Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Pharmacologic and Nonpharmacologic Therapies in Adult Patients With Exacerbation of COPD: A Systematic Review

Draft report available for public comment from March 23, 2019 to April 25, 2019.

Research Review Citation: Dobler CC, Morrow AS, Farah MH, Beuschel B, Majzoub AM, Wilson ME, Hasan B, Seisa MO, Daraz L, Prokop LJ, Murad MH, Wang Z. Pharmacologic and Nonpharmacologic Therapies in Adult Patients With Exacerbation of COPD: A Systematic Review. Comparative Effectiveness Review No. 221. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. 290-2015-00013-I.) AHRQ Publication No. 19(20)-EHC024-EF. Rockville, MD: Agency for Healthcare Research and Quality; October 2019. Posted final reports are located on the Effective Health Care Program search page. DOI: https://doi.org/10.23970/AHRQEPCCER221.

Comments to Draft Report

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Comments on draft reports and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final report 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.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. 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 Comments	Most of the studies cited have mortality, hospitalization rate and/or re-exacerbation rate as secondary rather than primary outcomes. This is important with respect to sample size estimates as, in most instances, the studies are not sufficiently powered to effectively detect differences in these secondary endpoints. Accordingly, conclusions regarding lack of difference in these endpoints are likely to be limited by large type 2 errors.	We agree that small number of studies per meta-analysis is an issue. We added this point to the limitation.
Peer reviewer #1	General Comments	In conjunction with this issue the review consistently states that there was "no statistical significance" where it would be much more scientifically sound to say that "no statistical difference was observed."	We agree and changed this.
Peer reviewer #1	General Comments	Suggest identifying the tool used to determine the SOE in the Abstract. I wanted to know that and had to go well into the Review before finding it.	We followed the steps outlined in the EPC methods guide, which is similar to the GRADE approach. However, we are restricted by the word count limits that were standardized to improve readability
Peer reviewer #1	General Comments	Suggest that noting 13,022 pts were included in the trials is not relevant given at this number includes numerous different interventions. Even providing the number of trials is of limited utility given that some treatments are well-studied and others are not.	To give an overview of the existing literature, we believe the information is still important to some readers.
Peer reviewer #1	General Comments	Agree that any or all of the treatments reviewed could have different results in different AECOPD phenotypes but this is only a theoretical concern - I know of no data documenting this to be the case. Accordingly, I suggest the point should be made but in the Limitations section, not in the Abstract.	We changed ""acute exacerbation of COPD (AECOPD)" to "exacerbation of COPD (ECOPD)". We agree with the reviewer that ECOPD phenotypes remain largely theoretical at this point with little implications for practical management of ECOPD. We have now made the point in the Limitations but not in the Abstract.
Peer reviewer #1	General Comments	Would be useful to also include a table of treatments organized by SOE. Or even just a table of interventions supported by high SOE. This makes your point more effectively.	We chose not to present results by SOE, instead presented by interventions and KQs. The flow works better for the whole report. This is also better from an end user perspective searching for evidence on specific interventions.

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Peer reviewer #1	General Comments	Interesting that you make a point that short-acting bronchodilators have not been studied. I cannot imagine any IRB approving an RCT of short-acting BDs vs placebo. Sort of like the absence of studies documenting that parachutes work.	The message that we aimed to convey was that it is unclear whether a combination of different short-acting bronchodilators is more effective than one short-acting bronchodilator alone. See Evidence Summary: "Short-acting beta adrenergic agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) are established treatments to relieve dyspnea and improve airflow obstruction during ECOPD, but the benefit of combination of short-acting beta agonists and short-acting muscarinic antagonists is unclear."
Peer reviewer #1	General Comments	It might be useful to define what "sufficient evidence" means (versus insufficient).	We added definitions of all SOE levels to the methods section.
Peer reviewer #2	General Comments	General Comments: Well-organized, comprehensive review of management of AECOPD.	We thank the reviewer for the comments.
Peer reviewer #3	General Comments	General Comments: Yes I think the key goals and questions are clear.	We thank the reviewer for the comments.
Peer reviewer #4	General Comments	This systematic review addresses an important topic and covers key questions that are relevant to a wide range of stakeholders. The authors stated that they followed the standard AHRQ EPC methods in searching for evidence, collecting data, assessing the risk of bias of included studies, and grading the certainty in evidence. However, the draft report contains numerous inconsistencies (including search date, wording, and description of methods), inaccuracies, and perhaps errors (e.g., numbers in the evidence tables). It appears that insufficient attention has been given to the context of the included studies analyzed and a thoughtful qualitative synthesis is missing. The key messages are unclear and difficult to follow. The report reads superficial and lacks depth. The clarity of writing and presentation can be improved significantly. The major issues are elaborated below.	We thank the reviewer for the comments. We followed the EPC methods guide for the methods and reporting and made changes to clarify the methods and reporting.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	General Comments	Issues around comparison Interventions: Several key questions included “standard care” as the comparator. Please define “standard care” early on in the report. Has “standard care” changed over time? If so, how did you handle this in the analysis?	We acknowledge that there is not a "standard care" for exacerbations of COPD that is the same across settings and over time. We had used the term "standard care" for groups that did not have a study intervention (e.g. chest physiotherapy) but still received some additional treatments (e.g. antibiotics, systemic corticosteroids) in the same way as the intervention group. To avoid any confusion we have now clearly labelled the comparator group in these instances as "management without [*insert intervention from intervention group*]" and no longer use the word "standard care" for comparator groups.
