VA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and the Department of Defense (DOD) guidelines are based on the best information available at the time of publication. The guidelines are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as such, nor should the guidelines be interpreted as prescribing an exclusive course of management.

This clinical practice guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when providers consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Therefore, every health care professional using these guidelines is responsible for evaluating the appropriateness of applying them in each unique clinical situation using a patient-centered approach.

These guidelines are not intended to represent VA or DOD policies. Further, inclusion of recommendations for specific testing, therapeutic interventions, or both, within these guidelines does not guarantee coverage of civilian sector care.

Version 4.0 – 2026

Prepared by:

The Management of Chronic Obstructive Pulmonary Disease Work Group

With support from:

Office of Quality and Patient Safety, Veterans Health Administration and Clinical Quality Improvement Program, Defense Health Agency

Version 4.0 – 2026

Based on evidence reviewed through December 5, 2025

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I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DOD) Evidence-Based Practice Work Group (EBPWG) was established in 2004, with a mission to use clinical and epidemiological evidence to improve population health within the Veterans Health Administration (VHA) and Military Health System (MHS) and develop clinical practice guidelines (CPGs) for the VA and DOD populations.(1) The development and updating of VA/DOD CPGs is funded by VA Evidence-Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based guidelines, including this CPG, is to guide providers in chronic obstructive pulmonary disease (COPD) management through pathways supported by evidence. This CPG is intended to provide health care providers with a practical framework by which to evaluate, treat, and manage COPD, address the individual needs and preferences of patients, and improve clinical outcomes.

In 2014, the VA and DOD published a CPG for the Management of Chronic Obstructive Pulmonary Disease (2014 VA/DOD COPD CPG), which was based on evidence reviewed through February 2014. This was updated in 2021 using the same process, based on evidence reviewed from January 2014 through February 2020 (2021 VA/DOD COPD CPG). Since then, a growing body of research has expanded the general knowledge and understanding of the impact of COPD. Consequently, a recommendation to update the 2021 VA/DOD COPD CPG was initiated in July 2025 using published data from February 1, 2020, to December 5, 2025. This updated CPG's use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach reflects a more rigorous application of the methodology than previous iterations.(2) Therefore, the strength of some recommendations might have been modified because of changes in the quality of the supporting evidence (see Evidence Quality and Recommendation Strength).

This CPG provides an evidence-based framework for evaluating and managing adult patients, 18 years or older, who are eligible for care in the VA and/or DOD healthcare systems and may benefit from COPD management to improve clinical outcomes. These guidelines were written to emphasize the role of:

- Utilizing patient-centered care;
- Decreasing preventable complications and morbidity;
- Improving health outcomes and quality of life; and
- Using shared decision-making frameworks in patient collaboration efforts.

II. Background

A. Description of COPD

COPD comprises a group of chronic, progressive respiratory disorders, including emphysema, small airway disease, and chronic bronchitis. Clinically, COPD is characterized by persistent respiratory symptoms and airflow limitation, most commonly demonstrated by not fully reversible reduction in maximal expiratory flow during forced exhalation.(3) COPD is caused by persistent exposure to tobacco smoking, occupational or other noxious exposures. Airflow limitation in COPD reflects structural airway and parenchymal abnormalities and is not fully reversible, which

distinguishes COPD from other obstructive lung diseases such as asthma, where airflow obstruction is often more variable and may be reversible with bronchodilators.(3) Contemporary professional society statements agree and emphasize that COPD is a heterogeneous disease with multiple clinical phenotypes and trajectories. COPD is a syndrome with overlapping phenotypes and treatable traits.

Symptoms may include dyspnea, chronic cough, sputum production, wheezing, and reduced exercise tolerance, and may vary over time. Patients also may have episodes of acute deterioration with worsening symptoms from baseline. These deteriorations are referred to as acute exacerbations of COPD (AECOPDs). They are often associated with increased inflammation, infection, pollution, or other insults to the lungs. AECOPDs are associated with significant morbidity and mortality. They are also associated with progression of disease and can result in persistent decline in lung function. Along with controlling chronic symptoms, treatment of exacerbations and reducing exacerbation risk are specific therapeutic targets for COPD management. Some patients may be more prone to exacerbations. Increasing recognition of disease heterogeneity has informed updated approaches to diagnosis, symptom assessment, and risk stratification.(4-6)

Recent evidence highlights accelerated lung aging and cellular senescence as contributors to COPD progression. Systemic inflammation is increasingly linked to cardiovascular risk. Biomarker-driven phenotyping, such as blood eosinophil counts, may be useful in fine-tuning COPD pharmacotherapy.

B. Pathology

Although COPD is primarily a disorder of the respiratory system, it is increasingly recognized as a condition associated with systemic inflammation and multisystem effects. COPD-related inflammation predominantly affects the distal airways and lung parenchyma and is believed to be mediated in part by oxidative stress and chronic exposure to various inhaled irritants.(3) Pathologic changes occur throughout the bronchial tree and the terminal respiratory units. The changes include airway wall thickening, mucus hypersecretion, loss of alveolar attachments, and parenchymal destruction. Small airways may narrow and become fibrotic, leading to airflow limitation and air trapping. Additional pathophysiologic consequences include lung hyperinflation, impaired gas exchange, ventilation–perfusion mismatch, and progressive decline in lung function, which collectively contribute to symptoms, exacerbations, and increased mortality.(3)

C. Etiology

In most cases, COPD develops as a result of prolonged exposure to lung irritants. In the United States (U.S.), cigarette smoking remains the primary etiologic factor and has been causally linked to the majority of COPD cases.(7-9) Despite declining smoking rates nationally, cigarette smoke exposure continues to account for a substantial proportion of COPD morbidity and mortality. Smoking also increases the risk of COPD-related complications, including pneumonia and acute exacerbations.

While cigarette smoking remains the leading modifiable risk factor for COPD, electronic cigarettes (vaping) have increasingly been recognized as an independent risk factor for airway injury and disease progression. Deployment-related airborne hazards, including burn pit smoke, geologic/desert particulate matter, engine exhaust, and other combustion sources such as biomass smoke from cooking heating fires, are significant concerns for VA/DOD populations.(10,11) Known genetic predispositions like alpha-1 anti-trypsine deficiency and lifetime household biomass fuel exposure should be assessed separately as an independent risk factor for chronic airflow obstruction.

Smoking cessation is the most effective intervention to prevent COPD development in at-risk individuals, slow disease progression, reduce exacerbation frequency, and decrease COPD-related mortality in those already diagnosed.(7,12) Evidence consistently demonstrates that cessation leads to a significant reduction in the rate of lung function decline, although established structural lung damage is typically not reversible.(3) Smoking prevalence remains higher among certain populations, including military personnel, particularly younger and enlisted Service members.(13) As a result, tobacco-related COPD continues to represent a substantial clinical and economic burden within the VA healthcare system.(7) For additional information, refer to the VA/DOD Tobacco Use Treatment CPG.

Centers for Disease Control and Prevention (CDC) 2025 reports age-adjusted prevalence of diagnosed COPD at 3.8% among U.S. adults, with approximately 120,000-130,000 annual deaths attributable specifically to COPD (International Classification of Diseases 10th Revision [ICD-10] J40-J44), exclusive of deaths related to chronic lower respiratory diseases.(14)

COPD is a systemic disease with co-occurring conditions and economic burden driven by exacerbations and hospitalizations. Other causes of COPD include occupational and environmental exposures to particulates, fumes, and noxious inhaled substances. Additional risk factors include household air pollution, secondhand smoke exposure, prior childhood respiratory infections, impaired lung growth, and genetic susceptibility.(3) Alpha-1 antitrypsin deficiency represents an important but less common inherited cause of COPD and should be considered in appropriate clinical settings.(3)

D. Epidemiology and Impact of COPD

COPD imposes a substantial public health burden in the U.S. and globally. It remains one of the leading causes of morbidity and mortality worldwide and is consistently ranked among the leading causes of death. Estimates of global prevalence suggest that approximately 10% of adults aged 40 and older have spirometry-confirmed COPD of any severity, with moderate-to-severe disease (post-bronchodilator [post-BD] $FEV_1 \leq 50\%$ of predicted) representing a substantial proportion of this burden, particularly among older individuals and those with significant exposure histories.

In the U.S., COPD represents a substantial and likely underestimated public health burden. In 2023, the age-adjusted prevalence of diagnosed COPD among adults was 3.8%,(15) corresponding to approximately 9.8 million individuals when applied to the U.S. adult population of roughly 263 million,(16) with prevalence increasing sharply with age, poorer health status, and geographic region — ranging from 3.3% to 15.8% across U.S. counties. However,

population-based spirometry studies estimate that approximately 50% of individuals with confirmable airflow obstruction remain undiagnosed, suggesting the true burden may approach 15-20 million adults. COPD and related chronic lower respiratory diseases contribute substantially to U.S. mortality, accounting for over 145,000 deaths annually at an age-adjusted rate of approximately 39.8 per 100,000 — placing COPD among the top 10 leading causes of death nationally.(15,17)

COPD-related mortality has increased over recent decades, with notable demographic shifts. Mortality rates among women have risen and now exceed those of men, a trend attributed in part to differences in lung size, hormonal influences, and susceptibility to tobacco smoke and environmental pollutants. COPD prevalence and outcomes vary across racial and ethnic groups; diagnosed prevalence is higher among non-Hispanic White individuals, though this likely reflects differences in smoking history, healthcare access, and diagnostic rates rather than biological susceptibility alone, and outcomes per diagnosed case may be disproportionately worse among non-Hispanic Black patients. Consistent with its chronic and progressive nature and cumulative exposure burden, COPD prevalence increases substantially with advancing age, with the sharpest rise occurring after the sixth decade of life.

COPD is associated with significant healthcare utilization and economic costs. U.S. expenditures related to COPD care are substantial and largely driven by hospitalizations, emergency care, and management of exacerbations. Although some data suggest stabilization or modest declines in age-adjusted prevalence, COPD continues to represent a major contributor to healthcare burden and disability. COPD is also recognized as an ambulatory care sensitive condition (ACSC) — a condition for which timely and effective outpatient care can prevent or reduce the need for hospitalization, making it a key target for primary care-based prevention, early intervention, and chronic disease management efforts.(18)

Veterans and Service members are at increased risk for COPD compared with the general U.S. population. Within the VA healthcare system, patients with COPD experience significantly higher all-cause and respiratory-related healthcare utilization than patients without COPD.

Military service may involve unique occupational and environmental exposures independent of the increased rate of smoking, including dust, combustion products, and deployment-related airborne hazards, which may increase the risk of developing chronic respiratory disease.(19) Additionally, the physical demands of military service may reveal respiratory limitations earlier in the disease course. As a result, Veterans and Service members may present with COPD symptoms at younger ages than civilians.(10,11)

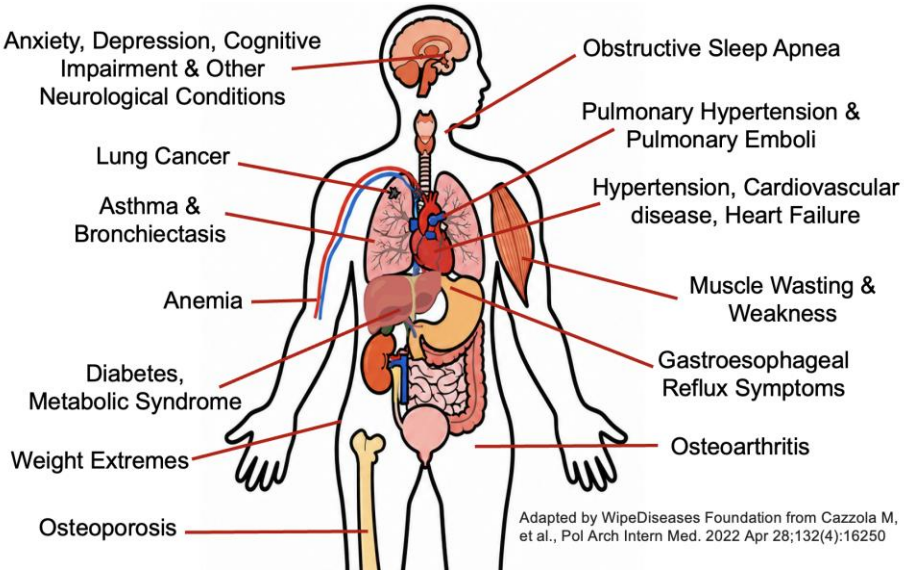
COPD can adversely affect military readiness, fitness for duty, and long-term disability outcomes. Consequently, primary care providers in both the VA and the DOD are likely to encounter individuals with established COPD or with symptoms suggestive of the condition requiring evaluation, diagnosis, and longitudinal management. This guideline is intended to support evidence-based diagnosis and management of COPD within these populations.

E. Effect of Co-Occurring Conditions on COPD

Roughly 94–96% of patients with COPD have at least one comorbidity that can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to the management of COPD.(20,21) Because COPD is sometimes accompanied by these conditions, it is often best to manage COPD in collaboration with other care providers as these conditions influence health status, hospitalizations, and mortality independently of the severity of airflow obstruction. COPD is associated with a wide range of comorbid conditions spanning cardiovascular, metabolic, respiratory, musculoskeletal, and neuropsychiatric domains. Established comorbidities include hypertension, coronary artery disease, pulmonary hypertension, diabetes, metabolic syndrome, osteoporosis, osteoarthritis, lung cancer, anxiety, depression, and cognitive impairment. For additional information on suicide prevention and mental health, refer to the VA/DOD CPGs on Assessment and Management of Patients at Risk for Suicide and Major Depressive Disorder. The recognized spectrum has further expanded to include asthma-COPD overlap, bronchiectasis, obstructive sleep apnea, peripheral muscle wasting, cachexia, anemia, gastroesophageal reflux disease, and peptic ulcer disease. Each contributes independently to disease burden, exacerbation risk, and reduced quality of life (QoL).(20-24) Lung cancer screening programs utilizing low-dose chest computed tomography (CT) represent an important opportunity for more timely identification of COPD-related findings, as these images frequently reveal incidental emphysema, airway wall thickening, and other structural abnormalities associated with elevated risk for future exacerbations and disease progression. Professional evidence-based strategy documents (e.g., Global Initiative for Chronic Obstructive Lung Disease [GOLD]) and emerging evidence support leveraging these imaging findings for COPD case-finding in high-risk screening populations.

Early specialist consultation may be indicated for some co-occurring conditions to determine recommended changes in treatment, establish a shared understanding of care coordination, assess mental health status to include suicidal ideation, and implement patient education strategies that may include complementary and integrative health (CIH) self-management practices.

Figure II. E-1: COPD Co-Occurring Conditions



Alternative text: Diagram of the human body illustrating health conditions related to COPD. Red lines point to affected regions, including Brain (Anxiety, Depression, Cognitive Impairment, Neurological Conditions); Lungs (Lung Cancer, Asthma); Heart (Pulmonary Hypertension, Cardiovascular Disease); Muscles (Wasting, Weakness); Digestive System (Gastroesophageal Reflux); Bones (Osteoporosis, Osteoarthritis); and Metabolic Issues (Diabetes, Anemia).

F. Patient and Caregiver Education and Support

Patient and caregiver education is a foundational component of patient-aligned care that supports shared decision-making and is widely recognized for its ability to promote desirable treatment outcomes and enhance QoL while posing minimal risk. Education may be delivered through printed materials, demonstrations, online resources, classes, or support groups. Randomized trials evaluating structured caregiver education models for COPD have demonstrated improvements in patient self-care, adherence behaviors, inhaler technique, and early symptom recognition—skills essential for preventing exacerbations and maintaining disease stability.(25,26) In a Miami VA study, a computerized clinical decision support system using the COPD Population Screener (COPD-PS) increased spirometry testing from 24% to 83% among high-risk Veterans, yielding new COPD diagnoses in 43%. This also identified that one-third of Veterans carrying a prior COPD label did not have spirometrically confirmed disease.(27)

Providing caregivers with structured education and practical tools, such as the COPD Caregiver's Toolkit, increases confidence in managing COPD at home and supports informed shared decision-making and continuity of care.(28) Given its low cost, minimal risk, feasibility, and alignment with whole health models of care, routine inclusion of patient and caregiver education should be considered a core component of COPD management.

G. Force Readiness

COPD can impact force readiness in several ways, including deployability, administrative burdens, and long-term force health protection. For retention purposes, COPD alone is not a disqualifying diagnosis in a Service member. It can become disqualifying if: (1) symptoms persist despite

appropriate treatment, and if it impairs function to preclude satisfactory performance of military duties necessitated by the warfighter's office, grade, community (e.g., flight status, special operations), rank or rating; (2) a warfighter cannot pass Service-specific pulmonary functional assessments, safely participate in Service-specific physical fitness testing, deployments, field exercises or other applicable exercises; (3) if post-BD FEV_1 is less than 50% of predicted despite optimal inhaler treatment; and/or (4) more than one required hospitalization for COPD in the previous 12 months. For further specifics, see the applicable DOD retention guideline for each of the armed services.(29)

A diagnosis of COPD may restrict where a Service member can be stationed or deployed, as air quality, high ambient particulate matter, extreme temperatures, or high-altitude operations may lead to exacerbation of symptoms, require increased monitoring, and necessary specialized care may not be available in all locations.

Finally, COPD is recognized as a presumptive condition associated with exposure to airborne hazards during deployments, prioritizing respiratory screening, occupational health monitoring, and exposure-informed care.

H. Trauma-Informed Care Approaches

Trauma-informed care (TIC) is an approach that recognizes how the experience of trauma can affect how patients with COPD perceive symptoms, interact with clinicians, and use healthcare services.(30) Individuals may experience emotional distress linked to their condition, worsening symptom management, and increased healthcare needs or dependency on caregivers; for instance, breathlessness can lead to catastrophic thinking and panic, amplifying dyspnea and distress.(31) Integrating TIC principles in policy, procedure, and practice lessens patient trauma-related responses, instills trust, and reinforces patient-centered care. Examples of TIC approaches as applied to COPD treatment include (32):

- Create a sense of physical and psychological safety during procedures, especially those involving physical touch, exposure, or breathlessness triggers.
- Use collaborative communication by explaining next steps and asking permission to proceed.
- Recognize signs of trauma-related distress, such as panic during dyspnea episodes, and integrate supportive strategies to avoid re-traumatization.
- Address structural trauma, including stigma, discrimination, and inequities that disproportionately affect marginalized COPD populations.
- Integrate Substance Abuse and Mental Health Services Administration's (SAMHSA's) 10 domains of TIC to improve patient experience and system outcomes.(33)

III. Scope of This Guideline

This CPG is based on published clinical evidence and related information available between February 1, 2020, to December 5, 2025. It is intended to provide general guidance on best evidence-based practices (see Appendix A for additional information on the evidence review methodology). Although this CPG is intended to improve the quality of care and clinical outcomes

(see Introduction), it is not intended to define a standard of care (i.e., mandated or strictly required care).

A. Guideline Audience

This CPG is designed to assist general health care professionals who manage, co-manage, or otherwise provide outpatient care for adults with COPD.

B. Guideline Population

This CPG is intended for adults (18 years or older) with COPD, who are eligible for outpatient care in the VA or DOD systems, including community care. This includes Veterans and Service members as well as their eligible adult dependents.

IV. Highlighted Features of This Guideline

A. Highlights in This Guideline Update

The current document is an update to the 2021 VA/DOD COPD CPG. The major strength of this CPG is in the coordination and collaboration of the multidisciplinary team, ensuring a broad representation of providers engaged in COPD management. The following significant updates highlight the importance of clinicians reviewing this version of the CPG:

1. Updated Algorithms;
    - Including the initial assessment of COPD, pharmacologic and non-pharmacologic management of COPD, and outpatient management of COPD exacerbations
2. Updated Sidebars; and
    - Including a guide to creating individualized management plans
3. Added 6 new recommendations, reviewed and replaced 3 recommendations, reviewed and amended 1 recommendation, carried over 2 recommendations that were reviewed and not changed, carried over 5 recommendations that were not reviewed and amended, and carried over 2 recommendations that were not reviewed and not changed from the 2021 VA/DOD COPD CPG.
    - Including a strong-for recommendation for long-acting beta 2-agonist/long-acting antimuscarinic agent (LABA/LAMA) dual therapy over monotherapy in patients with significant symptom burden
    - More specific recommendations for who/when to prescribe systemic corticosteroids and/or antibiotics in patients with acute COPD exacerbations
    - And the inclusion of telerehabilitation as a clinically effective alternative to in-person pulmonary rehabilitation

B. Components of This Guideline

This CPG provides clinical practice recommendations for the care of patients with COPD (see Recommendations). In addition, the Algorithm integrates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which list areas the Work Group identified as needing additional research. To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, patient

summary, and a quick reference guide, which can be found at https://www.healthquality.va.gov/index.asp.

C. Demographic Terminology in This Guideline

The demographic terms used in this guideline are derived from the published literature sources included in the systematic review (SR) and evidence base. The Work Group used terms such as Black rather than African American and White rather than Caucasian to avoid presumptions about ancestry and improve clarity and consistency. To accurately present the research evidence on which this CPG is based, the Work Group made every effort to use the same terminology as reported in the published literature base of SRs, clinical trials, and other studies. Consequently, usage of demographic terms in this CPG may vary and appear inconsistent.

V. Guideline Development Team

The VA Evidence-Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency, identified the following four providers to serve as Champions (i.e., leaders) of this CPG's Work Group: Amir Sharafhaneh, MD, PhD, and William C. (Claibe) Yarbrough, MD, MS, from VA; and Kimberly Fabyan, MD, FACP, and Christopher Shank, from DOD. The Work Group was comprised of individuals with the following areas of expertise: pulmonology, primary care, critical care, clinical social work, respiratory therapy, inpatient and clinical pharmacy, dietetics, internal medicine, physical medicine and rehabilitation, and medication management. Table 1 lists the Work Group and Guideline Development Team members.

This CPG Work Group, led by the Champions, was tasked with:

- Determining the scope of the CPG;
- Crafting clinically relevant key questions (KQs) to guide the systematic evidence review;
- Identifying discussion topics for the Patient Focus Group and considering the patient perspective;
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence; and
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation.

Sigma Health Consulting and Duty First Consulting were contracted by the VA to help develop this CPG.

Table 1. Guideline Work Group and Guideline Development Team

Organization	Names*
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*Additional contributor information is available in Appendix D.

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the Guideline for Guidelines, an internal document of the VA/DOD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DOD CPGs.(34) The Guideline for Guidelines is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of SR and external review).(35) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see Determining Recommendation Strength and Direction)(36):

1. Balance of desirable and undesirable outcomes;
2. Confidence in the quality of the evidence;
3. Patient or provider values and preferences; and

4. Other implications, as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup considerations).

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which incorporates the four domains.(37) A *Strong* recommendation generally indicates High or Moderate confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and an understood influence of other implications (e.g., resource use, feasibility). A recommendation's strength (i.e., *Strong* vs. *Weak*) does not reference its clinical importance (e.g., a *Weak* recommendation is evidence-based and still important to clinical care).

In some instances, the systematic evidence review might have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for a particular therapy or intervention. The way this finding is expressed in the CPG might vary. The Work Group might include a statement among its recommendations acknowledging insufficient evidence for or against a commonly practiced intervention, particularly if it lacks supporting clinical evidence and poses potential risks (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group might choose to remain silent in cases where evidence is lacking for a rarely used intervention or when an intervention, despite the absence of recent evidence, is considered the standard of care and has a favorable balance of benefits and harms.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text as shown in Table 2. The strength of each recommendation is shown in Recommendations.

Table 2. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend . . .
Weak for	We suggest …
Neither for nor against	There is insufficient evidence to recommend for or against . . .
Weak against	We suggest against . . .
Strong against	We recommend against . . .

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations; the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision-making. The confidence in the quality of the evidence is assessed using an objective, systematic approach independent of the clinical topic of interest. Therefore, recommendations on topics for which designing and conducting rigorous studies (e.g., randomized controlled trials [RCTs]) might be inherently more difficult are typically considered lower quality evidence and, in turn, are usually *Weak* recommendations. Recommendations on topics for which rigorous studies can be designed and conducted (e.g., RCTs) may more often be *Strong* recommendations. Per GRADE, if the

quality of evidence differs across the relevant critical outcomes, then the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(2,38) This stricter standard provides a consistent approach to determining recommendation strength. For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, staying current typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(39) For example, the U.S. Preventive Services Task Force (USPSTF) has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(40)

Recommendation categories are used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, United Kingdom [UK]).(41,42) Table 3 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2026 VA/DOD COPD CPG recommendation categories can be found in Recommendations. Appendix C outlines the 2021 VA/DOD COPD CPG's recommendation categories.

Table 3. Recommendation Categories and Definitions*

Evidence Reviewed	Recommendation Category	Definition
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG and has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, where the evidence has not been reviewed and the recommendation has not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG, where the evidence has not been reviewed and a minor amendment has been made

Evidence Reviewed	Recommendation Category	Definition
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012)(41) and Garcia, et al. (2014)(42)

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the Guideline for Guidelines.(34) Further, the Guideline for Guidelines refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care)(43) as well as to disclosure statements (i.e., standard disclosure form completed at least twice by CPG Work Group members and the guideline development team).(34) The disclosure form inquires about relevant financial and intellectual interests or other relationships with, for example, manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also asks about any other relationships or activities that could be perceived to have influenced, or give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COI among the CPG Work Group and Guideline Development Team were subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments, ProPublica).

D. Patient Perspective

When developing a CPG, consideration should be given to patients' perspectives and experiences, which often differ from those of providers.(38) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DOD Leadership arranged a virtual Patient Focus Group on October 17th, 2025. The focus group aimed to gain insights into the perspectives of individuals who received care in the VA and DOD healthcare systems for COPD and incorporated these insights into the CPG, as appropriate. Topics discussed included various interventions participants have used, challenges they have experienced, information they have received regarding their condition and care, and other strategies or resources they have employed to manage COPD.

The Patient Focus Group was comprised of a convenience sample of seven participants, which included one woman and six men. Participants were mixed in terms of receiving care from the VA and DOD, and one participant was a caregiver for their spouse who has COPD. Participants' severity of COPD and length of treatment ranged widely from as recent as 3 years to as long as 40 years, with two participants relying on continuous oxygen therapy. The Work Group acknowledges that this convenience sample is not representative of all individuals with COPD within the VA and DOD healthcare systems, and thus, findings are not generalizable and do not comprise evidence. For more information on the Patient Focus Group methods and findings, see Appendix E. Patient Focus Group participants were provided with the opportunity to review the final draft of this CPG and share additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group members completed a near-final draft, they identified individuals from VA and DOD healthcare systems and external organizations generally viewed as experts in their respective fields. The draft was sent to those experts for a 14-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review may be provided by the VA Office of Quality and Patient Safety.

F. Implementation

This CPG and algorithm are designed for adaptation by individual healthcare providers with respect to unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care of patients with COPD. The Work Group will submit suggested performance metrics for VA and DOD to use when assessing the implementation of this CPG. Robust implementation is identified in VA and DOD internal implementation plans and policies. Additionally, implementation will entail wide dissemination through publication in the medical literature, online access to the final CPG, educational programs, and ideally, electronic medical record programming in the form of clinical decision support tools at the point-of-care.

VII. Approach to Care in the Department of Veterans Affairs and the Department of Defense

A. Patient-Centered Care

VA and DOD encourage providers to be sensitive to demographic, cultural, and other differences that affect patients' values, needs, and preferences, aimed at treating the condition while also optimizing the individual's overall health and well-being. Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in providers, and improve treatment adherence.(44,45) A whole health approach (https:/www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and well-being goals. Clear communication is essential and should be supported by evidence-based information tailored to each patient's needs. Guideline recommendations should be applied in a holistic approach to care that is patient-centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. The focus is using an individual's risk factors and event history to guide the various treatment and management strategies among patients with COPD.

B. Shared Decision-Making

This CPG encourages providers to practice shared decision-making, a process in which providers, patients, and patient care partners (e.g., family, friends, caregivers) consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.(46) Shared decision-making is emphasized in "Crossing the Quality Chasm,"

an Institute of Medicine, now NAM, report in 2001 (47) and is a core component of a patient-centered, whole health approach. Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, possible outcomes, and levels and/or settings of care, especially where patient heterogeneity in weighing risks and benefits might exist. The VA and DOD have embraced shared decision-making. Providers are encouraged to use shared decision-making to individualize treatment goals and plans based on patient capabilities, needs, values, and preferences.

C. Patients with Co-Occurring Conditions

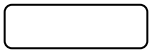
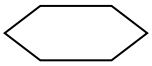
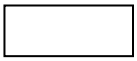
Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to COPD management. Many Veterans, Active-Duty Service members, and their families have one or more co-occurring conditions. Because COPD is often accompanied by co-occurring conditions, collaborative management with other care providers is often best. Some co-occurring conditions may require or would benefit from early specialist consultation to determine necessary changes in treatment or establish a common understanding of how care should be coordinated.

VIII. Algorithm

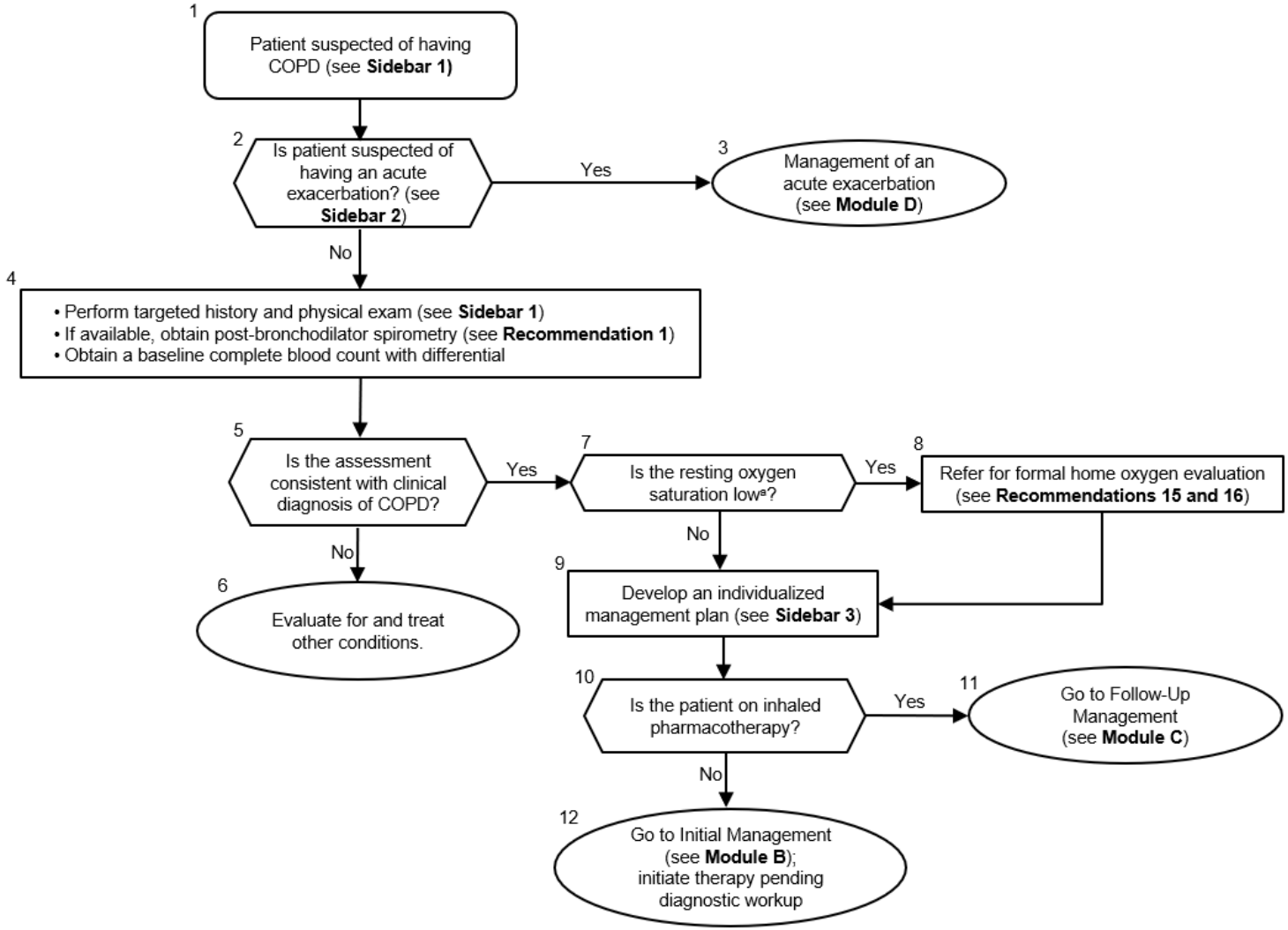
This CPG's algorithm is designed to facilitate an understanding of the clinical pathway and decision-making process used in managing patients with COPD. The algorithm format represents a simplified flow of the management of patients with COPD, helping to foster efficient decision-making by providers. It includes:

- An ordered sequence of steps of care;
- Recommended observations and examinations;
- Decisions to be considered; and
- Actions to be taken.

The algorithm is a step-by-step decision tree. Standardized symbols are used to display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(48) Sidebars provide more detailed information to assist in defining and interpreting elements in the boxes.

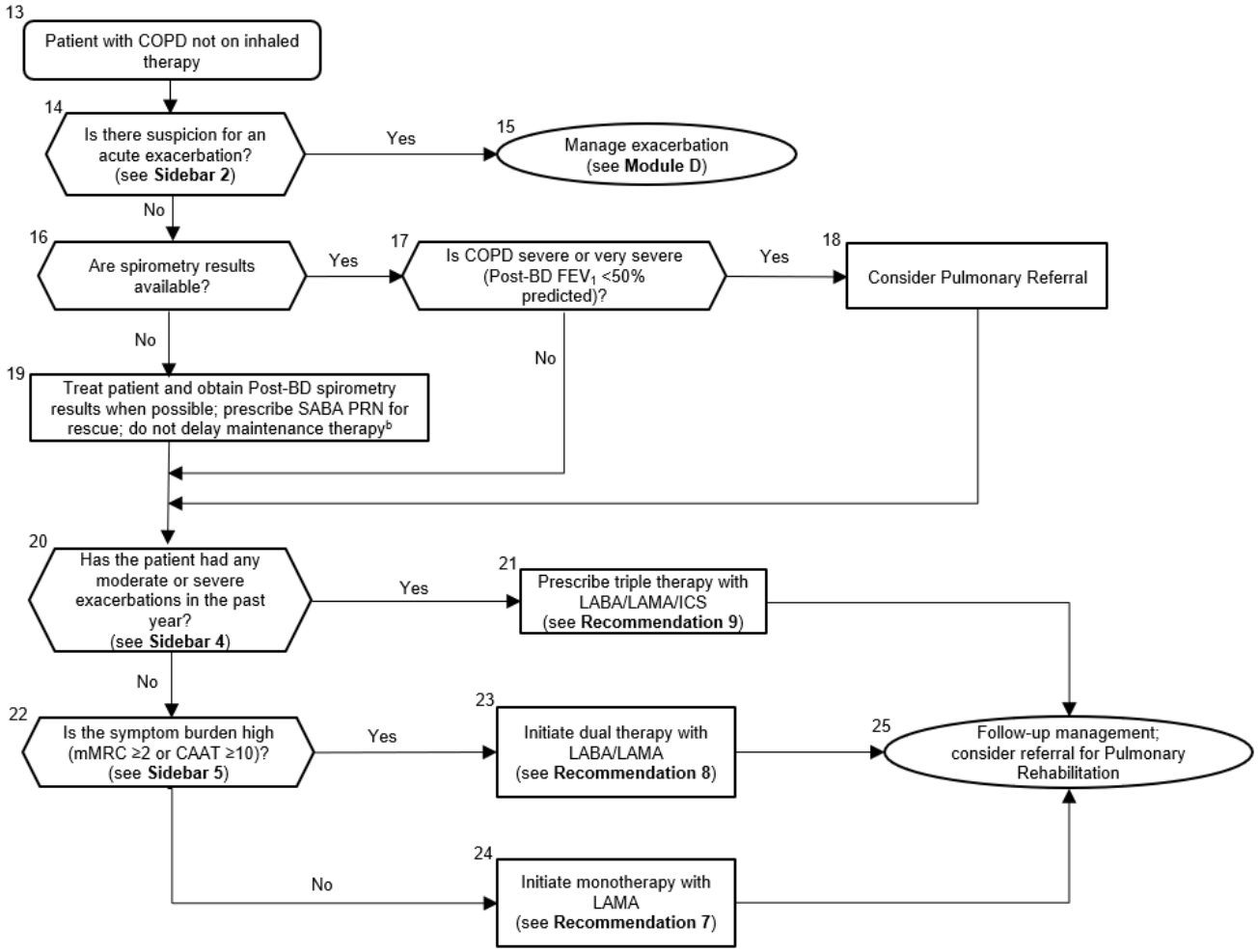
Shape	Description
	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered "Yes" or "No".
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the algorithm

Module A: Assessment of COPD



Abbreviations: COPD: chronic obstructive pulmonary disease

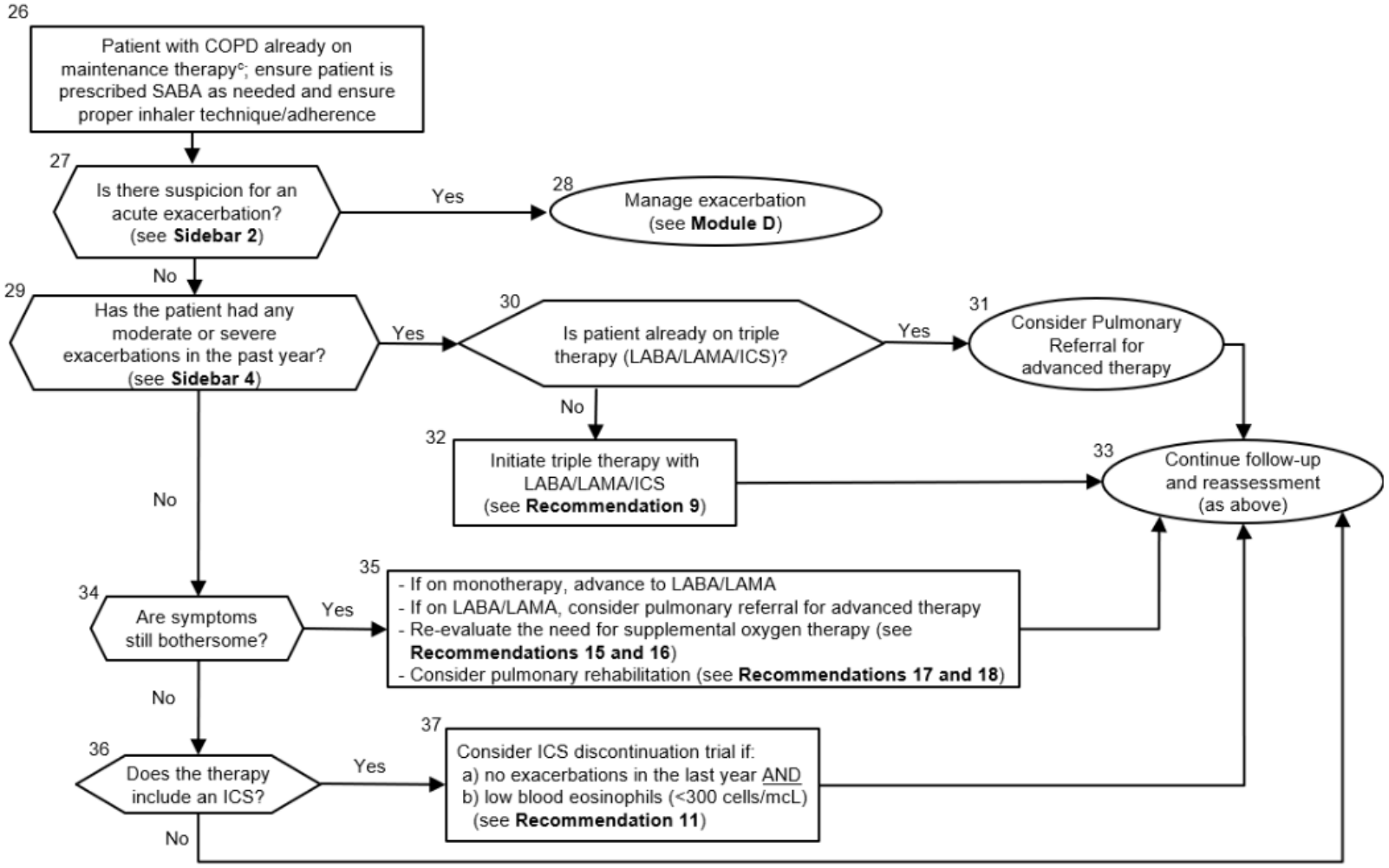
Module B: Initial Management of COPD



[b]: COPD exacerbations are treatment failures and exacerbations can result in disease progression

