



## Evidence-based Practice Center Systematic Review Protocol

### Project Title: Pharmacologic and Non-pharmacologic Therapies in Adult Patients with Acute Exacerbation of COPD: A Systematic Review

#### I. Background and Objectives for the Systematic Review

Chronic Obstructive Pulmonary Disease (COPD) is a common respiratory disease characterized by airflow limitation and chronic respiratory symptoms. The global prevalence is estimated to be greater than 10%, impacting approximately 380 million people worldwide.<sup>1</sup> In the United States, COPD affects approximately 15 million people, is the third leading cause of death, and costs more than \$32 billion annually.<sup>2, 3</sup> Patients with COPD experience chronic respiratory symptoms (including shortness of breath and cough), have decreased quality of life, and premature mortality.

Patients with COPD are at risk of experiencing acute exacerbations of COPD (AECOPD), defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as “an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.”<sup>4</sup> AECOPD are generally characterized by increased dyspnea, increased frequency and severity of cough, and/or increased sputum production.<sup>5</sup> Exacerbations may range in severity from mild to severe. The 2017 joint guidelines on the management of COPD exacerbations by the European Respiratory Society and the American Thoracic Society refer to mild exacerbations as exacerbations mild enough to be treated in an outpatient setting, and give recommendations on the use of systemic corticosteroids and antibiotics in these episodes.<sup>6</sup> The guidelines give conditional recommendations for a short course ( $\leq 14$  days) of oral corticosteroids and a course of antibiotics in mild AECOPD (very low quality of evidence and moderate quality of evidence respectively).

AECOPD are a leading independent cause of increased mortality and morbidity among patients with COPD. AECOPD are associated with a higher risk of dying during or shortly after the exacerbation, lower quality of life, hospital admission and readmission, depletion of financial resources, and a progressive decline in lung function.<sup>7-14</sup> Hospitalizations for AECOPD account for more than half of all costs associated with COPD.<sup>10, 15</sup>

Goals of management of AECOPD include addressing precipitating factors, improving expiratory airflow, reducing lung inflammation, improving gas exchange, and providing symptom relief. Pharmacologic treatment considerations for AECOPD include short-acting/long-acting inhaled bronchodilators, anti-inflammatory drugs such as systemic corticosteroids and phosphodiesterase-4 inhibitors, and antibiotics. Non-pharmacologic treatments include supplemental oxygen, cigarette cessation, nutritional support and

others.<sup>16-18</sup> In addition, several new pharmacologic agents with novel mechanisms of action in early stages of development may be of potential benefit to COPD patients including those in acute exacerbation.<sup>19</sup>

The area of AECOPD management has several uncertainties and necessitates an up to date evidence synthesis. Uncertainties relate to the benefits and harms of emerging pharmacologic and non-pharmacologic treatments, the benefits and harms of antibiotics and systemic corticosteroids in mild AECOPD, the benefits and harms of combinations of treatments that have been found to be individually effective, and—for antibiotics and systemic corticosteroids—the comparative effectiveness of different types of agents (e.g. broad-spectrum versus narrow-spectrum antibiotics), modes of application (e.g. intravenous, oral), and durations of treatment.

Examples of emerging treatments for AECOPD, some of which may have an established role in the treatment of stable COPD, include mucolytics, PDE4 inhibitors, and symptom palliation with opioids and benzodiazepins.

Mucolytics appear to have a small effect on reducing the frequency of AECOPD.<sup>20, 21</sup> In clinical practice, they are also used during an AECOPD, where the evidence for their effectiveness appears less clear.

PDE4 inhibitors have been shown to improve lung function and reduce the likelihood of exacerbations in patients with COPD.<sup>22</sup> Whether they have a role in treatment of AECOPD based on their properties to reduce airway inflammation and bronchoconstriction has not been systematically assessed to date.

Breathlessness is a common symptom of AECOPD. The role of treatments that can relieve breathlessness including opioids and benzodiazepines in patients with advanced COPD suffering from an episode of AECOPD is unclear, especially as these drugs can cause respiratory depression and have thus the potential to worsen hypercapnic respiratory failure.<sup>23</sup>

For non-pharmacological treatments there are a number of areas in which an update of the evidence is required to inform best practice management of AECOPD. There is increasing recognition that too much oxygen might do more harm than good, and not just in patients with chronic hypercapnic respiratory who are at risk of iatrogenic worsening of respiratory failure due to oversupply of oxygen.<sup>24, 25</sup> There is also the newer modality of oxygen therapy via high flow nasal cannula, which seems a promising approach in the treatment of AECOPD.<sup>26</sup>

Historically, physiotherapy during AECOPD has focused on clearance of secretions and breathing technique, but in more recent times a number of trials have explored the role of exercise/ pulmonary rehabilitation during an episode of AECOPD.<sup>27, 28</sup> Many COPD patients are in a state of hyper-metabolism in which their body consumes more calories per kilogram on calorimetric measures compared to a person without COPD, likely because of the increased work of breathing.<sup>29</sup> This hyper-metabolic state is even more

pronounced during episodes of AECOPD, posing questions about the optimal nutritional support for patients with AECOPD.<sup>30, 31</sup>

