strategies are explicit and clear. The authors could consider including a definition for ventilator associated pneumonia, or specify that they used the definitions in the primary studies. The statistical methods used were appropriate.	Thank you.
TEP Member 1	Methods	Methods are appropriate.	Thank you.
TEP Member 2	Methods	Inclusion/Exclusion criteria are justifiable. Search strategies are clearly and explicitly stated. Gray literature was included in the search strategy, but the results were not clear as to when that literature was used to draw conclusions and whether the inclusion of gray literature was additive or not to the overall review.	Thank you. The two information request strategies described in the report (contacts to device manufacturers and the U.S. Food and Drug Administration) did not result in any additional data for consideration. The final component of the grey literature search strategy (a search of the ClinicalTrials.gov trial registry) was performed to address the possibility of publication bias, by searching for completed but unpublished studies. The ClinicalTrials.gov search did not identify completed but unpublished studies, and this result is described in the Results section.
TEP Member 3	Methods	The criteria for inclusion into the study and for exclusion as well are clearly defined and are logical for the audience. All definitions are up to date and outcome measures are what clinicians need to know.	Thank you.
TEP Member 4	Methods	While it I would have perferred a larger body of research reviewed, the amount of sound research is limited for this topic. The inclusion and exclusion criteria are clearly stated so thereader does have assurance that the body of evidence reviewed is comprehensive and not a result of potential bias.	Noted.

Commentator & Affiliation	Section	Comment	Response
TEP Member 5	Methods	This section provides an excellent overview of their methods. Table 2 provides a concise summary of their research methods with clear criteria for their study characteristics, inclusion and exclusion criteria. The search strategy is comprehensive, including their description of the search of the "gray" literature. Definitions and diagnostic criteria are appropriate, although there are limited measures of functional status and health related quality of life since these were not routine areas of investigation.	Thank you.
TEP Member 6	Methods	agree wtih all	Thank you.
Peer Reviewer 1	Results	There are a few recent studies that might be considered. Su CL, Chiang LL, Yang SH, Lin HI, Cheng KC, Huang YC, Wu CP. Preventive use of noninvasive ventilation after extubation: a prospective, multicenter randomized controlled trial. Respir Care. 2012 Feb;57(2):204-10. Epub 2011 Jul 12. Anjos CF, Schettino GP, Park M, Souza VS, Scalabrini Neto A. A randomized trial of noninvasive positive end expiratory pressure in patients with acquired immune deficiency syndrome and hypoxemic respiratory failure. Respir Care. 2012 Feb;57(2):211-20. Epub 2011 Jul 12. Agarwal R, Aggarwal AN, Gupta D. Role of noninvasive ventilation in acute lung injury/acute respiratory distress syndrome: a proportion meta-analysis. Respir Care. 2010 Dec;55(12):1653-60.	These studies were evaluated, and Su et al. was identified and included during our search update. The study by Agarwal is a meta-analysis, and its bibliography was reviewed for relevant citations. The study by Anjos did not meet eligibility criteria.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Results	I do not agree with the analysis in the section on Key Question 3 - Early extubation to NPPV. The studies by Esteban and Keenan were designed to evaluate the use of NIV to rescue a failed extubation after a successful spontaneous breathing trial. Other studies were designed to evaluate the use of NIV to prevent extubation failure in patients at risk, again after a successful spontaneous breathing trial. In these studies, unlike the Esteban/Keenan studies, NIV was initiated immediately after extubation. These are different questions and should be evaluated separately, not lumped together. The study by Girault (VENISE Trial) must be interpreted carefully. On first read, it might appear that NIV did not decrease the risk of reintubation. But that is only because rescue NIV was allowed in the >conventional weaning and O2 groups. Had rescue NIV not been allowed in these 2 groups, it would have shown clear benefit for NIV. The rate of post-extubation respiratory failure was significantly lower in the NIV group.	Thank you for this comment. We have revised KQ3 to analyze 3 separated groups: NPPV used to wean from invasive ventilation, NPPV used to prevent acute respiratory failure following extubation and NPPV used to treat acute respiratory failure following extubation.
Peer Reviewer 2	Results	I read only the Executive Summary--figures and tables in this section are clear.	Thank you.
Peer Reviewer 3	Results	The results section is an excellent presentation of detail regarding the sub-divisions of studies and outcomes that provides a very clear picture of the data. The figures and tables are appropriately demonstrative. I am not aware of any data that should have been included. In the key questions, I prefer the format used in KQ2 with distinct bullet points for the different outcomes as I find this easier to read.	Thank you. Where feasible, we reported the outcomes in bulleted format.
Peer Reviewer 4	Results	1) I'd suggest organizing the studies in the Figures by year, which would make it easier to find individual studies, rather than by weight.	The studies have been reorganized to be grouped by population, and within these groups, by year.