Abbreviations: BD: bronchodilator; CAAT: COPD Airways Assessment Test; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; mMRC: Modified Medical Research Council Dyspnea Scale; PRN: pro re nata; SABA: short-acting beta-agonist

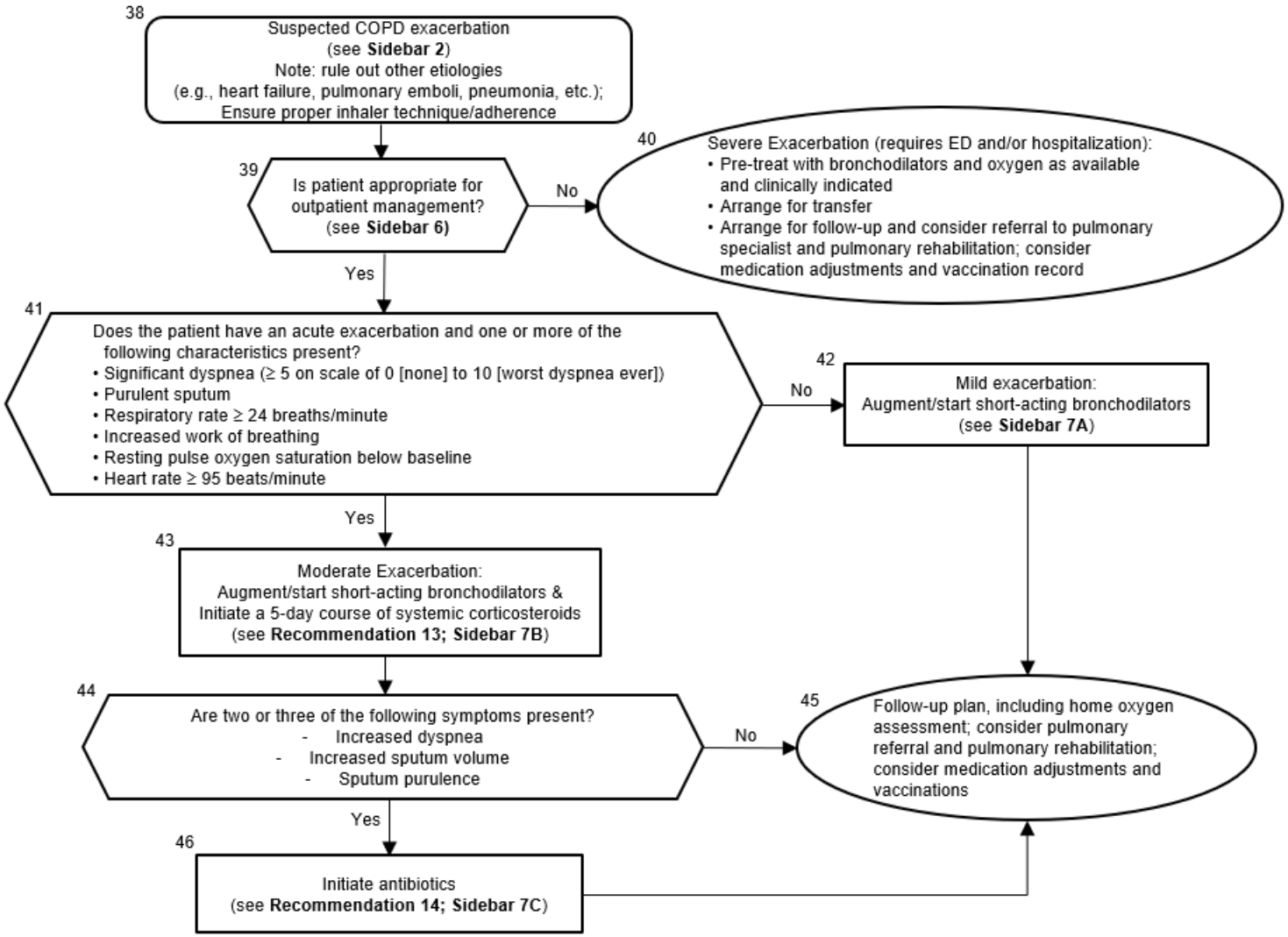
Module C: Follow Up Management of COPD



[c]: Stable patients on ICS/LABA, should be switched to either LABA/LAMA or triple therapy based on moderate/severe exacerbations and EOS ≥300 cells/mcL (see **Recommendation 8 and 9** narratives for details)

Abbreviations: COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; mcL: microliter; SABA: short-acting beta-agonist

Module D: Management of Acute COPD Exacerbations



Abbreviations: COPD: chronic obstructive pulmonary disease; ED: emergency department;

Sidebar 1: Definition of COPD

COPD is a respiratory condition associated with progressive decline in exercise tolerance and quality of life and increased mortality. In addition to genetic predisposition like alpha-1 antitrypsin deficiency, COPD results from long-term exposure to noxious stimuli including but not limited to cigarette smoking, biomass fuel, etc. Physiologically, the expiratory flow limitation is not fully reversible in COPD. Pathologically, COPD is an inflammatory condition encompassing a wide variety of findings including alveolar wall destruction, small airways disease, and mucus gland hypertrophy. The symptoms of COPD include one or more of the following:

- Shortness of breath (progressive)
- Chronic cough
- Chronic sputum production regardless of purulence
- Chronic Wheezing
- Fatigue
- Episodes of acute flares or worsening known as exacerbations
- Consider other conditions that may present similarly

Abbreviations: COPD: chronic obstructive pulmonary disease

Sidebar 2: When to Suspect an Acute COPD Exacerbation

Increased respiratory symptoms (i.e., increased shortness of breath, increased sputum volume, and/or sputum purulence — a change in sputum color from the patient's usual clear or white baseline to yellow or green) over a few days (<2 weeks) beyond the usual day-to-day variability and not fully explained by other differential diagnoses (e.g., heart failure, pulmonary emboli, pneumonia, etc.)

Abbreviations: COPD: chronic obstructive pulmonary disease

Sidebar 3: Individualized Management Plan

- Assess symptom burden with a patient-reported outcome measure – CAAT (6,49) and/or mMRC
- Assessment and management of modifiable risk factors
  - Tobacco smoking and cessation (see **Recommendations 4 and 5** and **VA/DOD Tobacco Use Treatment CPG**)
  - Vaccination (see **Recommendation 6**)
  - Nutrition (malnutrition)
  - Activity/Exercise
  - Mental health
  - Substance use including alcohol
  - Air quality
  - Housing insecurity
- Additional management considerations
  - Patient and/or caregiver education and support (for example see **Background F**; refer to Veterans Health Library)
  - Management of co-occurring conditions that may worsen COPD (see **CPG pg. 9**)
  - Lung cancer screening as appropriate
  - Pharmacological management (see **Module B and Module C**)
  - Oxygen therapy (see **Recommendations 15 and 16**)
  - Refer for in-person or tele-pulmonary rehabilitation (see **Recommendations 17-18**)
  - Telehealth support tools (see **Recommendation 19**)
  - Complimentary and Integrative Health support based on patient preferences
  - Palliative care

Abbreviations: CAAT: COPD Airways Assessment Test; COPD: chronic obstructive pulmonary disease; CPG: clinical practice guideline; DOD: Department of Defense; mMRC: Modified Medical Research Council Dyspnea Scale; VA: Department of Veterans Affairs

Sidebar 4: Severity of Prior Acute COPD Exacerbations

History of acute exacerbation of COPD within the last year treated in the following manner:

- History of Mild Exacerbation: Symptoms managed with inhaled bronchodilators alone. (see **Algorithm Box 42**)
- History of Moderate Exacerbation: Treatment included systemic corticosteroids and/or antibiotics. (see **Algorithm Box 43**)
- History of Severe Exacerbation: Management required hospitalization or emergency room visit. Severe exacerbations may also require additional ventilatory support including non-invasive ventilation or mechanical ventilator support. (see **Algorithm Box 40**)

Abbreviations: COPD: chronic obstructive pulmonary disease

Sidebar 5: mMRC Dyspnea Scale

Grade	Description of Breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

Abbreviation: mMRC: Modified Medical Research Council Dyspnea Scale

Sidebar 6: Criteria for Possible Admission to ED, Hospital, or ICU*

- In the opinion of the evaluating healthcare professional, inpatient or emergency department management is warranted
- Accessory muscle use or retractions
- Severe tachypnea or respiratory distress
- Acute, aberrant vitals (e.g., hypotension, severe tachycardia, etc.)
- Failure to respond to initial outpatient therapy
- Hypoxemia or hypercapnia compared to baseline
- Inability to complete ADLs due to acute symptoms
- Inability to take oral medications
- Altered mental status
- Presence of severe underlying COPD and/or serious co-occurring medical conditions

*Use clinical judgement

Abbreviations: ADLs: activities of daily living; COPD: chronic obstructive pulmonary disease; ED: emergency department; ICU: intensive care unit

Sidebar 7: Pharmacologic Treatment of Acute COPD Exacerbations in Outpatients

7a. Adjust bronchodilator therapy

- Augment (consider scheduling for a few days) short-acting bronchodilator therapy with SABA (e.g., albuterol, levalbuterol), then change back to as needed ***and***
- Start or change maintenance inhalers to triple therapy with ICS/LABA/LAMA (see **Algorithm Boxes 21 & 30**). Do NOT use maintenance inhalers for relief of acute symptoms and do NOT use more than the usual dose approved by the FDA,

7b. Systemic corticosteroids (see **Recommendation 13**)

- Start a short course of prednisone 40 mg daily or equivalent (recommended duration is 5 days but may extend to 14 days as clinically indicated).(50)

7c. Antibiotics (see **Recommendation 14**)

- Start a short (3-10 days) course of an antibiotic: choice based on local resistance patterns and prior patient culture data to cover, at minimum, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*.
- Consider adding coverage for *Pseudomonas* and other Gram-negative rods if Post-BD FEV_1 <50% predicted, recent antibiotic use, recent or frequent hospitalizations, or history of infection or colonization with resistant organisms.(51,52)

Abbreviations: BD: bronchodilator; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LABA: long-acting beta 2-agonist; LAMA: long-acting muscarinic antagonist; mg: milligram; SABA: short-acting beta 2-agonist

IX. Recommendations

The evidence-based clinical practice recommendations listed in the table below were developed using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Table 4. Evidence-Based Clinical Practice Recommendations with Strength and Category

While some of these recommendations may clearly be an element in a particular phase of care, others may require consideration throughout the continuum of care.

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Diagnosis & Monitoring		1.	We suggest post-bronchodilator spirometry to confirm clinical diagnosis of chronic obstructive pulmonary disease (COPD).	Weak for	Reviewed, Not Changed
		2.	There is insufficient evidence to recommend using a multidimensional schema to diagnose chronic obstructive pulmonary disease (COPD).	Neither for nor against	Reviewed, New-added
		3.	There is insufficient evidence to recommend for or against any frequency of testing (i.e., spirometry, symptom questionnaires, electronic health technology) in patients with chronic obstructive pulmonary disease (COPD) to reduce exacerbations, reduce mortality, and/or improve quality of life.	Neither for nor against	Reviewed, New-added
Risk Reduction		4.	We recommend smoking cessation with a goal of sustained abstinence for prevention and risk reduction of chronic obstructive pulmonary disease (COPD) (see the VA/DOD Tobacco Use Treatment CPG).	Strong for	Reviewed, Not changed
		5.	We suggest against electronic nicotine delivery systems (ENDS) as an alternative to tobacco smoking cessation for the reduction of chronic obstructive pulmonary disease (COPD) risk and exacerbation (see the VA/DOD Tobacco Use Treatment CPG).	Weak against	Reviewed, New-added
		6.	We suggest respiratory vaccinations with influenza, pneumococcal pneumonia, and coronavirus disease to reduce the risk of exacerbations of chronic obstructive pulmonary disease (COPD).	Weak for	Reviewed, New-replaced
Pharmacotherapy	Stable COPD	7.	We recommend inhaled long-acting muscarinic antagonists (LAMA) as initial therapy for patients with mild symptoms of chronic obstructive pulmonary disease (COPD).	Strong for	Not reviewed, Amended
		8.	In patients with moderate to severe symptom burden, we recommend initiating therapy with a long-acting beta-agonist and long-acting muscarinic antagonist (LABA/LAMA) over monotherapy.	Strong for	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Pharmacotherapy (cont.)	Stable COPD (cont.)	9.	In patients with chronic obstructive pulmonary disease (COPD) and a history of exacerbations requiring systemic corticosteroids and/or antibiotics in the past year, we recommend triple therapy with an inhaled corticosteroid, a long-acting beta-agonist, and a long-acting muscarinic antagonist (ICS/LABA/LAMA) for reducing exacerbations.	Strong for	Reviewed, New-replaced
		10.	We recommend against long-acting beta agonists with inhaled corticosteroids (LABA/ICS) as standalone therapy for patients with chronic obstructive pulmonary disease (COPD).	Strong against	Not reviewed, Amended
		11.	In select patients on inhaled corticosteroid-containing therapy who have not had an exacerbation in the prior year and have blood eosinophil count <300 cells/μL, we suggest discontinuation of inhaled corticosteroid with careful monitoring.	Weak for	Reviewed, Amended
		12.	In patients with chronic obstructive pulmonary disease (COPD), we suggest starting or continuing cardio-selective beta-blockers only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction).	Weak for	Not reviewed, Not changed
	COPD Exacerbations	13.	In outpatients experiencing an acute chronic obstructive pulmonary disease (COPD) exacerbation, we suggest selectively prescribing a short course of systemic corticosteroids based on clinical exacerbation severity and patient characteristics.	Weak for	Reviewed, New-added
		14.	In outpatients experiencing an acute chronic obstructive pulmonary disease (COPD) exacerbation, we recommend short-term antibiotics depending on patient characteristics.	Strong for	Reviewed, New-replaced
Other Management Interventions	Oxygen Therapy	15.	In outpatients with chronic obstructive pulmonary disease (COPD) and chronic severe resting hypoxemia or moderate resting hypoxemia with signs of chronic hypoxia-related cardiopulmonary or hematologic complications, we recommend providing long-term oxygen therapy.	Strong for	Not reviewed, Amended
		16.	In outpatients with chronic obstructive pulmonary disease (COPD) and isolated exercise hypoxemia, we suggest against providing long-term oxygen therapy.	Weak against	Not reviewed, Amended

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Other Management Interventions (cont.)	Rehabilitation	17.	We recommend offering pulmonary rehabilitation to stable, symptomatic patients on pharmacotherapy or post-hospitalization for chronic obstructive pulmonary disease (COPD) exacerbation.	Strong for	Not reviewed, Amended
		18.	We suggest offering telepulmonary rehabilitation as a clinically effective alternative to in-person pulmonary rehabilitation.	Weak for	Reviewed, New-added
	Tele-health	19.	We suggest offering telehealth support tools as an adjunct to usual care.	Weak for	Not reviewed, Not changed

[a] For additional information, please refer to Determining Recommendation Strength and Direction.
[b] For additional information, please refer to Recommendation Categorization.

A. Diagnosis & Monitoring

Recommendation

1. We suggest post-bronchodilator spirometry to confirm clinical diagnosis of chronic obstructive pulmonary disease (COPD).
   (Weak for | Reviewed, Not changed)

Discussion

Expiratory airflow obstruction is one of the most verifiable indicators of COPD. The Work Group's review of recent evidence suggests that post-BD spirometry remains the most accurate method to confirm the clinical diagnosis of COPD. Expiratory airflow obstruction is not fully reversible in COPD, and incomplete reversibility is confirmed by the spirometry final report confirming the finding of post-BD obstruction.

The studies in reference below evaluated the results of other methodological criteria and diagnostic testing to the accuracy of post-BD spirometry when using the fixed ratio criteria to diagnose COPD. One study comparing pre-bronchodilator (pre-BD) spirometry alone vs. pre-BD and post spirometry showed that 39% of patients would have been given a false positive diagnosis of having COPD.(53) Additionally, 5.5-21.8% of COPD diagnoses identified accurately with post-BD spirometry would have been missed if using only pre-BD spirometry.(54) Portable spirometry may be an acceptably accurate alternative in settings where post-BD spirometry is not feasible,(55) but in a direct comparison of portable spirometry to the accuracy of post-BD spirometry, there was a wide variation across studies in proportion of missed COPD diagnoses and false positive rates.(54) Standard quantitative measures with computed tomography (CT) imaging were found to have moderate diagnostic accuracy when compared to post-BD spirometry, but the focus of the study was on the use of automated software based on deep learning to interpret CT scans.(56)

Post-BD spirometry has been the standard in confirming persistent airflow limitations. The test is widely used as the reference to which nearly all other diagnostic methods are compared to when evaluating for COPD. Post-BD spirometry provides the criteria for clinicians to establish confirmation of their clinical diagnosis so they may begin evidence-based treatment modalities unique to COPD that improve critical outcomes; therefore, the Work Group assessed that the benefits outweigh the harm in making this recommendation. Harms that were considered include delays in care due to an over-reliance on diagnostic testing before initiating therapy, the potential for misdiagnosis or misclassification of severity could impact treatment methodology, QoL, and mortality if post-BD spirometry is interpreted inappropriately.

The Work Group systematically reviewed evidence related to this recommendation, and considered the evidence put forth in the 2021 and 2014 VA/DOD COPD CPG. In doing so, the Work Group arrived at the decision to move forward with a *Reviewed, Not Changed* recommendation. The strength of the 2026 evidence base is Very low due to serious limitations in quality, imprecision, and inconsistency.

Additional factors considered in making the recommendation were patient values and preferences in obtaining a post-BD spirometry analysis for confirmation of COPD. The Work Group proposed

that there would be some variation among patients, but the majority would prefer to have the ability to establish confidence in the diagnosis of COPD before taking on costly and time-consuming therapies. QoL and factors that affect mortality are of great concern among the population; therefore, accurate diagnosis would hold significant value among symptomatic patients to begin early treatment. In contrast, some of the population may prefer ease in management of their disease and might feel burdened by difficult access to care in situations where post-BD spirometry testing is not readily available, or at significant cost to the patient. Additionally, members from the DOD may be reluctant to seek further confirmation of their diagnosis due to the impact that COPD may have on suitability for military service.

Other implications exist in acceptability, feasibility, resource use, equity, and subgroup considerations when suggesting post-BD spirometry as the method to confirm diagnosis of COPD. The Work Group sees a high rate of acceptability among clinicians with this recommendation since post-BD spirometry has been the GOLD standard for nearly 25 years, and within the VA medical system, a referral to a pulmonologist is not required to obtain spirometry testing. There were concerns regarding feasibility and equity for patients with geographical challenges that limit access to care, and patients may experience slow access to care due to the referral process, scheduling, and availability of facilities that offer post-BD spirometry testing. Lastly, the Work Group recognizes that certain subgroup populations may be unable to complete spirometry testing due to co-occurring conditions (e.g., cognitive disability), language barriers, military status, and age.

The Work Group systematically reviewed evidence related to this recommendation and found no definitive evidence to suggest against or change the 2021 recommendation that post-BD spirometry is the most accurate method of confirming the clinical diagnosis of COPD.(53-59) Therefore, it is categorized as *Reviewed, Not Changed*. The Work Group's confidence in the quality of the evidence was Very low due to serious limitations in baseline differences in patient characteristics, high attrition, poor study quality per USPSTF criteria, and lack of clarity surrounding interpretation of test results.(57,59) Using post-BD spirometry to confirm clinical diagnosis of COPD improves diagnostic accuracy. This positively affects critical outcomes and outweighs the potential harms of delayed diagnosis while awaiting pulmonary function testing. Patient values and preferences somewhat vary, but the majority would prefer confirmation of their diagnosis over avoidance and the potential burdens that post-BD spirometry would place on them. Thus, the Work Group decided upon a *Weak for* strength of recommendation.

Recommendation

2. There is insufficient evidence to recommend using a multidimensional schema to diagnose chronic obstructive pulmonary disease (COPD).
   (Neither for nor against | Reviewed, New-added)

Discussion

This recommendation was developed after review of the work by Bhat et al.(60) The study by Bhat and colleagues, using longitudinal cohorts, evaluated whether COPD diagnosis can be improved by moving beyond spirometry alone by incorporating symptoms, respiratory QoL, and CT evidence of structural lung disease. The study considered CT emphysema, bronchial wall

thickening, dyspnea, poor respiratory QoL, and chronic bronchitis as minor criteria. The study suggested that COPD could be diagnosed either by airflow obstruction plus at least one minor criterion, or when airflow obstruction was absent, by at least three minor criteria. The approach newly classified 811 of 5,250 individuals without airflow obstruction as having COPD. These individuals did worse in outcomes than those classified as not having COPD, including higher all-cause mortality, respiratory-specific mortality, exacerbation risk, and faster FEV_1 decline. Conversely, 282 individuals with airflow obstruction but no symptoms or CT evidence of COPD were no longer classified as having COPD and had outcomes similar to those without airflow obstruction. The cohort provided partial validation, especially showing increased exacerbation risk among newly classified patients. The Work Group considered the strength of evidence as Moderate due to the large cohort study with adequate controls. The study also demonstrated that patients diagnosed under the multidimensional schema were more likely to have disease associated with higher mortality. Accurate diagnosis was also considered one of our critical outcomes, which led to this being an important study in our review. Potential benefit includes a more accurate framework for diagnosis of COPD, with potential harms being increased resource utilization and prolonged time to diagnosis.

The Work Group extensively discussed the value of the findings of this study for the general practice of primary care. External validation of the findings, in addition to nuances related to implementation in primary care settings, are among major concerns of the Work Group.

While there was some promise in this study of identifying higher risk patients, overruling the well-established standard of care based on a single cohort study was felt to be too early. We did, however, want to acknowledge the potential for this schema as a new diagnostic approach moving forward if the data is sustained in further studies. Thus, we decided to include a recommendation *Neither for nor against*, at this time to highlight this study. We believed that the increased visits, imaging, and diagnostic burden would not align with our patient's values, and the increased resource use may limit utilization of this schema in resource limited locations.

The Work Group systematically reviewed evidence related to this recommendation.(60) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations, including a single cohort study, albeit with a large pool of patients. The multidimensional diagnostic schema may identify higher-risk patients who would otherwise be missed, but it could also increase resource use and lengthen the time to diagnosis. Patient values and preferences varied largely, because some patients prioritized ease of diagnosis and care that would conflict with this more in-depth and follow-up-heavy schema. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

3. There is insufficient evidence to recommend for or against any frequency of testing (i.e., spirometry, symptom questionnaires, electronic health technology) in patients with chronic obstructive pulmonary disease (COPD) to reduce exacerbations, reduce mortality, and/or improve quality of life.
   (Neither for nor against | Reviewed, New-added)

Discussion

A key element in caring for patients with COPD is reassessment and monitoring of their disease. This clinical follow-up can include multiple different modalities, including laboratory monitoring, repeat spirometry, and symptom questionnaires. Some of this clinical surveillance can also be accomplished remotely through telemonitoring.

This CPG performed an expansive search covering a wide range of clinical monitoring tools and looked for studies evaluating the frequencies of these modalities. This literature search included spirometry, eosinophil count, pulse oximetry, multiple different symptom questionnaires, depression/anxiety screening, and Body-mass index, airflow Obstruction, Dyspnea, and Exercise capacity (BODE) index.

Our searches identified one SR (61) and two RCTs (62,63) that assessed the effectiveness of different tests in the monitoring and management of COPD. All three of the identified studies used telehealth as a vehicle with other tools (i.e., pulse oximetry, symptom questionnaires, spirometry). There were no identified studies that analyzed the benefits of frequency or type of monitoring that did not include these telehealth interventions.

Given the lack of relevant studies directly evaluating frequency and choice of disease monitoring, we cannot recommend for or against a specific monitoring strategy at this time.

The Work Group systematically reviewed evidence related to this recommendation and identified one SR (61) and two RCTs.(62,63) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations including all using telehealth as their primary vehicle for follow-up/monitoring. The benefits of frequent disease monitoring (e.g., faster detection of change of clinical course) were balanced with the potential harm (e.g., high resource use, high time/financial cost, and potential false positives leading to invasive testing). Patient values and preferences varied largely because their risk/benefit analysis of frequent testing also varied. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

B. Risk Reduction

Recommendation

4. We recommend smoking cessation with a goal of sustained abstinence for prevention and risk reduction of chronic obstructive pulmonary disease (COPD) (see the VA/DOD Tobacco Use Treatment CPG).
   (Strong for | Reviewed, Not changed)

Discussion

Cessation of smoking tobacco and avoidance of tobacco smoke are the cornerstones of COPD treatment. Smoking cessation interventions are widely accepted and available. In the 2021 VA/DOD COPD CPG, the evidence showed that avoidance of respiratory irritants can preserve lung function and slow progression of the disease more than any available medical treatment. According to the Scanlon et al. (2000) study, individuals with COPD who stopped smoking were

generally found to have improved FEV_1 the following year, a decreased rate of decline in FEV_1, and reduced mortality.(64) The retrospective cohort study by Kim et al. (2025) indicated that quitting smoking was associated with a decreased risk of both moderate to severe and severe COPD exacerbation.(65)

The Work Group systematically reviewed current evidence related to this recommendation and considered the assessment of the evidence put forth in the 2021 COPD CPG.(64,65) Therefore, this is a *Reviewed, Not changed* recommendation. The Work Group's confidence in the quality of evidence was Moderate. The benefits of slower decline in lung function; reduction of symptoms; alleviating risks for cardiovascular disease and/or cancer; and decreased mortality in the long term outweighed the harms associated with smoking cessation. The patients may have some variation in values about the contribution of smoking to illness due to different levels of dependency, mental status, COPD stages, and related symptoms. Smoking cessation interventions are widely available, have low resource use, and are widely accepted across providers. Providers should also consider barriers to cessation: (1) availability of some smoking cessation products; (2) co-pay costs for cessation products; and (3) some cessation programs may not include cognitive behavior therapy. Thus, the Work Group decided upon a *Strong for* recommendation for smoking cessation.

Recommendation

5. We suggest against electronic nicotine delivery systems (ENDS) as an alternative to tobacco smoking cessation for the reduction of chronic obstructive pulmonary disease (COPD) risk and exacerbation (see the VA/DOD Tobacco Use Treatment CPG). **(Weak against | Reviewed, New-added)**

Discussion

The evidence review identified a large study by Kim et al. (2025).(65) The study enrolled 23,262 individuals. Smoking cessation compared to continued smoking was significantly associated with reduced risk of moderate to severe exacerbations, reduced risk of severe exacerbations, and reduced all-cause mortality. Further, smoking cessation offered reductions in lung cancer and major adverse cardiac and cerebrovascular events (MACCE). However, switching to electronic delivery systems (ENDS) was not associated with any of the above beneficial outcomes compared to continued smoking except for MACCE. For additional information on ENDS, please see Recommendation 12 in the 2026 VA/DOD Tobacco Use Treatment CPG.

ENDS use has grown in popularity. Many individuals in the medical community consider ENDS as a less harmful option compared to smoking; however, the data is not supportive of this concept. Based on the Work Group's review of the above study, this recommendation is categorized as *Reviewed, New-added*.(65) The confidence in the quality of the study was Moderate. The Work Group considered the balance of desirable and undesirable outcomes and determined that harms slightly outweigh benefits. It was clear to the Work Group that this recommendation might enhance the use of cessation therapies and encourage complete tobacco and nicotine cessation. However, ENDS may have unfavorable effects on other outcomes like cardiovascular risk. Additionally, lack of ENDS use may result in more nicotine withdrawal symptoms. The Work Group felt that there will be significant variation in patient values and preferences. Some patients

may feel that ENDS is a safer and more practical option. Further, use of ENDS and subsequent reductions in smoking may be viewed favorably by patients and their significant others. Use of ENDS is associated with lighter, or no, nicotine withdrawal compared to smoking cessation. Thus, the Work Group decided upon a *Weak against* recommendation.

Recommendation

6. We suggest respiratory vaccinations with influenza, pneumococcal pneumonia, and coronavirus disease to reduce the risk of exacerbations of chronic obstructive pulmonary disease (COPD).
   (Weak for | Reviewed, New-replaced)

Discussion

Routine influenza vaccination can benefit patients with COPD by reducing COPD exacerbations. The overall strength of evidence is Low, and mixed results are seen in studies regarding the risk reduction with influenza vaccine.(66,67) This benefit of risk reduction was seen in COPD patients with FEV_1 <50%, and no significant reduction in the risk of exacerbation was seen in patients with FEV_1 >50%.(66) Although pneumococcal vaccination, together with influenza vaccination, may reduce the risk of severe exacerbations, no significant reduction in severe exacerbations was observed with pneumococcal vaccination alone.(67) A retrospective cohort study with Moderate strength of evidence showed that coronavirus disease 2019 (COVID-19) vaccination significantly reduced the risk of exacerbation in COPD patients.(68)

The Work Group found that routine respiratory virus vaccinations offer greater benefits than risks. Some benefits, in addition to reduced exacerbations and mortality among COPD patients, include reduced healthcare utilization, fewer missed days from work and school, and improved QoL. Harms are limited but include adverse vaccine reactions and the costs of the vaccine and its administration. The Work Group also noted some variation in patients' values and preferences regarding vaccinations, particularly increased hesitancy toward the COVID-19 vaccine. The routine vaccines against respiratory viruses such as influenza, pneumococcal, and COVID-19 are commonly available in the MHS and the VA, and generally well accepted across the medical community. However, patient preferences can vary with local and community beliefs and cultural practices. While our evidence synthesis did not include studies on respiratory syncytial virus (RSV), the Work Group recognizes that the Advisory Committee on Immunization Practice (ACIP) recommends RSV immunization for all adults aged ≥75 years and for adults aged 50-74 years who are at increased risk due to chronic medical conditions, such as COPD. Additionally, ACIP recommends starting recombinant zoster vaccine (RZV) to protect against the increased risk of shingles in COPD patients starting at age 50. Finally, the Work Group supports vaccination against pertussis in COPD patients, in line with CDC and ACIP.

The Work Group systematically reviewed evidence related to this recommendation (66-68) and considered the evidence assessment in the 2021 VA/DOD COPD CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of evidence was Very low. The body of evidence had some limitations. Evidence from one retrospective cohort study with a Moderate strength of evidence suggested that COVID-19 vaccination was associated with decreased risk of COPD exacerbation.(68) Eight studies in one

SR with a Low strength of evidence suggested influenza vaccinations were associated with decreased risk of COPD exacerbation.(66) Finally, one retrospective cohort study with a Very low strength of evidence did not find a significant benefit of pneumococcal vaccinations in reducing severe COPD exacerbations.(67) However, the overall benefits of reduced exacerbations outweigh the minimal side effects of vaccinating against respiratory infections. Patient values and preferences were somewhat varied, as some patients do not want to receive vaccinations. Thus, the Work Group decided upon a *Weak for* recommendation.

C. Pharmacotherapy

In this CPG, the majority of the pharmacotherapy recommendations address maintenance therapy for COPD; however, all patients with COPD should be prescribed a short-acting beta 2-agonist (SABA) for acute symptoms/rescue therapy, as needed. Our evidence showed that LAMAs are effective for maintenance; concomitant use of LAMAs and short-acting muscarinic antagonists (SAMAs) should be avoided.

Stable COPD

Recommendation

7. We recommend inhaled long-acting muscarinic antagonists (LAMA) as initial therapy for patients with mild symptoms of chronic obstructive pulmonary disease (COPD). **(Strong for | Not reviewed, Amended)**

Discussion

LAMAs remain the first-line maintenance therapy for symptomatic patients with confirmed and/or suspected COPD while awaiting confirmatory post-BD spirometry. Chen et al. (2017), compared the efficacy of LAMAs to LABAs in an SR and demonstrated that LAMAs were more effective in reducing the risk of acute exacerbations and were associated with fewer adverse events than LABAs.(69) Further supporting LAMAs over LABAs for first-line monotherapy, the SR by Maia et al. (2017), found that patients treated with LAMAs had a reduced risk of severe exacerbations leading to hospitalization.(70) The systematic evidence review carried out for this guideline update identified two SRs comparing the effectiveness of various LAMAs; neither review found that one LAMA was superior to another in terms of safety or efficacy.(71,72) Although not part of this review, it is important to note that LAMA is clearly superior to SAMA for maintenance of COPD with regard to symptoms and trough FEV_1.(73) Additionally, in patients with mild symptoms (COPD Airways Assessment Test [CAAT] <10), Maltais et al. (2022), found that there was no significant difference in improvement in symptoms (Self-Administered Computerized Transition Dyspnea Index [SAC-TDI]) when comparing patients on LABA/LAMA to patients on LAMA or LABA monotherapy.(74) However, those on LABA/LAMA had improved symptom control as manifested by SAC-TDI scores when having moderate-severe symptoms (CAAT >10 at baseline).

Despite general consistency in the evidence supporting first-line use of LAMA over LABA, there is some variability in patient preferences regarding this treatment. When a single long-acting bronchodilator is indicated, a LAMA is generally preferred over a LABA based on the comparative evidence above; the choice may reasonably shift toward a LABA in patients with contraindications

or intolerance to muscarinic antagonists. These can include patients with narrow-angle glaucoma and urinary retention.

This recommendation is categorized as *Not reviewed, Amended*. It was amended only to improve the clarity and simplicity of the language of the recommendation, and the substance of this recommendation from the 2021 VA/DOD COPD CPG is unchanged. The Work Group systematically reviewed the prior evidence related to these recommendations (69-72,75-79) and considered the assessment of the evidence put forth in the 2014 VA/DOD COPD CPG.(80,81) Therefore, this recommendation is categorized as *Not reviewed, Amended* from the 2021 guideline, by excluding the word "offering". The Work Group's confidence in the quality of the evidence was Moderate. The benefits of LAMA therapy, including reduced rates of exacerbations and hospitalizations and decreased adverse events, outweighed the harms, which were minimal. Patients have similar values and preferences for a medication that improves their symptoms and causes few side effects. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

8. In patients with moderate to severe symptom burden, we recommend initiating therapy with a long-acting beta-agonist and long-acting muscarinic antagonist (LABA/LAMA) over monotherapy.
   (Strong for | Reviewed, New-added)

Discussion

In the Work Group's review of the evidence base, there was considerable support for dual therapy (LABA/LAMA) over monotherapy in patients with moderate to severe burden. There was moderate-quality evidence favoring LABA/LAMA over LABA alone as well as LAMA alone, in improving dyspnea and cough as evidenced by clinical symptom scores such as the Generalized Anxiety Disorder scale (GAD), SAC-TDI, and Evaluating Respiratory Symptoms scale (ERS).(74,82) Although these studies used GAD, SAC-TDI, and ERS scoring to assess symptom burden, we chose to define moderate-severe symptoms using Modified Medical Research Council Dyspnea Scale (mMRC) score (≥2) or CAAT Score (≥10). We did so because these symptom-scoring methods are more commonly available in clinical practice. In these studies, there were no serious limitations, risk-of-bias, inconsistency, or imprecision, but there was some indirectness noted. Thus, this justified a rating of Moderate quality of evidence. The addition of a LABA to LAMA therapy is well-tolerated, and there is the benefit of improved QoL. Furthermore, with the addition of a LAMA to LABA therapy, there is improvement in dyspnea and cough, and harm only for select patients that have urinary retention or acute angle closure glaucoma. Given there was Moderate-quality evidence supporting LABA/LAMA over monotherapy and significant benefit relative to minimal harm, this allowed for a *Strong for* recommendation for this intervention.

The guideline's Patient Focus Group emphasized that symptom control was a high priority. It was especially noted that symptoms of breathlessness are worrisome to patients. The results of these studies speak to this symptom specifically. Additionally, the Patient Focus Group emphasized the preference for a single inhaler for multiple treatments. This can be accomplished with LABA/LAMA combined inhalers. The cost of dual inhaler therapy can be variable among healthcare systems but is less likely to be a barrier in the VA/DOD healthcare systems. Adequate support staff in

clinics will be important for inhaler training, especially when new inhalers are initiated as multiple treatments are consolidated into one inhaler. From a military readiness perspective, dual therapy is compatible with deployment to operational/austere settings as it does not require special storage or refrigeration.

Based on the relevant studies reviewed in the current CPG evidence base, this is a new recommendation based on Moderate strength of evidence. Furthermore, improved QoL and fewer inhalers were important to the Patient Focus Group, and better control of symptoms with single inhaler LABA/LAMA versus monotherapy aligns with this goal. Practically speaking, this dual therapy is generally available in the VA/DOD healthcare systems and suitable for use during operational deployments, but not all civilian healthcare systems may provide it. Thus, the Work Group made a *Strong for* recommendation for LABA/LAMA therapy compared to monotherapy in patients with significant symptom burden.

The Work Group systematically reviewed evidence related to this recommendation.(74,82) Therefore, it is categorized as *Reviewed, New-added.* The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations, including some indirectness.(74,82) The benefits of LABA/LAMA versus monotherapy in patients with significant symptom burden include improved dyspnea and QoL, which outweigh any minimal risks with the addition of a LABA or LAMA. Patient values and preferences are similar because patients reported wanting improved symptom control and a single inhaler during the focus group. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

9. In patients with chronic obstructive pulmonary disease (COPD) and a history of exacerbations requiring systemic corticosteroids and/or antibiotics in the past year, we recommend triple therapy with an inhaled corticosteroid, a long-acting beta-agonist, and a long-acting muscarinic antagonist (ICS/LABA/LAMA) for reducing exacerbations. **(Strong for | Reviewed, New-replaced)**

Discussion

The recommendation from the 2021 VA/DOD COPD CPG was reviewed and replaced to identify patients that would benefit from triple therapy without the idea of a stepwise escalation of therapies. The 2021 CPG used an underlying therapeutic structure that depended on using minimal therapies thought necessary to control symptoms and increasing the number of agents and dosage in a stepwise fashion if the initial therapy was not effective. The current literature suggests that initial therapy should be based more toward a phenotype of patients with COPD. This allows higher therapeutic measures as initial therapy to control patients' symptoms more readily and completely.

In the previous CPG, triple therapy with an inhaled corticosteroid (ICS), LABA, and LAMA had been compared with both single and combination therapy in numerous RCTs, which primarily involved patients with COPD with moderate to severe airflow obstruction and a history of one or more moderate to severe acute exacerbations (defined as exacerbations treated with antibiotics, oral corticosteroids, or those that result in hospitalization) within the prior year. There were four

SRs of these trials that served as the evidence base for this recommendation in the previous CPG.(83-86) Triple therapy decreased the frequency of moderate to severe exacerbations, improved QoL, and improved FEV_1 when compared to single or dual therapy.(83-86) The current literature review added strength to this finding,(87) using an SR of nine RCTs (N=19,603) to show triple therapy was favored over LABA/LAMA for patients who had a moderate to severe exacerbation in the previous year. Similarly, an SR of 16 RCTs (N=22,014) in patients with moderate to severe exacerbations in the past year favored triple therapy over ICS/LABA. These data addressed our critical outcome of improvement of exacerbations with Moderate strength of evidence, allowing a stronger recommendation. This same study showed an SR of 13 RCTs finding that triple therapy significantly decreased all-cause mortality compared to LABA/LAMA dual therapy, although this was not one of our critical criteria. The meta-analyses by Li and Ferguson both showed no significant differences between different combinations of ICS/LABA/LAMA.(87,88) This finding was also shown in the previous CPG literature.(83,86) Mammen et al. (2020) used 11 RCTs in an SR with meta-analysis, finding that triple therapy was not superior to long-acting bronchodilator therapy except in patients who had one or more exacerbations in the past year.(89) The decrease in exacerbations in this group outweighed any increased risk of pneumonia.