Peer reviewer #4	General Comments	Issues around outcomes: A fully defined outcome includes domain, measure, metric, method of aggregation, and timing (please see Zarin NEJM 2011;364:852-60 and Saldanha PlosOne 2014;9(10):e109400). Did you extract all these elements? (1) It would be useful to present this information in a Table. For example, each row contains information from one trial, each column represents one outcome of the review (i.e., domain), and in each cell, note down how the other four elements were specified (reported) and were available for analysis. A high-level summary of the Table can then be provided in the text.	We thank the reviewer for the comments. We extracted all of the five elements and included almost all of these in the report. The only missing items were specific measures for symptom scales and quality of life. We deemed those as not critical for clinical practice and tried to be concise with our report. We now added these in the report.

Commentator & Affiliation	Section	Comment	Response
		(2) Please describe in the Methods section how variations in outcome definition were handled in the analysis. For example, when data from multiple time points or from multiple instruments were available for an outcome domain, which one did you choose for analysis, and why?	We reported how we pooled time points for each outcome in the tables in the results. For majority of the outcomes, we extracted and pooled estimated at the end of intervention and the longest followup. For re-exacerbation, we extracted at the end of intervention, 1-month, 3 month, 6-month, 12-month, and longest followup, which were commonly used follow-up time points in studies that measured exacerbations. For hospital admission, we extracted 30-day admission and longest followup. Thirty-day hospital admissions were chosen because hospital admissions within 30 days of an index hospitalization count as a readmission in Medicare's Hospital Readmissions Reduction Program, which lowers payments to Inpatient Prospective Payment System hospitals with too many readmissions. We added the information in the methods.
		(3) Discuss how outcome heterogeneity may (may not) affect your overall interpretation of evidence.	We followed the EPC methods guide to rate the strength of evidence. Heterogeneity is a part of the evaluation. The information was presented in the Methods-Grading the Strength of Evidence (SOE) for Major Comparisons and Outcome. We also reported I^2 in the tables in the results.
		4) For adverse events, what was the unit for analysis (e.g., number of events, number of participants with at least one event)? How did you handle different definitions or descriptions of adverse events across trials? How was serious adverse event defined?	We used number of events as listed in the methods. The definition of AEs is listed in Table 3 in the methods. We used the definition of serious AEs listed by the original studies, which could have varied between studies. We recognize this as a limitation and added to the report.

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		(5) You used SMD to combine outcomes measured by different scales/instruments. Any idea of the psychometric properties of these instruments?	We only included quality of life and symptom measurement instruments that previously have been found to be reliable (i.e. measuring the construct of interest consistently and in a stable manner) and valid (i.e. accurately measuring the construct of interest). When combining outcomes measured by different instruments, we ensured that the construct of interest was identical or very similar. Evaluating or summarizing the psychometrics of these tools is beyond the scope of this report.
Peer reviewer #4	General Comments	Investigating heterogeneity Based on the descriptions of the PICOTS, it appears that there were substantial clinical and methodologic differences among the studies. Are such differences sufficiently large to preclude meta-analysis? Provide evidence to support whether clinical and methodologic differences may (may not) threaten the validity of meta-analysis. Discuss the implications of heterogeneity (if there is any).	Heterogeneity is always a concern for meta-analyses. We executed extra caution and used extra steps to ensure validity of the findings. Throughout the report and KQs, we conducted meta-analyses only when it's reasonable to do so. This is also the reason we didn't conduct network meta-analysis or pool systemic vs inhaled CS per suggestion by the reviewer. For example, in KQ2, we combined results for Aminophyllines vs. placebo; Magnesium sulfate vs placebo; Mucolytics vs placebo, etc. For Chest physiotherapy, we separated by breathing technique, vibration/ percussion, positive expiratory pressure, etc. As a result, despite of 95 studies included in the analyses, no meta-analyses included more than 4 studies. Nevertheless, heterogeneity still exists. We presented I^2 and incorporated heterogeneity in evaluating SOE. We also presented heterogeneity as a limitation.

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Peer reviewer #4	General Comments	Statistical issues: When the number of studies is small, DerSimonian and Laird random effect model is problematic and alternative models should be considered. Please see Cornell Ann Intern Med. 2014;160:267-270; and Veroniki JRSM 2015. (As a matter of fact, Annals would not publish any systematic review that used D-L random-effects model.)	In this report, we followed the latest EPC methods guide for comparative effectiveness reviews (Morton SC et al. Quantitative Synthesis-An Update. Methods Guide for Comparative Effectiveness Reviews. https://doi.org/10.23970/AHRQEPCMETHGUIDE3). We are aware of the alternative methods (such as profile likelihood, the Hartung-Knapp-Sidik-Jonkman modification (HKSJ), etc). These methods are not bulletproof. The profile likelihood doesn't always converge and may overestimate the confidence intervals when the number of studies is small and heterogeneity is low. The HKSJ modification often produces smaller confidence intervals and smaller P values and, sometimes, provides wider and unreasonable confidence intervals, in addition to other issues (Wiksten, et al Stat Med. 2016;35:2503-2515; Jackson, et al Stat Med. 2017 Nov 10; 36(25): 3923–3934; Copas, Stat Med. 2003;22:2667-2668). In this review, we used the DerSimonian and Laird random effect model because the heterogeneity is low (the largest I^2 was 20.33%), which followed the recommendations by the latest EPC methods guide. However, we added the HKSJ method and profile likelihood as sensitivity analysis and presented the findings in Appendix Table J.1.