Established treatments for AECOPD, such as antibiotics and systemic corticosteroids may not be indicated in every single episode of an AECOPD. One uncertainty relates to the need for antibiotics in mild and moderately severe AECOPD, especially in an outpatient setting.<sup>32</sup> While there is robust evidence supporting the role of antibiotics for treatment of severe AECOPD, the need for antibiotics in less severe forms of COPD is unclear.<sup>33</sup> Uncertainty regarding the use of systemic (oral, intravenous) corticosteroids relate to whether all patients stand to benefit from this treatment of AECOPD.<sup>33</sup> These questions are important to address in view of trying to reduce prescriptions of antibiotics, where safely possible, to reduce potential harms including development of antibiotic resistance, and to reduce potentially significant adverse effects from systemic corticosteroids, in particular hyperglycemia, in patients with glucose intolerance and diabetes.<sup>34</sup>

Short-acting beta adrenergic agonists and short-acting anticholinergics are established treatments to relieve dyspnea and improve airflow obstruction during AECOPD, but the benefit of combination of short-acting beta agonists and short-acting muscarinic antagonists is unclear.<sup>35</sup> Long-acting bronchodilators and inhaled corticosteroids have historically only be used in stable COPD, but there is emerging evidence that an increase in dosage of inhalation therapy with inhaled corticosteroids and long-acting beta agonists may be beneficial in early treatment of AECOPD when patients experience mild to moderate dyspnea and may result in no requirement of systemic corticosteroids in a large proportion of patients presenting with mild-to-moderate worsening of dyspnea.<sup>36</sup> The benefit of using a combination of long-acting beta agonists and long-acting muscarinic antagonists in the treatment of AECOPD is unclear.

For antibiotics and systemic corticosteroids, the comparative effectiveness of different agents (e.g. broad-spectrum versus narrow-spectrum antibiotics), modes of application and durations of treatment needs to be established.<sup>37-40</sup>

In summary, determining the optimal treatment plan for patients with AECOPD requires 1) a synthesis of existing knowledge regarding the efficacy of treatment options 2) a synthesis of existing knowledge regarding the harms of treatment options and 3) the ability to reliably and accurately apply that knowledge to the right patient. Currently, the comparative benefits and harms of these varied treatment approaches including the optimal combination or sequencing of these treatments to mitigate COPD exacerbation is unclear. A systematic review of current evidence will assist clinicians in understanding and determining optimal management for AECOPD. This review will focus on evidence from randomized controlled trials as the gold standard design for evaluating a therapeutic intervention. While observational studies are helpful to determine adverse effects (because they are longer and represent the real world experience), we will focus this review on randomized trials because 1) the clinical question is of acute nature; thus, adverse effects will be captured during the follow up of trials without the need for extended follow up; and 2) the clinical question focuses on patients with exacerbations

who usually who have high risk and multiple comorbidities; thus, the trials will unlikely to selectively enroll low risk patients.

## II. The Key Questions

KQ1. In adult patients with mild acute exacerbation of COPD, what are the benefits and harms of systemic corticosteroids and antibiotics compared with placebo or standard care?

KQ2. In adult patients with moderate to severe AECOPD, what are the benefits and harms of emerging pharmacologic and non-pharmacologic therapies compared with placebo or standard care?

KQ3. In adult patients with acute exacerbation of COPD, what are the benefits and harms of combinations of treatments that have been found to be individually effective?

KQ4. In adult patients with acute exacerbation of COPD, what is the comparative effectiveness of different regimens of antibiotics and systemic corticosteroids based on type of agents (e.g. broad-spectrum versus narrow-spectrum antibiotics), modes of application (e.g. intravenous, oral), and durations of treatment?

## PICOTS

- **Population(s)**
  - Adults with acute exacerbation of COPD

- **Interventions**
  - KQ 1 and 4
  - Antibiotics and systemic corticosteroids

KQ 2 and 3

Pharmacologic interventions include:

- Short- and long-acting beta adrenergic agonists
- Short- and long-acting anticholinergic agents
- Inhaled and systemic corticosteroid therapy
- Antibiotics
- Mucolytics
- Opioids
- Benzodiazepines
- PDE4 Inhibitors
- Aminophyllines
- Magnesium sulfate
- Immune-modifying therapies
- Combinations of the above, in particular the combination of short-acting beta adrenergic agonists and short-acting anticholinergic agents; and the combination of antibiotics and systemic corticosteroids with focus on the question whether there are episodes of AECOPD that can be safely treated with systemic corticosteroids alone without antibiotics or vice versa

(treatment with antibiotics alone without the need for systemic corticosteroids)

Non-pharmacologic interventions include:

- Oxygen therapy, delivered via conventional oxygen therapy, high flow nasal cannula
- Early pulmonary rehabilitation/exercise
- Chest physiotherapy
- Nutritional support
- Whole body vibration
- Neuromuscular electrical stimulation
- Combinations of the above

- **Comparators:**

KQ 1: Placebo or standard care

KQ 2: Placebo or standard care

KQ3: Placebo, standard care or active individual intervention

KQ4 : Different types, modes of application, and durations of treatment of antibiotics and systemic corticosteroids