Triple therapy did not increase the rates of serious adverse events or total adverse events. In fact, the meta-analysis by Chen involving 60 RCTs showed a decrease in all-cause mortality in patients on ICS-containing therapy, especially triple therapy, with exacerbations and presence of peripheral blood eosinophils as important predictors.(90) Similar findings on all-cause mortality was found by Hammadi with triple therapy compared to LABA/LAMA.(91) Studies inconsistently reported an association between triple therapy and an increased risk of pneumonia compared to LABA/LAMA dual therapy in the previous CPG.(83,85,86) A meta-analysis by Cazzola et al. (2018), estimated a number needed to treat (NNT) of 38 for triple therapy to prevent an acute exacerbation of COPD compared to LABA/LAMA dual therapy. Conversely, triple therapy was associated with a number needed to harm of 195 for pneumonia.(85)

While Patient Focus Group participants desired improvements in their risk of exacerbations, QoL, and functional status, some heterogeneity exists among patients when weighing the risks of pneumonia and the benefits of triple therapy with an inhaled steroid. Also, while the studies did not show any difference in the number of inhalers required to deliver triple therapy, the use of separate devices for triple therapy may require a patient to utilize multiple different inhaler types and techniques, thus limiting adherence to therapy. Pre-specified secondary analyses within triple therapy trials have shown benefit across all groups but suggest that the magnitude of benefit was heterogeneous amongst different COPD phenotypes and may be influenced by the frequency of exacerbations, active smoking status, and/or blood eosinophil counts.(84-86) The Work Group determined that the strength of evidence did not justify a recommendation to treat these subgroups differently. More research should be done to elucidate markers of COPD phenotypes that benefit from different therapeutic options.

The Work Group systematically reviewed evidence related to this recommendation (83-86) and considered the assessment of the evidence put forth in the 2021 VA/DOD COPD CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of

the evidence was Moderate, which is higher than the previous CPG, allowing for a *Strong for* recommendation. The body of current evidence (87-91) had less limitations and heterogeneity than the evidence used in the 2021 CPG. The benefits of increased QoL, decreased risk of exacerbation, and decreased mortality outweighed the harms of increased risks of pneumonia. Patients likely have similar values and preferences for avoiding pneumonia, exacerbation, and mortality. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

10. We recommend against long-acting beta agonists with inhaled corticosteroids (LABA/ICS) as standalone therapy for patients with chronic obstructive pulmonary disease (COPD). **(Strong against | Not reviewed, Amended)**

Discussion

Evidence showed that LABA/ICS is inferior to LAMA/LABA in COPD regardless of rate of exacerbation, severity of exacerbation, and time to first exacerbation.(92) The preferred treatment recommendation would be LABA/LAMA instead of LABA/ICS.

An SR by Oba et al. (2018), concluded that the combination of LABA/LAMA reduced COPD exacerbations compared to LABA/ICS. Oba et al. (2018) also showed that a combination of LABA/ICS had a higher incidence of severe pneumonia compared to other inhaler combinations. The Oba et al. (2018) SR included a review of the 2016 FLAME trial (Effect of Indacaterol Glycopyrronium Vs. Fluticasone Salmeterol on COPD Exacerbations), which also showed that dual bronchodilators (LABA/LAMA) were superior at preventing exacerbations compared to LABA/ICS. However, while not included in the current evidence base, thus not impacting the strength of this recommendation, Martinez et al. (2020), also highlighted that ICS increases pneumonia risk especially if eosinophils are low (<100 cells/µL).(93) Therefore, we recommend against LABA/ICS as a standalone therapy for patients with COPD.

The Work Group systematically reviewed evidence related to this recommendation from the 2021 VA/DOD COPD CPG.(92) Therefore, it is categorized as *Not reviewed, Amended.* The Work Group's confidence in the quality of the evidence for the dual therapy with LABA/ICS was Moderate. The Work Group came to this conclusion due to the harms/burden outweighing the benefits, similar patient values and preferences, and subgroup considerations. Thus, the Work Group decided upon a *Strong against* recommendation.

Recommendation

11. In select patients on inhaled corticosteroid-containing therapy who have not had an exacerbation in the prior year and have blood eosinophil count <300 cells/µL, we suggest discontinuation of inhaled corticosteroid with careful monitoring. **(Weak for | Reviewed, Amended)**

Discussion

The Work Group's recommendation regarding ICS discontinuation was informed by two SRs (94,95) and two observational cohort studies.(96,97) The strength of evidence for this recommendation was Very low. Both SRs contained RCTs with significant risk-of-bias, and

observational real-world studies have a high risk-of-bias. Evidence on the effect of blood eosinophil levels was also based on subgroup analysis. The SR by Pierra et al. (2024)(94) contained three RCTs and three observational studies comparing continuation of ICS-containing triple therapy versus stepping down to dual bronchodilator LABA/LAMA therapy. There was no increase in moderate to severe exacerbations in patients who stepped down to LABA/LAMA therapy except in the subgroup of patients with peripheral blood eosinophils ≥300 cells/μL.

The SR by Dalin et al. (2022)(95) contained 11 RCTs, of which six compared triple therapy to dual LABA/LAMA and 5 compared ICS/LABA to LABA monotherapy. Evidence from this SR was somewhat indirect as it was a mix of RCTs investigating the effect of ICS either as continued treatment or new treatment. Only some RCTs were actual discontinuation trials, while others compared ICS/bronchodilator therapy to bronchodilator therapy. Because more than 50% of the patients in these trials had received ICS prior to the start of the study, Dalin et al. (2022) considered these studies as approximating an ICS discontinuation study. Dalin et al. (2022) investigated the relationship of blood eosinophils on exacerbation rates after ICS discontinuation by stratifying eosinophil levels into three subgroups: <150, 150-300, and >300 cells/μL. It found a correlation between eosinophil level and the risk of moderate to severe exacerbations with ICS discontinuation. There was a statistically significant increase in the risk of moderate to severe exacerbations in all three subgroups: 12% for <150, 20% for 150-300, and 43% for >300 cells/μL. However, only the >300 cells/μL subgroup met the 25% prespecified threshold for minimal clinically important difference. Clinicians should recognize that risk of exacerbation with discontinuation increases progressively as eosinophil counts approach 300 cells/μL from below; the <300 threshold identifies a population where discontinuation is reasonable on average, not a population uniformly free of risk.

Blood eosinophil levels in the RCTs and cohorts were determined on enrollment into the study or cohort. Blood eosinophil levels, however, can vary within an individual over time. Repeat levels during clinically stable periods may more accurately characterize a patient's typical eosinophil profile. A single eosinophil count taken during stable disease may be sufficient to classify a patient as above or below a certain threshold. However, it should be noted that for patients whose true mean is close to the threshold, a second measurement will substantially increase the probability of correct classification.(98)

Along with avoiding ICS withdrawal in patients with elevated blood eosinophil levels, observational studies in the evidence review support avoiding ICS discontinuation in patients with a history of multiple exacerbations. Wu et al. (2024)(96) and Suissa et al. (2022)(97) showed no increase in overall rates of moderate to severe exacerbations with ICS withdrawal except in the subgroup of patients with ≥2 exacerbations in the prior year. The Pierra et al. (2024)(94) and Dalin et al. (2022)(95) SRs unfortunately provided limited information regarding prior exacerbation history and did not analyze the effect of prior exacerbations.

Offering a trial of ICS discontinuation in patients who are stable and at low risk for exacerbation is a reasonable approach to reduce the medication burden and potential harms of ICS. ICS are associated with an increased risk of pneumonia.(99,100) There is also a strong association of ICS with local effects of thrush and dysphonia. The effects of ICS on risk for diabetes and fractures are less certain and appear significant only at high doses of ICS.(100) The prior 2021

VA/DOD COPD CPG recommendation, which suggested ICS discontinuation in patients without exacerbation in the prior two years, was likely too conservative with respect to exacerbation history. This limited the number of patients who might otherwise benefit from ICS discontinuation. Our current recommendation also takes a conservative approach, suggesting limiting ICS discontinuation to patients without an exacerbation in the prior year. The Wu et al. (2024),(96) and Suissa et al. (2022)(97) cohort studies showed that patients with ≥2 exacerbations in the prior year were at an increased risk for exacerbations with ICS discontinuation. This observation was consistent with findings of an SR by Singh et al. (2020)(101) which showed that prior exacerbation history was a strong predictor of future exacerbations independent of eosinophil levels – zero exacerbations in the prior year having the lowest risk of exacerbations and ≥2 having the highest risk. In selecting patients for ICS discontinuation, providers may also want to account for other factors such the severity of prior exacerbations and the degree of airway obstruction. The Suissa 2022 study showed an increased incidence of moderate to severe exacerbations with ICS discontinuation in patients with an FEV_1 <30% predicted.(97) Patients with severe airway obstruction will likely have worse outcomes if they develop an exacerbation.

Patients' receptiveness to ICS discontinuation may be varied. Some patients may be eager to reduce medication burden and potential side effects of ICS, while others may be reluctant to make any changes that impact their exacerbation risk. Patients in the CPG's focus group expressed a strong desire to reduce the number of inhalers to manage their COPD. A patient-centered, shared decision-making approach should be taken by providers. ICS discontinuation trials require that patients are switched to appropriate long-acting bronchodilators and have adequate clinical follow-up. It is uncertain whether there is any difference between abrupt discontinuation of ICS versus tapering off ICS. ICS discontinuation strategies were not reported in the cohort studies. Only one RCT in the SRs used a tapering strategy.(102) In this RCT, patients were on a high dose of ICS fluticasone 500 mcg twice daily. For patients who are on high doses of ICS, it may be prudent to taper the ICS dose before discontinuation.

The Work Group systematically reviewed evidence related to factors associated with the risks and benefits of ICS discontinuation in patients with COPD. Prior exacerbation and blood eosinophil level thresholds were updated from the 2021 VA/DOD COPD CPG. Therefore, this recommendation is classified as *Reviewed, Amended*. Benefits of ICS discontinuation likely outweigh harms in select patients who are at low risk for exacerbations.

The Work Group's confidence in the quality of the evidence assessing the benefits and harms of ICS discontinuation and using specific blood eosinophil and prior exacerbation thresholds to select patients is Very low. Thus, this *Reviewed, Amended* recommendation is *Weak for*. The two SRs in the evidence review (94,95) used subgroup analysis to evaluate the effect of blood eosinophils and contained RCTs with a significant risk-of-bias. Evidence for using frequency of exacerbations in the prior year to determine which patients are appropriate for ICS discontinuation is also weak. Two observational cohort studies in the evidence review (96,97) demonstrated an increased risk of exacerbations in patients with ≥2 exacerbations in the prior year. An SR outside of the evidence review (101) demonstrated a relationship between exacerbations in the prior year and the likelihood of future exacerbations, which was independent of eosinophil levels. Although the current evidence review did not identify factors

associated with benefit from ICS discontinuation, SRs outside of the evidence base demonstrate a higher risk of pneumonia in patients receiving ICS. The Very low confidence in the quality of evidence and variability in patients' receptiveness to an ICS discontinuation trial warrants a weak recommendation. Shared decision-making between clinicians and patients is essential for implementation of this recommendation, and patients should be informed of the uncertainties in assessing the benefits and harms of ICS discontinuation. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

12. In patients with chronic obstructive pulmonary disease (COPD), we suggest starting or continuing cardio-selective beta-blockers only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction).
    (Weak for | Not reviewed, Not changed)

Discussion

In patients with COPD with a cardiovascular indication for cardio-selective beta-blockers, such as heart failure with reduced ejection fraction or recent myocardial infarction, observational and RCT data suggest that these agents are safe, improve mortality rates, and decrease COPD exacerbations. While metoprolol was the primary beta-blocker examined in the earlier evidence base, the Work Group extrapolated findings to all cardio-selective beta-blockers, as they all have at least some cross-reactivity with beta-2 receptors found in lung tissue.

The following studies, while not part of the systematic evidence review for this guideline, provide relevant clinical context regarding beta-blocker use in patients with co-occurring COPD and cardiovascular disease. A 2024 SR and meta-analysis of 20 studies found that beta-blocker use was associated with reduced mortality (odds ratio [OR]: 0.50; 95% confidence interval [CI]: 0.39 to 0.63) and fewer exacerbations (OR: 0.76; 95% CI: 0.62 to 0.92) compared with non-use.(103) A large real-world registry study of over 5,000 patients with heart failure with reduced ejection fraction and concomitant COPD found that beta-blocker use was independently associated with lower cardiovascular mortality and heart failure hospitalization, without a significant increase in severe COPD exacerbations.(104) A 2024 prospective multicenter cohort study of patients with COPD hospitalized for acute myocardial infarction found that beta-blocker prescription at discharge was not associated with increased risk of all-cause mortality, revascularization, hospitalization, or COPD-related respiratory events.(105) In contrast, evidence continues to confirm that beta-blockers should not be initiated in patients with COPD who lack a cardiovascular indication. The beta-blockers COPD RCT,(106) which was stopped early due to higher exacerbation and hospitalization risk in patients without cardiovascular indications, remains the most relevant high-quality evidence on this point, and subsequent reviews have not altered this conclusion. The Work Group also considered that the harms of using cardio-selective beta-blockers in patients with COPD and hypertension without any other cardiovascular requirements continue to outweigh the benefits.

Patient values and preferences were consistent with prior Patient Focus Group findings, with patients expressing high concern regarding QoL and medication-related side effects, particularly

fear of worsening breathlessness. These preferences support a conservative approach of avoiding beta-blocker use in those without established cardiovascular indications. The Work Group noted that despite the growing body of evidence supporting beta-blocker use in appropriate patients, these medications remain underused in patients with COPD and cardiovascular disease, representing an important equity and implementation concern for Veterans and Service members who frequently carry both diagnoses. The Work Group further considered reports that patients with COPD-asthma overlap may have poor outcomes on beta-blocker therapy; however, evidence in this subgroup remains insufficient to draw firm conclusions, and caution is warranted. These studies were outside the scope of the systematic evidence review and therefore did not influence the strength of the recommendation.

The Work Group categorized this recommendation as *Not reviewed, Not changed.* The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations including heterogeneity across study designs, reliance on observational data for several key outcomes, and limited generalizability of some trials to patients without cardiovascular indications.(107,108) The benefits of cardio-selective beta-blocker use in patients with established cardiovascular indications, including reduced cardiovascular mortality and heart failure hospitalization, outweighed the potential harms of adverse respiratory events in this subgroup. Patient values and preferences were similar in that patients consistently prioritized mortality benefit and minimization of adverse effects when considering beta-blocker therapy. Thus, the Work Group decided upon a *Weak for* recommendation.

COPD Exacerbations

Recommendation

13. In outpatients experiencing an acute chronic obstructive pulmonary disease (COPD) exacerbation, we suggest selectively prescribing a short course of systemic corticosteroids based on clinical exacerbation severity and patient characteristics.
    (Weak for | Reviewed, New-added)

Discussion

Overall, low-quality evidence from an RCT by Ramakrishnan et al. (2024), suggests using blood eosinophil counts to guide adding a short course of a systemic corticosteroid in outpatients experiencing an acute exacerbation of COPD.(109) This study used a point-of-care measure of eosinophils at the time of randomization and used two weeks of 30 mg prednisolone daily as the treatment. Both factors make it less likely to replicate in usual clinical practice. However, looking at past values of blood eosinophil counts to determine which patients might fit into a phenotype seems reasonable. All patients in this RCT received an antibiotic (doxycycline). Patients with elevated blood eosinophil counts of ≥300 cells/mcL (evaluated by point-of-care measure of blood eosinophil count at the time of randomization) derived the greatest benefit from a short course of a systemic corticosteroid. Biomarker-based subgroup analyses from this clinical trial demonstrated that improvements in lung function and symptoms were greatest among those with high eosinophil counts who received oral steroids. In contrast, those with lower eosinophil counts (<300 cells/mcL) derived no benefit and may have experienced harm. This study suggests that systemic corticosteroids may be safely withheld in patients with low blood

eosinophil counts. Approximately 19% of those managed with eosinophil-guided therapy experienced treatment failure versus 32% with standard care (risk ratio [RR]: 0.60; 95% CI: 0.33 to 1.04; p=0.07). A limitation of this RCT was that it was originally designed as a superiority study, but due to multiple factors (e.g., randomization coding error and limited enrollment during the COVID-19 pandemic), the trial was converted to a noninferiority study.(109)

Historically, the severity of COPD exacerbations has been classified retrospectively according to the intensity of treatment required: mild exacerbations were managed with an increase in bronchodilator therapy alone; moderate exacerbations required treatment with systemic corticosteroids and/or antibiotics; and severe exacerbations resulted in an emergency department (ED) visit or hospitalization. In contrast, the reviewed RCTs in outpatients used a prospective, pragmatic definition of exacerbation severity. Patients were enrolled when, in the opinion or at the discretion of the treating primary care provider, they were experiencing a clinically significant acute exacerbation of COPD requiring treatment with antibiotics and/or systemic corticosteroids while remaining in the outpatient setting. Of note, the management of exacerbations requiring ED or hospitalization therapy is outside of the scope of this CPG.

When systemic corticosteroids are prescribed non-selectively to outpatients with COPD experiencing an acute exacerbation, the potential harms may outweigh the potential benefits. Overall, very low-quality evidence from the RCT by Thebault et al. (2023), suggests against prescribing systemic corticosteroids indiscriminately to all outpatients with an acute exacerbation of COPD.(110) Similar to the Ramakrishnan trial, outpatients were enrolled based on the treating clinician's judgment that they were having symptoms of an exacerbation warranting treatment in the outpatient setting. This RCT enrolled 173 patients (43% of the planned sample size of 404 patients) to evaluate a five-day course of prednisone for patients with acute exacerbations of COPD in an ambulatory setting. This underpowered study, with wide confidence intervals and imprecision in the effect estimates, failed to demonstrate clinical benefit of systemic corticosteroids. In contrast, potential harms were suggested, with higher respiratory-related treatment failure in the prednisone group compared with placebo (27.6% vs. 13.6%; RR: 2.0; 95% CI: 1.15 to 3.57) even though the overall failure rate was not different. Urgent, unplanned healthcare utilization was numerically higher with prednisone but did not reach statistical significance. Overall, adverse events were similar, with four severe adverse events in each arm and no reported deaths. Therefore, these findings support an individualized approach to prescribing systemic corticosteroids for outpatients with acute COPD exacerbations rather than the routine use of corticosteroids for all patients. Treatment decisions should incorporate the clinician's assessment of exacerbation severity, including symptom burden and objective physiologic findings (e.g., tachypnea, tachycardia, or a decline from baseline oxygen saturation), together with the peripheral blood eosinophil count, particularly in patients with eosinophil counts ≥300 cells/mcL.(109,111)

Not included in this evidence report because they were published outside the prespecified inclusion window (i.e., 2020-2025) are RCTs by Aaron et al. (2003)(112) and Leuppi et al. (2013)(50) The study by Aaron demonstrated a significant reduction in treatment failure among patients with COPD exacerbations requiring ED management, from 31/73 (43%) in the placebo group to 20/74 (27%) in the prednisone group (OR: 0.48; 95% CI: 0.23 to 0.99; NNT ~ 6). Of

note, all patients enrolled in the Aaron trial who were discharged from the ED also received a course of an oral antibiotic.(112) The REDUCE trial (Reduction in the Use of Corticosteroids in Exacerbated COPD) by Leuppi et al. (2013) demonstrated that a five-day course of systemic corticosteroids for patients presenting to the ED with acute exacerbations of COPD was noninferior to a 14-day course with respect to recurrent exacerbation or relapse within six months, while significantly reducing cumulative corticosteroid exposure. Together with other studies outside the predefined evidence base,(112-114) these findings support the selective use of a short course of a systemic corticosteroid for outpatients with clinically significant acute exacerbations of COPD, particularly those with blood eosinophil counts ≥300 cells/mcL.(109,111)

When systemic corticosteroids are prescribed selectively to outpatients with COPD with clinically significant acute exacerbations, particularly with peripheral blood eosinophil counts ≥300 cells/mcL, the benefits outweigh the potential harms. Patient values and preferences are similar because exacerbations of COPD are associated with significant morbidity, and patients want to improve more quickly and minimize the possibility of adverse events.

Practically speaking, it is important for clinicians to interpret blood eosinophil counts within a clinical context. Ideally, identify a value obtained near the time of the exacerbation, if available. Reviewing a prior (baseline) absolute eosinophil count may better reflect the patient's typical inflammatory profile. Importantly, determine whether systemic corticosteroids were administered before the eosinophil count was measured, because steroid exposure may rapidly suppress eosinophil levels and lead to underestimation.

The Work Group systematically reviewed evidence related to this recommendation.(109,110) Therefore, it is categorized as a *Reviewed, New-added* recommendation that suggests assessing the clinical exacerbation severity and the peripheral blood eosinophil count to determine which patients may benefit from a short course (i.e., five days) of a systemic corticosteroid (i.e., prednisone 40 mg per day or equivalent) during an outpatient acute exacerbation of COPD. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had limitations, including RCTs that were underpowered with wide confidence intervals and imprecision in effect estimates. Overall, the balance of evidence suggests an individualized approach to prescribing a short course of a systemic corticosteroid in outpatients with an acute COPD exacerbation. In the outpatient setting, treatment decisions should be guided by clinical exacerbation severity and the peripheral blood eosinophil count, with the greatest benefit expected in patients with clinically significant exacerbations, particularly in those with blood eosinophil counts ≥300 cells/mcL. Patient values and preferences also favor treatment in select outpatients, as exacerbations of COPD are associated with substantial morbidity and most patients prioritize faster recovery and minimization of adverse events. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

14. In outpatients experiencing an acute chronic obstructive pulmonary disease (COPD) exacerbation, we recommend short-term antibiotics depending on patient characteristics. **(Strong for | Reviewed, New-replaced)**

Discussion

Overall, moderate-quality evidence from the SR by Suzuki et al. (2024) of four RCTs demonstrated that short courses of antibiotics (≤10 days) reduce treatment failure in outpatients with acute exacerbations of COPD.(113) The greatest benefit was seen in patients with two or three cardinal symptoms of acute exacerbations of COPD (i.e., increased shortness of breath, increased sputum volume, sputum purulence) based on the Anthonisen et al. (1987) criteria.(111) Across trials, antibiotics reduced treatment failure by about 12% (33.6% for placebo vs. 21.2% for antibiotic group; OR: 0.44; 95% CI: 0.28 to 0.70; p=0.0004), and adverse events were not increased.(113) A limitation is the inconsistent use of systemic corticosteroids. None of the Anthonisen trial participants and only 17% in Llor et al. (2012) received steroids,(111,114) whereas all patients within the Hassan et al (2015) and van Velzen et al. (2017) trials received systemic corticosteroids.(115,116) Despite this variability, antibiotics were associated with fewer treatment failures in moderate to severe outpatient COPD exacerbations, particularly when more cardinal symptoms are present.

When antibiotics are prescribed to patients with COPD with at least two of the three cardinal symptoms of an acute exacerbation or in those with just sputum purulence, the benefits of a short course of antibiotics in reducing treatment failure outweigh the potential harm. Adverse effects were similar between the antibiotic and placebo groups across these studies. Patient values and preferences are generally consistent with this recommendation because exacerbations of COPD are associated with significant morbidity, and patients want to get better and not fail therapy.

The Work Group systematically reviewed evidence related to this recommendation.(113) Therefore, it is categorized as a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations including indirectness, since the SR included four outpatient and two inpatient RCTs. Only the results from the outpatient trials were considered for this recommendation.(111,114-116) The benefits of a short course of antibiotics in reducing treatment failure in more severe exacerbations outweighed the potential harms. Patient values and preferences also favor treatment, as exacerbations of COPD are associated with substantial morbidity and most patients prioritize faster recovery and avoidance of treatment failure. Adverse effects were similar in the antibiotic groups and the placebo groups across these studies. Thus, the Work Group decided upon a *Strong for* recommendation.

D. Other Management Interventions

Oxygen Therapy

Recommendation

15. In outpatients with chronic obstructive pulmonary disease (COPD) and chronic severe resting hypoxemia or moderate resting hypoxemia with signs of chronic hypoxia-related cardiopulmonary or hematologic complications, we recommend providing long-term oxygen therapy.
    (Strong for | Not reviewed, Amended)

Discussion

Severe chronic hypoxemia in COPD is associated with substantial morbidity and mortality, and long-term oxygen therapy (LTOT) has been shown to reduce mortality in this population. LTOT is indicated for patients with chronic stable resting severe hypoxemia (117) (partial pressure of oxygen in arterial blood [PaO_2] <55 mmHg or arterial oxygen saturation [SaO_2] ≤88%) and for those with chronic stable resting moderate hypoxemia (PaO_2 56-59 mmHg or SaO_2 >88% to ≤90%) when there is evidence of *chronic* hypoxia-*related cardiopulmonary or hematologic complications*, such as hematocrit >55%, pulmonary hypertension, or cor pulmonale. Chronic stable hypoxemia should be confirmed by two qualifying measurements obtained at least six weeks apart and at least six weeks after recovery from any acute illness.

When oxygen is initiated after an acute respiratory illness, the need for continued therapy should be reassessed within 30-90 days, as up to half of these patients will no longer meet criteria for LTOT. Notably, prior randomized trials demonstrating a survival benefit with LTOT did not consistently re-evaluate oxygen requirements after initiation. In contrast, patients with established chronic hypoxemia who met criteria for LTOT prior to hospitalization generally do not require routine reassessment.

The Work Group did not systematically review new evidence related to this recommendation and instead, considered the assessment of the evidence put forth in the 2021 VA/DOD COPD CPG and modified the language of the recommendation for clarity.(118-120) Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was Moderate. The benefits of LTOT outweighed the potential harm of adverse events, such as trip hazards from oxygen tubing and fire hazards for smokers. Patient values and preferences were somewhat varied. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

16. In outpatients with chronic obstructive pulmonary disease (COPD) and isolated exercise hypoxemia, we suggest against providing long-term oxygen therapy.
    (Weak against | Not reviewed, Amended)

Discussion

Oxygen is essential for normal cellular and organ function. In individuals with COPD, impairments in ventilation and gas exchange can lead to hypoxemia at rest, with exertion, or during sleep.

Although it may appear reasonable to provide supplemental oxygen in any setting of hypoxemia, clinical benefit varies depending on severity and context. The benefit of oxygen therapy is well established in patients with severe resting hypoxemia (see Recommendation 15). However, giving oxygen in patients with stable COPD who experience only exercise-induced desaturation remains unproven. The Long-Term Oxygen Treatment Trial (LOTT)(121) provides evidence addressing this question. This randomized, controlled, unblinded study compared supplemental oxygen with no oxygen therapy in 738 patients with moderate resting or exertional hypoxemia (mean age >68 years). Approximately 65% of participants experienced oxygen desaturation below 88% during a six-minute walk test (6MWT). Only a small proportion had isolated resting hypoxemia, while less than half had isolated exertional hypoxemia. Most participants had moderate-to-severe airflow limitation (FEV_1 <50% predicted in over 60%). In patients with exercise-induced hypoxemia alone, oxygen was administered only during activity. The trial found no statistically significant difference in time to death or first hospitalization. Additionally, no durable or clinically meaningful improvements were observed in QoL or functional outcomes.

Additional evidence from SRs and meta-analyses are consistent with these findings. Liu and Gong, 2019, meta-analyzed seven trials and found no significant improvement in dyspnea or functional capacity with supplemental oxygen compared to room air or compressed air.(122) Ejiofor et al. (2016), similarly reported no meaningful differences in QoL or exercise performance after six weeks of oxygen therapy, although modest improvements were noted in fatigue and dyspnea scores on the Chronic Respiratory Disease Questionnaire.(123) Ameer et al. (2014), found no impact on mortality or exercise capacity across four trials, though some reduction in post-exercise dyspnea was observed.(124) Maldonado et al. (2014), evaluated short-term oxygen administration in a crossover randomized trial and found no significant effect on dyspnea, limb fatigue, or exercise endurance.(125)

While there does not seem to be any clinically significant benefit, there are certainly harms. In certain patients, excessive oxygen administration may exacerbate hypercapnia through mechanisms such as reduced ventilatory drive and worsening ventilation-perfusion mismatch. In addition, the use of oxygen equipment introduces practical safety concerns, including increased fall risk due to tubing and a heightened risk of fire, particularly in patients who continue to smoke.

The Work Group did not systematically review new evidence related to this recommendation and instead, considered the assessment of the evidence put forth in the 2021 VA/DOD COPD CPG.(122-125) Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was Very low. The balance of benefits and harms suggests that supplemental oxygen does not provide meaningful clinical benefit in patients with chronic stable isolated exercise-induced hypoxemia, while potential harms include worsening hypercapnia, reduced respiratory drive, and safety risks such as fire hazards and falls related to oxygen equipment. Patient values and preferences are variable, with some patients reluctant to use oxygen due to perceived stigma and reduced mobility. Additional considerations include resource use, feasibility, and safety concerns, particularly among older adults and Veterans. Thus, the Work Group decided upon a *Weak against* recommendation.

Rehabilitation

Recommendation

17. We recommend offering pulmonary rehabilitation to stable, symptomatic patients on pharmacotherapy or post-hospitalization for chronic obstructive pulmonary disease (COPD) exacerbation.
    (Strong for | Not reviewed, Amended)

Discussion

Pulmonary rehabilitation is a program for patients with exercise limitations attributed to COPD or recent acute exacerbation of COPD. Programs include exercise therapy with both aerobic and strength training, with or without patient/caregiver education and/or psychological support.

This recommendation originated with the 2014 VA/DOD COPD CPG. The methodology used in 2014 to determine the overall strength of evidence differed from current GRADE methodology and did not include outcome prioritization. The methodology in 2014 averaged the strength of evidence rather than taking the lowest strength of evidence of critical outcomes. We re-reviewed the original evidence chapter and found a consistent direction of effect and Moderate strength of evidence for all critical outcomes, including healthcare utilization and QoL, across studies. The overall strength of evidence was Moderate for all pre-decided critical outcomes.

The evidence base for this recommendation consisted of one SR with 26 RCTs.(125) Of those, 18 RCTs addressed the efficacy of pulmonary rehabilitation in patients with stable COPD, demonstrating that pulmonary rehabilitation improved exercise capacity, dyspnea, and QoL. There were an additional five RCTs focused on pulmonary rehabilitation after acute exacerbation of COPD, which demonstrated that pulmonary rehabilitation decreased hospital readmissions.

There may be co-pay requirements for patients referred by VA who attend in-person rehabilitation services at a VA facility or through Community Care. This co-pay varies by patient status and may be up to $50 dollars per session for up to 36 sessions. This can represent a significant financial burden and barrier to participation.

The Work Group found that benefits outweigh associated harms and burdens. The benefits of pulmonary rehabilitation include improved exercise tolerance, improved QoL, increased physical capacity, and decreased hospitalization. Additional benefits may be social support, improved outcomes for anxiety and depression, and patient education about disease management, breathing techniques, smoking cessation, and sleep hygiene. Potential burdens include time, cost, resource utilization, and travel. The Work Group identified some variation in patient values and preferences. While the outcomes of improved symptoms and disease control are consistent with those the Patient Focus Group identified as important, there is a significant time commitment required to participate in pulmonary rehabilitation, including obtaining prerequisite cardiac and pulmonary studies. Additionally, unless a patient lives close to a facility that offers pulmonary rehabilitation, there may be an increased burden on time and distance needed for travel to actively participate, as programs are not necessarily ubiquitous. Additional feasibility limitations include time away from work and childcare needs. In addition to feasibility limitations, there are equity implications, as access may be limited in rural and under-resourced areas.

After systematically reviewing the 2014 recommendation and its associated evidence, the Work Group amended this recommendation. Since no new evidence was reviewed, it is categorized as *Not reviewed, Amended.* The Work Group's confidence in the quality of evidence was Moderate. The body of evidence had some limitations, including lack of reporting about randomization methods, allocation concealment, and outcome assessor blinding.(125) The benefits of pulmonary rehabilitation include improved exercise tolerance, improved QoL, increased physical capacity, and decreased hospitalizations, which outweigh the potential burdens of time, cost, resource utilization, and travel. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

18. We suggest offering telepulmonary rehabilitation as a clinically effective alternative to in-person pulmonary rehabilitation.
    (Weak for | Reviewed, New-added)

Discussion

Pulmonary telerehabilitation is the delivery of rehabilitation services at a distance using information and communication technology. A systematic evidence review consistently identified no difference in critical outcomes (i.e., functional exercise capacity, dyspnea, QoL) between in-person, or center-based, pulmonary rehabilitation and tele-pulmonary rehabilitation in patients with COPD. In an SR of 15 RCTs by Cox et al. (2021),(126) five different models of telerehabilitation showed little or no difference between in-person pulmonary rehabilitation and telerehabilitation for exercise capacity measured by 6-Minute Walking Distance (6MWD) test. Additionally, when compared to a no-rehabilitation control group, trials of primary telerehabilitation were found to improve 6MWD, further supporting the exercise capacity benefits of telerehabilitation. Similarly, other studies found no between-group differences in exercise capacity after in-person or telerehabilitation.(127,128) Using the Chronic Respiratory Questionnaire or the mMRC dyspnea scale, three RCTs (126) and a prospective, single-blinded, multicenter, equivalence RCT with concealed allocation (127) found no difference in reported dyspnea whether the patient participated in in-person pulmonary rehabilitation or telerehabilitation. Finally, multiple studies showed no difference between the two interventions in QoL, as measured by St. George's Respiratory Questionnaire (SGRQ).(126-128)

The quality of the evidence when comparing in-person and tele-pulmonary rehabilitation was Low due to the relatively small number of studies, low participant sample size, and high risk of bias due to an inability to blind participants or healthcare professionals who delivered interventions. There were variation and heterogenicity in telerehabilitation models and types of technology used to deliver services, as well as variability in the duration of primary and maintenance telerehabilitation programs. Very few studies followed participants and their symptoms after the intervention was completed.(126) It should also be noted that telerehabilitation dropout rates were higher in patients with severe advanced lung disease.(128) Regarding QoL as an outcome, it is unclear whether socialization with other patients, which is typically experienced in in-person pulmonary rehabilitation programs, has an impact on QoL.(128)

There are several benefits to telerehabilitation for patients with COPD. Telerehabilitation provides an alternative to the very limited number of in-person pulmonary rehabilitation centers, potentially

reducing wait times and delays in care. The evidence demonstrates higher rates of telerehabilitation program completion (82-93%) when compared to in-person rehabilitation (70%).(126,128) Telerehabilitation reduces travel time and transportation costs and may overcome a lack of suitably qualified professionals to deliver in-person interventions. There may be no or reduced co-pay requirements for telerehabilitation, resulting in cost savings for patients. Telerehabilitation reduces the demand for physical space for services. In a post-pandemic era, telerehabilitation increases the accessibility of services during seasons of high respiratory activity to minimize exposure to communicable diseases. The CPG's Patient Focus Group also recognized that alternatives to in-person care could assist with education on various aspects of COPD self-management. While no potential harm to patients is identified in the literature, there are some burdens to participants that may impact their willingness to participate in telerehabilitation, such as requiring access to their own devices and understanding how to operate the technology. Additionally, some maintenance telerehabilitation models may be resource intensive.

The Patient Focus Group participants highlighted the value of non-pharmacologic treatments in improving symptoms, functional ability, and confidence in disease management. Pulmonary telerehabilitation provides an alternative method for patients to receive structured exercise training, education, and biopsychosocial support to improve lung function in their home or at a satellite location, using supervised, synchronous interventions. However, there is likely some variability in patient values and preferences regarding telerehabilitation. Telerehabilitation requires a certain degree of engagement in prescribed rehabilitation interventions. Patients must also have the willingness, comfort, and competency (physical and mental) to use telerehabilitation technologies.

Availability of technological devices to support telerehabilitation is not always equitable depending on geographic, financial, and infrastructural (i.e., internet access and bandwidth) factors. However, the reduced need to travel for services may make telerehabilitation more accessible and desirable for patients with COPD. When considering subgroups, certain characteristics such as musculoskeletal abnormalities, dizziness, substantial sensory or motor impairments, cognitive impairment, and other features may impede participation in telerehabilitation. Therefore, some patients were excluded from RCTs due to physically limiting co-occurring conditions or experiencing an acute or immediate post-acute COPD exacerbation.(126) Of note, the evidence does not demonstrate consistent benefits of telerehabilitation for adults with non-COPD chronic respiratory conditions.(126)

The Work Group systematically reviewed evidence related to this recommendation.(126-128) Therefore, it is categorized as *Reviewed, New-added.* The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations, including a small number of studies, small sample size, high risk-of-bias due to an inability to blind participants or healthcare professionals, variation and heterogenicity in telerehabilitation models, variability in duration of primary and maintenance telerehabilitation programs, and limited follow-up of participants' symptoms and function after the intervention was completed. The benefits of pulmonary telerehabilitation, as measured by functional exercise capacity, dyspnea, and QoL, outweighed the potential harms and burdens (e.g., requiring access to and knowledge of technological

devices). Patient values and preferences varied somewhat because telerehabilitation reduces the demand for travel and space, but it also requires comfort and competence to use technology (e.g., videoconferencing, mobile devices, virtual reality, biometric sensors) and engagement in prescribed interventions. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

19. We suggest offering telehealth support tools as an adjunct to usual care.
    (Weak for | Not reviewed, Not changed)

Discussion

Telehealth is a broad term for medical services using telecommunications and digital technology. While not included in the literature review, the Work Group discussed different telehealth services such as telemedicine, telehealth monitoring, and telehealth support tools for clarification:

- **Telemedicine** uses technology tools (e.g., videoconferencing, phone calls, and/or secure messaging) to connect medical providers with patients. This can include medical visits and/or therapeutic visits such as home-based telehealth pulmonary rehabilitation.
- **Telehealth monitoring** uses specialized equipment or smartphones to transmit patient's biomedical data that from devices (e.g., oximeter, blood pressure monitor, glucometer, weight scale, and/or spirometer) to a centralized system or telemedicine center. Physicians and healthcare providers are notified of abnormal readings to allow timely interventions, adjustment of individualized management plans and/or addition of CIH services to include physical, mental, and social health.
- **Telehealth support tools** (e.g., online platforms and phone applications) provide interactive education and training to increase health literacy, medication/treatment compliance, and understanding of COPD self-management pathway.

The systematic evidence review evaluated telehealth interventions including telemonitoring, mobile applications, and telerehabilitation in the context of self-management via telecommunications and digital technology. The confidence in the quality of the evidence was Low due to inconsistency in findings, as most studies were of fair or poor quality and varied with respect to their comparison groups and the timing of outcome assessments. The interventions reviewed were heterogeneous, but all would be considered supportive in nature and not a replacement for usual medical care.

The benefits of telehealth support are thought to outweigh the potential harms and burdens. Telehealth offers significant benefits by overcoming geographic barriers to care, which is particularly important for patients in rural areas or those who have physical limitations. This modality promotes engagement with the healthcare team, patient empowerment, and more timely recognition of potential problems like pre-exacerbation symptoms or poor inhaler techniques. Furthermore, telehealth provides expanded opportunities for education, exercise promotion, and self-management. During seasons of high respiratory virus activity (e.g., influenza, RSV, COVID-19), it also increases accessibility to care while minimizing the risk of exposure to communicable diseases in this vulnerable population.

Potential burdens include variability in patient compliance and the requirement for patients to have access to and some proficiency with personal technology (e.g., smartphones, internet service). The maintenance models for telehealth programs can also be resource-intensive for the healthcare system.

Findings from the Patient Focus Group highlighted nuanced perspectives. Participants favored face-to-face visits with providers over telehealth, citing that they could better communicate symptoms and receive information. However, they also acknowledged that telehealth had significant benefits. For instance, one participant who lived 60 miles from the nearest VA Hospital remarked that it takes a whole day for a 15-minute visit. They noted that their local clinic lacked consistent specialist coverage, whereas the quality of information provided by the hospital was more comprehensive. Thus, opting for telehealth would improve their accessibility to desired specialists and reduce travel time. Participants also noted that telehealth could facilitate care for individuals who were unable to walk longer distances due to breathlessness. Moreover, due to time constraints in-clinic, telehealth could be employed to better educate patients on how to breathe, eat well, and exercise. Comfort and competency in using the required technology also remain important factors.