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Peer reviewer #4	General Comments	Qualitative synthesis: Please provide an assessment and synthesis of the body of evidence that goes beyond factual descriptions of results to help readers to interpret the findings of the analyses. The purpose of the qualitative synthesis is to develop and convey a deeper understanding of how an intervention might be working (or not), for whom, and under what circumstances. It can include, for example, critique the strengths and weaknesses of the body of evidence, identify differences in the design and execution of the individual studies that may explain why their results differ, how flaws in the design or execution of the studies may bias the results, describe the study setting and its relevance to real-world practice, call attention to patient population that may be inadequately studied or for whom results may differ, describe how the systematic review findings contrast conventional wisdom, and interpret and assess the robustness of the meta-analysis results. Please see Standard 4.2 of the IOM report (http://www.nationalacademies.org/hmd/Reports/2011/Finding-What-Works-in-Health-Care-Standards-for-Systematic-Reviews/Standards.aspx).	Many of these pieces are already in the discussion section. We hesitate to describe the results of individual studies in text because we know that most readers will not read this text and in fact this text will reduce the usability of the report and may distract from the main messages. There is plenty of literature documenting lack of interest of various stakeholders (particularly health systems users) in more detailed and lengthy text describing individual studies and speculations about bias directions and heterogeneity. The current qualitative description is sufficient according to our clinical experts and other peer reviewers with clinical background.
Peer reviewer #4	General Comments	Global comment: you may want to replace “patients” with “participants” throughout the report.	All study participants were “patients” with ECOPD.
Peer reviewer #4	General Comments	Page 17/302, “acute exacerbation of COPD” should be abbreviated to AECOPD. Please do a global find and replace.	We changed ““acute exacerbation of COPD (AECOPD)” to “exacerbation of COPD (ECOPD)” in the report.
Peer reviewer #5	General Comments	The questions asked are clinically important - and populations are defined.	We thank the reviewer for the comments.
Peer reviewer #6	General Comments	The report clearly represents a heroic effort and summarizes a very large number of studies. Such a report is long overdue and will be received with interest.	We thank the reviewer for the comments.

Peer reviewer #6	General Comments	I do, however, have some suggestions to improve the presentation and utility of the report. Some of my comments may be because the final formatting of this report has not be done. I used the page numbers corresponding to the PDF, because I found the pager number formatting at the bottom of the report cumbersome to use. 1. The phrase “comparative effectiveness” or "effectiveness" is used in several areas of the report (e.g., in Key Questions, such as KQ4; Page 2, Purpose of review; Line 52, page 52 about oral mucolytics; and Title of Table 49). However, in most cases, the authors explicitly indicate they evaluate the “efficacy” of interventions in the title or abstracts. Comparative “effectiveness” assumes the study design is oriented towards understanding the "real-world" harms and benefits when the intervention is used by individuals in the manner that would be expected in routine (not research) settings. Such a concept needs to account for the multi-criteria efficacy to effectiveness study design continuum. For further information: a. Lieu TA, Au D, Krishnan JA, Moss M, Selker H, Harabin A, Taggart V, Connors A; Comparative Effectiveness Research in Lung Diseases Workshop Panel. Comparative effectiveness research in lung diseases and sleep disorders: recommendations from the National Heart, Lung, and Blood Institute workshop. Am J Respir Crit Care Med. 2011 Oct 1;184(7):848-56. b. Institute of Medicine. Initial national priorities for comparative effectiveness research. Washington, DC: National Academies Press, 2009.	We thank the reviewer for the comments. We agree that “effectiveness” should be used throughout the report and have changed it.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	General Comments	The PRECIS-2 group has proposed use of multiple criteria to assign studies across this continuum to facilitate planning and communication of the intended study design – was the PRECIS-2 tool used by the EPC investigators?	We did not use the PRECIS-2 tool. This tool that evaluates how explanatory or pragmatic clinical trials has not been used in previous AHRQ studies, and, as far as we know, is currently not endorsed by AHRQ. The PRECIS-2 is primarily meant to be used at the design stage of a trial in order to help trialists make the purpose of their trial explicit.
Peer reviewer #6	General Comments	Please note that RCTs can be mostly effectiveness oriented (so-called pragmatic trials) or mostly efficacy oriented (so-called explanatory trials), or lie somewhere along the continuum.	In the review, all of the studies were conducted in clinical settings and deemed to be "effectiveness oriented".
Peer reviewer #6	General Comments	I believe the phrase "comparative efficacy" is more appropriate in this EPC report given the design used in the systematic review and the available studies.	We determine that "effectiveness" is more appropriate in this case.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	General Comments	Propose replacing the phrase “acute exacerbations of COPD” to “exacerbations of COPD” or “COPD exacerbations” throughout the report. There are no “chronic” exacerbations of COPD. The phrase “acute exacerbations of COPD” is an older phrase in the literature, but increasingly the word “acute” has been dropped in publications and guidelines. For example, see: Patient Education / Informations series in ATS: https://www.thoracic.org/patients/patient-resources/resources/copd-exacerbation-ecopd.pdf; 2017 ERS/ATS guidelines: https://erj.ersjournals.com/content/49/3/1600791; and GOLD 2019 report: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf	We agree that the word “acute” can be considered superfluous. We removed “acute” in the report.
Peer reviewer #6	General Comments	3.Please note that the GOLD GLs has been updated in 2019	We have now used the definition of the 2019 GOLD report and updated the reference.