Peer Reviewer 4	Results	2) Page 18 line 18: "Relatively few studies compared CPAP to supportive care (18%)." Consider rephrasing since this category of studies has the second highest number.	Thank you. This has been rephrased to "The most common comparisons were between BPAP and supportive care (50 percent of comparisons), followed by CPAP versus supportive care (18 percent) and BPAP versus CPAP (15 percent). Relatively few studies compared any mode of NPPV to invasive ventilation or to conventional weaning (both 7 percent)."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	Results	The Results are thorough and well organized and clearly presented, overall. Figures and Tables are adequate and descriptive, apart from a few suggestions I have made below. The review has included all the important studies. The Key Points provide the key interpretations of the Results. However, the key points could be more practical (as could the whole report) by providing more guidance to clinicians as opposed to stopping at interpreting the results. Please consider the following:	Thank you. This report is intended to summarize the evidence. Our expectation is that clinical guideline developers and other groups will use these results to develop clinical guidance.
Peer Reviewer 5	Results	Page 51 [20], Key Points - line 9 – postoperative or post-transplant settings - is problematic since only 2 studies each. While there is a suggestion of a benefit, more research is clearly needed and it would be worthwhile to consider re-phrasing this statement accordingly.	We note that "limited evidence supports an effect in the postoperative and post-transplant settings." In the Future Research section, we identify the need for more studies in these populations.
Peer Reviewer 5	Results	Page 51 [20] – lines 16-17 – suggest the authors specify which populations have no studies as it is vague to say 'sparse or absent'	The sentence has been revised to specify the populations with no studies.
Peer Reviewer 5	Results	Page 51 [20] – lines 18-19 – please define mixed etiologies	"Mixed" has been defined as a footnote to the tables. In addition this sentence has been revised to specify "studies with mixed etiologies" rather than "patients with mixed etiologies."
Peer Reviewer 5	Results	Page 63 [32] – KQ2 – BPAP vs CPAP – please see my comment for this section in the comments for ES section above. Consider reframing this KQ to indicate that a primary analysis for patients with ACPE was conducted since this is what it represents.	The KQ included multiple populations with acute respiratory failure, but the studies were primarily conducted in those with ACPE. In one of the Key Points, we emphasize that all but one study was conducted in patients with ACPE and that the results may not be applicable to other populations with acute respiratory failure.
Peer Reviewer 5	Results	Page 69 [38] – Key Points – line 28 – please define mixed populations	"Mixed" has been defined as a footnote to the tables. The analyses in this section have been stratified by specific NPPV application and in some instances, by clinical subgroups. The key points have been revised to reflect these changes.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	Results	Page 79 [48] – the analysis comparing location of initiation is problematic and I am not sure if any clinically important statements can really be made. While NPPV is initiated in the ED, patients spend very little time there and NPPV use is more likely to represent use in an ICU setting. Hence, is there any real validity in this distinction within this subgroup analysis? I am not sure it represents anything meaningful and may be misleading. While the authors do state that the effects of NPPV are stronger when initiated in the ICU, I question whether this is a meaningful analysis in the first place.	We reviewed all articles identified as initiating NPPV in the ED. Of these, we confirmed that all but two delivered NPPV primarily or exclusively in the ED setting. For the other two, NPPV was initiated in the ED but it was unclear whether the majority of NPPV care was delivered in this setting. Although the concerned raise is appropriate, we have confirmed that the classification by setting is accurate and meaningful.
TEP Member 1	Results	Results are sufficiently detailed.	Thank you.
TEP Member 2	Results	Results section is clear and thorough. I was not able to identify studies excluded or included incorrectly.	Thank you.
TEP Member 3	Results	The detail in the results sections are sufficient. The studies selected are clearly described. Figures and tables, as well as references are adequate and easy to follow. New studies will continue to be published in this field and this review is current as of when written.	Thank you.
TEP Member 4	Results	The detail presented in the results section is concise, relevant, and objective.	Thank you.
TEP Member 5	Results	The data is presented in appropriate detail with the information further enhanced by the figures and tables. However, their interpretation of the study by Plant and colleagues further highlight the earlier comment on the subjective element of intubation. The study does report intubation rates, but the data presented in Figure 6 is NOT of intubation rates but of the number of patients in their study which met CRITERIA for intubation. These are obviously two very different conditions. The difference between NPPV and standard care is significant when comparing the criteria for intubation, but not when comparing the actual reported intubation rates (6% vs. 10%). However, given the consistent outcomes of other investigators in favor of NPPV, this technicality is not likely to changes their conclusions.	The decision to intubate is subjective and may show variability across physicians. Therefore, when studies presented both intubation rates and the rate of those meeting prespecified criteria for intubation, we preferentially analyzed the latter outcome.
TEP Member 6	Results	information is presented clearly.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Summary/ Discussion/ Conclusion	The Discussion and Conclusions are appropriate. However the Conclusions regarding post-extubation NIV might change if the data are analyzed differently, as suggested above.	Thank you. The conclusions have been updated to reflect the change in analysis approach for KQ3.
Peer Reviewer 2	Summary/ Discussion/ Conclusion	future research section is clear	Thank you.