The Work Group systematically reviewed the 2021 VA/DOD COPD CPG evidence related to this recommendation.(129-145) Therefore, it is categorized as *Not reviewed, Not changed.* The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations including inconsistency in findings across studies, which were often of fair or poor quality, and variability in comparison groups and outcome assessment timing. The benefits of telehealth, such as increased accessibility to care by overcoming geographic barriers, promoting patient engagement and self-management, and reducing disease transmission risk, outweighed the potential harms and burdens related to technology access and literacy, compliance variability, and resource-intensive maintenance models. Patient values and preferences varied somewhat because while many patients are open to telehealth and its conveniences (e.g., better access to specialists and reduced commute times), some still prefer in-person visits and have varying comfort levels with technology. Thus, the Work Group decided upon a *Weak for* recommendation.

X. Research Priorities

During the development of the 2026 VA/DOD COPD CPG, the Work Group identified areas needing additional research, including areas requiring stronger evidence to support current recommendations and research exploring new areas to guide future CPG updates.

A. Diagnosis and Monitoring

Further evaluation of diagnostic tool accuracy, such as portable spirometry, particularly in combination with clinical questionnaires (e.g., FEV_1/FEV6 criteria), is needed. While current evidence suggests portable spirometry as a strong alternative to post-BD spirometry, studies that include broader comparators and populations are needed to validate these findings. Similarly, external validation and implementation studies looking at multidimensional schema for COPD diagnosis are needed. Future research should prioritize identifying the optimal frequency of COPD monitoring that balances detection of disease progression with patient burdens and costs.

B. Prevention and Risk Reduction

Future research should strengthen COPD prevention and risk reduction strategies by evaluating smoking cessation modalities. Future research should also assess the long-term impact of RSV vaccination on exacerbations. Additionally, further epidemiological studies are needed to examine the impact of military/occupational and environmental exposures on COPD.

C. Intervention Strategies

Advancements in the role of biomarkers and phenotyping using fractional exhaled nitric oxide (FeNO), eosinophils, and other novel biomarkers are needed to improve patient stratification, detection of disease progression, and guide intervention strategies. For instance, future research should focus on the risks and benefits associated with ICS and antibiotic use based on biomarkers, phenotypes, and pneumonia risk. Additionally, large, well-designed studies on the role of eosinophils in stable COPD and COPD exacerbations are needed.

Moreover, future research should include larger and high-quality studies that compare triple versus dual LABA/LAMA therapies and evaluate the cardiovascular and respiratory safety of cardio-selective beta-blockers. More studies identifying when to change to fully nebulized regimen and guidance on prescribing short-term systemic corticosteroid based on eosinophil count for acute COPD are needed.

D. Care Delivery Models

More research is needed on the comparative effectiveness and safety of tele-pulmonary rehabilitation and other telehealth delivery models on clinical outcomes (e.g., symptoms, adherence, ED visits, and hospitalizations). Furthermore, research should better assess early post-exacerbation use, duration of benefits, patient characteristics (e.g., age and disease severity), barriers to resources, and health equity.

Lastly, it would be valuable to analyze cost-effective and comparative studies on various telehealth delivery models (e.g., telephone, web-based, video, and remote monitoring).

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 KQs on clinical topics of the highest priority for the VA and DOD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ) (see Table A-1).

Table A-1. PICOTS (146)

P	Patients, Population, or Problem	Patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
I	Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic/screening test used with the patient or population.
C	Comparison	Treatment(s) (e.g., placebo, different drugs) or approach(es) (e.g., different dose, different frequency, standard of care) that are being compared with the intervention or exposure of interest described above.
O	Outcome	Results of interest (e.g., mortality, morbidity, quality of life, complications). Outcomes can include short, intermediate, and long-term outcomes.
(T)	Timing, if applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
(S)	Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing, and setting

The Champions, Work Group, and Evidence Review Team carried out several iterations of this process, each time narrowing the scope of the CPG and literature review by prioritizing the topics of interest. Due to resource constraints, not all developed KQs could be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of highest priority to include in the review. Table A-2 contains the final set of KQs used to guide the systematic evidence review for this CPG.

a. Population(s)

The standard clinical population considered in this SR is adults (≥18 years of age) with COPD. Most of the KQs focused on this overall clinical population, while the KQs specified below focused on specific subgroups of the clinical population:

- KQ 1: Adults with suspected COPD.
- KQ 4: Standard population without a history of prior exacerbations.
- KQ 5: Standard population with a history of prior exacerbations.
- KQ 6: Standard population with any of the following co-occurring conditions/factors:
  - Patients with COPD and any of the following: asthma, significant changes in lung function with bronchodilator, elevated serum eosinophils (>150 or >300), elevated sputum eosinophils, history of allergic rhinitis/atopy/polyps
  - Patients with an exacerbation or not
  - Patients with mucopurulent bronchitis

    - Patients with severe obstruction and/or lung hyperinflation or predominant dyspnea without exacerbations
    - Patients with low level eosinophils (<100) and/or pneumonia
    - Patients with gastroesophageal reflux disease
- KQ 7: Adults ≥18 yrs with COPD and an acute exacerbation
- KQ 8: Adults with stable COPD on long-term inhaled corticosteroids, Patients on dual, or triple therapy that contains ICS, patients with previous pneumonia
- KQ 10: Adults with COPD with refractory symptoms

b. Interventions and Comparators

KQ	Intervention(s)	Comparator(s)
1	▪ Spirometry or repeat spirometry ▪ Symptom severity scales ▪ Smoking History ▪ Risk of exacerbations ▪ GOLD classification ▪ Imaging (CT scans) ▪ Peak expiratory flow and questionnaire ▪ Salzburg COPD-screening questionnaire ▪ Major and minor criteria as defined by the COPD GENE cohort	Usual care (COPD symptoms, FEV1/FVC ratio, or another diagnostic tool) or one or more of the other diagnostic tools/criteria
2	Factors that may predict prognosis (outcomes) ▪ Severity of FEV1 ▪ Vaccination ▪ Vaping, marijuana, and secondhand smoke ▪ Cigarette smoking history ▪ Exercise ▪ Oxygen levels ▪ Improving sleep ▪ Presence of a mental health condition ▪ Nutrition (including overweight, obesity, and malnutrition) ▪ Exacerbations ▪ Air quality ▪ Wearing masks ▪ Co-occurring physical conditions – heart failure, anemia, thyroid disease, kidney disease, lung cancer ▪ Infections ▪ Childhood pulmonary illness	Absence of factors that predict outcomes
3	Tests for monitoring and management ▪ Spirometry	▪ Usual care ▪ Lower frequency of testing

KQ	Intervention(s)	Comparator(s)
	▪ Eosinophil count/eosinophilia ▪ Pulse oximetry (resting and/or with exertion) ▪ Periodic questionnaires for change in symptom (CAT, CAN, St George's Respiratory Questionnaire (SGRQ), or mMRC) ▪ Depression and anxiety screening ▪ Increased frequency of testing (spirometry) ▪ BODE Index ▪ Smoking cessation	
4	Single or combination drug therapy from the following drug or drug classes: ▪ Short-acting beta agonists (SABA) ▪ Long-acting beta agonists (LABA) ▪ Short-acting anticholinergics ▪ Long-acting anticholinergics ▪ Inhaled corticosteroids ▪ Mucolytics ▪ Biologics ▪ Roflumilast ▪ Ensifentrine	Another medication or combination of medications
5	Single or combination drug therapy from the following drug or drug classes: ▪ Short-acting beta agonists (SABA) ▪ Long-acting beta agonists (LABA) ▪ Short-acting anticholinergics ▪ Long-acting anticholinergics ▪ Inhaled corticosteroids ▪ Mucolytics ▪ Biologics ▪ Roflumilast ▪ Ensifentrine	Another medication or combination of medications
6	Single or combination drug therapy from the following drug or drug classes: ▪ Short-acting beta agonists (SABA) ▪ Long-acting beta agonists (LABA) ▪ Short-acting anticholinergics ▪ Long-acting anticholinergics ▪ Inhaled corticosteroids ▪ Mucolytics	Another medication or combination of medications

KQ	Intervention(s)	Comparator(s)
	▪ Biologics ▪ Roflumilast ▪ Ensifentrine	
7	▪ Short-term antibiotic treatment ▪ Short-term Systemic steroids ▪ Combination of short-term antibiotics and short-term systemic steroids	Placebo
8	▪ Patient characteristics which increase probability of successful ICS discontinuation. ▪ Patients with low eosinophil counts ▪ No atopy ▪ Patients with a history of no exacerbations in the preceding 1-2 years ▪ Patients on ICS as part of dual or triple therapy ▪ Patients with previous pneumonia	▪ Patient characteristics that decrease probability of successful ICS discontinuation: ▪ Eosinophilia (high eosinophil count) ▪ atopy ▪ Patients with prior exacerbations ▪ Patients on single therapy ▪ No history of pneumonia ▪ Continued smoking
9	▪ Spacers with MDI or SMI ▪ Optimization techniques including nebulizers, slow-mist inhalers, dry-powder inhaler (DPI), or metered-dose, adherence devices (e.g. propeller devices)	No spacer or other optimization technique
10	▪ Palliative interventions ▪ Meeting with a multidisciplinary palliative care team ▪ Morphine ▪ Anxiolytics ▪ SSRIs or other antidepressants ▪ Fans or other equipment that blows air ▪ Nebulized COPD treatment ▪ Home PEFR	Usual care
11	Telerehabilitation (pulmonary rehabilitation)	In-person rehabilitation
12	Caregiver education, caregiver support, or both	Usual care (no or minimal education/support)

c. Outcomes

KQ	Critical Outcome(s)	Important Outcome(s)
1	▪ COPD accurate diagnosis ▪ Clinical classification (severity)	▪ Treatment adherence ▪ Treatment planning ▪ Mortality ▪ Test accuracy
2	▪ Exacerbation	▪ Decline in lung functioning over time: spirometry, PFTs

KQ	Critical Outcome(s)	Important Outcome(s)
	▪ Criteria/thresholds for moving COPD patients to intensive/advanced therapy (e.g., triple therapy, early use of steroids, and antibiotics)	▪ Dyspnea and cough ▪ Quality of life ▪ Functional capacity (e.g. 6-minute walk test, activities of daily living) ▪ Mortality
3	▪ Exacerbation	▪ Dyspnea and cough ▪ Quality of Life ▪ Functional capacity (e.g. 6-minute walk test, activities of daily living) ▪ Morbidity/harms ▪ Mortality
4	▪ Improvement of control (FEV1 lung function) ▪ Dyspnea and cough	▪ Quality of Life ▪ Functional capacity (e.g. 6-minute walk test, activities of daily living) ▪ Morbidity/harms ▪ Mortality ▪ Exacerbation
5	▪ Exacerbation	▪ Dyspnea and cough ▪ Quality of Life ▪ Functional capacity (e.g. 6-minute walk test, activities of daily living) ▪ Morbidity/harms ▪ Mortality
6	▪ Exacerbation ▪ Dyspnea and cough	▪ Quality of Life ▪ Functional capacity (e.g. 6-minute walk test, activities of daily living) ▪ Morbidity/harms ▪ Mortality
7	▪ Reduced ED visits/hospitalizations ▪ Treatment failure ▪ Dyspnea and cough	▪ Exacerbation ▪ Quality of Life ▪ Functional capacity (e.g. 6-minute walk test, activities of daily living) ▪ Morbidity/harms ▪ Mortality
8	▪ ED visits ▪ Exacerbation	▪ Spirometry for lung functioning ▪ Dyspnea and cough ▪ Functional capacity (e.g. 6-minute walk test, activities of daily living) ▪ Morbidity/harms ▪ Mortality
9	▪ Dyspnea and cough	▪ Spirometry for lung function ▪ Exacerbation

KQ	Critical Outcome(s)	Important Outcome(s)
		▪ Quality of Life ▪ Functional capacity (e.g. 6-minute walk test, activities of daily living) ▪ Mortality
10	▪ Quality of life	▪ Improvement in mental health outcomes ▪ ED utilization ▪ Patient satisfaction ▪ Dyspnea and cough ▪ Exacerbation ▪ Mortality
11	▪ Exercise capacity ▪ Functional capacity (e.g. 6-minute walk test, activities of daily living)	▪ Smoking cessation ▪ Dyspnea and cough ▪ Exacerbation ▪ Quality of life ▪ Mortality
12	▪ Adherence ▪ Quality of life (patient)	▪ Caregiver quality of life and mental health outcomes ▪ Dyspnea and cough ▪ Exacerbation ▪ Functional capacity (e.g. 6-minute walk test, activities of daily living) ▪ Mortality

d. Timing

KQ	Timing
KQs 1, 2	No minimum follow-up
KQs 3, 8	Minimum 6 months follow-up
KQs 4, 5, 6	Minimum 3 months of pharmacotherapy
KQ 7	Minimum 2 weeks of treatment
KQs 9, 10, 12	Minimum 3 months follow-up
KQ 11	Minimum 8 to 12 weeks of telehealth intervention

e. Setting(s)

The standard setting for KQs 1-12 is Ambulatory (outpatient) care.

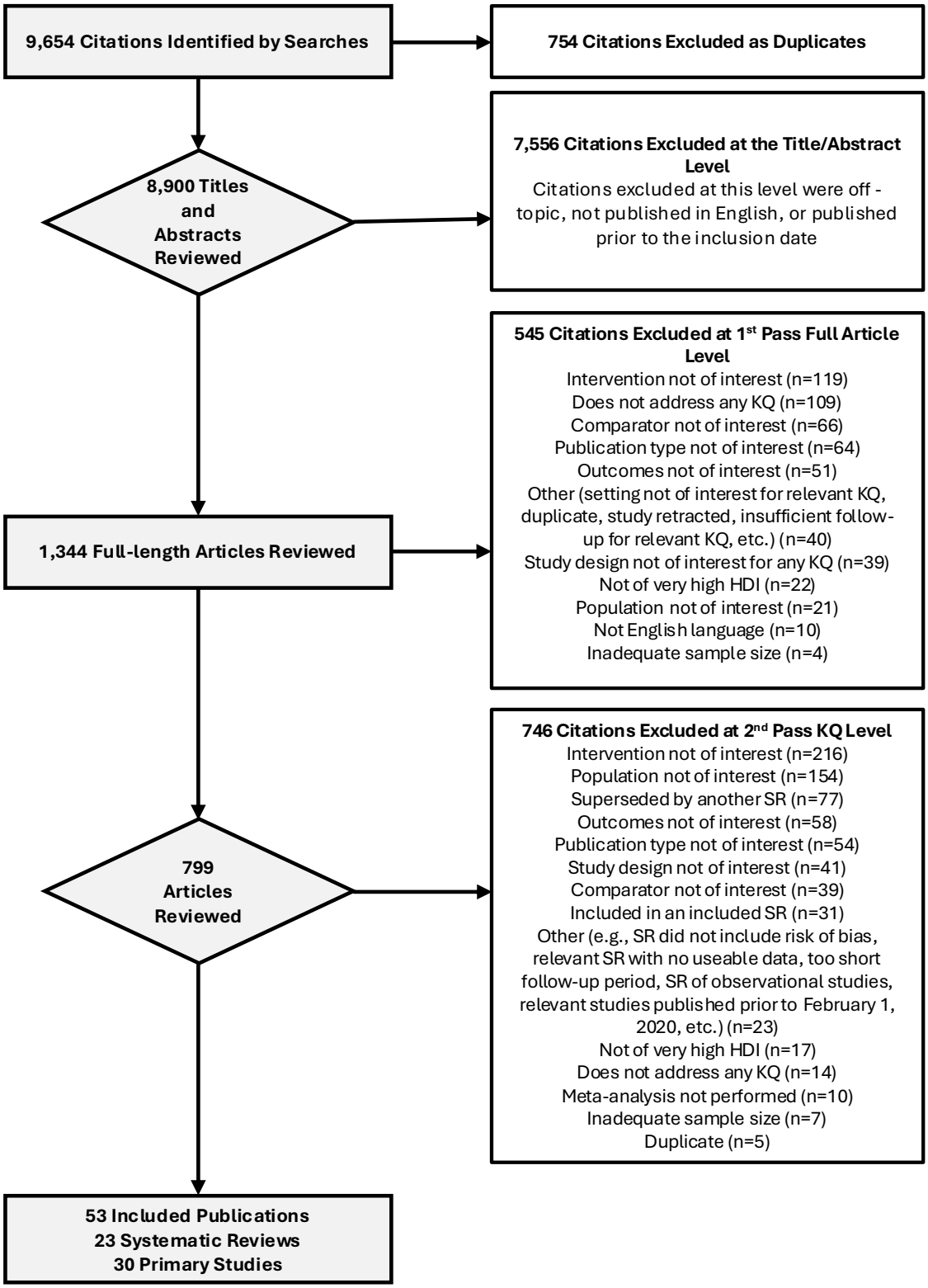
B. Conducting the Systematic Review

Literature searches identified 9,654 citations potentially addressing the KQs of interest for this evidence review. After 754 duplicates were removed, there were 8,900 citations. Of these, 7,556 were excluded upon title and abstract review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to the study inclusion publication date, or not a full-length article). A total of 1,344 full-length articles were reviewed. Of these, 545

were excluded at first pass review for the following reasons: intervention not of interest (119), does not address any KQ (109), comparator not of interest (66), publication type not of interest (64), outcomes not of interest (51), other (e.g., setting not of interest for relevant KQ, duplicate, study retracted, insufficient follow-up for relevant KQ, etc. [40]), study design not of interest for any KQ (39), not a country of very high Human Development Index (HDI) (22), population not of interest (21), not English language (10), or inadequate sample size (4). A total of 799 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 746 were ultimately excluded for the following reasons: intervention not of interest (216), population not of interest (154), superseded by another SR (77), outcomes not of interest (58), publication type not of interest (54), study design not of interest (41), comparator not of interest (39), study included in an included SR (31), other (e.g., SR did not include risk of bias, relevant SR with no useable data, too short follow-up period, SR of observational studies, relevant studies published prior to February 1, 2020, etc. [23]), not a country of very high HDI (17), does not address any KQ (14), meta-analysis not performed (10), inadequate sample size (7), or duplicate (5). Detailed information on inclusions and exclusions throughout the review process are provided in Figure A-1 below.

Overall, 53 publications addressed one or more of the KQs and were considered as evidence in this review, including 23 SRs and 30 primary studies. Table A-2 indicates the number of studies that addressed each of the questions, with some publications being used for more than one KQ.

Figure A-1. Study Flow Diagram



Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion-exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 9,654 citations identified by searches
    a. Right to Box 2: 754 citations Excluded as Duplicates
    b. Down to box 3
2. Box 3: 8,900 Titles and Abstracts reviewed
    a. Right to Box 4: 7,556 citations excluded at the title/abstract level. Citations excluded at this level were off topic, not published in English, or published prior to the inclusion date
    b. Down to Box 5
3. Box 5: 1,344 full-length articles reviewed
    a. Right to Box 6: 545 citations excluded at 1st full-article level
        i. 119 intervention not of interest
        ii. 109 does not address any KQ
        iii. 66 comparator not of interest
        iv. 64 publication type not of interest
        v. 51 outcomes not of interest
        vi. 40 other (setting not of interest for relevant KQ, duplicate, study retracted, insufficient follow-up for relevant KQ, etc.)
        vii. 39 study design not of interest for any KQ
        viii. 22 not of very high HDI
        ix. 21 population not of interest
        x. 10 not English language
        xi. 40 inadequate sample size
    b. Down to Box 7
4. Box 7: 799 articles reviewed
    a. Right to Box 8: 545 citations excluded at 2nd pass KQ level
        i. 216 intervention not of interest
        ii. 154 population not of interest
        iii. 77 superseded by another SR
        iv. 58 outcomes not of interest
        v. 54 publication type not of interest

vi. 41 study design not of interest
vii. 39 comparator not of interest
viii. 31 included in an included SR
ix. 23 other (e.g., SR did not include risk of bias, relevant SR with no useable data, too short follow-up period, SR of observational studies, relevant studies published prior to Feburary1, 2020, etc.)
x. 17 not of very high HDI
xi. 14 does not address any KQ
xii. 10 meta-analysis not performed
xiii. 7 inadequate sample size
xiv. 5 duplicate

b. Down to Box 9

5. Box 9: 53 included publications (23 systematic reviews and 30 primary studies)

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	For patients being evaluated for COPD, what is the optimal criteria for diagnosing and/or classifying COPD?	2 SRs, 2 RCTs, 7 observational studies
2	What modifiable factors predict the outcomes of COPD?	4 SRs, 10 observational studies
3	What tests and frequency of testing are effective for monitoring and management of COPD?	1 SR, 2 RCTs
4	In patients without a previous history of exacerbations of COPD, what is the comparative effectiveness of maintenance pharmacotherapy alone or in combination with the following drug classes to improve outcomes: SABA, LABA, LAMA, short/long-acting anticholinergics, mucolytics, biologics, ICS, PDE agents?	1 SR, 2 RCTs, 3 secondary analyses of an RCT
5	In patients with previous exacerbations of COPD, what is the comparative effectiveness of maintenance pharmacotherapy alone or in combination with the following drug classes to improve outcomes: SABA, LABA, LAMA, short/long-acting anticholinergics, mucolytics, biologics, ICS, PDE agents?	4 SRs, 3 NMA
6	Does pharmacotherapy have increased benefits or harms in specific subpopulations of patients with COPD?	1 NMA, 4 SRs, 1 post hoc analysis of an RCT
7	In patients with confirmed COPD experiencing an acute exacerbation, what is the evidence that administration of short-term antibiotics and/or systemic steroids are more effective than placebo in improving outcomes?	1 SR, 2 RCTs
8	In patients with confirmed COPD treated with long-term inhaled corticosteroids, what characteristics identify patients who can have ICS discontinued without risk of exacerbation or deterioration?	2 SRs, 6 RCTs
9	In patients with confirmed COPD does the use of spacers or other optimization of inhaler techniques improve patient adherence and outcomes?	1 SR, 1 crossover RCT
10	In patients with COPD with refractory symptoms, is palliative care effective in improving COPD outcomes?	3 RCTs (in 4 publications)
11	In patients with confirmed COPD, what is the comparative effectiveness of in person vs. telerehabilitation (pulmonary rehabilitation) in improving COPD outcomes?	1 SR, 2 RCTs
12	In patients with confirmed COPD, does caregiver education and support improve patient and caregiver outcomes?	1 RCT (in 3 publications)
Total Evidence Base		**70 publications*** (21 SRs, 20 RCTs, 4 NMA, 17 observational studies, 4 secondary analyses of an RCT, and 1 crossover RCT)

*Some publications addressed more than one KQ.

Abbreviations: COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; KQ: key question; LABA long-acting β2 agonist; LAMA: long-acting muscarinic antagonist; NMA: network meta-analysis; PDE: Phosphodiesterase; RCT: randomized controlled trial; SABA: short-acting beta agonist; SR: systematic review

a. General Criteria for Inclusion in Systematic Evidence Review

- RCTs or SRs of RCTs published on or after February 1, 2020, to December 5, 2025.
- Studies must have been published in English.
- Publication must have been a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, research protocols, and other publications that were not full-length clinical studies were not accepted as evidence.
- Systematic reviews must have been searched MEDLINE or EMBASE for eligible publications, performed a risk-of-bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the one used by the AHRQ Evidence-based Practice Centers [EPCs]). If an existing review did not assess the overall quality of the evidence, evidence from the review was reported in a manner that would allow us to judge the overall risk-of-bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were not able to assess the overall quality of the evidence in the review. If multiple SRs addressed a KQ, we selected the most recent and/or comprehensive review. In many cases, we used multiple SRs to address a single KQ, as each SR dealt with a different intervention or intervention-comparator combination.
- RCTs had an independent control group. Randomized crossover trials were only included if data from the first period (prior to treatment crossover) was reported separately or an adequate washout period was used.
- Study had enrolled at least 20 patients (10 per study group for RCTs and 20 for observational studies).
- Study had enrolled at least 85% of patients who met the study population criteria. If the patient population fell below this threshold but the relevant population of patients was reported separately, then that study was included.
- To ensure applicability to the VA/DOD healthcare systems, and ensure consistency across the CPG program, inclusion of individual studies were limited to very high HDI, countries with an index ≥0.8 where standards of healthcare were comparable (e.g., U.S., Canada, UK, Western Europe, Israel, Japan, Hong Kong, Australia, and New Zealand). Inclusion of the systematic reviews were limited to those including more than half of the studies from eligible regions.
    - These regions of interest are listed in Table 1 of the Statistical Annex of the 2023/24 Human Development Report produced by the United Nations Development Program.
- Study reported on at least one outcome of interest.

b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

- For KQ 1, diagnostic accuracy studies and SRs of diagnostic accuracy were included.
- For KQs 2 and 8, RCTs with pre-planned subgroup analyses, observational studies and SRs of observational studies that report on groups with and without potential prognostic factors were used to address the KQs.
- For all other KQs, only SRs of RCTs and individual RCTs were considered.

c. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table A-3, below. Additional information on the search strategies, including topic-specific search terms and search strategies can be found in Appendix F.

Table A-3. Bibliographic Database Information

Name		Date Limits	Platform/ Provider
Bibliographic Databases	Embase, Medline	February 1, 2020, to December 5, 2025	Elsevier
	PubMed in process	February 1, 2020, to December 5, 2025	National Library of Medicine
Name		**Date Limits**	**Platform/ Provider**
Gray Literature Databases	Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Center Reports	February 1, 2020, to December 5, 2025	AHRQ
	Cochrane Database of Systematic Reviews	February 1, 2020, to December 5, 2025	Cochrane Library
	Veterans Affairs Evidence Synthesis Program (VA ESP)	February 1, 2020, to December 5, 2025	VA ESP

d. Rating the Quality of Individual Studies and the Body of Evidence

Sigma Health Consulting assessed the methodological risk of bias of individual diagnostic, observational, and interventional studies using the USPSTF method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(147)

Next, Sigma Health Consulting assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, or *Very Low.*

C. Developing Evidence-Based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program within the Defense Health Agency, Sigma Health Consulting convened a 3.5 day in-person recommendation development meeting from March 31- April 3, 2026, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, Sigma Health Consulting finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting (see Determining Recommendation Strength and Direction).

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed the CPG's recommendations. The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications.

a. Determining Recommendation Strength and Direction

Per GRADE methodology, to assess the quality of the evidence base and assign a grade for the strength for each recommendation, the GRADE system uses the following four domains to assess the strength of each recommendation (36):

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease their strength. The evidence review used for the development of recommendations for COPD management, conducted by Sigma Health Consulting, assessed the confidence in the quality of the evidence base and assigned a rate of "High," "Moderate," "Low," or "Very low."

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

2. Balance of Desirable and Undesirable Outcomes

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid events, resolution of symptoms, improved QoL, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse events, impaired QoL, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that most clinicians will offer patients therapeutic or preventive measures if the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

3. Patient Values and Preferences

"Patient values and preferences" is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience

of the therapeutic or preventive measures in relation to one another. For some, the term “values” has the closest connotation to these processes. For others, the connotation of “preferences” best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having “similar values,” “some variation,” or “large variation” in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient’s values and preferences?
- Are the assumed or identified relative values similar across the target population?

4. Other Implications

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example, statin use in the frail elderly and others with multiple co-occurring conditions might not be effective and depending on the societal benchmark for willingness to pay, might not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practicality of the recommendation.

The framework below (Table A-4) was used by the Work Group to guide discussions on each domain.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgement
Balance of desirable and undesirable outcomes	▪ What is the magnitude of the anticipated desirable outcomes? ▪ What is the magnitude of the anticipated undesirable outcomes? ▪ Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	▪ Benefits outweigh harms/burdens ▪ Benefits slightly outweigh harms/burdens ▪ Benefits and harms/burden are balanced ▪ Harms/burden slightly outweigh benefits ▪ Harms/burden outweigh benefits
Confidence in the quality of evidence	▪ Among the designated critical outcomes, what is the lowest quality of relevant evidence? ▪ How unlikely is further research to change the confidence in the estimate of effect?	▪ High ▪ Moderate ▪ Low ▪ Very low
Patient values and preferences	▪ Are you confident about the typical values and preferences and are they similar across the target population? ▪ What are the patient's values and preferences? ▪ Are the assumed or identified relative values similar across the target population?	▪ Similar values ▪ Some variation ▪ Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	▪ Are the resources worth the expected net benefit from the recommendation? ▪ What are the costs per resource unit? ▪ Is this intervention generally available? ▪ Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? ▪ Is there lots of variability in resource requirements across settings?	▪ Various considerations

b. Recommendation Categorization

1. Recommendation Categories and Definitions

For use in the 2026 COPD CPG, a set of recommendation categories was adapted from those used by the UK's NICE.(41,42) These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2021 VA/DOD COPD CPG. The categories and definitions can be found in Table 3.

2. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether they were based on an updated review of the evidence. If evidence had been reviewed, recommendations were categorized as "New-added," "New-replaced," "Not changed," "Amended," or "Deleted."

"Reviewed, New-added" recommendations were original, new recommendations that were not in the 2021 VA/DOD COPD CPG. "Reviewed, New-replaced" recommendations were in the

previous version of the guideline but were modified to align with the updated review of the evidence. These recommendations could have also included clinically significant changes to the previous version. Recommendations categorized as “Reviewed, Not changed” were carried forward from the previous version of the CPG unchanged.

Recommendations could have also been designated “Reviewed, Deleted.” These were recommendations from the previous version of the CPG that were not brought forward to the updated guideline after review of the evidence. This occurred if the evidence supporting the recommendations was out of date, to the extent that there was no longer any basis to recommend a particular course of care and/or new evidence suggests a shift in care, rendering recommendations in the previous version of the guideline obsolete.

3. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous version of the CPG without a review of the evidence. Due to time and budget constraints, the update of the COPD CPG could not review all available evidence on COPD management, but instead, focused its KQs on new or updated scientific research or areas that were not previously covered in the CPG.

For areas of research that have not changed, and for which recommendations made in the previous version of the guideline were still relevant, recommendations could have been carried forward to the updated guideline without an updated review of the evidence. The support for these recommendations in the updated CPG was thus also carried forward from the previous version of the CPG. These recommendations were categorized as “Not reviewed.” If evidence had not been reviewed, recommendations could have been categorized as “Not changed,” Amended,” or “Deleted.”

“Not reviewed, Not changed” recommendations refer to recommendations from the previous version of the COPD CPG that were carried forward unchanged to the updated version. The category of “Not reviewed, Amended” was used to designate recommendations which were modified from the 2021 VA/DOD COPD CPG with the updated GRADE language, as explained above.

Recommendations could also have been categorized as “Not reviewed, Deleted” if they were determined to be out of scope. A recommendation was out of scope if it pertained to a topic (e.g., population, care setting, treatment, condition) outside of the scope for the updated CPG as defined by the Work Group.

The categories for the recommendations included in the 2026 version of the guideline are noted under the Recommendations. The categories for the recommendations from the 2021 VA/DOD COPD CPG are noted in Appendix C.

c. Drafting and Finalizing the Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations and/or to update discussion sections from the 2021 VA/DOD COPD CPG to support the amended “carried forward” recommendations. The Work Group also considered tables, appendices, and other

sections from the 2021 VA/DOD COPD CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithm, as necessary.

After developing the initial draft of the updated CPG, an iterative review process was used to solicit feedback for and revise the CPG. Once developed, the first two drafts of the CPG were posted on the COPD Wiki Website for a period of 10-15 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group, and appropriate revisions were made to the CPG.

Appendix B: Evidence Table

Table B-1. 2026 COPD Evidence Table [a, b, c, d]

#	2026 Recommendation	2021 Strength of Recommendation	Evidence	2026 Strength of Recommendation	2026 Recommendation Category
1.	We suggest post-bronchodilator spirometry to confirm clinical diagnosis of chronic obstructive pulmonary disease (COPD).	Weak for	(53-59)	Weak for	Reviewed, Not Changed
2.	There is insufficient evidence to recommend using a multidimensional schema to diagnose chronic obstructive pulmonary disease (COPD).	N/A	(60)	Neither for nor against	Reviewed, New-added
3.	There is insufficient evidence to recommend for or against any frequency of testing (i.e., spirometry, symptom questionnaires, electronic health technology) in patients with chronic obstructive pulmonary disease (COPD) to reduce exacerbations, reduce mortality, and/or improve quality of life.	N/A	(61-63)	Neither for nor against	Reviewed, New-added
4.	We recommend smoking cessation with a goal of sustained abstinence for prevention and risk reduction of chronic obstructive pulmonary disease (COPD) (see the VA/DOD Tobacco Use Treatment CPG).	Strong for	(64,65)	Strong for	Reviewed, Not changed
5.	We suggest against electronic nicotine delivery systems (ENDS) as an alternative to tobacco smoking cessation for the reduction of chronic obstructive pulmonary disease (COPD) risk and exacerbation (see the VA/DOD Tobacco Use Treatment CPG).	N/A	(65)	Weak against	Reviewed, New-added
6.	We suggest respiratory vaccinations with influenza, pneumococcal pneumonia, and coronavirus disease to reduce the risk of exacerbations of chronic obstructive pulmonary disease (COPD).	Weak for	(66-68)	Weak for	Reviewed, New-replaced

#	2026 Recommendation	2021 Strength of Recommendation	Evidence	2026 Strength of Recommendation	2026 Recommendation Category
7.	We recommend inhaled long-acting muscarinic antagonists (LAMA) as initial therapy for patients with mild symptoms of chronic obstructive pulmonary disease (COPD).	Strong for	(69-72,75-81) **Additional References** (73,74)	Strong for	Not reviewed, Amended
8.	In patients with moderate to severe symptom burden, we recommend initiating therapy with a long-acting beta-agonist and long-acting muscarinic antagonist (LABA/LAMA) over monotherapy.	N/A	(74,82)	Strong for	Reviewed, New-added
9.	In patients with chronic obstructive pulmonary disease (COPD) and a history of exacerbations requiring systemic corticosteroids and/or antibiotics in the past year, we recommend triple therapy with an inhaled corticosteroid, a long-acting beta-agonist, and a long-acting muscarinic antagonist (ICS/LABA/LAMA) for reducing exacerbations.	Weak for	(83-91)	Strong for	Reviewed, New-replaced
10.	We recommend against long-acting beta agonists with inhaled corticosteroids (LABA/ICS) as standalone therapy for patients with chronic obstructive pulmonary disease (COPD).	Strong for	(92) **Additional Evidence** (93)	Strong against	Not reviewed, Amended
11.	In select patients on inhaled corticosteroid-containing therapy who have not had an exacerbation in the prior year and have blood eosinophil count <300 cells/μL, we suggest discontinuation of inhaled corticosteroid with careful monitoring.	Weak for	(94-97,102) **Additional Evidence** (98-101)	Weak for	Reviewed, Amended
12.	In patients with chronic obstructive pulmonary disease (COPD), we suggest starting or continuing cardio-selective beta-blockers only in	Weak for	(107,108) **Additional Evidence**	Weak for	Not reviewed, Not changed

#	2026 Recommendation	2021 Strength of Recommendation	Evidence	2026 Strength of Recommendation	2026 Recommendation Category
	those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction).		(103-106)		
13.	In outpatients experiencing an acute chronic obstructive pulmonary disease (COPD) exacerbation, we suggest selectively prescribing a short course of systemic corticosteroids based on clinical exacerbation severity and patient characteristics.	N/A	(109,110) **Additional Evidence** (50,111-114)	Weak for	Reviewed, New-added
14.	In outpatients experiencing an acute chronic obstructive pulmonary disease (COPD) exacerbation, we recommend short-term antibiotics depending on patient characteristics.	Neither for nor against	(111,113-116)	Strong for	Reviewed, New-replaced
15.	In outpatients with chronic obstructive pulmonary disease (COPD) and chronic severe resting hypoxemia or moderate resting hypoxemia with signs of chronic hypoxia-related cardiopulmonary or hematologic complications, we recommend providing long-term oxygen therapy.	Strong for	(118-120) **Additional Evidence** (117)	Strong for	Not reviewed, Amended
16.	In outpatients with chronic obstructive pulmonary disease (COPD) and isolated exercise hypoxemia, we suggest against providing long-term oxygen therapy.	Weak against	(122-125) **Additional Evidence** (121)	Weak against	Not reviewed, Amended
17.	We recommend offering pulmonary rehabilitation to stable, symptomatic patients on pharmacotherapy or post-hospitalization for chronic obstructive pulmonary disease (COPD) exacerbation*.	Strong for	(125)	Strong for	Not reviewed, Amended

#	2026 Recommendation	2021 Strength of Recommendation	Evidence	2026 Strength of Recommendation	2026 Recommendation Category
18.	We suggest offering telepulmonary rehabilitation as a clinically effective alternative to in-person pulmonary rehabilitation.	N/A	(126-128)	Weak for	Reviewed, New-added
19.	We suggest offering telehealth support tools as an adjunct to usual care.	Weak for	(129-145)	Weak for	Not reviewed, Not changed

[a] 2021 Strength of Recommendation column: "N/A" indicates that the 2026 VA/DOD COPD CPG recommendation was a new recommendation and therefore, does not have an associated 2021 strength of recommendation.

[b] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through a systematic evidence review carried out as part of the initial development or update of this CPG. The second set of references in the evidence column (called "Additional References") includes references that provide additional information related to the recommendation but were not identified through a systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

[c] 2026 Strength of Recommendation column: The 2026 VA/DOD COPD CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Grading Recommendations section for more information.

[d] Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category

[*] Although this recommendation was deleted in the 2021 VA/DOD COPD CPG, the 2026 Work Group chose to carry forward this recommendation from the 2014 VA/DOD COPD CPG due to its importance.

Appendix C: 2021 Recommendation Categorization

2021 CPG Recommendation #	2021 Recommendation Text[1]	2021 CPG Strength of Recommendation	2021 CPG Recommendation Category[2]	2026 CPG Recommendation Category[3]	2026 CPG Recommendation #
1	We suggest post-bronchodilator spirometry to confirm clinical diagnosis of COPD.	Weak for	Reviewed, New-replaced	Reviewed, Not Changed	1
2	There is insufficient evidence to recommend for or against any specific clinical criteria to inform decision-making regarding advancing pharmacologic therapy for COPD.	Neither for nor against	Reviewed, New-added	N/A Deleted recommendation	
3	We recommend smoking cessation for prevention and risk reduction of COPD.	Strong for	Reviewed, New-replaced	Reviewed, Not Changed	4
4	We suggest routine vaccination for influenza and pneumococcal pneumonia for prevention and risk reduction of COPD exacerbations.	Weak for	Reviewed, New-replaced	Reviewed, New-replaced	5
5	We recommend offering inhaled long-acting muscarinic antagonists as first-line therapy in patients with symptomatic COPD.	Strong for	Reviewed, New-replaced	Not reviewed, Amended	7
6	We recommend against offering an inhaled long-acting beta agonist as first-line therapy in patients with symptomatic COPD, unless a long- acting muscarinic antagonist is not tolerated or is contraindicated.	Strong against	Reviewed, New-added	N/A Deleted recommendation	
7	We recommend against offering an inhaled corticosteroid in patients with symptomatic COPD as a first-line therapy.	Strong against	Not reviewed, Amended	N/A Deleted recommendation	
8	For patients with moderate to severe obstruction who continue to report significant dyspnea or decreased quality of life despite using a long-acting muscarinic antagonist, we suggest adding a long-acting beta agonist to long-acting antimuscarinic agent therapy.	Weak for	Reviewed, New-replaced	N/A Deleted recommendation	

2021 CPG Recommendation #	2021 Recommendation Text[1]	2021 CPG Strength of Recommendation	2021 CPG Recommendation Category[2]	2026 CPG Recommendation Category[3]	2026 CPG Recommendation #
9	If choosing dual therapy, we recommend against offering long-acting beta agonists with inhaled corticosteroids for patients with COPD.	Strong against	Reviewed, New-added	Not reviewed, Amended	11
10	In patients with COPD who are on combination therapy with a long- acting antimuscarinic agent/long-acting beta agonist and continue to have COPD exacerbations, we suggest adding an inhaled corticosteroid as a third medication.	Weak for	Reviewed, New-replaced	Reviewed, New-replaced	12
11	There is insufficient evidence to recommend for or against the use of eosinophilia or suspicion of asthma-COPD overlap syndrome to guide choice of additional therapy.	Neither for nor against	Reviewed, New-added	N/A Deleted recommendation	
12	We suggest considering withdrawal of inhaled corticosteroids in patients with COPD without moderate to severe exacerbations in the last two years.	Weak for	Reviewed, New-added	Reviewed, Amended	9
13	There is insufficient evidence to recommend for or against the use of N- acetylcysteine preparations available in the United States for patients with stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	Neither for nor against	Reviewed, Amended	N/A Deleted recommendation	
14	There is insufficient evidence to recommend for or against the use of antibiotics for outpatient COPD exacerbations (C-reactive protein guided or not).	Neither for nor against	Reviewed, New-replaced	Reviewed, New-replaced	13
15	We recommend providing long-term oxygen therapy to patients with chronic stable resting severe hypoxemia (PaO2 <55 mm Hg and/or SaO2 ≤88%) or chronic stable resting moderate hypoxemia (PaO2 56 – 59 mm Hg or SaO2 >88% and ≤90%) with signs of tissue hypoxia (hematocrit >55%, pulmonary hypertension, or cor pulmonale).	Strong for	Not reviewed, Not changed	Not reviewed, Amended	16

2021 CPG Recommendation #	2021 Recommendation Text[1]	2021 CPG Strength of Recommendation	2021 CPG Recommendation Category[2]	2026 CPG Recommendation Category[3]	2026 CPG Recommendation #
16	We suggest against routinely offering ambulatory long-term supplemental oxygen for patients with chronic stable isolated exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen.	Weak against	Reviewed, Not changed	Not reviewed, Amended	17
17	In patients with COPD, we suggest starting or continuing cardio- selective beta-blockers only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction).	Weak for	Reviewed, Amended	Not reviewed, Not changed	10
18	We suggest offering a supported self-management program that includes a written action plan with exacerbation management, smoking cessation, and exercise.	Weak for	Reviewed, New-replaced	N/A Deleted recommendation	
19	We suggest offering telehealth support that includes telemonitoring and/or mobile applications.	Weak for	Reviewed, New-replaced	Not reviewed, Not changed	20
36*	We recommend offering pulmonary rehabilitation to stable patients with exercise limitation despite pharmacologic treatment and to patients who have recently been hospitalized for an acute exacerbation.	Strong for	Reviewed, [not specified in 2014 VA/DOD COPD CPG]	Not reviewed, Amended	18

[1] The 2021 Recommendation Text column contains the wording of each recommendation from the 2021 VA/DOD COPD CPG.