- **Outcomes:**

KQ 1,2,3 & 4: Intermediate outcomes

- Symptom scores;
- FEV1, FEV1/FVC ratio

KQ 1,2,3 & 4: Final health outcomes

- Resolution of exacerbation/treatment failure;
- Repeat exacerbations;
- Mortality;
- Quality of life;
- Hospital admission;
- ICU admission;
- Physical capacity (timed walking tests, endurance tests)
- Number of intubations

KQ 1, 2,3 & 4: Adverse effects of interventions (harms)

- **Timing:**

- All

- **Setting:**

- Outpatient, hospital

- **Study Design:**

- Randomized controlled trials

- **Exclusions:**

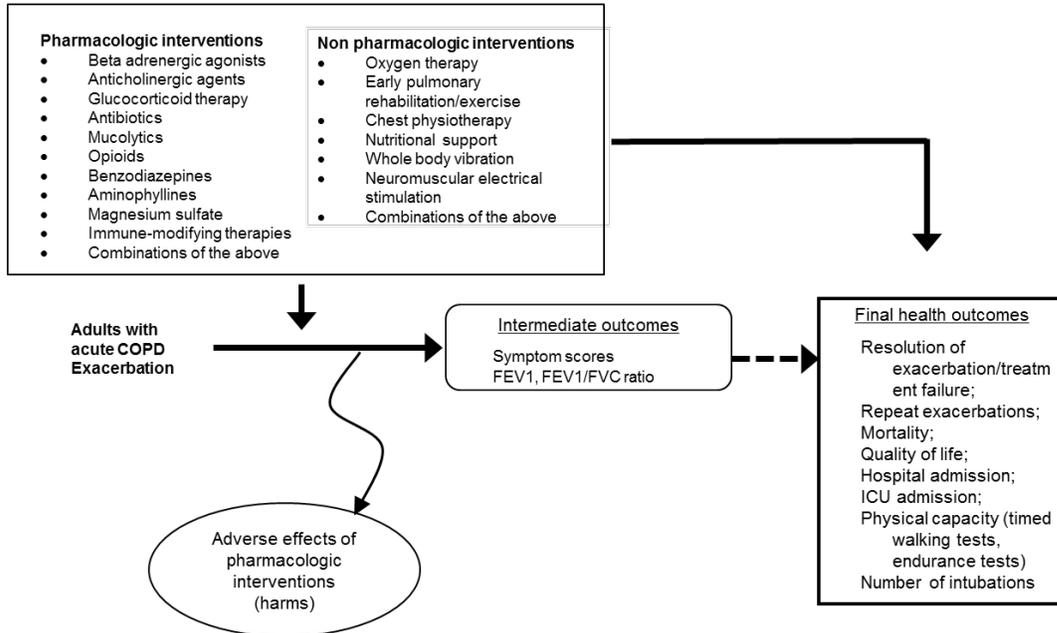
- Invasive and non-invasive mechanical ventilation

- Complementary and alternative interventions
- **Subgroup Analysis:**
  - COPD severity
  - COPD phenotype
  - Severity of exacerbation
  - Cause of exacerbation (respiratory infection, air pollution, failure to adhere to chronic therapy, pulmonary embolism, etc.)
  - Comorbidities (tobacco abuse, pulmonary hypertension, congestive heart failure, morbid obesity, gastroesophageal reflux disease, depression and anxiety, overlap with asthma or interstitial lung disease, etc)
  - Current baseline chronic treatment regimen (home noninvasive ventilation, chronic oral steroid use, inhalers, etc.)
  - Medication dosage
  - Agents within a drug class
  - Treatment duration
  - Delivery mode
  - Sex
  - Age group (18-40, 40-65, 65>)
  - Race/ethnicity
  - Socioeconomic status

### III. Analytic Framework

#### Analytic Framework

Figure 1. Draft analytic framework for key questions 1, 2, 3 and 4



**IV. Methods Criteria for Inclusion/Exclusion of Studies in the Review** - We will apply the following inclusion and exclusion criteria for the studies identified in the literature search (Table 1).

**Table 1. Inclusion and exclusion criteria**

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Populations	<ul style="list-style-type: none"> <li>• Patients with acute exacerbation of COPD</li> <li>• Adults 18 years and older</li> </ul>	<ul style="list-style-type: none"> <li>• Animals</li> <li>• Children (age &lt; 18 years)</li> <li>• Patients with stable COPD not in a current exacerbation</li> </ul>