Peer Reviewer 3	Summary/ Discussion/ Conclusion	The main findings are clearly delineated; although I would utilize bullet points for the main outcomes. In terms of limitations, I would emphasize that NPPV is not used in a standard fashion and differences in monitoring and titration may lead to different outcomes; future studies should be much more rigorous in defining how NPPV was used. The conclusion (page 60, sentence 3, lines 9 -12) mentions "potential benefit" of NPPV in a couple of clinical scenarios, but I'm unclear as to why only these were selected. The text of the manuscript mentions several conditions/situations in which NPPV may have benefit, but there is insufficient evidence at this time, i.e. asthma, OHS, etc. I would amend this sentence to emphasize the importance of further studies in many conditions/situations to better characterize the role of NPPV. I think the specifics should remain in the "Research Gaps" section.	We utilized the format recommended by AHRQ. Main outcomes are summarized in bullet form in the Results section for each KQ. In the summary section, we use a strength of evidence table along with accompanying text. We have revised the concluding paragraph to further specify that NPPV needs further evaluation in understudied patient populations and studies to evaluate the effectiveness in routine care.
Peer Reviewer 4	Summary/ Discussion/ Conclusion	1) The authors critique the Burns systematic review of NIV for weaning by noting that it includes trials quasi-randomized trials. The main problem with quasi-randomized studies is that they lack allocation concealment and are thus prone to selection bias. There is hence no difference between a quasi-randomized study and a randomized one that does not conceal allocation (for example, one that openly displays the randomly generated allocation list to the persons enrolling patients in the trial). I would delete this criticism unless all trials included in this review adequately concealed allocation.	Since only one of the studies included in the Burns review was a quasi-experimental study, we have dropped this criticism.
Peer Reviewer 4	Summary/ Discussion/ Conclusion	2) Similarly, the critique of non-English and abstract publications presumably relates to concerns about internal validity. I would frame the criticism as related to potential lack of internal validity; otherwise, these exclusions appear arbitrary.	This section has been substantially rewritten as we changed our analysis approach. We have dropped the critique of non-English publications.
Peer Reviewer 4	Summary/ Discussion/ Conclusion	3) Finally, it does not seem consistent to criticize the Burns review for including non-English trials (as did the Canadian guideline) and yet identify the exclusion of non-English literature as a limitation of the comparative effectiveness review.	We have dropped the criticism of the Burns article for including non-English studies.
Peer Reviewer 4	Summary/ Discussion/ Conclusion	4) In general, the implications and limitations of the review are clearly discussed and the future research section is clearly written.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	Summary/ Discussion/ Conclusion	The implications of the major findings are clearly stated, overall. The investigators did not omit any important literature. The section on Research Gaps is very thoughtful and will guide priorities for research in this area. I would like the authors to consider the following to improve an already very strong document and Discussion section.	Thank you.
Peer Reviewer 5	Summary/ Discussion/ Conclusion	The Discussion could be strengthened and made more clinically useful to bedside clinicians. I suggest being more directive in recommending the use of NPPV for patients where there is little evidence of effect. While this is not a clinical practice guideline, the second paragraph on page 83 [52], for example, may confuse the reader in the context of presenting tables 17 and 18 as a summary of all studies including all patient populations. Can the authors revise this section beyond interpretation of the findings to providing direction to the reader regarding the use of NPPV in patients other than COPD and ACPE?	We have revised the summary tables to show the effects by diagnosis when they vary substantially across these groups.
Peer Reviewer 5	Summary/ Discussion/ Conclusion	Similarly with weaning and post-extubation respiratory failure in the section that follows on page 84 [53] and 85 [54].	This section has been revised to reflect that change in analysis approach. That is, results are given by specific population
Peer Reviewer 5	Summary/ Discussion/ Conclusion	Under the section on Findings in Relationship to What is Already Known, please reference the recent BTS, Indian Society and German guidelines in this section.	In this section, we primarily cite systematic reviews. However, we have now added citations to the BTS guidelines and the recent Canadian guidelines as the most relevant non-U.S. sources.
TEP Member 1	Summary/ Discussion/ Conclusion	The conclusions are clearly described.	Thank you.
TEP Member 2	Summary/ Discussion/ Conclusion	Implications are clearly stated as are the limitations. Since the findings largely confirmed prior data, this is not unexpected. Important analysis regarding the benefits in ACPE are offered.	Thank you.
TEP Member 3	Summary/ Discussion/ Conclusion	The discussion is clear and concise. The section on future research clearly outlines what is needed to complete what this review has set out to discuss.	Thank you.
TEP Member 4	Summary/ Discussion/ Conclusion	I find this section to be very comprehensive and relevent.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 5	Summary/ Discussion/ Conclusion	This is an excellent summary of their findings, which incidentally are not disparate from those of other investigators who have performed systematic reviews and meta-analyses on NPPV. The authors acknowledge the limitations of the studies reviewed which in turn represents a limitation of their own analysis. There is a limit to which study conditions will translate to general use and in this case, training and provider experience remain unknowns that will vary throughout. All pertinent literature was reviewed and Table 22 provides a succinct summary of the need and direction for future research.	Thank you.
TEP Member 6	Summary/ Discussion/ Conclusion	evidence is clear, feel there are no limitations in the study	Thank you.