[2] The Recommendation Category column indicates the way in which each 2021 VA/DOD COPD CPG recommendation was updated.

[3] For recommendations that were carried forward to the 2026 VA/DOD COPD CPG, this column indicates the new recommendation(s) to which they correspond.

[*] Although this recommendation was deleted in the 2021 VA/DOD COPD CPG, the 2026 Work Group chose to carry forward this recommendation from the 2014 VA/DOD COPD CPG due to its importance.

Appendix D: Participant List

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Appendix E: Patient Focus Group Methods and Findings

A. Methods

VA and DOD Leadership recruited seven participants for the focus group with support from the Champions and other Work Group members. The goal of recruitment for this Patient Focus Group was to have a group of engaging, diverse patients receiving VA or DOD healthcare services, who could cogently explain their experience with COPD. Participants were mixed in terms of receiving care from the VA and DOD, and one participant was a caregiver for their spouse who has COPD. Participants' severity of COPD and length of treatment ranged widely from as recent as 3 years to as long as 40 years, with two participants relying on continuous oxygen therapy. Participants reported using multiple different prescriptions to manage their COPD, including rescue medications in addition to their standard treatments. Many participants also noted that they had several co-occurring conditions along with their COPD. Several participants attributed their COPD to exposures they experienced while serving on active duty in the military.

The Work Group, with support from Sigma Health Consulting, identified topics on which participants' input was important to consider in developing the CPG. Sigma Health Consulting developed, and the Work Group approved, an interview guide covering these topics. The focus group facilitator who led the discussion used the guide to elicit participants' perspectives about their treatment and overall care. Not all questions included in the Moderator's Guide for the COPD Patient Focus Group were addressed by participants, but because the moderator encouraged conversation between the Patient Focus Group members, most topics were covered.

Patient Focus Group Findings

a. Participants expressed a strong desire for a single treatment that combines all necessary COPD medications into one.

- Several participants noted their desire for a single COPD-specific inhaler. They wished to reduce the complexity and number of inhalers and medications.
- Participants desired limiting medications, emphasizing that a single combination treatment would reduce stress, improve medication adherence, and enhance daily QoL.

b. Participants emphasized the importance of non-pharmacologic treatment to support COPD management and overall well-being.

- Many participants highlighted the value of non-pharmacologic treatment such as pulmonary rehabilitation and holistic medicine.
- Participants emphasized the need for accessible mental health support to manage the anxiety associated with managing COPD symptoms.

c. Participants emphasized the critical role of accurate diagnosis and understanding the cause in ensuring effective treatment and better patient outcomes.

- Participants stressed that the lack of an early, accurate diagnosis negatively impacted their access to appropriate medications, patient education, and tailored treatment regimens, contributing to disease progression.

- A comprehensive diagnostic evaluation is essential to ensure the timely and effective management of COPD.
- Participants expressed a need for increased provider education on non-smoking-related causes and compounding factors, such as occupational and environmental exposures and adverse health events.

d. Participants recognized the importance of patient and provider education in improving COPD management.

- There is a desire for improved education on proper inhaler and spacer use, including correct techniques for using spacers.
- Participants agreed that COPD education efforts should extend beyond patients to include family members or caregivers.

e. Participants' main treatment goals were to breathe easier, perform activities of daily living without breathlessness, and partake in social activities.

- Breathlessness significantly hindered the participants' capacity to climb stairs, sleep through the night, exercise, and perform household chores.
- When asked about their primary motivation for treatment, many participants prioritized the ability to spend more time with family, including playing with grandchildren.

f. Participants expressed a preference for in-person care while recognizing the benefits of telehealth.

- Participants preferred face-to-face visits with their provider for treatment information.
- Telehealth can provide valuable access to specialists who may not be available locally, as well as facilitate care for individuals with limited mobility.
- Telehealth can potentially assist with the educational aspects of adopting a treatment plan.

Appendix F: Literature Review Search Terms and Strategy

A. Resources Searched

Sigma's Information Specialist searched the following databases for relevant information (see Table F-1).

Table F-1. Databases Searched

Bibliographic Database	Date Limits	Platform/Provider
EMBASE	February 1, 2020, to December 5, 2025	Elsevier
MEDLINE	February 1, 2020, to December 5, 2025	Elsevier
PubMed (in process, publisher, PubMed not MEDLINE record subsets)	February 1, 2020, to December 5, 2025	National Library of Medicine
Gray Literature Resources	**Date Limits**	**Platform/Provider**
Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Center Reports	February 1, 2020, to December 5, 2025	AHRQ
Veterans Affairs Evidence Synthesis Program (VA ESP)	February 1, 2020, to December 5, 2025	VA ESP
Cochrane Database of Systematic Reviews	February 1, 2020, to December 5, 2025	Cochrane Library

B. Search Strategies

The search strategies for bibliographic databases employed combinations of free-text keywords as well as controlled vocabulary terms including, but not limited to, the concepts detailed in Tables F-2 through F-6.

Table F-2. EMBASE and MEDLINE Search Strategy (Embase.com Syntax)

Line No.	Concept	Query	Results
KQ1: For patients being evaluated for COPD, what is the optimal criteria for diagnosing COPD?			
#1	Chronic obstructive lung disease	'chronic obstructive lung disease'/mj	100636
#2	Disease acronyms	aecb:ab,ti OR coad:ab,ti OR cobd:ab,ti OR copd*:ab,ti	136750
#3	Chronic bronchitis	'chronic bronchitis'/exp OR ((chronic* NEAR/3 bronch*):ab,ti)	30727
#4	Emphysema	'emphysema'/exp OR emphysem*:ab,ti	85654
#5	Obstructive lung diseases	(obstruct* NEAR/3 (airflow* OR airway* OR bronch* OR lung* OR pulmonary OR respirat*)):ab,ti	180257
#6	Combined population set	#1 OR #2 OR #3 OR #4 OR #5	385442

Line No.	Concept	Query	Results
#7	Diagnosis	'diagnosis'/mj OR 'diagnostic accuracy'/mj OR 'diagnostic procedure'/mj OR accuracy:ti OR accurate*:ti OR assess*:ti OR diagnos*:ti OR evaluat*:ti OR identif*:ti OR predict*:ti OR screen*:ti OR sensitiv*:ti OR specificity:ti OR valid*:ti	4893507
#8	Comorbidities, COPDgene, smoking history	'comorbidity'/mj OR 'people by smoking status'/exp OR 'co morbid*':ti OR comorbid*:ti OR copdgene*:ti OR smoke*:ti OR smoking:ti	201864
#9	Diagnosis title keywords	diagnos*:ti	1024464
#10	GOLD classification	'global initiative for obstructive lung disease':ti OR gold:ti	57726
#11	Imaging (CT scans)	'computer assisted tomography'/mj OR 'cat scan*':ti OR 'comput* tomograph*':ti OR 'ct scan*':ti OR imaging:ti	645994
#12	Lung function testing	fev1:ti OR 'forced expiratory volume':ti OR (((lung* OR pulmonary OR respiratory) NEAR/3 function* NEAR/3 test*):ti)	6391
#13	Peak expiratory flow	'peak expiratory flow'/mj OR 'peak expiratory flow*':ti	2198
#14	Questionnaires	'questionnaire'/mj OR questionnaire*:ti	87193
#15	Exacerbations	'disease exacerbation'/mj OR exacerbat*:ti	59933
#16	Spirometry	'spirometer'/mj OR 'spirometry'/mj OR spiromet*:ti	11251
#17	Symptom severity	'disease severity'/mj OR 'disease severity assessment'/mj OR 'symptom severity'/mj OR (((copd OR disease* OR symptom*) NEAR/3 sever*):ti)	76873
#18	Combined interventions	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	1961971
#19	Population and diagnosis and interventions	#6 AND #7 AND #18	18882
#20	Populations diagnosis subheadings	'chronic bronchitis'/exp/dm_di OR 'chronic obstructive lung disease'/exp/dm_di OR 'emphysema'/exp/dm_di	24616
#21	Population diagnosis subheadings combined with interventions	#18 AND #20	6397
#22	KQ1 combined results set	#19 OR #21	21847
#23	RCTs	#22 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ab,ti OR 'phase iii':ab,ti OR random*:ab,ti OR rct:ab,ti)	1495

Line No.	Concept	Query	Results
#24	Systematic reviews	#22 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ab,ti OR metaanaly*:ab,ti OR 'meta analy*':ab,ti OR (search*:ab,ti AND (cinahl*:ab,ti OR databases:ab,ti OR ebsco*:ab,ti OR embase*:ab,ti OR medline*:ab,ti OR psychinfo*:ab,ti OR psycinfo*:ab,ti OR 'science direct*':ab,ti OR sciencedirect*:ab,ti OR scopus*:ab,ti OR systematic*:ab,ti OR 'web of knowledge*':ab,ti OR 'web of science':ab,ti)) OR ((systematic* NEAR/3 review*):ab,ti))	525
#25	Observational studies	#22 AND ('cohort analysis'/exp OR 'comparative study'/exp OR 'controlled study'/exp OR 'diagnostic accuracy'/exp OR 'evaluation study'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'observational study'/de OR 'prospective study'/de OR 'sensitivity and specificity'/exp OR 'between groups':ti,ab OR 'case control*':ti,ab OR 'clinical utility':ti,ab OR cohort*:ti,ab OR comparison:ti,ab OR comparative:ti,ab OR 'control group*':ti,ab OR 'controlled study':ti,ab OR 'controlled trial':ti,ab OR 'cross over':ti,ab OR crossover:ti,ab OR 'diagnostic accuracy':ti,ab OR 'double blind':ti,ab OR 'double blinded':ti,ab OR longitudinal:ti,ab OR 'matched controls':ti,ab OR ((observational NEXT/3 study):ti,ab) OR prospective:ti,ab OR sensitivity:ti,ab OR specificity:ab,ti OR versus:ti OR vs:ti)	13015
#26	RCTs, systematic reviews, or observational studies	#23 OR #24 OR #25	13367
#27	Date limit	#26 AND [01-02-2020]/sd NOT [06-12-2025]/sd AND [2020-2025]/py	5538
#28	Remove out of scope publication types	#27 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	4073
#29	Remove animal studies	#28 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti	4028

		OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ab,ti OR patient*:ab,ti)))	
#30	Remove out of scope age ranges	#29 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	3920
#31	Remove out of scope record sources	#30 AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	3736
#32	English language records	#31 AND [english]/lim	2815
KQ2: What modifiable factors predict the outcomes of COPD?			
#33	Chronic obstructive lung disease	'chronic obstructive lung disease'/mj	100636
#34	Disease acronyms	aecb:ab,ti OR coad:ab,ti OR cobd:ab,ti OR copd*:ab,ti	136750
#35	Chronic bronchitis	'chronic bronchitis'/exp OR ((chronic* NEAR/3 bronch*):ab,ti)	30727
#36	Emphysema	'emphysema'/exp OR emphysem*:ab,ti	85654
#37	Obstructive lung diseases	(obstruct* NEAR/3 (airflow* OR airway* OR bronch* OR lung* OR pulmonary OR respirat*)):ab,ti	180257
#38	Combined population set	#33 OR #34 OR #35 OR #36 OR #37	385035
#39	Modifiable risk factors	anemia:ab,ti OR anemic:ab,ti OR cannabis:ab,ti OR cormorbid*:ab,ti OR exercis*:ab,ti OR 'heart failure':ab,ti OR infection*:ab,ti OR 'kidney disease*':ab,ti OR 'lung cancer':ab,ti OR malnourish*:ab,ti OR malnutrition:ab,ti OR marijuana:ab,ti OR 'mental health*':ab,ti OR nutrition:ab,ti OR obes*:ab,ti OR 'over weight':ab,ti OR overweight:ab,ti OR oxygen:ab,ti OR 'physical activit*':ab,ti OR 'risk factor*':ab,ti OR ((smoke* OR smoking) NEAR/3 (expos* OR history OR status)):ab,ti OR 'secondhand smok*':ab,ti OR sleep*:ab,ti OR 'thyroid disease*':ab,ti OR vaccinat*:ab,ti OR vape*:ab,ti OR vaping:ab,ti OR ((childhood NEAR/3 (condition* OR disease* OR illness*)):ab,ti)	7913075
#40	Risk factors	'risk factor'/exp/mj OR ((risk* NEAR/3 (factor* OR modif*)):ti)	309102
#41	Combine population and risk factors	#38 AND #39 AND #40	3421

Line No.	Concept	Query	Results
#42	RCTs	#41 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ab,ti OR 'phase iii':ab,ti OR random*:ab,ti OR rct:ab,ti)	248
#43	Systematic reviews	#41 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ab,ti OR metaanaly*:ab,ti OR 'meta analy*':ab,ti OR (search*:ab,ti AND (cinahl*:ab,ti OR databases:ab,ti OR ebsco*:ab,ti OR embase*:ab,ti OR medline*:ab,ti OR psychinfo*:ab,ti OR psycinfo*:ab,ti OR 'science direct*':ab,ti OR sciencedirect*:ab,ti OR scopus*:ab,ti OR systematic*:ab,ti OR 'web of knowledge*':ab,ti OR 'web of science':ab,ti)) OR ((systematic* NEAR/3 review*):ab,ti))	228
#44	Observational studies	#41 AND ('cohort analysis'/exp OR 'comparative study'/exp OR 'controlled study'/exp OR 'diagnostic accuracy'/exp OR 'evaluation study'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'observational study'/de OR 'prospective study'/de OR 'sensitivity and specificity'/exp OR 'between groups':ti,ab OR 'case control*':ti,ab OR 'clinical utility':ti,ab OR cohort*:ti,ab OR comparison:ti,ab OR comparative:ti,ab OR 'control group*':ti,ab OR 'controlled study':ti,ab OR 'controlled trial':ti,ab OR 'cross over':ti,ab OR crossover:ti,ab OR 'diagnostic accuracy':ti,ab OR 'double blind':ti,ab OR 'double blinded':ti,ab OR longitudinal:ti,ab OR 'matched controls':ti,ab OR ((observational NEXT/3 study):ti,ab) OR prospective:ti,ab OR sensitivity:ti,ab OR specificity:ab,ti OR versus:ti OR vs:ti)	2818
#45	RCTs, systematic reviews, or observational studies	#42 OR #43 OR #44	2938
#46	Date limit	#45 AND [01-02-2020]/sd NOT [06-12-2025]/sd AND [2020-2025]/py	1167
#47	Remove out of scope publication types	#46 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	1325
#48	Remove animal studies	#47 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti	1320

		OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ab,ti OR patient*:ab,ti)))	
#49	Remove out of scope age ranges	#48 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	1288
#50	Remove out of scope record sources	#49 AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	1265
#51	English language records	#50 AND [english]/lim	1293
KQ3: What tests and frequency of testing are effective for monitoring and management of COPD?			
#52	Chronic obstructive lung disease	'chronic obstructive lung disease'/mj	100636
#53	Disease acronyms	aecb:ab,ti OR coad:ab,ti OR cobd:ab,ti OR copd*:ab,ti	136750
#54	Chronic bronchitis	'chronic bronchitis'/exp OR ((chronic* NEAR/3 bronch*):ab,ti)	30727
#55	Emphysema	'emphysema'/exp OR emphysem*:ab,ti	85654
#56	Obstructive lung diseases	(obstruct* NEAR/3 (airflow* OR airway* OR bronch* OR lung* OR pulmonary OR respirat*)):ab,ti	179400
#57	Combined population set	#52 OR #53 OR #54 OR #55 OR #56	385442
#58	BODE index	'bode index':ab,ti OR 'body-mass index, airflow obstruction, dyspnea, and exercise':ab,ti	1209
#59	Depression and anxiety screening	((anxiety OR depress*) NEAR/5 (assess* OR screen* OR test*)):ab,ti	116296
#60	Eosinophil count/eosinophilia	(eosinophil* NEAR/5 (assess* OR count* OR screen* OR test*)):ab,ti	23712
#61	Frequency of testing	(frequen* NEAR/3 (assess* OR screen* OR test*)):ab,ti	63231
#62	Pulse oximetry	'pulse oximet*':ab,ti	19738
#63	Periodic questionnaires	'camberwell assessment of need':ab,ti OR 'copd assessment test':ab,ti OR mmrc:ab,ti OR 'modified medical research council dyspnea scale':ab,ti OR 'st. georges respiratory questionnaire':ab,ti OR sgrq:ab,ti	11872
#64	Spirometry	'spirometer'/exp OR 'spirometry'/exp OR spiromet*:ab,ti	84661
#65	Tests	test*:ti	656357

Line No.	Concept	Query	Results
#66	Combine tests	#58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65	951197
#67	Combine COPD and tests	#57 AND #66	45877
#68	RCTs	#67 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ab,ti OR 'phase iii':ab,ti OR random*:ab,ti OR rct:ab,ti)	7213
#69	Systematic reviews	#67 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ab,ti OR metaanaly*:ab,ti OR 'meta analy*':ab,ti OR (search*:ab,ti AND (cinahl*:ab,ti OR databases:ab,ti OR ebsco*:ab,ti OR embase*:ab,ti OR medline*:ab,ti OR psychinfo*:ab,ti OR psycinfo*:ab,ti OR 'science direct*':ab,ti OR sciencedirect*:ab,ti OR scopus*:ab,ti OR systematic*:ab,ti OR 'web of knowledge*':ab,ti OR 'web of science':ab,ti)) OR ((systematic* NEAR/3 review*):ab,ti))	1539
#70	RCTs or systematic reviews	#68 OR #69	8073
#71	Date limit	#70 AND [01-02-2020]/sd NOT [06-12-2025]/sd AND [2020-2025]/py	2989
#72	Remove out of scope publication types	#71 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	2075
#73	Remove animal studies	#72 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ab,ti OR patient*:ab,ti)))	2065
#74	Remove out of scope age ranges	#73 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	2022

#75	Remove out of scope record sources	#74 AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	1730
#76	English language records	#75 AND [english]/lim	1534
Line No.	**Concept**	**Query**	**Results**
KQ4: In patients without a previous history of exacerbations of COPD, what is the comparative effectiveness of pharmacotherapy alone or in combination with the following drug classes to improve outcomes: SABA, LABA, LAMA, short/long-acting anticholinergics, mucolytics, biologics, ICS, PDE agents? **KQ5: In patients with previous exacerbations of COPD, what is the comparative effectiveness of pharmacotherapy alone or in combination with the following drug classes to improve outcomes: SABA, LABA, LAMA, short/long-acting anticholinergics, mucolytics, biologics, ICS, PDE agents?** **KQ6: Does pharmacotherapy have increased benefits or harms in specific subpopulations of patients with COPD?**			
#77	Chronic obstructive lung disease	'chronic obstructive lung disease'/mj	100636
#78	Disease acronyms	aecb:ab,ti OR coad:ab,ti OR cobd:ab,ti OR copd*:ab,ti	136750
#79	Chronic bronchitis	'chronic bronchitis'/exp OR ((chronic* NEAR/3 bronch*):ab,ti)	30727
#80	Emphysema	'emphysema'/exp OR emphysem*:ab,ti	85654
#81	Obstructive lung diseases	(obstruct* NEAR/3 (airflow* OR airway* OR bronch* OR lung* OR pulmonary OR respirat*)):ab,ti	179400
#82	Combined population set	#77 OR #78 OR #79 OR #80 OR #81	385035
#83	Anticholinergics	'cholinergic receptor blocking agent'/exp OR (((acetylcholine OR cholinergic) NEAR/3 (antagonist* OR block*)):ab,ti) OR 'anti cholinergic*':ab,ti OR anticholinergic*:ab,ti	416719
#84	Beta agonists	'beta 2 adrenergic receptor stimulating agent'/exp OR 'long acting beta 2 agonist'/exp OR 'short acting beta 2 agonist'/exp OR laba:ab,ti OR labas:ab,ti OR 'long-acting beta* agonist*':ab,ti OR 'long-acting beta 2 agonist*':ab,ti OR 'longacting beta* agonist*':ab,ti OR 'longacting beta 2 agonist*':ab,ti OR saba:ab,ti OR sabas:ab,ti OR 'short-acting beta*-agonist*':ab,ti OR 'short-acting beta 2-agonist*':ab,ti OR 'shortacting beta* agonist*':ab,ti OR 'shortacting beta 2 agonist*':ab,ti	110177
#85	Biologics	'biological product'/exp OR biologic:ab,ti OR biologics:ab,ti	1197613
#86	Combination drug therapy	'drug combination'/exp OR 'polypharmacy'/exp OR '1 drug':ab,ti OR '2 drug*':ab,ti OR '3 drug*':ab,ti OR '4 drug*':ab,ti OR 'drug* combin*':ab,ti OR 'multi* drug*':ab,ti OR multidrug*:ab,ti OR 'one drug*':ab,ti OR polypharm*:ab,ti OR polypill:ab,ti OR polytherap*:ab,ti OR 'two drug':ab,ti OR (((single OR double OR dual OR	764133

		quadruple OR subsequent* OR triple) NEAR/2 (agent* OR combo* OR combin* OR drug* OR medicat* OR pharma* OR regimen* OR therap*)):ab,ti)	
#87	Ensifentrine	ensifentrine:ab,ti	149
#88	Inhaled corticosteroids	'corticosteroid'/exp OR corticosteroid*:ab,ti	1378529
#89	Mucolytics	'mucolytic agent'/exp OR mucolytic*:ab,ti	117437
#90	Roflumilast	'roflumilast'/exp OR roflumilast:ab,ti	3161
#91	Combined pharmacologic interventions	#83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90	3656978
#92	Pharmacologic interventions combined with COPD	#82 AND #91	71082
#93	Date limit	#92 AND [01-02-2020]/sd NOT [06-12-2025]/sd AND [2020-2025]/py	23271
#94	Remove out of scope publication types	#93 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	13364
#95	Remove animal studies	#94 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ab,ti OR patient*:ab,ti)))	12816
#96	Remove out of scope age ranges	#95 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	12432
#97	Remove out of scope record sources	#96 AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	11873

#98	English language records	#97 AND [english]/lim	11537
#99	RCTs	#98 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ab,ti OR 'phase iii':ab,ti OR random*:ab,ti OR rct:ab,ti)	1650
#100	Systematic Reviews	#98 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ab,ti OR metaanaly*:ab,ti OR 'meta analy*':ab,ti OR (search*:ab,ti AND (cinahl*:ab,ti OR databases:ab,ti OR ebsco*:ab,ti OR embase*:ab,ti OR medline*:ab,ti OR psychinfo*:ab,ti OR psycinfo*:ab,ti OR 'science direct*':ab,ti OR sciencedirect*:ab,ti OR scopus*:ab,ti OR systematic*:ab,ti OR 'web of knowledge*':ab,ti OR 'web of science':ab,ti)) OR ((systematic* NEAR/3 review*):ab,ti))	850
#101	RCTs or systematic reviews	#99 OR #100	1545
KQ7: In patients with confirmed COPD experiencing an acute exacerbation, what is the evidence that administration of short-term antibiotics and/or systemic steroids are more effective than placebo in improving outcomes?			
#102	Chronic obstructive lung disease	'chronic obstructive lung disease'/mj	100636
#103	Disease acronyms	aecb:ab,ti OR coad:ab,ti OR cobd:ab,ti OR copd*:ab,ti	136750
#104	Chronic bronchitis	'chronic bronchitis'/exp OR ((chronic* NEAR/3 bronch*):ab,ti)	30727
#105	Emphysema	'emphysema'/exp OR emphysem*:ab,ti	85654
#106	Obstructive lung diseases	(obstruct* NEAR/3 (airflow* OR airway* OR bronch* OR lung* OR pulmonary OR respirat*)):ab,ti	179400
#107	Combined population set	#102 OR #103 OR #104 OR #105 OR #106	385442
#108	Exacerbations	'disease exacerbation'/exp OR exacerbat*:ab,ti	443164
#109	Antibiotics	'antibiotic agent'/exp OR amoxicillin:ab,ti OR 'anti-bacterial*':ab,ti OR antibacterial*:ab,ti OR antibiotic*:ab,ti OR 'anti infectiv*':ab,ti OR antiinfectiv*:ab,ti OR 'anti-mycobacterial*':ab,ti OR antimycobacterial*:ab,ti OR bacteriocid*:ab,ti OR clarithromycin:ab,ti OR doxycycline:ab,ti OR erythromycin:ab,ti OR levofloxacin:ab,ti OR moxifloxacin:ab,ti	2506320
#110	Steroids	'corticosteroid'/exp OR corticosteroid*:ab,ti OR glucocorticoid*:ab,ti OR prednisone*:ab,ti OR steroid*:ab,ti	1690668

#111	Combine	#107 AND #108 AND (#109 OR #110)	19342
#112	Date limit	#111 AND [01-02-2020]/sd NOT [06-12-2025]/sd AND [2020-2025]/py	6232
#113	Remove out of scope publication types	#112 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	3617
#114	Remove animal studies	#113 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ab,ti OR patient*:ab,ti)))	3560
#115	Remove out of scope age ranges	#114 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	3500
#116	Remove out of scope record sources	#115 AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	3312
#117	English language records	#116 AND [english]/lim	3203
#118	RCTs	#117 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ab,ti OR 'phase iii':ab,ti OR random*:ab,ti OR rct:ab,ti)	600
#119	Systematic Reviews	#117 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ab,ti OR metaanaly*:ab,ti OR 'meta analy*':ab,ti OR (search*:ab,ti AND (cinahl*:ab,ti OR databases:ab,ti OR ebsco*:ab,ti OR embase*:ab,ti OR medline*:ab,ti OR psychinfo*:ab,ti OR psycinfo*:ab,ti OR 'science direct*':ab,ti OR sciencedirect*:ab,ti OR scopus*:ab,ti OR systematic*:ab,ti OR 'web of knowledge*':ab,ti OR 'web of science':ab,ti)) OR ((systematic* NEAR/3 review*):ab,ti))	275
#120	RCTs or systematic reviews	#118 OR #119	669

Line No.	Concept	Query	Results
KQ8: In patients with confirmed COPD treated with long-term inhaled corticosteroids, what characteristics identify patients who can have ICS discontinued?			
#121	Chronic obstructive lung disease	'chronic obstructive lung disease'/mj	100636
#122	Disease acronyms	aecb:ab,ti OR coad:ab,ti OR cobd:ab,ti OR copd*:ab,ti	136750
#123	Chronic bronchitis	'chronic bronchitis'/exp OR ((chronic* NEAR/3 bronch*):ab,ti)	30806
#124	Emphysema	'emphysema'/exp OR emphysem*:ab,ti	85959
#125	Obstructive lung diseases	(obstruct* NEAR/3 (airflow* OR airway* OR bronch* OR lung* OR pulmonary OR respirat*)):ab,ti	180257
#126	Combined population set	#121 OR #122 OR #123 OR #124 OR #125	386311
#127	Steroids	'corticosteroid'/exp OR corticosteroid*:ab,ti OR glucocorticoid*:ab,ti OR prednisone*:ab,ti OR steroid*:ab,ti	1693186
#128	Discontinuation	discontin*:ab,ti OR end*:ab,ti OR stop*:ab,ti OR withdraw*:ab,ti	5666306
#129	Combine	#126 AND #127 AND #128	8592
#130	RCTs	#129 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ab,ti OR 'phase iii':ab,ti OR random*:ab,ti OR rct:ab,ti)	2067
#131	Systematic reviews	#129 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ab,ti OR metaanaly*:ab,ti OR 'meta analy*':ab,ti OR (search*:ab,ti AND (cinahl*:ab,ti OR databases:ab,ti OR ebsco*:ab,ti OR embase*:ab,ti OR medline*:ab,ti OR psychinfo*:ab,ti OR psycinfo*:ab,ti OR 'science direct*':ab,ti OR sciencedirect*:ab,ti OR scopus*:ab,ti OR systematic*:ab,ti OR 'web of knowledge*':ab,ti OR 'web of science':ab,ti)) OR ((systematic* NEAR/3 review*):ab,ti))	395
#132	Observational studies	#129 AND ('cohort analysis'/exp OR 'comparative study'/exp OR 'controlled study'/exp OR 'diagnostic accuracy'/exp OR 'evaluation study'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'observational study'/de OR 'prospective study'/de OR 'sensitivity and specificity'/exp OR 'between groups':ti,ab OR 'case control*':ti,ab OR 'clinical utility':ti,ab OR cohort*:ti,ab OR comparison:ti,ab OR comparative:ti,ab OR 'control group*':ti,ab OR 'controlled study':ti,ab OR 'controlled trial':ti,ab OR 'cross over':ti,ab OR crossover:ti,ab OR 'diagnostic accuracy':ti,ab OR 'double blind':ti,ab OR 'double blinded':ti,ab OR longitudinal:ti,ab OR 'matched controls':ti,ab OR ((observational NEXT/3 study):ti,ab) OR	4564

		prospective:ti,ab OR sensitivity:ti,ab OR specificity:ab,ti OR versus:ti OR vs:ti)	
#133	RCTs, systematic reviews, or observational studies	#130 OR #131 OR #132	4848
#134	Date limit	#133 AND [01-02-2020]/sd NOT [06-12-2025]/sd AND [2020-2025]/py	1912
#135	Remove out of scope publication types	#134 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	1258
#136	Remove animal studies	#135 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ab,ti OR patient*:ab,ti)))	1232
#137	Remove out of scope age ranges	#136 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	1198
#138	Remove out of scope record sources	#137 AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	1078
#139	English language records	#138 AND [english]/lim	703
KQ9: In patients with confirmed COPD does the use of spacers or other optimization of inhaler technique improve patient adherence and outcomes?			
#140	Chronic obstructive lung disease	'chronic obstructive lung disease'/mj	100636
#141	Disease acronyms	aecb:ab,ti OR coad:ab,ti OR cobd:ab,ti OR copd*:ab,ti	136750
#142	Chronic bronchitis	'chronic bronchitis'/exp OR ((chronic* NEAR/3 bronch*):ab,ti)	30727
#143	Emphysema	'emphysema'/exp OR emphysem*:ab,ti	85654

Line No.	Concept	Query	Results
#144	Obstructive lung diseases	(obstruct* NEAR/3 (airflow* OR airway* OR bronch* OR lung* OR pulmonary OR respirat*)):ab,ti	179400
#145	Combined population set	#140 OR #141 OR #142 OR #143 OR #144	385442
#146	Combine population with interventions	#145 AND ('inhaler'/exp OR 'metered dose inhaler'/exp OR 'nebulizer'/exp OR 'adherence device*':ab,ti OR dpi:ab,ti OR 'dry powder':ab,ti OR inhaler*:ab,ti OR 'inhalation therap*':ab,ti OR 'metered dose':ab,ti OR mdi:ab,ti OR nebuliz*:ab,ti OR optimiz*:ab,ti OR 'propeller device*':ab,ti OR 'soft mist':ab,ti OR spacer*:ab,ti)	8628
#147	Date limit	#146 AND [01-02-2020]/sd NOT [06-12-2025]/sd AND [2020-2025]/py	26863
#148	Remove out of scope publication types	#147 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	20434
#149	Remove animal studies	#148 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ab,ti OR patient*:ab,ti)))	17064
#150	Remove out of scope age ranges	#149 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	16213
#151	Remove out of scope record sources	#150 AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	15592
#152	English language records	#151 AND [english]/lim	15305
#153	RCTs	#152 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ab,ti OR 'phase iii':ab,ti OR random*:ab,ti OR rct:ab,ti)	1323

Line No.	Concept	Query	Results
#154	Systematic Reviews	#152 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ab,ti OR metaanaly*:ab,ti OR 'meta analy*':ab,ti OR (search*:ab,ti AND (cinahl*:ab,ti OR databases:ab,ti OR ebsco*:ab,ti OR embase*:ab,ti OR medline*:ab,ti OR psychinfo*:ab,ti OR psycinfo*:ab,ti OR 'science direct*':ab,ti OR sciencedirect*:ab,ti OR scopus*:ab,ti OR systematic*:ab,ti OR 'web of knowledge*':ab,ti OR 'web of science':ab,ti)) OR ((systematic* NEAR/3 review*):ab,ti))	469
#155	RCTs or systematic reviews	#153 OR #154	1681
KQ10: In patients with COPD with refractory symptoms, is palliative care effective in improving COPD outcomes?			
#156	Chronic obstructive lung disease	'chronic obstructive lung disease'/mj	100636
#157	Disease acronyms	aecb:ab,ti OR coad:ab,ti OR cobd:ab,ti OR copd*:ab,ti	136750
#158	Chronic bronchitis	'chronic bronchitis'/exp OR ((chronic* NEAR/3 bronch*):ab,ti)	30727
#159	Emphysema	'emphysema'/exp OR emphysem*:ab,ti	85654
#160	Obstructive lung diseases	(obstruct* NEAR/3 (airflow* OR airway* OR bronch* OR lung* OR pulmonary OR respirat*)):ab,ti	179400
#161	Combined population set	#156 OR #157 OR #158 OR #159 OR #160	385442
#162	Palliative care interventions	'anti depressant*':ab,ti OR antidepressant*:ab,ti OR anxiolytic*:ab,ti OR fan:ab,ti OR fans:ab,ti OR morphine:ab,ti OR ((('multi disciplinary' OR multidisciplinary) NEAR/3 (care OR team*)):ab,ti) OR ssri*:ab,ti OR 'serotonin uptake inhibitor*':ab,ti	346509
#163	Palliative care	'palliative therapy'/exp OR 'comfort care':ab,ti OR palliativ*:ab,ti OR 'supportive care':ab,ti	262031
#164	Combine COPD with palliative care interventions	#161 AND (#162 OR #163)	8857
#165	Date limit	#164 AND [01-02-2020]/sd NOT [06-12-2025]/sd AND [2020-2025]/py	3511
#166	Remove out of scope publication types	#165 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR	1657

		[letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	
#167	Remove animal studies	#166 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ab,ti OR patient*:ab,ti)))	1640
#168	Remove out of scope age ranges	#167 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	1580
#169	Remove out of scope record sources	#168 AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	1476
#170	English language records	#169 AND [english]/lim	1426
#171	RCTs	#170 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ab,ti OR 'phase iii':ab,ti OR random*:ab,ti OR rct:ab,ti)	177
#172	Systematic Reviews	#170 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ab,ti OR metaanaly*:ab,ti OR 'meta analy*':ab,ti OR (search*:ab,ti AND (cinahl*:ab,ti OR databases:ab,ti OR ebsco*:ab,ti OR embase*:ab,ti OR medline*:ab,ti OR psychinfo*:ab,ti OR psycinfo*:ab,ti OR 'science direct*':ab,ti OR sciencedirect*:ab,ti OR scopus*:ab,ti OR systematic*:ab,ti OR 'web of knowledge*':ab,ti OR 'web of science':ab,ti)) OR ((systematic* NEAR/3 review*):ab,ti))	151
KQ11: In patients with confirmed COPD, what is the comparative effectiveness of in person vs. telerehab (pulmonary rehab) in improving COPD outcomes?			
#174	Chronic obstructive lung disease	'chronic obstructive lung disease'/mj	100636
#175	Disease acronyms	aecb:ab,ti OR coad:ab,ti OR cobd:ab,ti OR copd*:ab,ti	136750
#176	Chronic bronchitis	'chronic bronchitis'/exp OR ((chronic* NEAR/3 bronch*):ab,ti)	30727
#177	Emphysema	'emphysema'/exp OR emphysem*:ab,ti	85654
#178	Obstructive lung diseases	(obstruct* NEAR/3 (airflow* OR airway* OR bronch* OR lung* OR pulmonary OR respirat*)):ab,ti	179400
#179	Combined population set	#174 OR #175 OR #176 OR #177 OR #178	385442