Interventions	<p>KQ 1,4:</p> <ul style="list-style-type: none"> <li>• Antibiotics</li> <li>• Systemic corticosteroids</li> </ul> <p>KQ 2,3: Pharmacologic interventions include:</p> <ul style="list-style-type: none"> <li>• Beta adrenergic agonists</li> <li>• Anticholinergic agents</li> <li>• Glucocorticoid therapy</li> <li>• Antibiotics</li> <li>• Mucolytics</li> <li>• PDE4 Inhibitors</li> <li>• Opioids</li> <li>• Benzodiazepines</li> <li>• Aminophyllines</li> <li>• Magnesium sulfate</li> <li>• Immune-modifying therapies</li> <li>• Combinations of the above</li> </ul> <p>KQ 2,3: Non-pharmacologic interventions include:</p> <ul style="list-style-type: none"> <li>• Oxygen therapy</li> <li>• Early pulmonary rehabilitation/exercise</li> <li>• Chest physiotherapy</li> <li>• Nutritional support</li> <li>• Whole body vibration</li> <li>• Neuromuscular electrical stimulation</li> <li>• Combinations of the above</li> <li>•</li> </ul>	<ul style="list-style-type: none"> <li>• Invasive and non-invasive mechanical ventilations</li> <li>• Complementary and alternative medicine interventions</li> <li>• Investigational drugs and drugs that are only available outside of the U.S.</li> <li>• Interventions to prevent future COPD exacerbations</li> </ul>
Comparators	<p>KQ 1: Placebo or standard care  KQ 2: Placebo or standard care  KQ 3: Placebo, standard care or active individual intervention  KQ 4: Different types of antibiotics and systemic corticosteroids, different modes of application and durations of treatment</p>	None

Outcomes	Intermediate outcomes <ul style="list-style-type: none"> <li>• Symptom scores;</li> <li>• FEV1, FEV1/FVC</li> </ul> Final health outcomes <ul style="list-style-type: none"> <li>• Resolution of exacerbation/treatment failure;</li> <li>• Repeat exacerbations;</li> <li>• Mortality;</li> <li>• Quality of life;</li> <li>• Hospital admission;</li> <li>• ICU admission;</li> <li>• Physical capacity (timed walking tests, endurance tests)</li> <li>• Number of intubations</li> </ul>	None
Timing	All	None
Settings	Outpatient, hospital, emergency department	ICU, chronic ventilator unit or respiratory care unit (RCU)
Study design	<ul style="list-style-type: none"> <li>• Original data</li> <li>• Any sample size</li> <li>• RCTs</li> <li>• Relevant systematic reviews, or meta-analyses (used for identifying additional studies)</li> </ul>	<ul style="list-style-type: none"> <li>• <i>In vitro</i> studies</li> <li>• Non-original data (e.g. narrative reviews, editorials, letters, or erratum)</li> <li>• Observational studies, case series</li> <li>• Qualitative studies</li> <li>• Cost-benefit analysis</li> <li>• Cross-sectional (i.e., non-longitudinal) studies</li> <li>• Before-after studies</li> <li>• Survey</li> </ul>
Publications	Studies published in English only.	Foreign language studies
Abbreviations: KQ = key question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial		

**Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions** - We plan to conduct a comprehensive database search, including Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from database inception to the present. We have developed a preliminary database search strategy (Appendix A) and found that these databases can adequately identify the relevant literature. We will use relevant systematic reviews and meta-analysis to identify additional existing and new literature. We will also search FDA, ClinicalTrials.gov, Health Canada,

Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ's Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant publications will be conducted. The search strategy will be peer-reviewed by an independent information specialist. An experienced librarian will conduct the search. All citations identified through the process will be imported to a reference management system (EndNote® Version X7; Thomson Reuters, Philadelphia, PA).

Independent reviewers, working in pairs, will screen the titles and abstracts of all citations using pre-specified inclusion and exclusion criteria. Studies included by either reviewer will be retrieved for full-text screening. Independent reviewers, again working in pairs, will screen the full-text version of eligible references. Discrepancies between the reviewers will be resolved through discussions and consensus. If consensus can't be reached, a third reviewer will resolve the difference. We will use a web-based systematic review software, DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), to facilitate study selection process.

**Data Abstraction and Data Management** - At the beginning of data abstraction, we will develop a standardized data extraction form to extract study characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, intervention, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form will be pilot-tested by all study team members using 10 studies. We will iteratively continue testing the form until no additional items or unresolved questions exist. After we finalize the form, reviewers will work independently to extract study details. A second reviewer will review data extraction, and resolve conflicts. DistillerSR will also be used to create data extraction forms and facilitate data extraction.

**Assessment of the Risk of Bias of Individual Studies** - We will evaluate the risk of bias of each included study using the Cochrane Collaboration's Risk of Bias tool to assess sequence generation; allocation concealment; participant, personnel, and outcome assessor blinding; attrition bias; incomplete outcome data; selective outcome reporting; and other sources of bias.<sup>41</sup> Additional criteria will be adopted from other quality appraisal tools if deemed necessary.

**Data Synthesis** - We will qualitatively summarize key features/characteristics (e.g. study populations, design, intervention, outcomes, and conclusions) of the included studies and present in evidence tables for each KQs.

We will determine whether meta-analysis is appropriate (i.e., more than 2 studies address the same PICOTS and provide point estimates and dispersion measures) to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. If meta-analysis is deemed appropriate, we plan to use the DerSimonian and Laird random effect method to combine direct comparisons between treatments if the number of studies included in the analysis is larger than 2<sup>42</sup>; otherwise, the fixed effect method based on the Mantel and Haenszel method will be adopted. We will evaluate heterogeneity between studies using I<sup>2</sup> indicator. To further explore heterogeneity, we plan to conduct subgroup

analyses based on factors listed in Section II. We will conduct sensitivity analyses to evaluate robustness of our findings by excluding studies with high risk of bias.