Peer reviewer #6	General Comments	4.Page 17, line 48, KQ4: what defines “emerging” therapies. Later on in the report, we see aminophyllines, chest physiotherapy, and magnesium sulfate are included in this category of therapies. Merriam-Webster defines “Emerging” as “newly formed or prominent”. Most experts will say that aminophyllines and chest physiotherapy (and are not new or prominent therapies. How about using the phrase “other therapies” for KQ4?	We changed the phrase to “emerging and other therapies”.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Key messages	Page 2/302, Key Messages: When reading the key messages for the first time, it was unclear whether they were based on pair-wise meta-analysis or network meta-analysis. The key messages were stated without considering the certainty in evidence?	We did not conduct a network meta-analysis. SOE is not included in the key messages because it makes them less user friendly (according to AHRQ guidance). The abstract does include SOE.
Peer reviewer #4	Structured Abstract	Does the methods section of the structured abstract mention that a network meta-analysis was conducted?: No	We didn't conduct network meta-analysis.
Peer reviewer #4	Structured Abstract	Is there any discussion of whether a network meta-analysis would add value?: No	We didn't conduct network meta-analysis.
Peer reviewer #4	Structured Abstract	Page 8/302, Structured Abstract: Search date is inconsistent with that in the main text of the report.	We corrected it.
Peer reviewer #4	Structured Abstract	Consider rewording "we were unable to demonstrate a difference…" to "there is no/insufficient evidence suggesting a difference…" Please edit all descriptions of results using a consistent style and sentence structure (here and throughout the report).	We changed the words.
Peer reviewer #4	Structured Abstract	"Clinical failure rate" is undefined.	Clinical failure was defined in the methods of the full report.
Peer reviewer #4	Structured Abstract	"SABAs, SAMAs, LABAs, and LAMAs" – undefined abbreviations.	The abbreviations are included in the List of Abbreviations and Acronyms (page 69). The abbreviations were explained at the time of their first use in the Evidence Summary and the Main Report, but not the Abstract. We have now referred to the group of "SABAs, SAMAs, LABAs, and LAMAs" in the abstract as "inhaled bronchodilators."
Peer reviewer #4	Structured Abstract	"(Low SOE)" – please use consistent style to present the certainty in evidence throughout the report (see another example on 16/302, line 14).	We now used consistent style.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Evidence Summary	Page 15/302, Evidence Summary: Text describing the effectiveness of interventions in the Background reads like discussion; will benefit from some careful editing. Please describe here the state of knowledge, uncertainty, controversies, and evidence gaps prior to this systematic review.	In the background section, we carefully outlined the state of knowledge, uncertainty and evidence gaps before the systematic review was conducted. This section was written (and published as part of the protocol) before information from the current systematic review was available, and is therefore distinct from the discussion. The current discussion section expands on the results by commenting on uncertainty, controversies, limitations and recommendations for future research.
Peer reviewer #4	Evidence Summary	What are the outcomes you planned to examine in the systematic review? At what time points? It is unclear which outcomes were pre-planned but without any data. Please describe all outcome in the Evidence Summary and note the gaps in knowledge (in terms of outcomes).	The information was presented in the methods of the full report. We aim to present a concise summary in the evidence summary.
Peer reviewer #6	Evidence Summary	Page 17, line 48, KQ4: what defines “emerging” therapies. Later on in the report, we see aminophyllines, chest physiotherapy, and magnesium sulfate are included in this category of therapies. Merriam-Webster defines “Emerging” as “newly formed or prominent”. Most experts will say that aminophyllines and chest physiotherapy (and are not new or prominent therapies. How about using the phrase “other therapies” for KQ4?	We changed the phrase to “emerging and other therapies”.
Peer reviewer #6	Evidence Summary	Text presented on pages 18 to 21 (Executive summary): Can I suggest using a table to list (in separate columns, landscape format) each KQ, comparison, findings, strength of evidence for each comparison, and page numbers in the report (or hyperlinks to tables later in the report) for further information so that readers can find what they are looking for at-a-glance? The current formatting is difficult to read and not scannable – inconsistent with the concept behind an Executive Summary	We thank the reviewer for the comments. However, one table with all of the information can be too complex.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Evidence Summary	There are several types of fonts in this report, including in the Exec Summary – would simplify. On page 21, line 14, the large font and bolded sentence starting with "Inhaled Budesonide 40 mg…. " should it be included in the previous paragraph?	We corrected these issues.
Peer reviewer #6	Evidence Summary	Executive Summary discussion - seems repetitious with Results and less of a discussion. More high-level synthesis by KQ about findings and gaps would be better.	We have now deleted the repetitious results. The high-level synthesis can be found under "Findings in Relation to What Is Known" in the Discussion.