Line No.	Concept	Query	Results
#180	Pulmonary rehabilitation	'pulmonary rehabilitation'/exp OR ((('air flow*' OR airflow* OR 'air way*' OR airway* OR bronch* OR lung* OR pulmonary OR respirat*) NEAR/5 rehab*):ab,ti)	18354
#181	Telerehabilitation	((computer* OR mobile OR phone OR smartphone* OR web*) NEAR/3 (app OR apps OR application*)):ab,ti	58162
#182	Telerehabilitation	cellphone*:ab,ti OR chat*:ab,ti OR computer*:ab,ti OR device*:ab,ti OR 'home based':ab,ti OR phone*:ab,ti OR remote*:ab,ti OR smartphone*:ab,ti OR tablet*:ab,ti OR telephone*:ab,ti OR 'video conferenc*':ab,ti OR virtual*:ab,ti OR 'web site*':ab,ti OR website*:ab,ti	2137788
#183	Telerehabilitation	#180 AND (#181 OR #182)	1988
#184	Telerehabilitation	'telehealth'/exp OR 'tele health*':ab,ti OR telehealth*:ab,ti OR 'tele medicine':ab,ti OR telemedicine:ab,ti OR 'tele rehab*':ab,ti OR telerehab*:ab,ti	128137
#185	Combine COPD with telerehabilitation interventions	#179 AND (#183 OR #184)	3751
#186	RCTs	#185 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ab,ti OR 'phase iii':ab,ti OR random*:ab,ti OR rct:ab,ti)	1089
#187	Systematic Reviews	#185 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ab,ti OR metaanaly*:ab,ti OR 'meta analy*':ab,ti OR (search*:ab,ti AND (cinahl*:ab,ti OR databases:ab,ti OR ebsco*:ab,ti OR embase*:ab,ti OR medline*:ab,ti OR psychinfo*:ab,ti OR psycinfo*:ab,ti OR 'science direct*':ab,ti OR sciencedirect*:ab,ti OR scopus*:ab,ti OR systematic*:ab,ti OR 'web of knowledge*':ab,ti OR 'web of science':ab,ti)) OR ((systematic* NEAR/3 review*):ab,ti))	433
#188	RCTs or systematic reviews	#186 OR #187	1332
#189	Date limit	#188 AND [01-02-2020]/sd NOT [06-12-2025]/sd AND [2020-2025]/py	687
#190	Remove out of scope publication types	#189 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	553
#191	Remove animal studies	#190 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR	553

		feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ab,ti OR patient*:ab,ti)))	
#192	Remove out of scope age ranges	#191 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	551
#193	Remove out of scope record sources	#192 AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	437
#194	English language limit	#193 AND [english]/lim	339
KQ12: In patients with confirmed COPD, does caregiver education and support improve patient and caregiver outcomes?			
#195	Chronic obstructive lung disease	'chronic obstructive lung disease'/mj	100636
#196	Disease acronyms	aecb:ab,ti OR coad:ab,ti OR cobd:ab,ti OR copd*:ab,ti	136750
#197	Chronic bronchitis	'chronic bronchitis'/exp OR ((chronic* NEAR/3 bronch*):ab,ti)	30727
#198	Emphysema	'emphysema'/exp OR emphysem*:ab,ti	85654
#199	Obstructive lung diseases	(obstruct* NEAR/3 (airflow* OR airway* OR bronch* OR lung* OR pulmonary OR respirat*)):ab,ti	179400
#200	Combined population set	#195 OR #196 OR #197 OR #198 OR #199	385442
#201	Caregiver education, support interventions	'caregiver support'/exp OR ((('care giver*' OR caregiver* OR family OR families OR patient*) NEAR/2 (educat* OR info* OR learn* OR support* OR teach* OR train*)):ab,ti)	349720
#202	Combine COPD with caregiver education interventions	#200 AND #201	6325
#203	RCTs	#202 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ab,ti OR 'phase iii':ab,ti OR random*:ab,ti OR rct:ab,ti)	1298
#204	Systematic Reviews	#202 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ab,ti OR metaanaly*:ab,ti OR 'meta analy*':ab,ti OR (search*:ab,ti AND (cinahl*:ab,ti OR databases:ab,ti OR ebsco*:ab,ti OR embase*:ab,ti OR	403

		medline*:ab,ti OR psychinfo*:ab,ti OR psycinfo*:ab,ti OR 'science direct*':ab,ti OR sciencedirect*:ab,ti OR scopus*:ab,ti OR systematic*:ab,ti OR 'web of knowledge*':ab,ti OR 'web of science':ab,ti)) OR ((systematic* NEAR/3 review*):ab,ti))	
#205	RCTs or systematic reviews	#203 OR #204	1536
#206	Date limit	#205 AND [01-02-2020]/sd NOT [06-12-2025]/sd AND [2020-2025]/py	549
#207	Remove out of scope publication types	#206 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	438
#208	Remove animal studies	#207 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ab,ti OR patient*:ab,ti)))	437
#209	Remove out of scope age ranges	#208 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	431
#210	Remove out of scope record sources	#209 AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	296
#211	English language limit	#210 AND [english]/lim	217
Combine all KQs			
#212	Combine all KQ results sets	#32 OR #51 OR #76 OR #101 OR #120 OR #139 OR #155 OR #173 OR #194 OR #211	7439

Table F-3. PubMed Search Strategy (PubMed Syntax)

Search No.	Query	Results
KQ1	(((((("pulmonary disease, chronic obstructive"[MeSH Major Topic] OR ("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract]) OR ("bronchitis, chronic"[MeSH Terms] OR "chronic	473

Search No.	Query	Results
	bronchitis"[Title/Abstract]) OR ("Pulmonary Emphysema"[MeSH Terms] OR "emphysem*"[Title/Abstract]) OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("Diagnosis"[MeSH Major Topic] OR "diagnostic tests, routine"[MeSH Terms] OR "accuracy"[Title] OR "accurate*"[Title] OR "assess*"[Title] OR "diagnos*"[Title] OR "evaluat*"[Title] OR "identif*"[Title] OR "predict*"[Title] OR "screen*"[Title] OR "sensitiv*"[Title] OR "specificity"[Title] OR "valid*"[Title]) AND ("co morbid*"[Title] OR "comorbid*"[Title] OR "copdgene*"[Title] OR "smoke*"[Title] OR "smoking"[Title] OR "diagnos*"[Title] OR ("global initiative for obstructive lung disease"[Title] OR "gold"[Title]) OR ("tomography, x ray computed"[MeSH Terms] OR "cat scan*"[Title] OR "comput* tomograph*"[Title] OR "ct scan*"[Title] OR "imaging"[Title]) OR ("fev1"[Title] OR "forced expiratory volume"[Title] OR "lung function test*"[Title] OR "pulmonary function test*"[Title] OR "respiratory function test*"[Title]) OR ("Peak Expiratory Flow Rate"[MeSH Terms] OR "peak expiratory flow*"[Title]) OR ("Surveys and Questionnaires"[MeSH Terms] OR "questionnaire*"[Title] OR "survey*"[Title]) OR ("Disease Progression"[MeSH Terms] OR "Symptom Flare Up"[MeSH Terms] OR "exacerbat*"[Title]) OR ("Spirometry"[MeSH Terms] OR "spiromet*"[Title]) OR ("Patient Acuity"[MeSH Terms] OR "disease severity"[Title] OR "symptom severity"[Title]))) OR ("pulmonary disease, chronic obstructive/classification"[MeSH Terms] OR "pulmonary disease, chronic obstructive/diagnosis"[MeSH Terms] OR "pulmonary disease, chronic obstructive/diagnostic imaging"[MeSH Terms] OR "bronchitis, chronic/classification"[MeSH Terms] OR "bronchitis, chronic/diagnosis"[MeSH Terms] OR "bronchitis, chronic/diagnostic imaging"[MeSH Terms] OR "pulmonary emphysema/classification"[MeSH Terms] OR "pulmonary emphysema/diagnosis"[MeSH Terms] OR "pulmonary emphysema/diagnostic imaging"[MeSH Terms])) AND ((((((("random sample"[All Fields] AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomization"[All Fields]) AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomized controlled trial"[All Fields]) AND "exp"[All Fields]) OR "phase 3"[Title/Abstract] OR "phase iii"[Title/Abstract] OR "random*"[Title/Abstract] OR "rct"[Title/Abstract])) OR ((((("pulmonary disease, chronic obstructive"[MeSH Major Topic] OR ("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract]) OR ("bronchitis, chronic"[MeSH Terms] OR "chronic bronchitis"[Title/Abstract]) OR ("Pulmonary Emphysema"[MeSH Terms] OR "emphysem*"[Title/Abstract]) OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("Diagnosis"[MeSH Major Topic] OR "diagnostic tests, routine"[MeSH Terms] OR "accuracy"[Title] OR "accurate*"[Title] OR "assess*"[Title] OR "diagnos*"[Title] OR "evaluat*"[Title] OR "identif*"[Title] OR "predict*"[Title] OR "screen*"[Title] OR "sensitiv*"[Title] OR "specificity"[Title] OR "valid*"[Title]) AND ("co morbid*"[Title] OR "comorbid*"[Title] OR "copdgene*"[Title] OR "smoke*"[Title] OR "smoking"[Title] OR "diagnos*"[Title] OR ("global initiative for obstructive lung disease"[Title] OR "gold"[Title]) OR ("tomography, x ray computed"[MeSH Terms] OR "cat scan*"[Title] OR "comput* tomograph*"[Title] OR "ct scan*"[Title] OR "imaging"[Title]) OR ("fev1"[Title] OR "forced expiratory volume"[Title] OR "lung function test*"[Title] OR "pulmonary function test*"[Title] OR "respiratory function test*"[Title]) OR ("Peak Expiratory Flow Rate"[MeSH Terms] OR "peak expiratory flow*"[Title]) OR ("Surveys and Questionnaires"[MeSH Terms] OR "questionnaire*"[Title] OR "survey*"[Title]) OR ("Disease Progression"[MeSH Terms] OR "Symptom Flare Up"[MeSH Terms] OR "exacerbat*"[Title]) OR ("Spirometry"[MeSH Terms] OR "spiromet*"[Title]) OR ("Patient Acuity"[MeSH Terms] OR "disease severity"[Title] OR "symptom severity"[Title]))) OR ("pulmonary disease, chronic obstructive/classification"[MeSH	

Search No.	Query	Results
	Terms] OR "pulmonary disease, chronic obstructive/diagnosis"[MeSH Terms] OR "pulmonary disease, chronic obstructive/diagnostic imaging"[MeSH Terms] OR "bronchitis, chronic/classification"[MeSH Terms] OR "bronchitis, chronic/diagnosis"[MeSH Terms] OR "bronchitis, chronic/diagnostic imaging"[MeSH Terms] OR "pulmonary emphysema/classification"[MeSH Terms] OR "pulmonary emphysema/diagnosis"[MeSH Terms] OR "pulmonary emphysema/diagnostic imaging"[MeSH Terms])) AND ("cochrane*"[Title/Abstract] OR "metaanaly*"[Title/Abstract] OR "meta analy*"[Title/Abstract] OR ("search*"[Title/Abstract] AND ("cinahl*"[Title/Abstract] OR "databases"[Title/Abstract] OR "ebsco*"[Title/Abstract] OR "embase*"[Title/Abstract] OR "medline"[Title/Abstract] OR "psychinfo*"[Title/Abstract] OR "psycinfo*"[Title/Abstract] OR "science direct*"[Title/Abstract] OR "sciencedirect*"[Title/Abstract] OR "scopus*"[Title/Abstract] OR "systematic review*"[Title/Abstract] OR "web of knowledge*"[Title/Abstract] OR "web of science"[Title/Abstract])) OR "systematic"[Title])) OR ((((("pulmonary disease, chronic obstructive"[MeSH Major Topic] OR ("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract]) OR ("bronchitis, chronic"[MeSH Terms] OR "chronic bronchitis"[Title/Abstract]) OR ("Pulmonary Emphysema"[MeSH Terms] OR "emphysem*"[Title/Abstract]) OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("Diagnosis"[MeSH Major Topic] OR "diagnostic tests, routine"[MeSH Terms] OR "accuracy"[Title] OR "accurate*"[Title] OR "assess*"[Title] OR "diagnos*"[Title] OR "evaluat*"[Title] OR "identif*"[Title] OR "predict*"[Title] OR "screen*"[Title] OR "sensitiv*"[Title] OR "specificity"[Title] OR "valid*"[Title]) AND ("co morbid*"[Title] OR "comorbid*"[Title] OR "copdgene*"[Title] OR "smoke*"[Title] OR "smoking"[Title] OR "diagnos*"[Title] OR ("global initiative for obstructive lung disease"[Title] OR "gold"[Title]) OR ("tomography, x ray computed"[MeSH Terms] OR "cat scan*"[Title] OR "comput* tomograph*"[Title] OR "ct scan*"[Title] OR "imaging"[Title]) OR ("fev1"[Title] OR "forced expiratory volume"[Title] OR "lung function test*"[Title] OR "pulmonary function test*"[Title] OR "respiratory function test*"[Title]) OR ("Peak Expiratory Flow Rate"[MeSH Terms] OR "peak expiratory flow*"[Title]) OR ("Surveys and Questionnaires"[MeSH Terms] OR "questionnaire*"[Title] OR "survey*"[Title]) OR ("Disease Progression"[MeSH Terms] OR "Symptom Flare Up"[MeSH Terms] OR "exacerbat*"[Title]) OR ("Spirometry"[MeSH Terms] OR "spiromet*"[Title]) OR ("Patient Acuity"[MeSH Terms] OR "disease severity"[Title] OR "symptom severity"[Title]))) OR ("pulmonary disease, chronic obstructive/classification"[MeSH Terms] OR "pulmonary disease, chronic obstructive/diagnosis"[MeSH Terms] OR "pulmonary disease, chronic obstructive/diagnostic imaging"[MeSH Terms] OR "bronchitis, chronic/classification"[MeSH Terms] OR "bronchitis, chronic/diagnosis"[MeSH Terms] OR "bronchitis, chronic/diagnostic imaging"[MeSH Terms] OR "pulmonary emphysema/classification"[MeSH Terms] OR "pulmonary emphysema/diagnosis"[MeSH Terms] OR "pulmonary emphysema/diagnostic imaging"[MeSH Terms])) AND ("between groups"[Title/Abstract] OR "case control*"[Title/Abstract] OR "clinical utility"[Title/Abstract] OR "cohort*"[Title/Abstract] OR "comparison"[Title/Abstract] OR "comparative"[Title/Abstract] OR "control group*"[Title/Abstract] OR "controlled study"[Title/Abstract] OR "controlled trial"[Title/Abstract] OR "cross over"[Title/Abstract] OR "crossover"[Title/Abstract] OR "diagnostic accuracy"[Title/Abstract] OR "double blind"[Title/Abstract] OR "double blinded"[Title/Abstract] OR "longitudinal"[Title/Abstract] OR "matched controls"[Title/Abstract] OR "observational study"[Title/Abstract] OR "placebo*"[Title/Abstract] OR "prospective"[Title/Abstract] OR "random*"[Title/Abstract] OR "sensitivity"[Title/Abstract] OR "sham"[Title/Abstract] OR (("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "specificity"[All	

Search No.	Query	Results
	Fields] OR "specific"[All Fields] OR "specifically"[All Fields] OR "specification"[All Fields] OR "specifications"[All Fields] OR "specificities"[All Fields] OR "specifics"[All Fields] OR "specifities"[All Fields] OR "specifity"[All Fields]) AND ti, ab[Author]) OR "versus"[Title] OR "vs"[Title]))) NOT ("hascommenton"[All Fields] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "case report"[Title] OR "comment"[Title] OR "conference proceeding"[Title] OR "editorial"[Title] OR "letter"[Title])) NOT (("animal"[Title] OR "animals"[Title] OR "canine*"[Title] OR "dog"[Title] OR "dogs"[Title] OR "feline"[Title] OR "hamster*"[Title] OR "lamb"[Title] OR "lambs"[Title] OR "mice"[Title] OR "monkey"[Title] OR "monkeys"[Title] OR "mouse"[Title] OR "murine"[Title] OR "pig"[Title] OR "piglet*"[Title] OR "pigs"[Title] OR "porcine"[Title] OR "primate*"[Title] OR "rabbit*"[Title] OR "rat"[Title] OR "rats"[Title] OR "rodent*"[Title] OR "sheep*"[Title] OR "swine"[Title] OR "veterinar*"[Title] OR ("vitro"[Title] NOT "vivo"[Title])) NOT ("human*"[Title/Abstract] OR "patient*"[Title/Abstract]))) AND 2020/02/01:2025/12/05[Date - Publication] AND ("medlinestatus in process"[All Fields] OR "medlinestatus publisher"[All Fields] OR "medlinestatus pubmed not medline"[All Fields])	
KQ2	(((((("pulmonary disease, chronic obstructive"[MeSH Major Topic] OR ("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract]) OR ("bronchitis, chronic"[MeSH Terms] OR "chronic bronchitis"[Title/Abstract]) OR ("Pulmonary Emphysema"[MeSH Terms] OR "emphysem*"[Title/Abstract]) OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("anemia"[Title/Abstract] OR "anemic"[Title/Abstract] OR "cannabis"[Title/Abstract] OR "cormorbid*"[Title/Abstract] OR "exercis*"[Title/Abstract] OR "heart failure"[Title/Abstract] OR "infection*"[Title/Abstract] OR "kidney disease*"[Title/Abstract] OR "lung cancer"[Title/Abstract] OR "malnourish*"[Title/Abstract] OR "malnutrition"[Title/Abstract] OR "marijuana"[Title/Abstract] OR "mental health*"[Title/Abstract] OR "nutrition"[Title/Abstract] OR "obes*"[Title/Abstract] OR "over weight"[Title/Abstract] OR "overweight"[Title/Abstract] OR "oxygen"[Title/Abstract] OR "physical activit*"[Title/Abstract] OR "risk factor*"[Title/Abstract] OR "smoke expos*"[Title/Abstract] OR "smoking history"[Title/Abstract] OR "smoking status"[Title/Abstract] OR "secondhand smok*"[Title/Abstract] OR "sleep*"[Title/Abstract] OR "thyroid disease*"[Title/Abstract] OR "vaccinat*"[Title/Abstract] OR "vape*"[Title/Abstract] OR "vaping"[Title/Abstract] OR "childhood condition*"[Title/Abstract] OR "childhood disease*"[Title/Abstract] OR "childhood illness*"[Title/Abstract]) AND ("risk*"[Title] OR "risk factor*"[Title/Abstract]) AND ((((((("random sample"[All Fields] AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomization"[All Fields]) AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomized controlled trial"[All Fields]) AND "exp"[All Fields]) OR "phase 3"[Title/Abstract] OR "phase iii"[Title/Abstract] OR "random*"[Title/Abstract] OR "rct"[Title/Abstract])) OR (("pulmonary disease, chronic obstructive"[MeSH Major Topic] OR ("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract]) OR ("bronchitis, chronic"[MeSH Terms] OR "chronic bronchitis"[Title/Abstract]) OR ("Pulmonary Emphysema"[MeSH Terms] OR "emphysem*"[Title/Abstract]) OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("anemia"[Title/Abstract] OR "anemic"[Title/Abstract] OR "cannabis"[Title/Abstract] OR "cormorbid*"[Title/Abstract] OR "exercis*"[Title/Abstract] OR "heart failure"[Title/Abstract] OR	1,106

Search No.	Query	Results
	"infection*"[Title/Abstract] OR "kidney disease*"[Title/Abstract] OR "lung cancer"[Title/Abstract] OR "malnourish*"[Title/Abstract] OR "malnutrition"[Title/Abstract] OR "marijuana"[Title/Abstract] OR "mental health*"[Title/Abstract] OR "nutrition"[Title/Abstract] OR "obes*"[Title/Abstract] OR "over weight"[Title/Abstract] OR "overweight"[Title/Abstract] OR "oxygen"[Title/Abstract] OR "physical activit*"[Title/Abstract] OR "risk factor*"[Title/Abstract] OR "smoke expos*"[Title/Abstract] OR "smoking history"[Title/Abstract] OR "smoking status"[Title/Abstract] OR "secondhand smok*"[Title/Abstract] OR "sleep*"[Title/Abstract] OR "thyroid disease*"[Title/Abstract] OR "vaccinat*"[Title/Abstract] OR "vape*"[Title/Abstract] OR "vaping"[Title/Abstract] OR "childhood condition*"[Title/Abstract] OR "childhood disease*"[Title/Abstract] OR "childhood illness*"[Title/Abstract]) AND ("risk*"[Title] OR "risk factor*"[Title/Abstract]) AND ("cochrane*"[Title/Abstract] OR "metaanaly*"[Title/Abstract] OR "meta analy*"[Title/Abstract] OR ("search*"[Title/Abstract] AND ("cinahl*"[Title/Abstract] OR "databases"[Title/Abstract] OR "ebsco*"[Title/Abstract] OR "embase*"[Title/Abstract] OR "medline"[Title/Abstract] OR "psychinfo*"[Title/Abstract] OR "psycinfo*"[Title/Abstract] OR "science direct*"[Title/Abstract] OR "sciencedirect*"[Title/Abstract] OR "scopus*"[Title/Abstract] OR "systematic review*"[Title/Abstract] OR "web of knowledge*"[Title/Abstract] OR "web of science"[Title/Abstract])) OR "systematic"[Title])) OR (("pulmonary disease, chronic obstructive"[MeSH Major Topic] OR ("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract]) OR ("bronchitis, chronic"[MeSH Terms] OR "chronic bronchitis"[Title/Abstract]) OR ("Pulmonary Emphysema"[MeSH Terms] OR "emphysem*"[Title/Abstract]) OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("anemia"[Title/Abstract] OR "anemic"[Title/Abstract] OR "cannabis"[Title/Abstract] OR "cormorbid*"[Title/Abstract] OR "exercis*"[Title/Abstract] OR "heart failure"[Title/Abstract] OR "infection*"[Title/Abstract] OR "kidney disease*"[Title/Abstract] OR "lung cancer"[Title/Abstract] OR "malnourish*"[Title/Abstract] OR "malnutrition"[Title/Abstract] OR "marijuana"[Title/Abstract] OR "mental health*"[Title/Abstract] OR "nutrition"[Title/Abstract] OR "obes*"[Title/Abstract] OR "over weight"[Title/Abstract] OR "overweight"[Title/Abstract] OR "oxygen"[Title/Abstract] OR "physical activit*"[Title/Abstract] OR "risk factor*"[Title/Abstract] OR "smoke expos*"[Title/Abstract] OR "smoking history"[Title/Abstract] OR "smoking status"[Title/Abstract] OR "secondhand smok*"[Title/Abstract] OR "sleep*"[Title/Abstract] OR "thyroid disease*"[Title/Abstract] OR "vaccinat*"[Title/Abstract] OR "vape*"[Title/Abstract] OR "vaping"[Title/Abstract] OR "childhood condition*"[Title/Abstract] OR "childhood disease*"[Title/Abstract] OR "childhood illness*"[Title/Abstract]) AND ("risk*"[Title] OR "risk factor*"[Title/Abstract]) AND ("between groups"[Title/Abstract] OR "case control*"[Title/Abstract] OR "clinical utility"[Title/Abstract] OR "cohort*"[Title/Abstract] OR "comparison"[Title/Abstract] OR "comparative"[Title/Abstract] OR "control group*"[Title/Abstract] OR "controlled study"[Title/Abstract] OR "controlled trial"[Title/Abstract] OR "cross over"[Title/Abstract] OR "crossover"[Title/Abstract] OR "diagnostic accuracy"[Title/Abstract] OR "double blind"[Title/Abstract] OR "double blinded"[Title/Abstract] OR "longitudinal"[Title/Abstract] OR "matched controls"[Title/Abstract] OR "observational study"[Title/Abstract] OR "placebo*"[Title/Abstract] OR "prospective"[Title/Abstract] OR "random*"[Title/Abstract] OR "sensitivity"[Title/Abstract] OR "sham"[Title/Abstract] OR (("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "specificity"[All Fields] OR "specific"[All Fields] OR "specifically"[All Fields] OR "specification"[All Fields] OR "specifications"[All Fields] OR "specificities"[All Fields] OR "specifics"[All	

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	Fields] OR "specifities"[All Fields] OR "specifity"[All Fields]) AND ti, ab[Author]) OR "versus"[Title] OR "vs"[Title]))) NOT ("hascommenton"[All Fields] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "case report"[Title] OR "comment"[Title] OR "conference proceeding"[Title] OR "editorial"[Title] OR "letter"[Title])) NOT (("animal"[Title] OR "animals"[Title] OR "canine*"[Title] OR "dog"[Title] OR "dogs"[Title] OR "feline"[Title] OR "hamster*"[Title] OR "lamb"[Title] OR "lambs"[Title] OR "mice"[Title] OR "monkey"[Title] OR "monkeys"[Title] OR "mouse"[Title] OR "murine"[Title] OR "pig"[Title] OR "piglet*"[Title] OR "pigs"[Title] OR "porcine"[Title] OR "primate*"[Title] OR "rabbit*"[Title] OR "rat"[Title] OR "rats"[Title] OR "rodent*"[Title] OR "sheep*"[Title] OR "swine"[Title] OR "veterinar*"[Title] OR ("vitro"[Title] NOT "vivo"[Title])) NOT ("human*"[Title/Abstract] OR "patient*"[Title/Abstract]))) AND 2020/02/01:2025/12/05[Date - Publication] AND ("medlinestatus in process"[All Fields] OR "medlinestatus publisher"[All Fields] OR "medlinestatus pubmed not medline"[All Fields])	
KQ3	((((((("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("bode index"[Title/Abstract] OR "body mass index airflow obstruction dyspnea and exercise"[Title/Abstract] OR (("anxiety"[Title/Abstract] OR "depress*"[Title/Abstract]) AND ("assess*"[Title/Abstract] OR "screen*"[Title/Abstract] OR "test*"[Title/Abstract])) OR ("eosinophil*"[All Fields] AND ("assess*"[Title/Abstract] OR "count*"[Title/Abstract] OR "screen*"[Title/Abstract] OR "test*"[Title/Abstract])) OR "pulse oximet*"[Title/Abstract] OR ("camberwell assessment of need"[Title/Abstract] OR "copd assessment test"[Title/Abstract] OR "mmrc"[Title/Abstract] OR "modified medical research council dyspnea scale"[Title/Abstract] OR "st georges respiratory questionnaire"[Title/Abstract] OR "sgrq"[Title/Abstract]) OR "spiromet*"[Title/Abstract] OR "test*"[Title]) AND ((((((("random sample"[All Fields] AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomization"[All Fields]) AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomized controlled trial"[All Fields]) AND "exp"[All Fields]) OR "phase 3"[Title/Abstract] OR "phase iii"[Title/Abstract] OR "random*"[Title/Abstract] OR "rct"[Title/Abstract])) OR (("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("bode index"[Title/Abstract] OR "body mass index airflow obstruction dyspnea and exercise"[Title/Abstract] OR (("anxiety"[Title/Abstract] OR "depress*"[Title/Abstract]) AND ("assess*"[Title/Abstract] OR "screen*"[Title/Abstract] OR "test*"[Title/Abstract])) OR ("eosinophil*"[All Fields] AND ("assess*"[Title/Abstract] OR "count*"[Title/Abstract] OR "screen*"[Title/Abstract] OR "test*"[Title/Abstract])) OR "pulse oximet*"[Title/Abstract] OR ("camberwell assessment of need"[Title/Abstract] OR "copd assessment test"[Title/Abstract] OR "mmrc"[Title/Abstract] OR "modified medical research council dyspnea scale"[Title/Abstract] OR "st georges respiratory questionnaire"[Title/Abstract] OR "sgrq"[Title/Abstract]) OR "spiromet*"[Title/Abstract] OR "test*"[Title]) AND ("cochrane*"[Title/Abstract] OR "metaanaly*"[Title/Abstract] OR "meta analy*"[Title/Abstract] OR ("search*"[Title/Abstract] AND ("cinahl*"[Title/Abstract] OR "databases"[Title/Abstract] OR "ebsco*"[Title/Abstract] OR "embase*"[Title/Abstract] OR "medline"[Title/Abstract] OR	364

Search No.	Query	Results
	"psychinfo*"[Title/Abstract] OR "psycinfo*"[Title/Abstract] OR "science direct*"[Title/Abstract] OR "sciencedirect*"[Title/Abstract] OR "scopus*"[Title/Abstract] OR "systematic review*"[Title/Abstract] OR "web of knowledge*"[Title/Abstract] OR "web of science"[Title/Abstract])) OR "systematic"[Title])))) AND 2020/02/01:2025/12/05[Date - Publication]) NOT ("hascommenton"[All Fields] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "case report"[Title] OR "comment"[Title] OR "conference proceeding"[Title] OR "editorial"[Title] OR "letter"[Title])) NOT (("animal"[Title] OR "animals"[Title] OR "canine*"[Title] OR "dog"[Title] OR "dogs"[Title] OR "feline"[Title] OR "hamster*"[Title] OR "lamb"[Title] OR "lambs"[Title] OR "mice"[Title] OR "monkey"[Title] OR "monkeys"[Title] OR "mouse"[Title] OR "murine"[Title] OR "pig"[Title] OR "piglet*"[Title] OR "pigs"[Title] OR "porcine"[Title] OR "primate*"[Title] OR "rabbit*"[Title] OR "rat"[Title] OR "rats"[Title] OR "rodent*"[Title] OR "sheep*"[Title] OR "swine"[Title] OR "veterinar*"[Title] OR ("vitro"[Title] NOT "vivo"[Title])) NOT ("human*"[Title/Abstract] OR "patient*"[Title/Abstract]))) AND ("medlinestatus in process"[All Fields] OR "medlinestatus publisher"[All Fields] OR "medlinestatus pubmed not medline"[All Fields])	
KQ4-6	((((((("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("anti cholinergic*"[Title/Abstract] OR "anticholinergic*"[Title/Abstract] OR "acetylcholine"[Title/Abstract] OR "cholinergic*"[Title/Abstract] OR ("short acting beta 2 agonist*"[Title/Abstract] OR "laba"[Title/Abstract] OR "labas"[Title/Abstract] OR "long acting beta* agonist*"[Title/Abstract] OR "long acting beta 2 agonist*"[Title/Abstract] OR "longacting beta* agonist*"[Title/Abstract] OR "saba"[Title/Abstract] OR "sabas"[Title/Abstract] OR "short acting beta* agonist*"[Title/Abstract] OR "short acting beta 2 agonist*"[Title/Abstract]) OR ("biologic"[Title/Abstract] OR "biologics"[Title/Abstract]) OR ((("1 drug"[Title/Abstract] OR "2 drug*"[Title/Abstract] OR "3 drug*"[Title/Abstract] OR "4 drug*"[Title/Abstract] OR "dual agent*"[Title/Abstract] OR "dual combin*"[Title/Abstract] OR "dual drug*"[Title/Abstract] OR "drug* combin*"[Title/Abstract] OR "multi* drug*"[Title/Abstract] OR "multidrug*"[Title/Abstract] OR "one drug*"[Title/Abstract] OR "polypharm*"[Title/Abstract] OR "polypill"[Title/Abstract] OR "polytherap*"[Title/Abstract] OR "single agent*"[Title/Abstract]) AND "single drug"[Title/Abstract]) OR "subsequent drug*"[Title/Abstract] OR "two drug"[Title/Abstract]) OR "ensifentrine"[Title/Abstract] OR "corticosteroid*"[Title/Abstract] OR "mucolytic*"[Title/Abstract] OR "roflumilast"[Title/Abstract]) AND ((((((("random sample"[All Fields] AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomization"[All Fields]) AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomized controlled trial"[All Fields]) AND "exp"[All Fields]) OR "phase 3"[Title/Abstract] OR "phase iii"[Title/Abstract] OR "random*"[Title/Abstract] OR "rct"[Title/Abstract])) OR (("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("anti cholinergic*"[Title/Abstract] OR "anticholinergic*"[Title/Abstract] OR "acetylcholine"[Title/Abstract] OR "cholinergic*"[Title/Abstract] OR ("short acting beta 2 agonist*"[Title/Abstract] OR "laba"[Title/Abstract] OR "labas"[Title/Abstract] OR "long acting beta*	138

Search No.	Query	Results
	agonist*"[Title/Abstract] OR "long acting beta 2 agonist*"[Title/Abstract] OR "longacting beta* agonist*"[Title/Abstract] OR "saba"[Title/Abstract] OR "sabas"[Title/Abstract] OR "short acting beta* agonist*"[Title/Abstract] OR "short acting beta 2 agonist*"[Title/Abstract]) OR ("biologic"[Title/Abstract] OR "biologics"[Title/Abstract]) OR ((("1 drug"[Title/Abstract] OR "2 drug*"[Title/Abstract] OR "3 drug*"[Title/Abstract] OR "4 drug*"[Title/Abstract] OR "dual agent*"[Title/Abstract] OR "dual combin*"[Title/Abstract] OR "dual drug*"[Title/Abstract] OR "drug* combin*"[Title/Abstract] OR "multi* drug*"[Title/Abstract] OR "multidrug*"[Title/Abstract] OR "one drug*"[Title/Abstract] OR "polypharm*"[Title/Abstract] OR "polypill"[Title/Abstract] OR "polytherap*"[Title/Abstract] OR "single agent*"[Title/Abstract]) AND "single drug"[Title/Abstract]) OR "subsequent drug*"[Title/Abstract] OR "two drug"[Title/Abstract]) OR "ensifentrine"[Title/Abstract] OR "corticosteroid*"[Title/Abstract] OR "mucolytic*"[Title/Abstract] OR "roflumilast"[Title/Abstract]) AND ("cochrane*"[Title/Abstract] OR "metaanaly*"[Title/Abstract] OR "meta analy*"[Title/Abstract] OR ("search*"[Title/Abstract] AND ("cinahl*"[Title/Abstract] OR "databases"[Title/Abstract] OR "ebsco*"[Title/Abstract] OR "embase*"[Title/Abstract] OR "medline"[Title/Abstract] OR "psychinfo*"[Title/Abstract] OR "psycinfo*"[Title/Abstract] OR "science direct*"[Title/Abstract] OR "sciencedirect*"[Title/Abstract] OR "scopus*"[Title/Abstract] OR "systematic review*"[Title/Abstract] OR "web of knowledge*"[Title/Abstract] OR "web of science"[Title/Abstract])) OR "systematic"[Title]))) AND 2020/02/01:2025/12/05[Date - Publication]) NOT ("hascommenton"[All Fields] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "case report"[Title] OR "comment"[Title] OR "conference proceeding"[Title] OR "editorial"[Title] OR "letter"[Title])) NOT (("animal"[Title] OR "animals"[Title] OR "canine*"[Title] OR "dog"[Title] OR "dogs"[Title] OR "feline"[Title] OR "hamster*"[Title] OR "lamb"[Title] OR "lambs"[Title] OR "mice"[Title] OR "monkey"[Title] OR "monkeys"[Title] OR "mouse"[Title] OR "murine"[Title] OR "pig"[Title] OR "piglet*"[Title] OR "pigs"[Title] OR "porcine"[Title] OR "primate*"[Title] OR "rabbit*"[Title] OR "rat"[Title] OR "rats"[Title] OR "rodent*"[Title] OR "sheep*"[Title] OR "swine"[Title] OR "veterinar*"[Title] OR ("vitro"[Title] NOT "vivo"[Title])) NOT ("human*"[Title/Abstract] OR "patient*"[Title/Abstract]))) AND ("medlinestatus in process"[All Fields] OR "medlinestatus publisher"[All Fields] OR "medlinestatus pubmed not medline"[All Fields])	
KQ7	((((((("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND "exacerbat*"[Title/Abstract] AND ("amoxicillin"[Title/Abstract] OR "anti bacterial*"[Title/Abstract] OR "antibacterial*"[Title/Abstract] OR "antibiotic*"[Title/Abstract] OR "anti infectiv*"[Title/Abstract] OR "antiinfectiv*"[Title/Abstract] OR "anti mycobacterial*"[Title/Abstract] OR "antimycobacterial*"[Title/Abstract] OR "bacteriocid*"[Title/Abstract] OR "clarithromycin"[Title/Abstract] OR "doxycycline"[Title/Abstract] OR "erythromycin"[Title/Abstract] OR "levofloxacin"[Title/Abstract] OR "moxifloxacin"[Title/Abstract] OR ("corticosteroid*"[Title/Abstract] OR "glucocorticoid*"[Title/Abstract] OR "prednisone*"[Title/Abstract] OR "steroid*"[Title/Abstract])) AND ((((((("random sample"[All Fields] AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomization"[All Fields]) AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomized controlled trial"[All Fields])	75

Search No.	Query	Results
	AND "exp"[All Fields]) OR "phase 3"[Title/Abstract] OR "phase iii"[Title/Abstract] OR "random*"[Title/Abstract] OR "rct"[Title/Abstract])) OR (("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND "exacerbat*"[Title/Abstract] AND ("amoxicillin"[Title/Abstract] OR "anti bacterial*"[Title/Abstract] OR "antibacterial*"[Title/Abstract] OR "antibiotic*"[Title/Abstract] OR "anti infectiv*"[Title/Abstract] OR "antiinfectiv*"[Title/Abstract] OR "anti mycobacterial*"[Title/Abstract] OR "antimycobacterial*"[Title/Abstract] OR "bacteriocid*"[Title/Abstract] OR "clarithromycin"[Title/Abstract] OR "doxycycline"[Title/Abstract] OR "erythromycin"[Title/Abstract] OR "levofloxacin"[Title/Abstract] OR "moxifloxacin"[Title/Abstract] OR ("corticosteroid*"[Title/Abstract] OR "glucocorticoid*"[Title/Abstract] OR "prednisone*"[Title/Abstract] OR "steroid*"[Title/Abstract])) AND ("cochrane*"[Title/Abstract] OR "metaanaly*"[Title/Abstract] OR "meta analy*"[Title/Abstract] OR ("search*"[Title/Abstract] AND ("cinahl*"[Title/Abstract] OR "databases"[Title/Abstract] OR "ebsco*"[Title/Abstract] OR "embase*"[Title/Abstract] OR "medline"[Title/Abstract] OR "psychinfo*"[Title/Abstract] OR "psycinfo*"[Title/Abstract] OR "science direct*"[Title/Abstract] OR "sciencedirect*"[Title/Abstract] OR "scopus*"[Title/Abstract] OR "systematic review*"[Title/Abstract] OR "web of knowledge*"[Title/Abstract] OR "web of science"[Title/Abstract])) OR "systematic"[Title]))) AND 2020/02/01:2025/12/05[Date - Publication]) NOT ("hascommenton"[All Fields] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "case report"[Title] OR "comment"[Title] OR "conference proceeding"[Title] OR "editorial"[Title] OR "letter"[Title])) NOT (("animal"[Title] OR "animals"[Title] OR "canine*"[Title] OR "dog"[Title] OR "dogs"[Title] OR "feline"[Title] OR "hamster*"[Title] OR "lamb"[Title] OR "lambs"[Title] OR "mice"[Title] OR "monkey"[Title] OR "monkeys"[Title] OR "mouse"[Title] OR "murine"[Title] OR "pig"[Title] OR "piglet*"[Title] OR "pigs"[Title] OR "porcine"[Title] OR "primate*"[Title] OR "rabbit*"[Title] OR "rat"[Title] OR "rats"[Title] OR "rodent*"[Title] OR "sheep*"[Title] OR "swine"[Title] OR "veterinar*"[Title] OR ("vitro"[Title] NOT "vivo"[Title])) NOT ("human*"[Title/Abstract] OR "patient*"[Title/Abstract]))) AND ("medlinestatus in process"[All Fields] OR "medlinestatus publisher"[All Fields] OR "medlinestatus pubmed not medline"[All Fields])	
KQ8	((((((("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("corticosteroid*"[Title/Abstract] OR "glucocorticoid*"[Title/Abstract] OR "prednisone*"[Title/Abstract] OR "steroid*"[Title/Abstract]) AND ("discontin*"[Title/Abstract] OR "end"[Title/Abstract] OR "ends"[Title/Abstract] OR "ending"[Title/Abstract] OR "ended"[Title/Abstract] OR "stop*"[Title/Abstract] OR "withdraw*"[Title/Abstract]) AND ((((((("random sample"[All Fields] AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomization"[All Fields]) AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomized controlled trial"[All Fields]) AND "exp"[All Fields]) OR "phase 3"[Title/Abstract] OR "phase iii"[Title/Abstract] OR "random*"[Title/Abstract] OR "rct"[Title/Abstract])) OR (("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR	26

Search No.	Query	Results
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Search No.	Query	Results
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KQ10	(((((("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("anti depressant*"[Title/Abstract] OR "antidepressant*"[Title/Abstract] OR "anxiolytic*"[Title/Abstract] OR "fan"[Title/Abstract] OR "fans"[Title/Abstract] OR	33