We will evaluate potential publication bias by evaluating funnel plots symmetry and using statistical tests such as Egger linear regression test if the number of studies included in a direct comparison is large ( $n \geq 20$ ).

### **Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes**

We will grade the strength of the body of evidence (SOE) as per the EPC methods guide on assessing SOE. We will grade SOE for health outcomes we classified as most important or critical such as mortality, hospitalization. These outcomes are chosen because they are either clinically important from a patient's perspective or highly relevant for stakeholders' decision making.

RCTs start as high SOE. The domains to be used for all KQs will be: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias.

We will lower SOE grading when sensitivity analyses 1) show substantial difference in estimates derived from high or unclear risk of bias studies vs. estimates derived from studies at low risk of bias; or 2) when all the available studies (in a particular comparison) have high or unclear risk of bias. SOE grading will be also lowered when important heterogeneity is identified.

Based on this assessment and the initial study design, we will assign SOE rating as high, moderate, low, or 'insufficient evidence to estimate an effect'. We will produce summary of evidence tables that will provide for each comparison and for each outcome: data source, effect size, SOE rating; and rationale for judgments made on each domain of evidence rating.

**Assessing Applicability** - We will follow the procedures outlined in the EPC Methods Guide for Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies<sup>43</sup>. Applicability for each outcome will be summarized and presented qualitatively using the PICOTS framework and not a specific checklist or scale. We will focus on whether the populations, interventions, and comparisons in existing studies are representative of current practice. The literature suggest that COPD trials enroll highly specific populations that differ from the usual patients seen in practice in terms of their lung function tests, comorbidities (particularly cardiac comorbidities), age or the presence of concomitant other lung disease<sup>44</sup>. We will look for these characteristics, systematically abstract such factors and evaluate their impact on how applicable the evidence is to the question of interest. We will report any limitations in applicability of

individual studies in evidence tables and limitations of applicability of the whole body of evidence in the summary of evidence tables.

## V. References

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## VI. Definition of Terms

**COPD**, Chronic obstructive pulmonary disease: a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with a chronic inflammatory response of the lungs to noxious particles or gases.<sup>45</sup>

**AECOPD**, Acute exacerbation of COPD: episode of increasing respiratory symptoms, particularly dyspnea, cough and sputum production, and increased sputum purulence.<sup>6</sup>

## VII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the key questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

## VIII. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high

priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **IX. Technical Experts**

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **X. Peer Reviewers**

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

#### **XI. EPC Team Disclosures**

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

#### **XII. Role of the Funder**

This project was funded under Contract No. HHS A290201500013I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

#### **XIII. Registration**

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

## Appendix A. Search Strategies

### Ovid

Database(s): Embase 1988 to 2018 Week 16, EBM Reviews - Cochrane Central Register of Controlled Trials March 2018, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to April 11, 2018, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present  
Search Strategy:

#	Searches	Results
1	exp Pulmonary Disease, Chronic Obstructive/dh, dt, px, rh, th or exp Lung Diseases, Obstructive/dh, dt, px, rh, th	79195
2	exp chronic obstructive lung disease/dm, dt, rh, th	26021
3	((chronic* adj3 bronchiti*) or (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or aecb or "chronic airflow disease*" or "chronic airflow disorder*" or "chronic airflow limitation*" or "chronic airflow obstruction*" or "chronic airway disease*" or "chronic airway disorder*" or "chronic airway limitation*" or "chronic airway obstruction*" or "chronic bronchitis" or "chronic obstructive airflow disease*" or "chronic obstructive airflow disorder*" or "chronic obstructive airway disease*" or "chronic obstructive airway disorder*" or "chronic obstructive bronchitis" or "chronic obstructive bronchopulmonary disease*" or "chronic obstructive broncho-pulmonary disease*" or "chronic obstructive bronchopulmonary disorder*" or "chronic obstructive broncho-pulmonary disorder*" or "chronic obstructive lung disease*" or "chronic obstructive lung disorder*" or "chronic obstructive pulmonary disease*" or "chronic obstructive pulmonary disorder*" or "chronic obstructive respiratory disease*" or "chronic obstructive respiratory disorder*" or coad or cobd or copd or emphysema* or "obstructive lung disease" or "obstructive lung disorder*" or "obstructive pulmonary disease*" or "obstructive pulmonary disorder*" or "obstructive pulmonary tract disease*" or "obstructive pulmonary tract disorder*" or "obstructive respiratory disease*" or "obstructive respiratory disorder*" or "obstructive respiratory tract disease*" or "obstructive respiratory tract disorder*").ti,ab,hw,kw.	361641
4	((increas* adj3 (severity or seriousness)) or exacerbation* or worsen*).ti,ab,hw,kw.	409125
5	(1 or 2 or 3) and 4	49731
6	exp Bronchodilator Agents/ or exp Adrenergic beta-2 Receptor Agonists/ or exp Cholinergic Antagonists/ or exp Phosphodiesterase 4 Inhibitors/ or exp Antibiotic Prophylaxis/ or exp Anti-Bacterial Agents/ or exp antibiotic agent/ or exp Benzodiazepines/ or exp Respiration, Artificial/ or exp Adrenal Cortex Hormones/ or exp corticosteroid/ or exp corticosteroid therapy/ or exp Expectorants/ or exp narcotic analgesic agent/ or exp Analgesics, Opioid/ or exp Smoking Cessation/ or exp Respiratory Therapy/ or exp exercise/ or exp Exercise Therapy/ or exp Breathing Exercises/ or exp Exercise Movement Techniques/ or exp Nutrition Therapy/ or exp Influenza Vaccines/ or exp Pneumococcal Vaccines/ or exp vaccination/ or exp Psychotherapy/ or exp Cognitive Therapy/ or exp Cognitive	6840812