Peer reviewer #6	Evidence Summary	Table 1 (page 22+): The content is not linked to KQ nor SOE descriptions; suggest replacing with the table described in #5 above.	The content of Table 1 is linked to KQ1 and 2 and has now been deleted.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Evidence Summary	Suggestions for future research in Exec Summary and end of report (page 26, lines 15+, and on page 99, lines 13+): Patients hospitalized with COPD exacerbations are at high risk for hospital readmissions and death after hospital discharge, which has led payers (particularly CMS) to promote the design and implementation of programs to improve the hospital-to-home continuum of care. At hospital discharge, patients generally require days or weeks of supportive care as they convalesce. Patients, health systems, and payers are seeking evidence-based approaches to reduce the risk of adverse outcomes following hospital discharge – this report should call attention to this gap in evidence. A recent publication found the highest risk of hospital readmission or death to occur within the first few days after hospital discharge, with a time-related reduction in risk over a 12 month period. (Lindenauer PK, Dharmarajan K, Qin L, Lin Z, Gershon AS, Krumholz HM. Risk trajectories of readmission and death in the first year after hospitalization for chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2018;197:1009–1017.)	Our systematic review did not include health services interventions, such as community care after hospital discharge, and we focused on the most acute phase of an exacerbation rather than the convalescence. Nevertheless, the reviewer makes an important point about the need to improve the hospital-to-home continuum in care and we have included a comment in the “Suggestions for Future Research” in the ES and the main report.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Evidence Summary	Further research focused on improving supportive care (e.g., use of home action plans, patient and caregiver self-management education, care coordination with home-based and medical facility-based providers, promoting physical activity, re-assessing needs for home oxygen therapy) as patients with COPD exacerbations convalesce following hospital discharge are needed. The management of exacerbations should include evidence-based interventions and strategies during the high-risk period of transition from acute care for COPD exacerbations in hospital settings to outpatient care for stable COPD.	Our systematic review did not include health services interventions, and we focused on the initial most acute phase of an exacerbation only rather than the convalescence period. We have included a comment about the need to improve the hospital-to-home continuum in care in the "Suggestions for Future Research" in the ES and the main report. We have now also specified in "Scope of Review" that we excluded health services interventions and interventions during convalescence.
Peer reviewer #6	Evidence Summary	If this type of research is out of scope, then the scope should be made more clear - the title for the EPC report is very broad.	We have now specified in the "Scope of Review" that we excluded health services interventions and interventions during convalescence.
Peer reviewer #6	Evidence Summary	10. Page 61, line 24, "Early pulmonary rehabilitation". The term "early" is not defined – what does "during AECOPD" mean.	We changed "AECOPD" to "ECOPD". We have now defined that "Early pulmonary rehabilitation" refers to pulmonary rehabilitation commenced before hospital discharge and that during ECOPD refers to the initial most acute phase of exacerbation (hospitalization period for inpatients) rather than the convalescence period.
Peer reviewer #6	Evidence Summary	11. Page 62, line 33. Please define whole body vibration. The term "early" is not defined – what does "during AECOPD" mean.	We changed ""AECOPD" to "ECOPD". We have now defined that "early" refers to whole body vibration commenced before hospital discharge and that during ECOPD refers to the most acute phase of exacerbation (hospitalization period for inpatients) rather than the convalescence period.
Peer reviewer #6	Evidence Summary	12.References. 2-column format is difficult to scan and find relevant studies – suggest 1 column. Suggest 1 list of references at the end of the report, rather than different lists.	We followed the AHRQ reference format.
Peer reviewer #1	Introduction	Yes - but could add that defining when an AECOPD has resolved is very hard to do as is separating poor resolution from re-exacerbation.	We agree with the reviewer that defining resolution of an exacerbation and differentiating poor resolution from re-exacerbation can be challenging. We have added a comment on this in the limitations.
Peer reviewer #2	Introduction	Introduction: Well done	We thank the reviewer for the comments.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #3	Introduction	Introduction: It might be worth spending a little more time both more crisply defining exacerbations for your purposes in the background as well as better describing the breadth of exacerbation definitions in the literature. This could also go into methods but I didn't see it there either.	We have now added a comment on various definitions of ECOPD in the introduction and have included the definition of ECOPD from the 2019 GOLD report.
Peer reviewer #5	Introduction	Introduction lays out main issues reasonably clearly.	We thank the reviewer for the comments.
Peer reviewer #6	Introduction	Introduction: 1. For the structured abstract: Abbreviations should be spelled out before their use, even if there is a list of abbreviations elsewhere in the report (reduces cognitive burden for readers). Especially important in abstract since it will be often the initial text read (or the only text read) by most readers. For example, SOE, AECOPD, SABAs.	We deleted these abbreviations.
Peer reviewer #6	Introduction	Page 15: Line 13 (and in the Introduction, page 33, lines 13-14): Chronic lower respiratory diseases are now the fourth (not the third) leading cause of death in the U.S. for the past few years, of which COPD is the largest contributing condition; CDC leading causes of death 2016 https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm NCHS Data Brief ■ No. 328 ■ November 2018 https://www.cdc.gov/nchs/data/databriefs/db328-h.pdf	We have adjusted the text as suggested by the reviewer and included a reference to the NCHS Data Brief.
Peer reviewer #5	Evidence Summary	Key Questions appear appropriate (Acronym AECOPD used inconsistently in KQ in the ES).	We changed it.
Peer reviewer #1	Methods	Methods: Yes with the exceptions of the statistical issue I raised above and that separating intervention by severity of AECOPD.	We agree that small number of studies per meta-analysis is an issue. We added this point to the limitation. We also changed the sentence to “no statistical difference was observed”. The results by severity of ECOPD were presented in Appendix G.
Peer reviewer #2	Methods	Methods: Yes, justifiable.	We thank the reviewer for the comments.