Search No.	Query	Results
	"morphine"[Title/Abstract] OR "multi disciplinary care"[Title/Abstract] OR "multi disciplinary team*"[Title/Abstract] OR "multidisciplinary care"[Title/Abstract] OR "multidisciplinary team"[Title/Abstract] OR "ssri*"[Title/Abstract] OR "serotonin uptake inhibitor*"[Title/Abstract] OR ("comfort care"[Title/Abstract] OR "palliativ*"[Title/Abstract] OR "supportive care"[Title/Abstract])) AND ((((((("random sample"[All Fields] AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomization"[All Fields]) AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomized controlled trial"[All Fields]) AND "exp"[All Fields]) OR "phase 3"[Title/Abstract] OR "phase iii"[Title/Abstract] OR "random*"[Title/Abstract] OR "rct"[Title/Abstract])) OR (("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("anti depressant*"[Title/Abstract] OR "antidepressant*"[Title/Abstract] OR "anxiolytic*"[Title/Abstract] OR "fan"[Title/Abstract] OR "fans"[Title/Abstract] OR "morphine"[Title/Abstract] OR "multi disciplinary care"[Title/Abstract] OR "multi disciplinary team*"[Title/Abstract] OR "multidisciplinary care"[Title/Abstract] OR "multidisciplinary team"[Title/Abstract] OR "ssri*"[Title/Abstract] OR "serotonin uptake inhibitor*"[Title/Abstract] OR ("comfort care"[Title/Abstract] OR "palliativ*"[Title/Abstract] OR "supportive care"[Title/Abstract])) AND ("cochrane*"[Title/Abstract] OR "metaanaly*"[Title/Abstract] OR "meta analy*"[Title/Abstract] OR ("search*"[Title/Abstract] AND ("cinahl*"[Title/Abstract] OR "databases"[Title/Abstract] OR "ebsco*"[Title/Abstract] OR "embase*"[Title/Abstract] OR "medline"[Title/Abstract] OR "psychinfo*"[Title/Abstract] OR "psycinfo*"[Title/Abstract] OR "science direct*"[Title/Abstract] OR "sciencedirect*"[Title/Abstract] OR "scopus*"[Title/Abstract] OR "systematic review*"[Title/Abstract] OR "web of knowledge*"[Title/Abstract] OR "web of science"[Title/Abstract])) OR "systematic"[Title]))) NOT ("hascommenton"[All Fields] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "case report"[Title] OR "comment"[Title] OR "conference proceeding"[Title] OR "editorial"[Title] OR "letter"[Title])) NOT (("animal"[Title] OR "animals"[Title] OR "canine*"[Title] OR "dog"[Title] OR "dogs"[Title] OR "feline"[Title] OR "hamster*"[Title] OR "lamb"[Title] OR "lambs"[Title] OR "mice"[Title] OR "monkey"[Title] OR "monkeys"[Title] OR "mouse"[Title] OR "murine"[Title] OR "pig"[Title] OR "piglet*"[Title] OR "pigs"[Title] OR "porcine"[Title] OR "primate*"[Title] OR "rabbit*"[Title] OR "rat"[Title] OR "rats"[Title] OR "rodent*"[Title] OR "sheep*"[Title] OR "swine"[Title] OR "veterinar*"[Title] OR ("vitro"[Title] NOT "vivo"[Title])) NOT ("human*"[Title/Abstract] OR "patient*"[Title/Abstract]))) AND 2020/02/01:2025/12/05[Date - Publication] AND ("medlinestatus in process"[All Fields] OR "medlinestatus publisher"[All Fields] OR "medlinestatus pubmed not medline"[All Fields])	
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Search No.	Query	Results
	OR "web"[Title/Abstract] OR "web based"[Title/Abstract] OR "website*"[Title/Abstract]) AND ("app"[Title/Abstract] OR "apps"[Title/Abstract] OR "application*"[Title/Abstract])) OR ("cellphone*"[Title/Abstract] OR "chat*"[Title/Abstract] OR "computer*"[Title/Abstract] OR "device*"[Title/Abstract] OR "home based"[Title/Abstract] OR "phone*"[Title/Abstract] OR "remote*"[Title/Abstract] OR "smartphone*"[Title/Abstract] OR "tablet*"[Title/Abstract] OR "telephone*"[Title/Abstract] OR "video conferenc*"[Title/Abstract] OR "virtual*"[Title/Abstract] OR "web site*"[Title/Abstract] OR "website*"[Title/Abstract])) OR ("tele health*"[Title/Abstract] OR "telehealth*"[Title/Abstract] OR "tele medicine"[Title/Abstract] OR "telemedicine"[Title/Abstract] OR "tele rehab*"[Title/Abstract] OR "telerehab*"[Title/Abstract])) AND ((((((("random sample"[All Fields] AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomization"[All Fields]) AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomized controlled trial"[All Fields]) AND "exp"[All Fields]) OR "phase 3"[Title/Abstract] OR "phase iii"[Title/Abstract] OR "random*"[Title/Abstract] OR "rct"[Title/Abstract])) OR (("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ((("air flow*"[Title/Abstract] OR "airflow*"[Title/Abstract] OR "air way*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]) AND "rehab*"[Title/Abstract] AND ((("computer*"[Title/Abstract] OR "mobile"[Title/Abstract] OR "phone"[Title/Abstract] OR "smartphone*"[Title/Abstract] OR "web"[Title/Abstract] OR "web based"[Title/Abstract] OR "website*"[Title/Abstract]) AND ("app"[Title/Abstract] OR "apps"[Title/Abstract] OR "application*"[Title/Abstract])) OR ("cellphone*"[Title/Abstract] OR "chat*"[Title/Abstract] OR "computer*"[Title/Abstract] OR "device*"[Title/Abstract] OR "home based"[Title/Abstract] OR "phone*"[Title/Abstract] OR "remote*"[Title/Abstract] OR "smartphone*"[Title/Abstract] OR "tablet*"[Title/Abstract] OR "telephone*"[Title/Abstract] OR "video conferenc*"[Title/Abstract] OR "virtual*"[Title/Abstract] OR "web site*"[Title/Abstract] OR "website*"[Title/Abstract])) OR ("tele health*"[Title/Abstract] OR "telehealth*"[Title/Abstract] OR "tele medicine"[Title/Abstract] OR "telemedicine"[Title/Abstract] OR "tele rehab*"[Title/Abstract] OR "telerehab*"[Title/Abstract])) AND ("cochrane*"[Title/Abstract] OR "metaanaly*"[Title/Abstract] OR "meta analy*"[Title/Abstract] OR ("search*"[Title/Abstract] AND ("cinahl*"[Title/Abstract] OR "databases"[Title/Abstract] OR "ebsco*"[Title/Abstract] OR "embase*"[Title/Abstract] OR "medline"[Title/Abstract] OR "psychinfo*"[Title/Abstract] OR "psycinfo*"[Title/Abstract] OR "science direct*"[Title/Abstract] OR "sciencedirect*"[Title/Abstract] OR "scopus*"[Title/Abstract] OR "systematic review*"[Title/Abstract] OR "web of knowledge*"[Title/Abstract] OR "web of science"[Title/Abstract])) OR "systematic"[Title]))) AND 2020/02/01:2025/12/05[Date - Publication]) NOT ("hascommenton"[All Fields] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "case report"[Title] OR "comment"[Title] OR "conference proceeding"[Title] OR "editorial"[Title] OR "letter"[Title])) NOT (("animal"[Title] OR "animals"[Title] OR "canine*"[Title] OR "dog"[Title] OR "dogs"[Title] OR "feline"[Title] OR "hamster*"[Title] OR "lamb"[Title] OR "lambs"[Title] OR "mice"[Title] OR "monkey"[Title] OR "monkeys"[Title] OR "mouse"[Title] OR "murine"[Title] OR "pig"[Title] OR "piglet*"[Title] OR "pigs"[Title] OR "porcine"[Title] OR "primate*"[Title] OR "rabbit*"[Title] OR "rat"[Title] OR "rats"[Title] OR "rodent*"[Title] OR "sheep*"[Title] OR "swine"[Title] OR "veterinar*"[Title] OR	

Search No.	Query	Results
	("vitro"[Title] NOT "vivo"[Title])) NOT ("human*"[Title/Abstract] OR "patient*"[Title/Abstract]))) AND ("medlinestatus in process"[All Fields] OR "medlinestatus publisher"[All Fields] OR "medlinestatus pubmed not medline"[All Fields])	
KQ12	((((((("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("care giver*"[Title/Abstract] OR "caregiver*"[Title/Abstract]) AND ((((((("random sample"[All Fields] AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomization"[All Fields]) AND ("drug effects"[MeSH Subheading] OR ("drug"[All Fields] AND "effects"[All Fields]) OR "drug effects"[All Fields] OR "de"[All Fields])) OR "randomized controlled trial"[All Fields]) AND "exp"[All Fields]) OR "phase 3"[Title/Abstract] OR "phase iii"[Title/Abstract] OR "random*"[Title/Abstract] OR "rct"[Title/Abstract])) OR (("aecb"[Title/Abstract] OR "coad"[Title/Abstract] OR "cobd"[Title/Abstract] OR "copd*"[Title/Abstract] OR "chronic bronchitis"[Title/Abstract] OR "emphysem*"[Title/Abstract] OR ("obstruct*"[Title/Abstract] AND ("airflow*"[Title/Abstract] OR "airway*"[Title/Abstract] OR "bronch*"[Title/Abstract] OR "lung*"[Title/Abstract] OR "pulmonary"[Title/Abstract] OR "respirat*"[Title/Abstract]))) AND ("care giver*"[Title/Abstract] OR "caregiver*"[Title/Abstract]) AND ("cochrane*"[Title/Abstract] OR "metaanaly*"[Title/Abstract] OR "meta analy*"[Title/Abstract] OR ("search*"[Title/Abstract] AND ("cinahl*"[Title/Abstract] OR "databases"[Title/Abstract] OR "ebsco*"[Title/Abstract] OR "embase*"[Title/Abstract] OR "medline"[Title/Abstract] OR "psychinfo*"[Title/Abstract] OR "psycinfo*"[Title/Abstract] OR "science direct*"[Title/Abstract] OR "sciencedirect*"[Title/Abstract] OR "scopus*"[Title/Abstract] OR "systematic review*"[Title/Abstract] OR "web of knowledge*"[Title/Abstract] OR "web of science"[Title/Abstract])) OR "systematic"[Title]))) AND 2020/02/01:2025/12/05[Date - Publication]) NOT ("hascommenton"[All Fields] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "case report"[Title] OR "comment"[Title] OR "conference proceeding"[Title] OR "editorial"[Title] OR "letter"[Title])) NOT (("animal"[Title] OR "animals"[Title] OR "canine*"[Title] OR "dog"[Title] OR "dogs"[Title] OR "feline"[Title] OR "hamster*"[Title] OR "lamb"[Title] OR "lambs"[Title] OR "mice"[Title] OR "monkey"[Title] OR "monkeys"[Title] OR "mouse"[Title] OR "murine"[Title] OR "pig"[Title] OR "piglet*"[Title] OR "pigs"[Title] OR "porcine"[Title] OR "primate*"[Title] OR "rabbit*"[Title] OR "rat"[Title] OR "rats"[Title] OR "rodent*"[Title] OR "sheep*"[Title] OR "swine"[Title] OR "veterinar*"[Title] OR ("vitro"[Title] NOT "vivo"[Title])) NOT ("human*"[Title/Abstract] OR "patient*"[Title/Abstract]))) AND ("medlinestatus in process"[All Fields] OR "medlinestatus publisher"[All Fields] OR "medlinestatus pubmed not medline"[All Fields])	18

Table F-4. AHRQ EPC Reports Search Strategy

Query
COPD
chronic obstructive pulmonary
emphysema
bronchitis

Table F-5. VA ESP Reports Search Strategy

Query
COPD
chronic obstructive pulmonary
emphysema
bronchitis

Table F-6. Cochrane Library Search Strategy

Line No.	Query	Results
#1	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees	8246
#2	(aecb OR "chronic bronchitis" OR "chronic obstructive pulmonary disease" OR coad OR cobd OR copd* OR emphysem*):ti,ab,kw	26631
#3	MeSH descriptor: [Bronchitis, Chronic] explode all trees	211
#4	MeSH descriptor: [Emphysema] explode all trees	318
#5	#1 OR #2 OR #3 OR #4	27184

Appendix G. Alternative Text Description of Algorithm

The following outline narratively describe Module A, Module B, and Module C. An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the Algorithm section. The sidebars referenced within these outlines can also be found in the Algorithm section.

Module A: Assessment of COPD

1. Module A begins with Box 1, in the shape of a rounded rectangle: "Patient suspected of having COPD (see **Sidebar 1**)"
2. Box 1 connects to Box 2, in the shape of a hexagon, asks the question: "Is patient suspected of having an acute exacerbation? (see **Sidebar 2**)"
    a. If the answer is "Yes" to Box 2, then Box 3, in the shape of an oval: "Management of an acute exacerbation (see **Module D**)
    b. If the answer is "No" to Box 2, then Box 4, in the shape of a rectangle:
    "• Perform targeted history and physical exam (see **Sidebar 1**).
    • If available, obtain post-bronchodilator spirometry (see **Recommendation 1**)
    • Obtain a baseline complete blood count with differential"
3. Box 4 connects to Box 5, in the shape of a hexagon, asks the question: "Is the assessment consistent with clinical diagnosis of COPD?"
    a. If the answer is "Yes" to Box 5, then Box 7.
    b. If the answer is "No" to Box 5, then Box 6, in the shape of an oval: "Evaluate for and treat other conditions."
4. Box 7, in the shape of a hexagon, asks the question: "Is the resting oxygen saturation low[a]?"
    a. If the answer is "Yes" to Box 7, then Box 8, in the shape of a rectangle: "Refer for formal home oxygen evaluation (see **Recommendations 15 and 16**)
        i. Box 7 connects to Box 9.
    b. If the answer is "No" to Box 7, then Box 9, in the shape of a rectangle: "Develop an individualized management plan (see **Sidebar 3**)
        i. Box 9 connects to Box 10.
5. Box 10, in the shape of a hexagon, asks the question: "Is the patient on inhaled pharmacotherapy?"
    a. If the answer is "Yes" to Box 10, then Box 10, in the shape of an oval: "Go to Follow-Up Management (see Module C)
    b. If the answer is "No" to Box 10, then Box 12, in the shape of an oval: "Go to Initial Management (see Module B); initiate therapy pending diagnostic workup"

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[a]: oxygen saturation ≤80%, or moderate resting hypoxemia with signs of chronic hypoxia-related cardiopulmonary or hematologic complications

Module B: Initial Management of COPD

1. Module B begins with Box 13, in the shape of a rounded rectangle: "Patient with COPD not on inhaled therapy"

2. Box 13 connects to Box 14, in the shape of a hexagon, asks the question: "Is there suspicion of an acute exacerbation? (see **Sidebar 2**)"
    a. If the answer is "Yes" to Box 14, then Box 15, in the shape of an oval: "Manage exacerbation (see **Module D**)"
    b. If the answer is "No" to Box 9, then Box 16.
3. Box 16, in the shape of a hexagon, asks the question: "Are spirometry results available?"
    a. If the answer is "Yes" to Box 16, then Box 17.
    b. If the answer is "No" to Box 16, then Box 19, in the shape of a rectangle: "Treat patient and obtain PBD spirometry results when possible; prescribe SABA for PRN rescue; do not delay maintenance therapy[b]"
4. Box 17, in the shape of a hexagon, asks the question: "Is COPD severe or very severe (FEV_1 <50% predicted)?"
    a. If the answer is "Yes" to Box 17, then Box 18, in the shape of a rectangle: "Consider Pulmonary Referral"
        i. Box 18 connects to Box 20.
    b. If the answer is "No" to Box 17, then Box 20.
5. Box 20, in the shape of a hexagon, asks the question: "Has the patient had any moderate or severe exacerbations in the past year? (see **Sidebar 4**)"
    a. If the answer is "Yes" to Box 20, then Box 21, in the shape of a rectangle: "Prescribe triple therapy with LABA/LAMA/ICS (see **Recommendation 9**)"
        i. Box 21 connects to Box 25.
    b. If the answer is "No" to Box 20, then Box 22.
6. Box 22, in the shape of a hexagon, asks the question: "Is the symptom burden high (mMRC ≥2 or CAT ≥10)? (see **Sidebar 5**)"
    a. If the answer is "Yes" to Box 22, then Box 23, in the shape of a rectangle: "Initiate dual therapy with LABA/LAMA (see **Recommendation 8**)"
        i. Box 23 connects to Box 25.
    b. If the answer is "No" to Box 22, then Box 24, in the shape of a rectangle" "Initiate monotherapy with LAMA (see **Recommendation 7**)"
        i. Box 24 connects to Box 25.
7. Box 25, in the shape of an oval: "Follow-Up Management; consider referral for Pulmonary Rehabilitation"

---

[b]: COPD exacerbations are treatment failures and exacerbations can result in disease progression

Module C: Follow Up Management of COPD

1. Module C begins with Box 26, in the shape of a rounded rectangle: "Patient with COPD already on maintenance therapy[c]; ensure patient is prescribed SABA as needed and ensure proper inhaler technique/adherence"
8. Box 26 connects to Box 27, in the shape of a hexagon, asks the question: "Is there suspicion of an acute exacerbation? (see **Sidebar 2**)"
    a. If the answer is "Yes" to Box 27, then Box 28, in the shape of an oval: "Manage exacerbation (see **Module D**)"
    b. If the answer is "No" to Box 9, then Box 29.

2. Box 29, in the shape of a hexagon, asks the question: "Has the patient had any moderate or severe exacerbations in the past year? (see **Sidebar 4**)"
    a. If the answer is "Yes" to Box 29, then Box 30.
    b. If the answer is "No" to Box 29, then Box 34.
3. Box 30, in the shape of a hexagon, asks the question: "Is the patient already on triple therapy (LABA/LAMA/ICS)?"
    a. If the answer is "Yes" to Box 30, then Box 31, in the shape of an oval: "Consider Pulmonary Referral for advanced therapy."
        i. Box 31 connects to Box 33.
    b. If the answer is "No" to Box 30, then Box 32, in the shape of a rectangle: "Initiate triple therapy with LABA/LAMA/ICS (see **Recommendation 9**)"
        i. Box 32 connects to Box 33.
4. Box 34, in the shape of a hexagon, asks the question: "Are symptoms still bothersome?"
    a. If the answer is "Yes" to Box 34, then Box 35, in the shape of a rectangle:
    "- If on monotherapy, advance to LABA/LAMA
    - If on LABA/LAMA, consider pulmonary referral for advanced therapy
    - Re-evaluate the need for supplemental oxygen therapy (see **Recommendations 15 and 16**)
    - Consider pulmonary rehabilitation (see **Recommendations 17 and 18**)"
        i. Box 35 connects to Box 33.
    b. If the answer is "No" to Box 34, then Box 36.
5. Box 36, in the shape of a hexagon, asks the question: "Does the therapy include an ICS?"
    a. If the answer is "Yes" to Box 36, then Box 37, in the shape of a rectangle:
    "Consider ICS discontinuation trial if:
    a) No exacerbations in the last year AND
    b) Low blood eosinophils (<300 cells/mcL) (see **Recommendation 11**)"
        i. Box 37 connects to Box 33.
    b. If the answer is "No" to Box 35, then Box 33.
6. Box 33, in the shape of an oval: "Continue follow-up and reassessment (as above)"

---

[c]: Stable patients on ICS/LABA, should be switched to either LABA/LAMA or triple therapy based on moderate/severe exacerbations and EOS ≥300 cells/mcL (see **Recommendation 8 and 9** narratives for details)

Module D: Management of Acute COPD Exacerbations

1. Module C begins with Box 38, in the shape of a rounded rectangle: "Suspected COPD exacerbation (See **Sidebar 2**). Note: Rule out other etiologies (e.g., heart failure, pulmonary emboli, pneumonia, etc.); ensure proper inhaler technique/adherence"
2. Box 38 connects to Box 39, in the shape of a hexagon, asks the question: "Is patient appropriate for outpatient management? (see **Sidebar 6**)"
    a. If the answer is "No" to Box 39, then Box 40, in the shape of an oval:
    "Severe Exacerbation (requires ED and/or hospitalization):
    • Pre-treat with bronchodilators and oxygen as available and clinically indicated
    • Arrange for transfer
    • Arrange for follow-up and consider referral to pulmonary specialist and pulmonary rehabilitation; consider medication adjustments and vaccination record"

   b. If the answer is "Yes" to Box 39, then Box 41.
3. Box 41, in the shape of a hexagon, asks the question:
   "Does the patient have an acute exacerbation and one or more of the following characteristics present?
   • Significant dyspnea (≥ 5 on scale of 0 [none] to 10 [worst dyspnea ever])
   • Purulent sputum
   • Respiratory rate ≥ 24 breaths/minute
   • Increased work of breathing
   • Resting pulse oxygen saturation below baseline
   • Heart rate ≥ 95 beats/minute)"
      a. If the answer is "No" to Box 41, then Box 42, in the shape of rectangle: "Mild Exacerbation: Augment/start short-acting bronchodilators (see **Sidebar 7A**)"
         i. Box 42 connects to Box 45, in the shape of an oval: "Follow-up plan, including home oxygen assessment; consider pulmonary referral and pulmonary rehabilitation; consider medication adjustments and vaccinations"
      b. If the answer is "Yes" Box 41, then Box 43, in the shape of a rectangle: "Moderate Exacerbation: Augment/start short-acting bronchodilators & initiate a 5-day course of systemic corticosteroids (see **Recommendation 13; Sidebar 7B**)"
4. Box 43 connects to Box 44, in the shape of a hexagon, asks: "Are two or three of the following symptoms present
   - Increased dyspnea
   - Increased sputum volume
   - Sputum purulence?"
      a. If the answer is "No" to Box 44, then Box 45.
      b. If the answer is "Yes" to Box 44, then Box 46, in the shape of a rectangle: "Initiate antibiotics (see **Recommendation 14; Sidebar 7C**)"
         i. Box 46 connects to Box 45.

Appendix H. Pharmacotherapy

Refer to current product information for additional prescribing information.

Table H-1. Short-Acting Beta 2-agonist (SABA) Products

Product		Delivery	Strength	Dosing	Doses per Unit
Hand-held Devices	Albuterol ProAir Respiclick	DPI	90 mcg	2 inhalations every 4-6 hours as needed (Max: 2 inhalations every 4 hours)	200
	Albuterol ProAir HFA Proventil HFA Ventolin HFA	MDI			
	Levalbuterol Xopenex HFA	MDI	45 mcg	1 or 2 inhalations every 4-6 hours as needed (Max: 2 inhalations every 4 hours)	
Nebulizers	Albuterol sulfate solution	Neb	2.5 mg/3 mL	Inhale contents of 1 vial every 6-8 hours as needed over 5-15 minutes (Max: 10 mg/day)	30
	Levalbuterol solution Xopenex	Neb	0.63 mg/3 mL	Inhale contents of 1 vial every 6-8 hours as needed for 3 doses/day (Max: 3.75 mg/day)	25
			1.25 mg/3 mL		

Abbreviations: DPI: dry powder inhaler; HFA: hydrofluoroalkane; mcg: microgram; MDI: metered-dose inhaler; mg: milligram; mL: milliliter; Neb: nebulized solution; SABA: short-acting beta 2-agonist

Table H-2. Short-Acting Muscarinic Antagonist (SAMA)(148) Products

Product		Delivery	Strength	Dosing	Doses per Unit
Hand-held Devices	Ipratropium Atrovent HFA	MDI	17 mcg	2 inhalations 4 times/day (Max: 12 inhalations/day)	200
Nebulizers	Ipratropium bromide solution	Neb	500 mcg/25 mL	Inhale contents of 1 vial every 6-8 hours (Max: 2000 mcg/day)	30

Abbreviations: HFA: hydrofluoroalkane; mcg: microgram; MDI: metered-dose inhaler; mg: milligram; mL: milliliter; Neb: nebulized solution; SAMA: short-acting muscarinic antagonist

Table H-3. SABA + SAMA (148) Products

Product		Delivery	Strength	Dosing	Doses per Unit
Hand-held Devices	Ipratropium/Albuterol Combivent Respimat	SMI	20/100 mcg	1 inhalation 4 times/day (Max: 6 inhalations/day)	120
Nebulizers	Ipratropium/Albuterol solution DuoNeb	Neb	0.5/3 mg/3 mL	Inhale contents of 1 vial (3 mL) every 6 hours (Max: 3/18 mg/day)	30

Abbreviations: mcg: microgram; mg: milligram; mL: milliliter; Neb: nebulized solution; SABA: short-acting beta 2-agonist; SAMA: short-acting muscarinic antagonist; SMI: slow mist inhaler

Table H-4. Long-Acting Beta 2-Agonist (LABA) Products

Product		Delivery	Strength	Dosing	Doses per Unit
Hand-held Devices	Indacaterol Arcapta Neohaler	DPI	75 mcg	Inhale contents of 1 capsule once daily (Max: 300 mcg/day)	30
	Olodaterol Striverdi Respimat	SMI	2.5 mcg	2 inhalations once daily (Max: 5 mcg/day)	60
	Salmeterol Serevent Diskus	DPI	50 mcg	1 inhalation twice daily (Max: 100 mcg/day)	60
Nebulizers	Arformoterol solution Brovana	Neb	15 mcg/2 mL	Inhale contents of 1 vial twice daily (Max: 30 mcg/day)	60
	Formoterol solution Perforomist	Neb	20 mcg/2 mL	Inhale contents of 1 vial twice daily (Max: 40 mcg/day)	60

Abbreviations: DPI: dry powder inhaler; LABA: long-acting beta 2-agonist; mcg: microgram; mg: milligram; mL: milliliter; Neb: nebulized solution; SMI: slow mist inhaler

Table H-5. Long-Acting Muscarinic Antagonists (LAMA) Products

Product		Delivery	Strength	Dosing	Doses per Unit
Hand-held Devices	Aclidinium Tudorza Pressair	DPI	400 mcg	1 inhalation twice daily (Max: 800 mcg/day)	60
	Tiotropium Spiriva Handihaler	DPI	18 mcg	Inhale contents of 1 capsule once daily (Max: 18 mcg/day)	30
	Tiotropium Spiriva Respimat	SMI	2.5 mcg	2 inhalations once daily (Max: 5 mcg/day)	60
	Umeclidinim Incruse Ellipta	DPI	62.5 mcg	1 inhalation once daily (Max: 62.5 mcg/day)	30
Nebulizers	Revefenacin solution Yupelri	Neb	175 mcg/3 mL	Inhale contents of 1 vial once daily (Max: 175 mcg/day)	30

Abbreviations: DPI: dry powder inhaler; mcg: microgram; mL: milliliters; Neb: nebulized solution; SMI: slow mist inhaler

Table H-6. LAMA + LABA Products

Product		Delivery	Strength	Dosing	Doses per Unit
Hand-held devices	Aclidinium/Formoterol Duaklir Pressair	DPI	400/12 mcg	1 inhalation twice daily (Max: 2 inhalations/day)	60
	Glycopyrrolate/Formoterol Bevespi Aerosphere	MDI	9/4.8 mcg	2 inhalations twice daily (Max: 4 inhalations/day)	120
	Tiotropium/Olodaterol	SMI	2.5/2.5 mcg	2 inhalations once daily	60

Product		Delivery	Strength	Dosing	Doses per Unit
	Stiolto Respimat			(Max: 2 inhalations/day)	
	Umeclidinium/Vilanterol Anoro Ellipta	DPI	62.5/25 mcg	1 inhalation once daily (Max: 1 inhalation/day)	30

Abbreviations: DPI: dry powder inhaler; LABA: long-acting beta 2-agonist; LAMA: long-acting muscarinic antagonist; mcg: microgram; MDI: metered-dose inhaler; mg: milligram; mL: milliliter; SMI: slow mist inhaler

Table H-7. Inhaled Corticosteroids (ICS) Products*

Product		Delivery	Strength	Dosing	Potency of Steroid	Doses per Unit
Hand-held devices	Beclomethasone Qvar RediHaler	Breath-actuated MDI	40 mcg	1 or 2 inhalations twice daily	Low	120
			80 mcg	1 or 2 inhalations twice daily (Max: 320 mcg twice daily)	Low/Med/ High	
	Budesonide Pulmicort Flexhaler	DPI	90 mcg	1 or 2 inhalations twice daily	Low	60
			180 mcg	1 or 2 inhalations twice daily (Max: 720 mcg twice daily)	Low/Med/ High	120
	Ciclesonide Alvesco HFA	MDI	80 mcg	1 or 2 inhalations twice daily	Low/Med	60
			160 mcg	1 or 2 inhalations twice daily (Max: 320 mcg twice daily)	Med/High	
	Fluticasone furoate Arnuity Ellipta	DPI	100 mcg	1 or 2 inhalations once daily (Max: 200 mcg/day)	Low/High	30
			200 mcg	1 inhalation once daily (Max: 200 mcg/day)	High	
	Fluticasone propionate ArmonAir Digihaler Flovent Diskus	DPI	55 mcg	1 or 2 inhalations twice daily	Low	60
			113 mcg	1 or 2 inhalations twice daily (Max: 223 mcg twice daily)	Low/Med	
			232 mcg	1 inhalation twice daily (Max: 223 mcg twice daily)	Med	
			50 mcg	1 or 2 inhalations twice daily	Low	
			100 mcg	1 or 2 inhalations twice daily	Low/Med	
			250 mcg	1 or 2 inhalations twice daily (Max: 1000 mcg twice daily)	Med/High	
	Fluticasone propionate Flovent HFA	MDI	44 mcg	1 or 2 inhalations twice daily	Low	120
			110 mcg	1 or 2 inhalations twice daily	Low/Med	
			220 mcg	1 or 2 inhalations twice daily (Max: 880 mcg twice daily)	Med/High	

Product		Delivery	Strength	Dosing	Potency of Steroid	Doses per Unit
Hand-held devices (cont.)	Mometasone Asmanex HFA Asmanex Twisthaler	MDI	100 mcg	1 or 2 inhalations twice daily	Low	120
			200 mcg	1 or 2 inhalations twice daily (Max: 800 mcg/day)	Med/High	
		DPI	110 mcg	1 or 2 inhalations daily	Low	60
			220 mcg	1 or 2 inhalations daily (Max: 440 mcg/day)	Low/Med	
Nebulizers	Budesonide suspension Pulmicort	Neb	0.25 mg/2 mL	Inhale contents of 1 respule once daily	Low	30
			0.5 mg/2 mL	Inhale contents of 1 or 2 respules once or twice daily	Med/High	

*Not to be used alone in COPD; use in combination with LAMA and LABA (as triple therapy in one or two inhalers)
Abbreviations: DPI: dry powder inhaler; HFA: hydrofluoroalkane; mcg: microgram; Med: medium; MDI: metered-dose inhaler; mg: milligram; mL: milliliter; Neb: nebulized solution

Table H-8. ICS + LABA devices recommended for use with LAMA (See Table H-5) Products*

Product		Delivery	Strength	Dosing	Potency of Steroid	Doses per Unit
Hand-held devices	Budesonide/ Formoterol Symbicort Breyna authorized generic	MDI	80/4.5 mcg	2 inhalations twice daily	Low	120
			160/4.5 mcg	2 inhalations twice daily (Max: 320/9 mcg twice daily)	Med	
	Fluticasone furoate/ Vilanterol Breo Ellipta	DPI	100/25 mcg	1 inhalation once daily	Low	30
			200/25 mcg	1 inhalation once daily (Max: 200/25 mcg daily)	High	
	Fluticasone propionate/ Salmeterol Advair Diskus Wixela Inhub Authorized generic	DPI	250/50 mcg	1 inhalation twice daily (Max: 250/50 mcg twice daily) (FDA approved for this dose)	Med	60
Hand-held devices (cont.)	Fluticasone propionate/ Salmeterol Advair HFA	MDI	45/21 mcg	2 inhalations twice daily	Low	120
			115/21 mcg	2 inhalations twice daily	Med	
			230/21 mcg	2 inhalations twice daily (Max: 460/42 mcg twice daily)	High	
	Mometasone/ Formoterol Dulera	MDI	100/5 mcg	2 inhalations twice daily	Med	120
			200/5 mcg	200/5 mcg: 2 inhalations twice daily (Max: 400/10 mcg twice daily)	High	

*Must be used with LAMA in COPD (as triple therapy)
Abbreviations: DPI: dry powder inhaler; HFA: hydrofluoroalkane; ICS: inhaled corticosteroid; LABA: long-acting beta 2-agonist; LAMA: long-acting muscarinic antagonist; mcg: microgram; MDI: metered-dose inhaler; mg: milligram; mL: milliliter

Table H-9. ICS + LABA + LAMA Products

Product		Delivery	Strength	Dosing	Potency of Steroid	Doses per Unit
Single Inhalers	Budesonide/ Glycopyrrolate/ Formoterol fumarate Breztri Aerosphere	MDI	160/9/4.8 mcg	2 inhalations twice daily	Med	120
	Fluticasone furoate/Vilanterol/ Umeclidinium Trelegy Ellipta	DPI	100/25/62.5 mcg	1 inhalation once daily	Low	30
	Beclomethasone dipropionate / Formoterol fumarate / Glycopyrrolate Trimbow	MDI	86/4.9/10.6/86 mcg	2 inhalations twice daily	Medium	120
Multiple Inhalers*	Fluticasone furoate Arnuity Ellipta + Tiotropium/ Olodaterol Stiolto Respimat	DPI	100 mcg	1 inhalation once daily	Low	30
		SMI	2.5/2.5 mcg	2 inhalations once daily		60
	Fluticasone propionate Flovent Diskus + Umeclidinium/ Vilanterol Anoro Ellipta	DPI	100 mcg	1 or 2 inhalations twice daily	Low/Med	60
		DPI	62.5/25 mcg	1 inhalation once daily		30
	Mometasone Asmanex Twisthaler + Tiotropium/ Olodaterol Stiolto Respimat	DPI	220 mcg	1 or 2 inhalations daily	Low/Med	60
		SMI	2.5/2.5 mcg	2 inhalations once daily		60

*Based on individual formularies, cost, and preferences, triple therapy may be achieved by using a single inhaler (LABA+LAMA+ICS) or by using a 2-drug fixed-dose combination (LAMA+LABA preferred in COPD) + a single inhaler (ICS preferred in COPD) (e.g., see below [NOT an all-inclusive list])

Abbreviations: COPD: chronic obstructive pulmonary disease; DPI: dry powder inhaler; ICS: inhaled corticosteroid; LABA: long- acting beta 2-agonist; LAMA: long-acting muscarinic antagonist; mcg: microgram; SMI: slow mist inhaler

Table H-10. Comments by Drug Class*

Drug Class	Comments
Beta 2-Agonists	LABAs increase the risk of asthma-related death; do not use as monotherapy in asthma
	May cause palpitations, chest pain, rapid heart rate, increased blood pressure, tremor, nervousness
	Decreases in potassium levels have occurred

Drug Class	Comments
	SABAs are used for acute treatment of bronchospasm; LABAs are used for chronic treatment of bronchospasm
	Indacaterol: capsules are for oral inhalation only; capsules should not be swallowed; administer using supplied inhalation device only
Muscarinic Antagonist Agents	Use with caution in patients with narrow angle glaucoma, prostatic hyperplasia, or bladder neck obstruction
	Caution patients against getting product in eyes; temporary blurred vision may result
	For relief of dry mouth, suggest use of saliva substitute, practice of good oral hygiene, rinsing of mouth after inhalation; instruct patient to take sips of water frequently, suck on ice chips or sugarless hard candy, or chew sugarless gum
	Tiotropium: capsules are for oral inhalation only; capsules should not be swallowed; administer using supplied inhalation device only
Inhaled Glucocorticoids	Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported
	Increased risk of pneumonia
	Advise patients to rinse mouth after inhalation to reduce risk of oral fungal infections (e.g., oropharyngeal candidiasis)

Note: Each drug class has agents available in a dry powder formulation, appropriate for patients with adequate inspiratory flow. Dry powder formulations contain lactose and small amounts of milk proteins; do not use in patients with severe hypersensitivity to milk proteins.

* Table not intended as a comprehensive list of all warnings, precautions, and risks. Abbreviations: LABA: long-acting beta 2-agonist; SABA: short-acting beta 2-agonist

Appendix I: Standardized Questionnaires

Standardized questionnaires may help clinicians assess symptom burden. Two commonly used questionnaires are the mMRC and the CAT. The mMRC is a simple tool that can be used to assess dyspnea in multiple medical conditions.(6) The CAAT is a more complex questionnaire that is specific to COPD.(49)

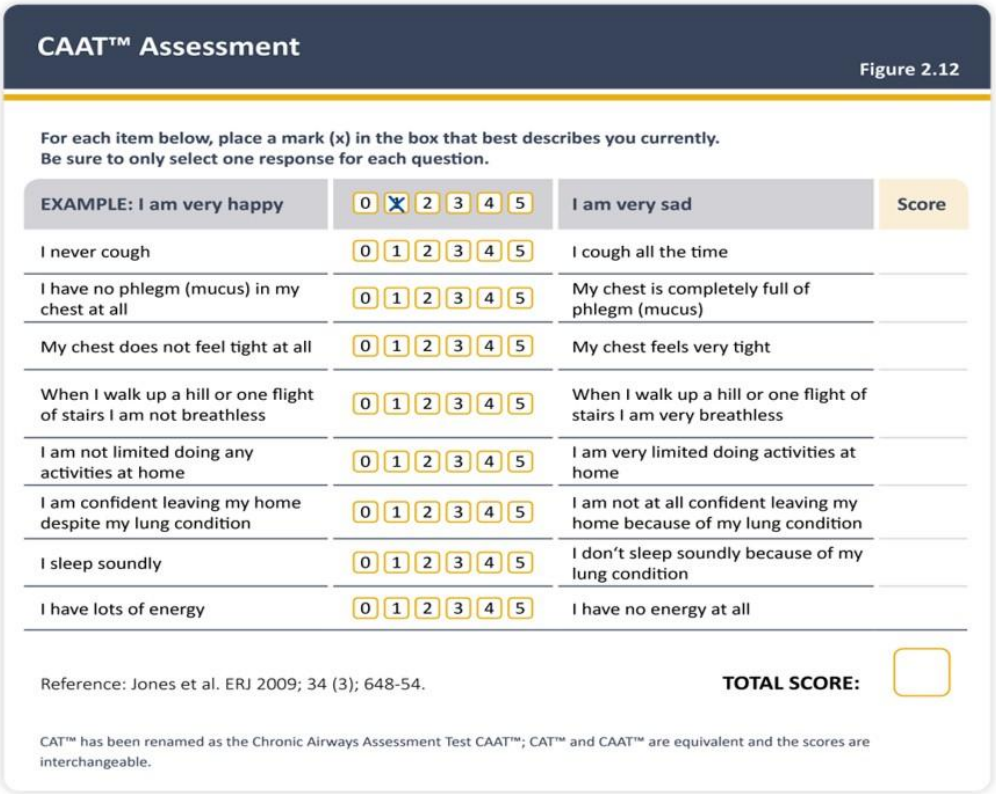
A. Modified Medical Research Council Questionnaire

Table I-1. mMRC (6)

Grade	Description of Breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

B. COPD Airways Assessment Test

Figure I-1. CAAT (49)



CAAT™ Assessment

Figure 2.12

For each item below, place a mark (x) in the box that best describes you currently.
Be sure to only select one response for each question.

EXAMPLE: I am very happy	0 X 2 3 4 5	I am very sad	Score
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

Reference: Jones et al. ERJ 2009; 34 (3); 648-54.

TOTAL SCORE:

CAT™ has been renamed as the Chronic Airways Assessment Test CAAT™; CAT™ and CAAT™ are equivalent and the scores are interchangeable.

Alternative Text: Figure I-1. Screenshot of the COPD Airways Assessment Test (CAAT) questionnaire. The form includes eight labeled questions with a 0-5 scale for responses, an example marked answer at the top of the questionnaire, and a section for total score at the bottom of the questionnaire. The questions address cough, phlegm, chest tightness, breathlessness, activity limitations, confidence with leaving home, sleep, and energy.

Appendix J: Inhaler Techniques

It is very common to discover patients not using their inhaler(s) as they are designed. Incorrect inhaler technique can lead to an assumption of treatment failure. It is critical to assess a patient's inhaler technique before the determination of treatment failure.

Instructional graphics for meter-dose inhalers (MDI), dry powder inhalers (DPI), Respimat inhalers as well as inhaler demonstration videos can be found within Appendix J in the following pages below.