Behavior Therapy/ or exp Mindfulness/ or exp Mind-Body Therapies/ or exp Self Care/ or exp Acupuncture exp Complementary Therapies/ or exp Electric Stimulation Therapy/

((action adj3 plan\*) or (disease adj2 manag\*) or (management adj1 program\*) or Acupuncture or "Adrenal Cortex Hormone\*" or "Adrenergic beta-2 Receptor Agonist\*" or "Adrenergic beta-2 Receptor Antagonist\*" or "alternative medicine\*" or antibacterial\* or "Anti-Bacterial\*" or antibiotic\* or Anticholinergic\* or "artificial respiration" or behavior\* or behaviour\* or Benzodiazepine\* or "Beta adrenergic agonist\*" or "Beta adrenergic Antagonist\*" or "Breathing Exercise\*" or Bronchodilator\* or chemotherap\* or "Chest physiotherap\*" or "Cholinergic agonist\*" or "Cholinergic Antagonist\*" or "Cognitive Behavior Therap\*" or

7 "Cognitive Therap\*" or "Complementary Therap\*" or corticosteroid\* or diet or drug\* or educat\* or "Electric Stimulation\*" or empower\* or exercise\* or Expectorant\* or Glucocorticoid\* or instruct\* or "management plan\*" or "Mind-Body" or Mindfulnes\* or narcotic\* or Nutrition\* or opioid\* or "Oxygen therap\*" or "patient cent\*" or "patient educat\*" or "patient focus\*" or pharmacotherap\* or "Phosphodiesterase 4 Inhibitor\*" or Psychotherap\* or respirator\* or "Respiratory Therap\*" or "Self Car\*" or "self-efficac\*" or "self-manag\*" or "Smoking Cessation" or steroid\* or train\* or Vaccin\* or ventilation or ventilator\*).ti,ab,hw,kw. 18738979

8 6 or 7 20404291

9 5 and 8 41472

10 limit 9 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained] 34470

11 limit 10 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] 19126

12 limit 9 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") [Limit not valid in Embase,CCTR,CDSR; records were retained] 29935

13 limit 12 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] 6074

14 13 not 11 1733

15 9 not 14 39739

16 limit 15 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid 1608

in Embase,CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]

17 from 16 keep 1188-1266	79
18 (15 not 16) or 17	38210
19 limit 18 to yr="2017 -Current"	3781
20 remove duplicates from 19	2822
21 limit 18 to yr="2016"	3419
22 remove duplicates from 21	2406
23 limit 18 to yr="2015"	3204
24 remove duplicates from 23	2403
25 limit 18 to yr="2014"	3101
26 remove duplicates from 25	2294
27 limit 18 to yr="2013"	3052
28 remove duplicates from 27	2359
29 limit 18 to yr="2012"	2541
30 remove duplicates from 29	1974
31 limit 18 to yr="2010-2011"	4305
32 remove duplicates from 31	3307
33 limit 18 to yr="2008-2009"	2736
34 remove duplicates from 33	1877
35 limit 18 to yr="2003 -2007"	5548
36 remove duplicates from 35	3759
37 limit 18 to yr="2000 -2002"	2116
38 remove duplicates from 37	1373
39 limit 18 to yr="1946 -1999"	4348
40 remove duplicates from 39	2890
41 20 or 22 or 24 or 26 or 28 or 30 or 32 or 34 or 36 or 38 or 40	27464
42 exp Guideline/ or exp Practice Guideline/	478469
43 ("consensus development" or guideline* or "position statement*").mp.pt.	1038953
44 42 or 43	1129629
45 41 and 44	3171
46 exp meta analysis/	229891
47 exp Meta-Analysis as Topic/	54003
48 exp "systematic review"/	165306
49 ((meta adj analys*) or (systematic* adj3 review*)).mp.pt.	606754
50 46 or 47 or 48 or 49	606754
51 (41 not 45) and 50	1072