Peer reviewer #3	Methods	Methods: Well it's not really outlined here, the authors point reader to a website. It might be nice to try to provide a brief overview of the search strategy within the actual document.	The search strategy is included in Appendix B of this report.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Methods	Page 22/302, Table 1. What are the comparison interventions for each row? The text in the previous page suggests that the standard of care is "standard therapy with antibiotics" (also see major comment #1). Please include comparison interventions here. The findings presented in this table rely entirely on the statistical significance without any context of the trials analyzed and risk of bias information.	The title stated the comparison. For the table, we intended to present the results in a simple concise matter. The clinical context of the findings in Table 1 was discussed in the following paragraphs. Now, we removed Table 1 from the ES.
Peer reviewer #4	Methods	Geometry of the network - Are the methods appropriate?: Yes	Network meta-analysis is not applicable in the study.
Peer reviewer #4	Methods	Geometry of the network Are the methods reported clearly and accurately?: No	Network meta-analysis is not applicable in the study.
Peer reviewer #4	Methods	Summary measures Are the methods appropriate?: No Summary measures Are the methods reported clearly and accurately?: No Assessment of inconsistency Are the methods appropriate?: Yes Assessment of inconsistency Are the methods reported clearly and accurately?: No Methods of analysis Are the methods appropriate?: No	We followed the EPC methods guide for the methods and reporting and made changes to clarify the methods and reporting.
Peer reviewer #4	Methods	Methods of analysis Are the methods reported clearly and accurately?: No Additional analyses Are the methods appropriate?: No Additional analyses Are the methods reported clearly and accurately?: No	We followed the EPC methods guide for the methods and reporting and made changes to clarify the methods and reporting.
Peer reviewer #5	Methods	Methods: Inclusion and exclusion criteria appear reasonable and appropriate to the scope of this review. The search strategies is included. Outcomes are defined.	We thank the reviewer for the comments.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #5	Methods	On pg 8, 2nd paragraph, (regarding cross-over RCTs) the sentence is confusing, it appears to be missing some words? O/w methodology appears clear.	The crossover randomized trials included in the study suffered methodological issues. We chose not to include those studies in the meta-analyses. We clarified this in the methods.
Peer reviewer #6	Methods	Methods: 1. Strongly recommend briefly defining Low, Moderate, and High SOE, as it is used throughout the Exec Summary to increase the usability of the report to readers, most of whom will not be reading the rest of the report or have prior knowledge.	We agree and added in the evidence summary.
Peer reviewer #6	Methods	Page 39, Table 2: Categories of severity. The severity categories are not mutually exclusive – for example, both "mild" and "moderate" can include ED visits. Also, not consistent with GOLD 2019 report (mild treated with bronchodilators only; moderate treated with bronchodilators plus abx or oral corticosteroids; severe requires hospitalization or ED visit).	There is a lot of variation in the classification of severity of ECOPD across the literature and no consensus about the "correct" classification. The severity classification in the latest GOLD report is controversial, as an ED visit may not be a marker of severity but may indicate health service availability in certain regions (e.g. no after-hours primary care cover and therefore patient might attend ED even with a non-severe ECOPD). The fact that we accepted the severity classification of the original studies (as outlined in the methods), also meant that there would be some overlap between categories. We believe that this correctly reflects the complex nature of severity classifications in ECOPD. This strategy also aligns with the input from our Key Informants and Technical Expert Panel.
Peer reviewer #6	Methods	Page 41, Strength of evidence: Not clear how the various criteria (e.g., methodological limitations, precision, directness) were combined to assign SOE as high, moderate, low, or insufficient. Suspect most readers will not know where to find the "EPC methods" (page 41, line 8) or have the time to. Would indicate why data from observational studies with control groups (e.g., cohort studies) were not included – explanation can be simple, but should be provided as there is increasing interest .	We thank the reviewer for the comments. We added the SOE definition and added the reference. We have also explicitly provided a rationale for depending in this review solely on randomized trials.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Methods	Page 66, line 50, indicates that patients without evidence of airflow limitation were excluded. It is often difficult to obtain spirometry in patients with COPD exacerbations, so frequently not done. This exclusion seems very important – suggest including this in the Abstract and Executive summary.	We agree with the reviewer that the exclusion of patients without evidence of airflow limitation is an important feature of our systematic review and distinguishes it from other systematic reviews on ECOPD. This meant that we excluded patients with AE of bronchitis, who did not have evidence of airflow limitation on spirometry (at any time, including during a stable state). We have now included a statement on this in the section on inclusion and exclusion criteria.
Peer reviewer #1	Results	In the Results section you separate cure rates from failures. They seem to be the same outcome to me.	We used the direction of reporting (positive, cure, or negative, failure) from the original studies. Episodes of ECOPD could have been reported as treatment failure at one time point (i.e. requiring additional treatment or a change in treatment) but eventually as cure at another time point.
Peer reviewer #1	Results	Results: See above comments	We used the direction of reporting (positive, cure, or negative, failure) from the original studies. Episodes of EOCPD could have been reported as treatment failure at one time point (i.e. requiring additional treatment or a change in treatment) but eventually as cure at another time point.
Peer reviewer #2	Results	Results: Well-done.	We thank the reviewer for the comments.
Peer reviewer #3	Results	Results: Results are pretty sparse on details. If possible, would be nice to reference Tables and some more detailed info at the back at the report. The key messages are clear, but the evidence for those conclusions really aren't present	We listed more detailed information in Appendix tables F1-F4.
Peer reviewer #3	Results	Page 71, Figure 2, I don't understand the arrows	Each arrow represents a comparison between two treatments reported by the literature. We added a footnote to the figure.