52 41 not (45 or 51)	23221
53 exp controlled study/	5984322
54 exp Randomized Controlled Trial/	940129
55 exp triple blind procedure/	184
56 exp Double-Blind Method/	410008
57 exp Single-Blind Method/	73673
58 exp latin square design/	352
((control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or	
59 "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square").mp.pt.	7724844
60 or/53-59	7724941
61 52 and 60	5717
62 52 not 61	17504
63 controlled study/	5837966
64 exp comparative study/	2793772
65 exp Cross-Sectional Studies/	515415
66 exp Cohort Studies/	2229295
67 exp longitudinal study/	350987
68 exp retrospective study/	1315698
69 exp prospective study/	988112
70 exp population research/	89341
71 exp observational study/	183368
72 clinical study/	106193
73 exp Evaluation Studies/	281440
74 exp quantitative study/	37673
75 exp validation studies/	158014
76 exp quasi experimental study/	4825
77 exp field study/	8023
78 in vivo study/	298460
79 exp panel study/	725
80 exp prevention study/	3403
81 exp replication study/	1788
82 exp Feasibility Studies/	154012
83 exp trend study/	22570
84 exp correlational study/	28879
85 exp case-control studies/	1063205
86 exp confidence interval/	163081

87	exp regression analysis/	790965
88	exp proportional hazards model/ ((control* adj3 study) or "comparative study" or "comparative survey" or "comparative analysis" or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or cohort* or longitudinal* or retrospectiv* or prospectiv* or (population adj3 (stud* or survey* or analys* or research)) or (("follow-up" or followup) adj (stud* or survey or analysis)) or ((observation or observational) adj (study or survey or analysis)) or "clinical study" or "evaluation study" or "evaluation survey" or "evaluation analysis" or "quantitative study" or "quantitative analys*" or "numerical study" or "validation study" or "validation survey" or "validation analysis" or "quasi experimental study" or "quasi experimental analysis" or "quasiexperimental study" or "quasiexperimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or ((prevention or preventive) adj3 (trial or study or analysis or survey)) or "replication study" or "replication analysis " or "replication trial" or "feasibility study" or "feasibility analysis" or "trend study" or "trend survey" or "trend analysis" or ((correlation* adj2 study) or (correlation* adj2 analys*)) or "case control study" or "case base study" or "case referent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "confidence interval" or "regression analysis" or "least square" or "least squares" or (hazard* adj (model or analys* or regression or ratio or ratios)) or "Cox model" or "Cox multivariate analyses" or "Cox multivariate analysis" or "Cox regression" or "Cox survival analyses" or "Cox survival analysis" or "Cox survival model" or ((study or trial or random* or control*) and compar*).mp.pt.	155815
89		18108958
90	or/63-89	18493501
91	62 and 90	8019

## Scopus

- 1 TITLE-ABS-KEY((chronic\* W/3 bronchiti\*) or (obstruct\* W/3 (pulmonary or lung\* or airway\* or airflow\* or bronch\* or respirat\*)) or aecb or "chronic airflow disease\*" or "chronic airflow disorder\*" or "chronic airflow limitation\*" or "chronic airflow obstruction\*" or "chronic airway disease\*" or "chronic airway disorder\*" or "chronic airway limitation\*" or "chronic airway obstruction\*" or "chronic bronchitis" or "chronic obstructive airflow disease\*" or "chronic obstructive airflow disorder\*" or "chronic obstructive airway disease\*" or "chronic obstructive airway disorder\*" or "chronic obstructive bronchitis" or "chronic obstructive bronchopulmonary disease\*" or "chronic obstructive broncho-pulmonary disease\*" or "chronic obstructive bronchopulmonary disorder\*" or "chronic obstructive broncho-pulmonary disorder\*" or "chronic obstructive lung disease\*" or "chronic obstructive lung disorder\*" or "chronic obstructive pulmonary disease\*" or "chronic obstructive pulmonary disorder\*" or "chronic obstructive respiratory disease\*" or "chronic obstructive respiratory disorder\*" or coad or cobd or copd or emphysema\* or "obstructive lung disease" or "obstructive lung disorder\*" or "obstructive pulmonary disease\*" or "obstructive pulmonary disorder\*" or "obstructive pulmonary tract disease\*" or "obstructive pulmonary tract disorder\*" or "obstructive respiratory disease\*" or "obstructive respiratory disorder\*" or "obstructive respiratory tract disease\*" or "obstructive respiratory tract disorder\*")
- 2 TITLE-ABS-KEY((increas\* W/3 (severity or seriousness)) or exacerbation\* or worsen\*)
- 3 TITLE-ABS-KEY((action W/3 plan\*) or (disease W/2 manag\*) or (management W/1 program\*) or Acupuncture or "Adrenal Cortex Hormone\*" or "Adrenergic beta-2 Receptor Agonist\*" or "Adrenergic beta-2 Receptor Antagonist\*" or "alternative medicine\*" or antibacterial\* or "Anti-Bacterial\*" or antibiotic\* or Anticholinergic\* or "artificial respiration" or behavior\* or behaviour\* or Benzodiazepine\* or "Beta adrenergic agonist\*" or "Beta adrenergic Antagonist\*" or "Breathing Exercise\*" or Bronchodilator\* or chemotherap\* or "Chest physiotherap\*" or "Cholinergic agonist\*" or "Cholinergic Antagonist\*" or "Cognitive Behavior Therap\*" or "Cognitive Therap\*" or "Complementary Therap\*" or corticosteroid\* or diet or drug\* or educat\* or "Electric Stimulation\*" or empower\* or exercise\* or Expectorant\* or Glucocorticoid\* or instruct\* or "management plan\*" or "Mind-Body" or Mindfulnes\* or narcotic\* or Nutrition\* or opioid\* or "Oxygen therap\*" or "patient cent\*" or "patient educat\*" or "patient focus\*" or pharmacotherap\* or "Phosphodiesterase 4 Inhibitor\*" or Psychotherap\* or respirator\* or "Respiratory Therap\*" or "Self Car\*" or "self-efficac\*" or "self-manag\*" or "Smoking Cessation" or steroid\* or train\* or Vaccin\* or ventilation or ventilator\*)
- 4 1 and 2 and 3
- 5 TITLE-ABS-KEY(newborn\* or neonat\* or infant\* or toddler\* or child\* or adolescent\* or paediatric\* or pediatric\* or girl or girls or boy or boys or teen or teens or teenager\* or preschooler\* or "pre-schooler\*" or preteen or preteens or "pre-teen" or "pre-teens" or youth or youths) AND NOT TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" OR elderly OR geriatric\* OR "old people" OR "old person\*" OR "older people" OR "older person\*" OR "very old")
- 6 4 and not 5
- 7 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
- 8 6 and not 7
- 9 PMID(0\*) OR PMID(1\*) OR PMID(2\*) OR PMID(3\*) OR PMID(4\*) OR PMID(5\*) OR PMID(6\*) OR PMID(7\*) OR PMID(8\*) OR PMID(9\*)
- 10 8 and not 9
- 11 TITLE-ABS-KEY("consensus development" or guideline\* or "position statement\*")

- 12 10 and not 11
- 13 TITLE-ABS-KEY((meta W/1 analys\*) or (systematic\* W/3 review\*))
- 14 12 and 13
- 15 12 and not 14
- 16 TITLE-ABS-KEY((control\* W/3 study) or (control\* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl\* W/1 blind\*) or (doubl\* W/1 mask\*) or (singl\* W/1 blind\*) or (singl\* W/1 mask\*) or (tripl\* W/1 blind\*) or (tripl\* W/1 mask\*) or (trebl\* W/1 blind\*) or (trebl\* W/1 mask\*) or "latin square")
- 17 15 and 16
- 18 15 and not 17
- 19 TITLE-ABS-KEY((control\* W/3 study) or "comparative study" or "comparative survey" or "comparative analysis" or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or cohort\* or longitudinal\* or retrospectiv\* or prospectiv\* or (population W/3 (stud\* or survey\* or analys\* or research)) or (("follow-up" or followup) W/1 (stud\* or survey or analysis)) or ((observation or observational) W/1 (study or survey or analysis)) or "clinical study" or "evaluation study" or "evaluation survey" or "evaluation analysis" or "quantitative study" or "quantitative analys\*" or "numerical study" or "validation study" or "validation survey" or "validation analysis" or "quasi experimental study" or "quasi experimental analysis" or "quasiexperimental study" or "quasiexperimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or ((prevention or preventive) W/3 (trial or study or analysis or survey)) or "replication study" or "replication analysis" or "replication trial" or "feasibility study" or "feasibility analysis" or "trend study" or "trend survey" or "trend analysis" or ((correlation\* W/2 study) or (correlation\* W/2 analys\*)) or "case control study" or "case base study" or "case referent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "confidence interval" or "regression analysis" or "least square" or "least squares" or (hazard\* W/1 (model or analys\* or regression or ratio or ratios)) or "Cox model" or "Cox multivariate analyses" or "Cox multivariate analysis" or "Cox regression" or "Cox survival analyses" or "Cox survival analysis" or "Cox survival model" or ((study or trial or random\* or control\*) and compar\*))
- 20 18 and 19

ClinicalTrials.Gov

(aecb OR "airflow obstruction" OR "airway obstruction" OR "bronchial obstruction" OR "bronchus obstruction" OR "chronic airflow disease") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic airflow disorder" OR "chronic airflow limitation" OR "chronic airflow obstruction" OR "chronic airway disease" OR "chronic airway disorder" OR "chronic airway limitation") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic airway obstruction" OR "chronic bronchitis" OR "chronic obstructive airflow disease" OR "chronic obstructive airflow disorder" OR "chronic obstructive airway disease" OR "chronic obstructive airway disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic obstructive bronchitis" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive broncho-pulmonary disease" OR "chronic obstructive bronchopulmonary disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic obstructive broncho-pulmonary disorder" OR "chronic obstructive lung disease" OR "chronic obstructive lung disorder" OR "chronic obstructive pulmonary disease" OR "chronic obstructive pulmonary disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic obstructive respiratory disease" OR "chronic obstructive respiratory disorder" OR coad OR cobd OR copd OR emphysema OR "lung obstruction" OR "obstructive lung disease" OR "obstructive lung disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("obstructive pulmonary disease" OR "obstructive pulmonary disorder" OR "obstructive pulmonary tract disease" OR "obstructive pulmonary tract disorder" OR "obstructive respiratory disease") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("obstructive respiratory disorder" OR "obstructive respiratory tract disease" OR "obstructive respiratory tract disorder" OR "pulmonary obstruction" OR "respiratory obstruction") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

All limited to adults.