Peer reviewer #4	Results	Page 39/302: How did you reach an overall risk of bias (as presented in Appendix D)?	Descriptions were presented at the end of study description for each KQ, pages 13, 22, 42, 45.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Results	Page 40/302: Is there are reason for using odds ratio (instead of relative risk) for binary outcomes? Were you able to extract incidence rate of adverse events and subsequently calculate a rate ratio? Why not a relative risk?	There are pros and cons for odds ratio versus relative risk and there is no preferred way for sure. This is left to the discretion of the researchers. Odds ratio has better statistical properties than relative risk such as being symmetrical when converting outcomes (e.g. changing death to survival). For AEs, almost all studies reported incidence of events, not the number of patients; hence, we had to use a rate ratio.
Peer reviewer #4	Results	Page 42/302: Current description of the Evidence Base is superficial and does not provide the context for synthesis. Please see major comment 4. This comment applies to the description of evidence base for all key questions.	In the background section, we carefully outlined the state of knowledge, uncertainty and evidence gaps before the systematic review was conducted. This section was written (and published as part of the protocol) before information from the current systematic review was available, and is therefore distinct from the discussion. The current discussion section expands on the results by commenting on uncertainty, controversies, limitations and recommendations for future research.
Peer reviewer #4	Results	Page 46/302: Table 5 – Why SMD is used for cough and other symptoms? It would be useful to show the "raw data" somewhere.	Symptoms, including cough, were reported using scales. When multiple scales used, we used SMD. When only one scale reported, we used WMD.
Peer reviewer #4	Results	Presentation of network structure Is the network structure reported clearly and accurately? If you answer no, please elaborate in the Other Comments text box at the end of the form.: No	Network meta-analysis is not applicable in the study.
Peer reviewer #4	Results	Summary of network geometry Is the network geometry reported clearly and accurately? If you answer no, please elaborate in the Other Comments text box at the end of the form.: No	Network meta-analysis is not applicable in the study.
Peer reviewer #4	Results	Describe the implications of the network geometry on the validity of the network meta-analysis.: Not applicable because no NMA was conducted.	Network meta-analysis is not applicable in the study.
Peer reviewer #4	Results	Exploration for consistency/inconsistency Are the results reported clearly and accurately? If you answer no, please elaborate in the Other Comments text box at the end of the form.: No	Network meta-analysis is not applicable in the study.

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Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Results	Describe the implications of the result of the analysis (or of diagnostics) on the validity of the network meta-analysis.: Not applicable because no NMA was conducted.	Network meta-analysis is not applicable in the study.
Peer reviewer #5	Results	Would it be appropriate to do a meta-analysis of systemic vs inhaled CS? Would it be appropriate to do a meta-analysis of systemic vs IV CS?	For the comparison of systemic CS vs inhaled CS, the systemic CS included variable routes of administration (subcutaneous, oral, intravenous, oral with iv step down) and different agents (prednisone and methylprednisone). For the comparison of oral vs iv CS, different agents were used in different studies (prednisone and methylprednisone). Thus, for both comparisons the interventions were too heterogeneous for meaningful meta-analysis.
Peer reviewer #5	Results	Otherwise, the detail and clarity appears appropriate Fow chart A - Not clear why in lower Right box 39 clinical trials were excluded - it appears they were excluded because they were clinical trials	We updated the flowchart.
Peer reviewer #6	Results	Results: 1. For KQ2, was the following sham-controlled RCT of high frequency chest wall oscillation included (e.g., Table 24 and 25)? Does not appear so. This study was unique in using a sham-control and blinded assessments of patient-reported outcomes, including dyspnea using the Borg instrument. Mahajan AK, Diette GB, Hatipoğlu U, Bilderback A, Ridge A, Harris VW, Dalapathi V, Badlani S, Lewis S, Charbeneau JT, Naureckas ET, Krishnan JA. High frequency chest wall oscillation for asthma and chronic obstructive pulmonary disease exacerbations: a randomized sham-controlled clinical trial. Respir Res. 2011 Sep 10;12:120. doi: 10.1186/1465-9921-12-120.	We excluded this study after full text screening as the study included patients with asthma and COPD, asthma only, or COPD only and outcomes were not reported for COPD separately.
Peer reviewer #6	Results	Page 47, Table 6. Was the following study in 271 participants included in the evidence table? Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, Anderson P, Morgan NA. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med. 1999 Jun 24;340(25):1941-7.	Yes, this is ref.77

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #6	Results	Page 63, line 40. For supplemental oxygen studies. Please define the study population – what was their SpO2 or PaO2 in whom supplemental oxygen vs. air was tested? Unless the patient has severe hypoxemia (SpO2<89%), the likelihood of benefit is low.	The reviewer makes an important point. Hypoxemia at rest was not a requirement for inclusion in this study, and baseline mean PaO2 measurements were relatively high, ranging from 72-80 mmHg in different groups. This might well explain the lack of a demonstrated effect of oxygen. We have added this information in the results section.
Peer reviewer #6	Results	Page 67, line 48, KQ3. This question seems to refer to combining treatments that "have been found to be individually effective." First, the term "efficacious" is probably a better descriptor. Also, KQ3 suggest that the individual treatments were known to benefit in AE-COPD; that does not seem to be the case. Perhaps KQ3 should be re-worded to say "….known to be efficacious in stable COPD"?	Our systematic review showed indeed that no RCTs have been performed to assess the effect of a SABA or SAMA vs placebo. This is likely the case because there is overwhelming evidence from clinical practice that these medications relieve breathlessness. We changed KQ3 to "In adult patients with exacerbation of COPD, what are the benefits and harms of combinations of treatments that are individually effective (based on empirical evidence in stable COPD)"
Peer reviewer #6	Results	. Page 69, KQ4, suggest clarifying in the subsequent text if the trials of antibiotics were based on empiric initial therapy in all patients or based on clinical suspicion of pneumonia or other infection or if the antibiotics were selected on the basis of other testing (e.g., sputum cultures or blood cultures).	The trials of antibiotics were based on empirical initial therapy for ECOPD (in the absence of pneumonia). We have added this information in the results section.
Peer reviewer #6	Results	Page 90, Table 79. Why was the study with reference #68 considered to have a high risk of bias? Also, how was severe imprecision defined – for example, if the ends of the 95% CI crossed no difference but were within the MID, that would not be considered as imprecision.	We used the Cochrane Risk of Bias tool. We could not find information on how randomization was conducted (unclear random sequence generation and allocation concealment) and whether outcome assessors knew the treatments patients received. After reviewing the protocol and this manuscript, we judged it as high risk of bias. In terms of imprecision, the outcomes in table 79 are binary and the concept of MID is not applied here.
Peer reviewer #1	Discussion	Discussion/ Conclusion: Yes	We thank the reviewer for the comments.
Peer reviewer #2	Discussion	Discussion/ Conclusion: Yes	We thank the reviewer for the comments.
Peer reviewer #3	Discussion	Discussion/ Conclusion: Yes implications are clearly stated.	We thank the reviewer for the comments.
Peer reviewer #3	Discussion	Limitations are relatively briefly stated. Perhaps could be emphasized more.	We revised the section.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Discussion	Is there adequate discussion of the strength and limitations of the network meta-analysis?: No	Network meta-analysis is not applicable in the study.
Peer reviewer #4	Discussion	Do the authors give any comments on the validity of the assumptions, such as transitivity and consistency, and any comments on concerns regarding network geometry (e.g., avoidance of certain comparisons)?: No	Network meta-analysis is not applicable in the study.
Peer reviewer #5	Discussion	Summary (Table 81) Lays out key statements of effectiveness for each intervention.	We thank the reviewer for the comments.
Peer reviewer #5	Discussion	New research section calls out the importance of patient-important outcomes.	We thank the reviewer for the comments.
Peer reviewer #6	Discussion	Discussion/ Conclusion: 1. Figures 3 and 4 in Discussion. Probably among the most important findings – for most interventions, the literature is inadequate or non-existing. Suggest providing the reference number for each study that was identified (e.g., 1 RCT with superscript for reference number) to help readers quickly see which studies were included for what analysis.	We thank the reviewer for the comments. We intended to present concise information in Figure 3 and 4 to show the distribution of the evidence. The reference numbers would have added too much information making the figures less readable.
Peer reviewer #4	Appendix	Page 71/302: Figure 2 – Have you considered a network meta-analysis?	Due to heterogeneity, we didn't conduct network meta-analysis.
Peer reviewer #4	Appendix	Page 92/302: you may want to consider moving Figures 3, 4 to the Results.	The evidence maps show the distribution of the evidence by KQs. We decided to keep them.
Peer reviewer #4	Appendix	Page 117/302: Flow chart: The reasons for excluding "full-text articles" are oddly and unclearly worded. "Abstract" – do you mean full text not available? "Article not available" – what do you mean?	These are studies published as conference abstracts only. We clarified this now.
Peer reviewer #4	Appendix	"Clinical Trials"? "Duplicate study"? I thought you are only excluding full text articles at this stage. Please discuss the limitations of excluding trials published in non-English language. Can you provide a quick summary of the other 54 systematic reviews and meta-analyses on this topic?	Those are completed studies identified from ClinicalTrials.gov. We used those studies to identify additional studies. "Excluding non-English study" is listed as a limitation. Summarizing systematic review/meta-analyses is not in the KQs and the protocol.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Appendix	Page 185/302: Appendix D How did you reach an overall risk of bias? Last column on "patient characteristics" – are numbers presented by treatment group or overall? It seems you have both, but very confusing. Please re-work this column.	The reasons on how we summarized overall risk of bias varied by KQs and presented at the beginning of each KQ. For the number of patients, we presented by the arms. However, we have crossover randomized controlled trials (RCTs), in which the same group of patients received different treatments. We now combined these cells in the table.
Peer reviewer #1	Clarity and Usability	Clarity and Usability: Yes	We thank the reviewer for the comments.
Peer reviewer #2	Clarity and Usability	Clarity and Usability: Yes, well-structured	We thank the reviewer for the comments.
Peer reviewer #3	Clarity and Usability	Clarity and Usability: I almost feel like too much of the actual detail is in the appendices at the end. The conclusions within the main report don't feel well substantiated.	This systematic review had a very broad focus. The numerous analyses conducted make it impossible to present all information in the main report. The appendices will be published with the main report, which will allow readers to look at the details if so desired. A relatively concise main report will allow readers to gain a quicker overview over the relevant outcomes.
Peer reviewer #5	Clarity and Usability	Clarity and Usability: Overall, well organized.	We thank the reviewer for the comments.
Peer reviewer #5	Clarity and Usability	There are a few places where typographic issues appeared to cause text body to show up as header text. Pg ES-5, ES-7	We changed these errors.
Peer reviewer #5	Clarity and Usability	Clarity and Usability: Various sections could be improved in terms of clarity and usability - see above.	We thank the reviewer for the comments.