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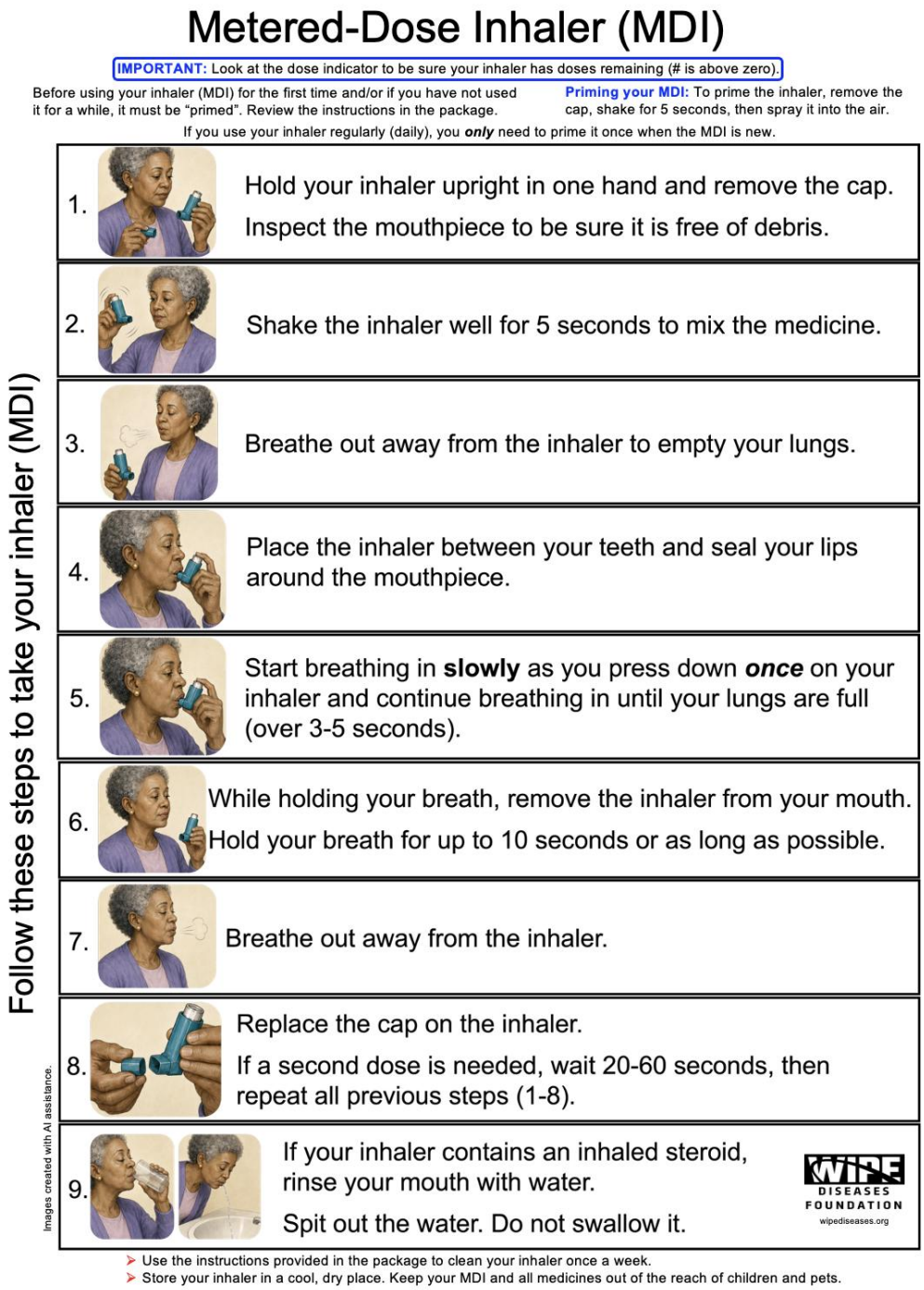
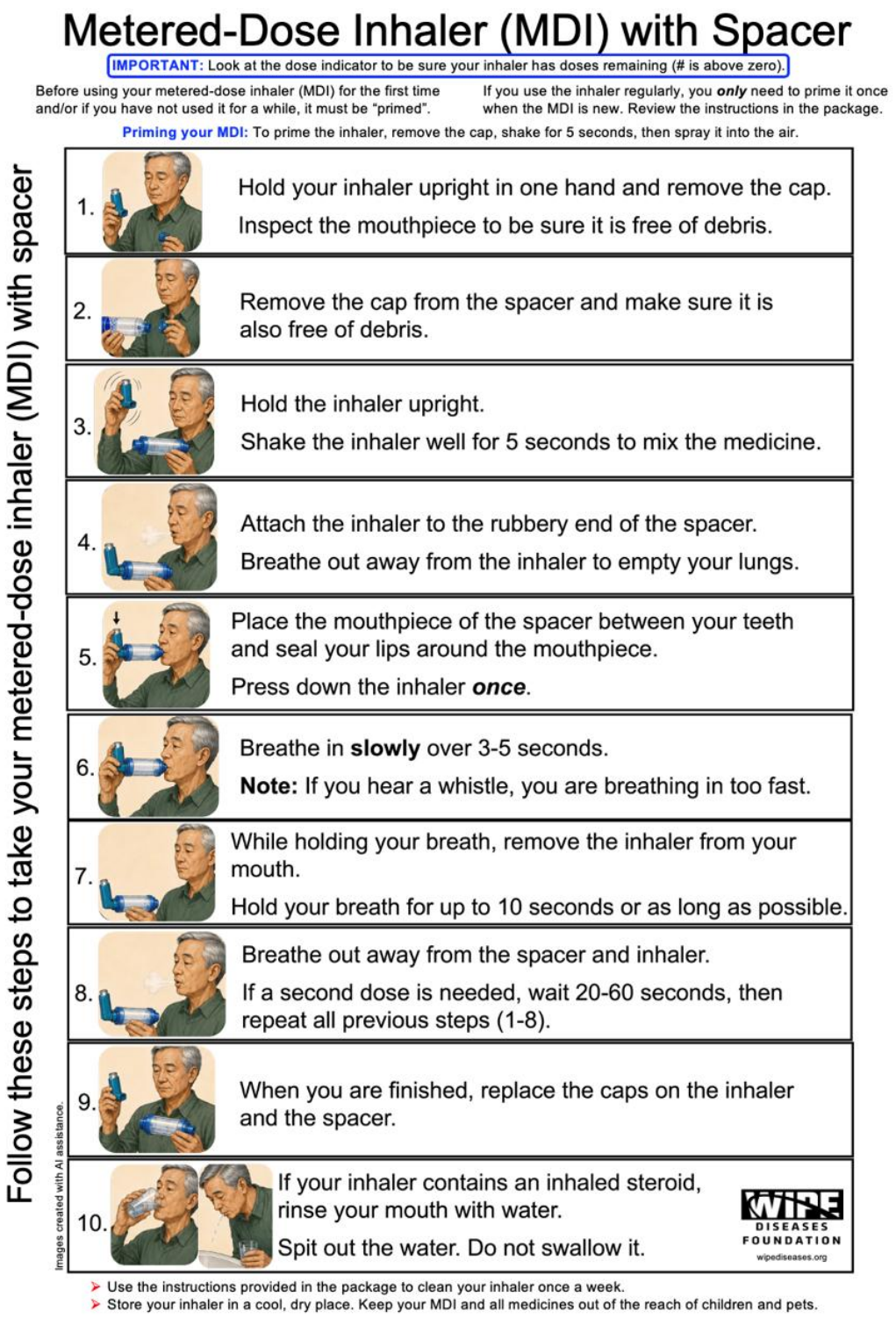
A. Metered-Dose Inhaler

Figure J-1. How to correctly use a metered-dose inhaler (MDI)(149)



Alternative Text: Figure J-1. Instructional graphic illustrating nine sequential steps for proper use of a metered-dose inhaler (MDI), featuring labeled boxes with photos of a person demonstrating each step. Key steps include priming instructions, slow-inhalation timing, breath-holding guidance, and cleanup after use.

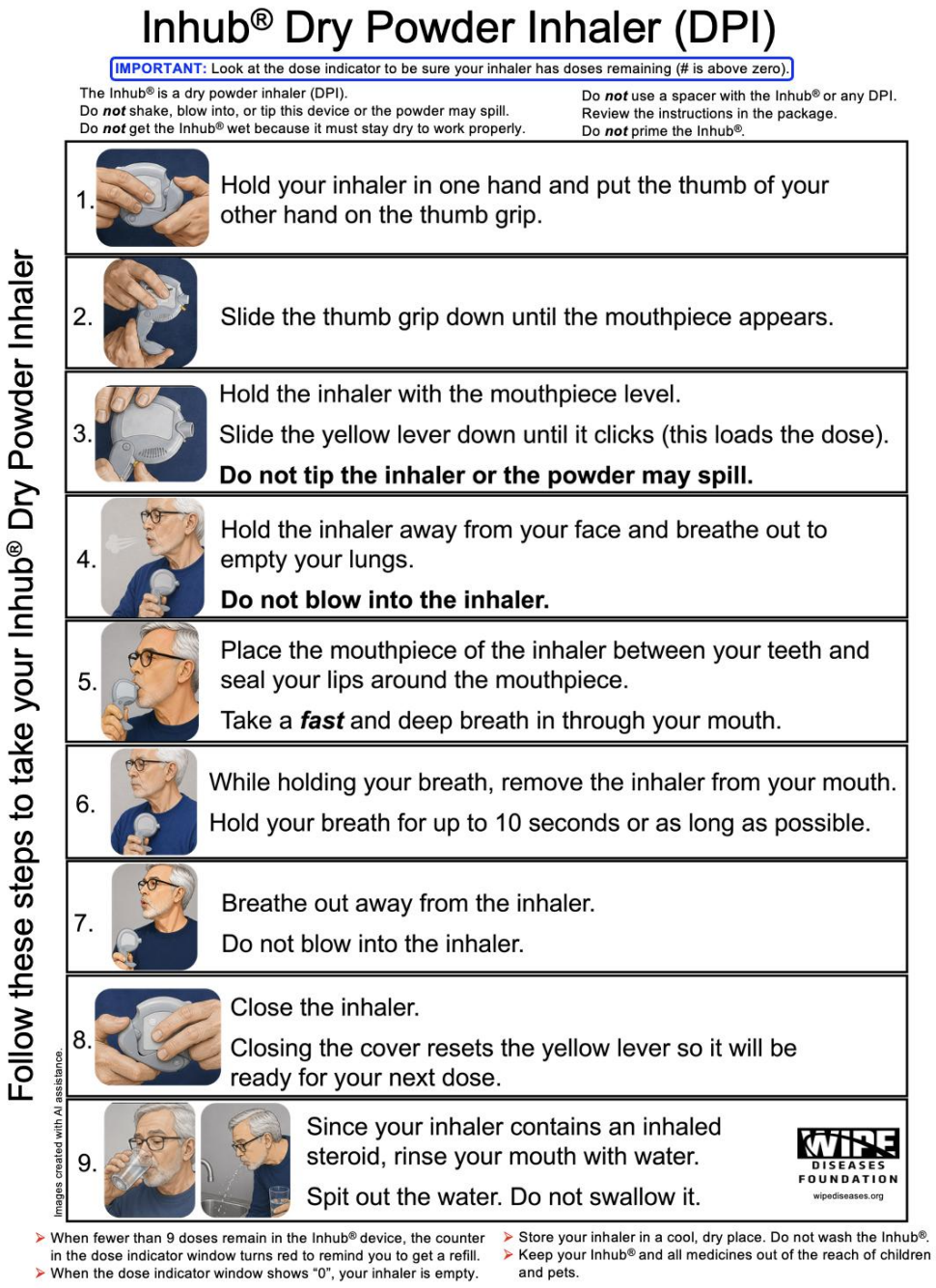
Figure J-2. How to correctly use an MDI with a spacer (149)



Alternative Text: Figure J-2. Instructional graphic illustrating 10 sequential steps for proper use of a metered-dose inhaler (MDI) with spacer, featuring labeled boxes with photos of a person demonstrating each step. Key steps include priming instructions, slow-inhalation timing, breath-holding guidance, and cleanup after use.

B. Dry Powder Inhalers

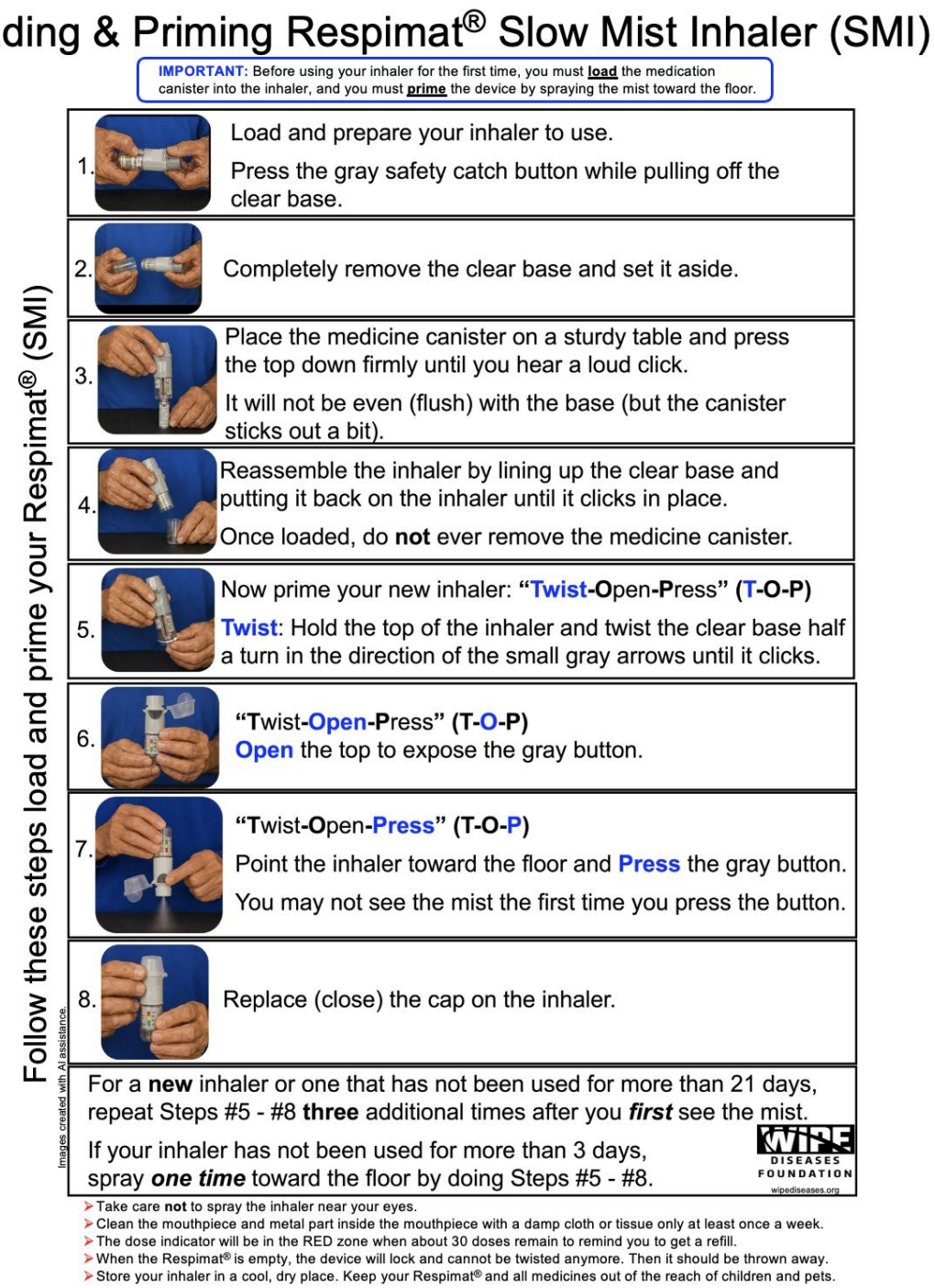
Figure J-3. How to correctly use an Inhub dry powder inhaler (DPI)([149])



Alternative Text: Figure J-3. Instructional graphic illustrating 9 sequential steps for proper use of an inhub dry powder inhaler (DPI), featuring labeled boxes with photos of a person demonstrating each step. Key steps include griping instructions, fast-inhalation timing, breath-holding guidance, and cleanup after use.

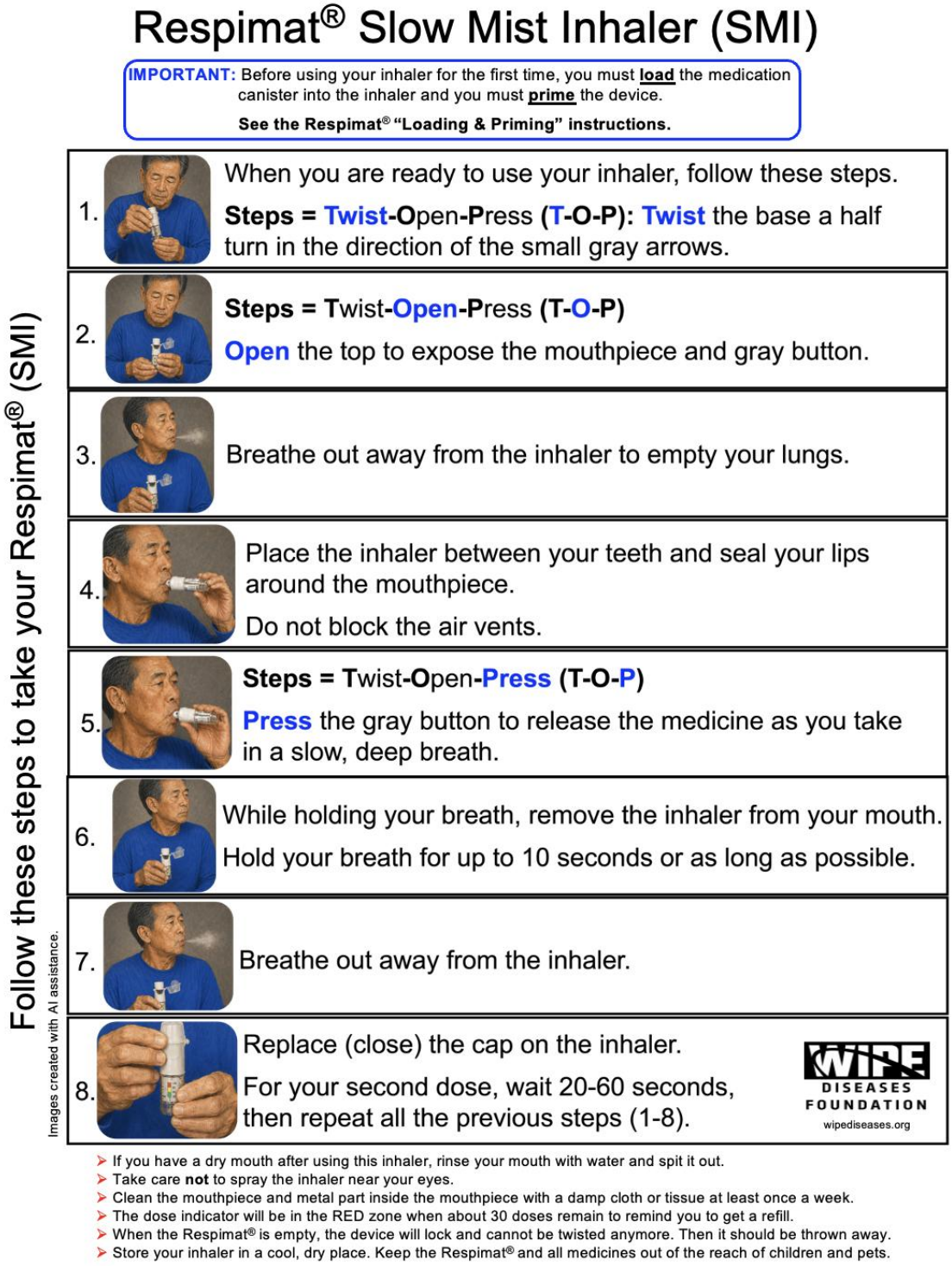
C. Respimat Inhalers

Figure J-4. How to correctly load and prime a Respimat Slow Mist Inhaler (SMI)(149)



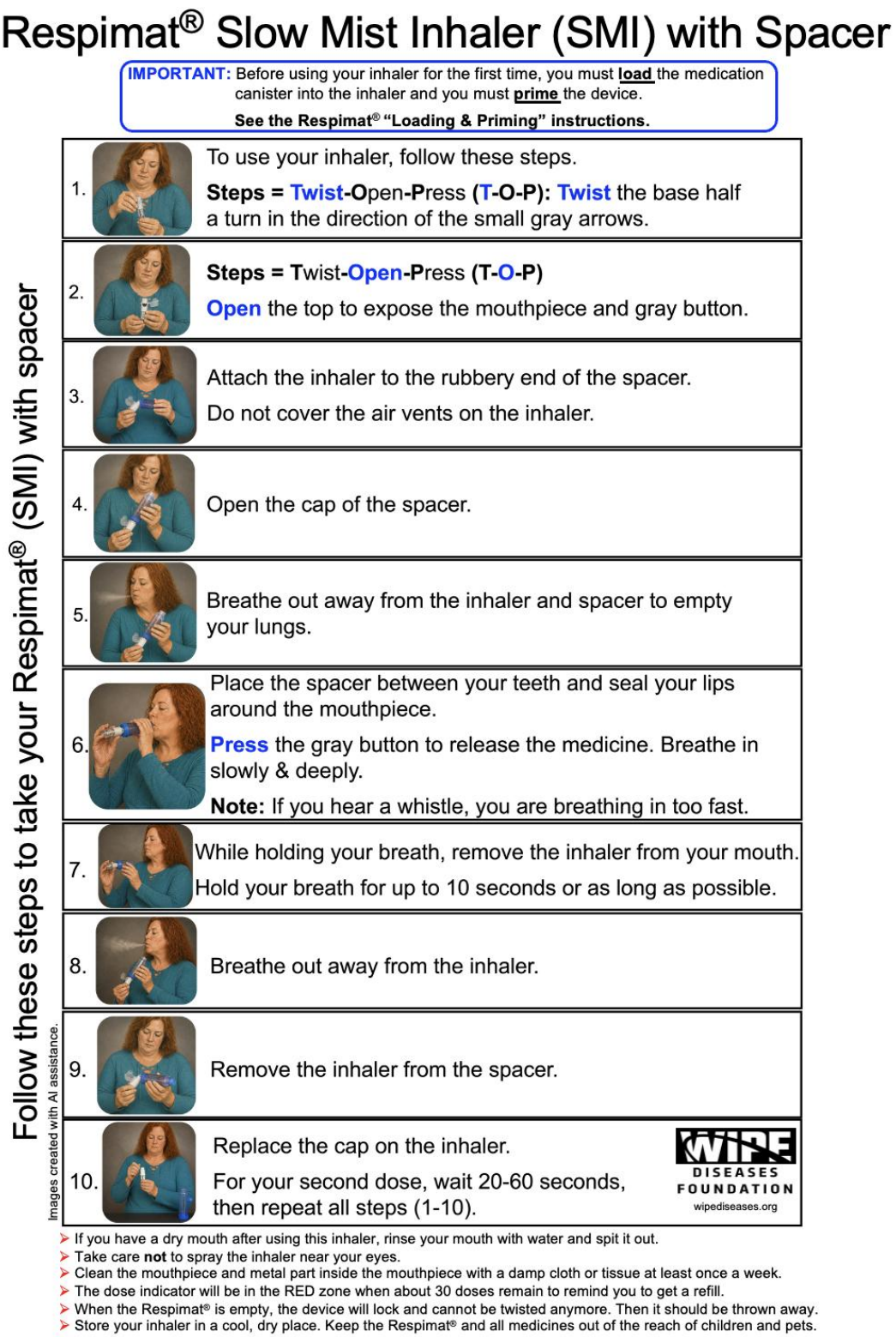
Alternative Text: Figure J-4. Instructional graphic illustrating 8 sequential steps for proper loading and priming of a Respimat slow mist inhaler (SMI), featuring labeled boxes with photos of a person demonstrating each step. Key steps include base removal, medication insertion, and twisting instructions to prime the inhaler.

Figure J-5. How to correctly use a Respimat Slow Mist Inhaler (SMI)(149)



Alternative Text: Figure J-5. Instructional graphic illustrating 8 sequential steps for proper use of Respimat slow mist inhaler (SMI), featuring labeled boxes with photos of a person demonstrating each step. Key steps include opening of the SMI and inhalation instructions, breath-holding guidance, and second-dose use instructions.

Figure J-6. How to correctly use a Respimat Slow Mist Inhaler (SMI) with spacer (149)

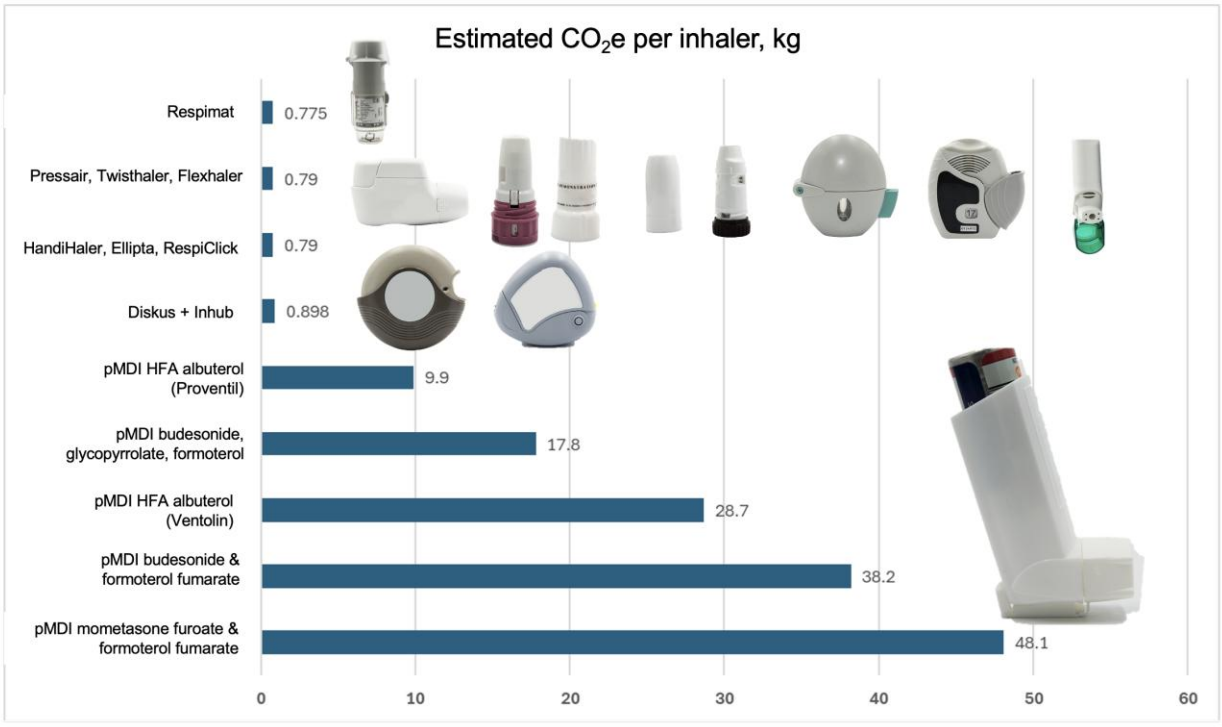


Alternative Text: Figure J-6. Instructional graphic illustrating 10 sequential steps for proper use of Respimat slow mist inhaler (SMI) with spacer, featuring labeled boxes with photos of a person demonstrating each step. Key steps include opening of the SMI and spacer attachment instructions, breath-holding guidance, and second-dose use instructions.

D. Inhaler Emissions

DPIs: Diskus, Ellipta, Flexhaler, HandiHaler, Inhub, Pressair, Respiclick and SMI: Respimat each produce less than 1 kg of carbon dioxide equivalents (CO_2e) per inhaler (ranging from 0.775 to 0.898 kg). In contrast, the pressurized metered dose inhalers (pMDIs) produce 10 to 48 times more emissions (ranging from 9.9 kg CO_2e for one of the albuterol formulations (Proventil) to 28.7 kg CO_2e for Ventolin and up to 48.1 kg CO_2e for mometasone/formoterol).(150,151)
For reference, 10 kg of CO_2e equals 25.6 miles driven in an average gasoline-powered passenger vehicle.(152)

Figure J-7. Estimated CO_2e per Inhaler (152)

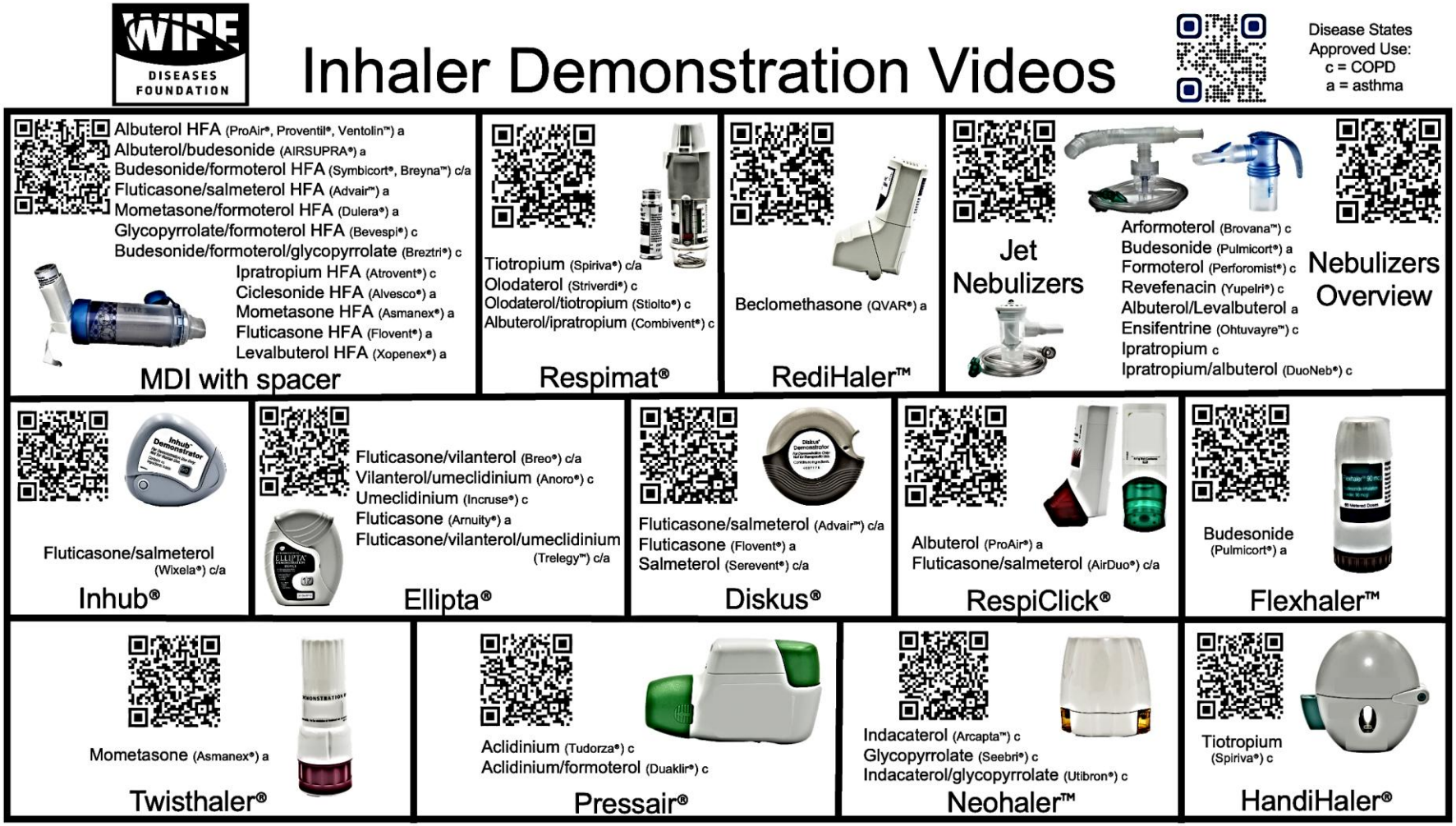


Data sourced from: Tirumalasetty J, Miller SA, Prescott HC, et al. Greenhouse Gas Emissions and Costs of Inhaler Devices in the US. *JAMA*. 2024;332(12):1017–1019. doi:10.1001/jama.2024.1533

Alternative Text: Figure J-7. Bar chart comparing estimated CO2 emissions per inhaler in kilograms, with images of each inhaler type displayed above their respective bars. The data indicates that dry powder inhalers (DPIs) and soft mist inhalers have lower emissions, ranging from 0.775 to 0.896 kg, while pressurized metered-dose inhalers (pMDIs) produce much higher emissions, between 9.9 and 48.1 kg.

E. Inhaler Demonstration Videos

Figure J-8. QR codes for WipeDiseases Foundation Demonstration Videos (153)



Alternative Text: Figure J-8. A diagram displaying images of various respiratory inhaler devices, including MDI with spacer, Respimat, RediHaler, Jet Nebulizers, and multiple branded inhalers like Inhub, Ellipta, Diskus, RespiClick, Flexhaler, Twisthaler, Pressair, Neohaler, and HandiHaler. Each inhaler lists its active ingredients and includes QR codes linking directly to instructional videos.

VHA Links to Inhaler Demonstration Videos

English Versions

- HOW TO USE NEBULIZER: https://youtu.be/UKUClmyRC2Q
- HOW TO USE MDI: https://youtu.be/yQiGzELcMg4
- HOW TO USE RESCUE: Proper Inhaler Use - Albuterol - YouTube
- HOW TO USE RESPIMAT: https://youtu.be/In6zmUHVdfE
- HOW TO USE TWISTHALER: https://youtu.be/-VBAvheKvM0
- HOW TO USE HANDIHALER: https://youtu.be/8TYU73CZvi0
- HOW TO USE DISK: How to use your Fluticasone/Salmeterol Inhaler (Wixela Inhub) - YouTube

Spanish Versions

- HOW TO USE NEBULIZER: Cómo Utilizar su Nebulizador - YouTube
- HOW TO USE MDI: https://youtu.be/yQiGzELcMg4
- HOW TO USE RESPIMAT: Cómo Utilizar su Inhalador Respimat - YouTube
- HOW TO USE TWISTHALER: Cómo utilizar su Twisthaler - YouTube
- HOW TO USE HANDIHALER: Cómo Utilizar su Handihaler - YouTube

Appendix K: Individualized Management Plan

The individualized management plan (IMP) can provide positive patient engagement and help patients develop skills in the daily management of COPD. Physicians and/or health professionals should include the patient in the development of their IMP to increase understanding of COPD condition, medication, exacerbation risks, exacerbation action plan, and to help improve QoL. Positive patient engagement and motivation will increase knowledge, skills, and adjustment to COPD condition. The IMP may include the following:

Assessment and Management of Modifiable Risk Factors

- Tobacco smoking and cessation (see **Recommendations 4 and 5** and **VA/DOD Tobacco Use Treatment CPG**)
- Vaccination (see **Recommendation 6**)
- Nutrition (malnutrition)
- Activity/Exercise
- Mental health
- Substance use including alcohol
- Air quality
- Housing insecurity

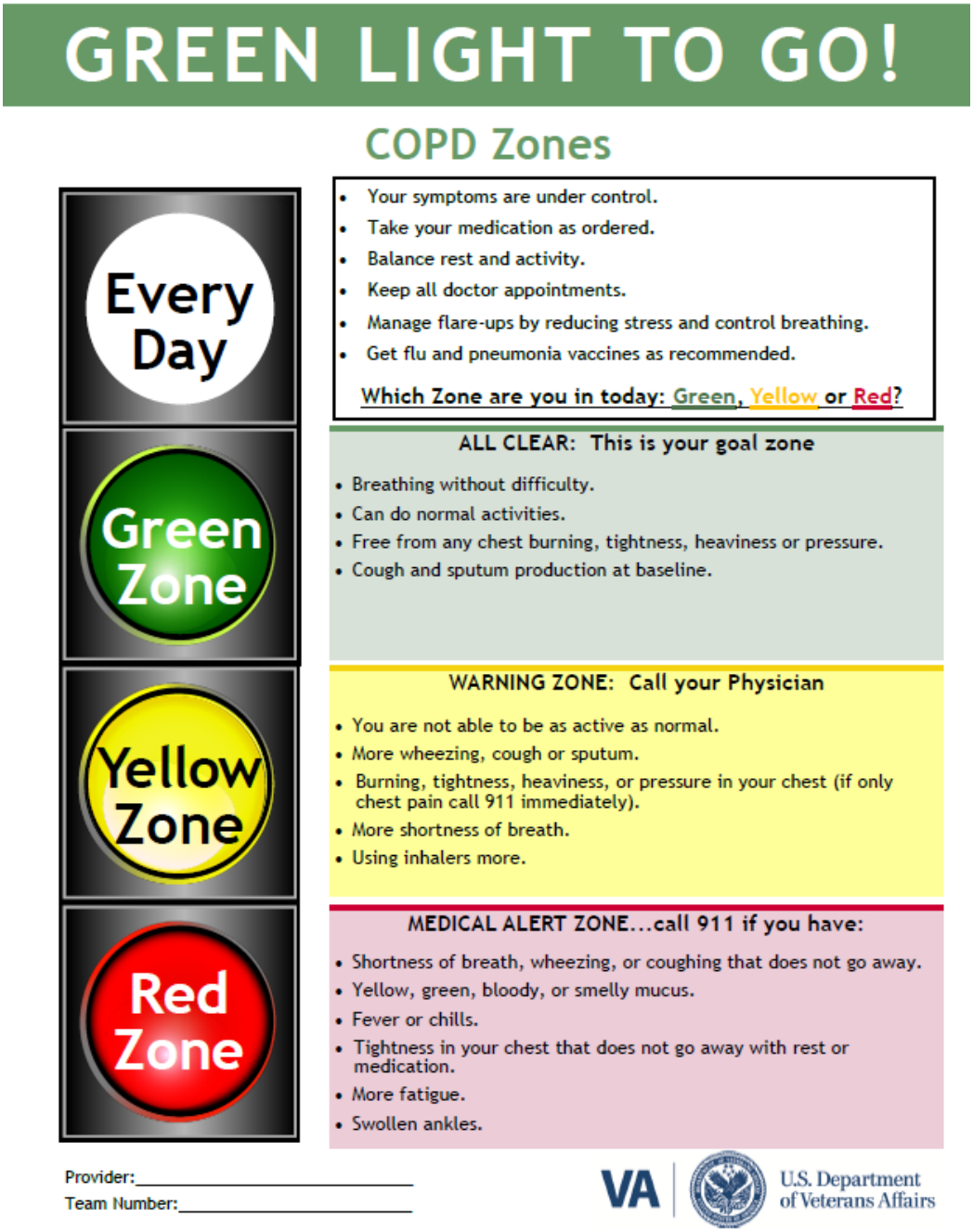
Assessment of Symptoms by CAAT and/or mMRC (see Appendix I, Figures A & B)

Additional Management Considerations

- Patient and/or caregiver education and support (for example see **Background F**; refer to Veterans Health Library)
- Management of co-occurring conditions that may worsen COPD (see **CPG pg. 9**)
- Lung cancer screening as appropriate
- Pharmacological management (see **Module B and Module C**)
- Oxygen therapy (see **Recommendations 15 and 16**)
- Refer for in-person or tele-pulmonary rehabilitation (see **Recommendations 17-18**)
- Telehealth support tools (see **Recommendation 19**)
- CIH support based on patient preferences
- Palliative care

Written COPD Self-Management or Action Plan (see samples below)

Figure K-1. VA COPD Management Plan



Alternative Text: Figure K-1. A printable, structured COPD Management Plan from the VA. The document is divided into four sections and uses a color-coded traffic light system (green, yellow, and red zones) to help patients monitor and manage their symptoms. The first section includes everyday COPD management guidance, followed by three colored zones of increasing urgency, detailing the actions that patients are recommended to take depending on which zone the patient's symptoms fall under. The Green Zone describes baseline symptoms and activities, the Yellow Zone describes worsening symptoms that require calling a physician, and the Red Zone describes severe symptoms that require calling 911.

Appendix L: Abbreviation List

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practice
ACSC	ambulatory care sensitive condition
ADL	activities of daily living
AECOPDs	acute exacerbations of COPD
AHRQ EPC	Agency for Healthcare Research and Quality Evidence-based Practice Center
ATS	American Thoracic Society
BMI	body mass index
BODE	Body-mass index, airflow Obstruction, Dyspnea, and Exercise capacity (Index)
CAN	Chronic Airways Assessment Test
CAT	COPD Assessment Test
CAAT	COPD Airways Assessment Test
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIH	complimentary integrative health
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
COPD-PS	COPD Population Screener
COVID-19	coronavirus disease of 2019
CO_2e	carbon dioxide equivalents
CPG	clinical practice guideline
CT	computed tomography
DOD	U.S. Department of Defense
DPI	dry powder inhaler
EBPWG	Evidence-Based Practice Work Group
ED	emergency department
EMBASE	Excerpta Medica Database
ENDS	electronic nicotine delivery system
ERS	Evaluating Respiratory Symptoms scale
FDA	U.S. Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV1 or FEV_1	forced expiratory volume at 1 second
FEV6	forced expiratory volume at 6 seconds
FLAME	Effect of Indacaterol Glycopyrronium Vs. Fluticasone Salmeterol on COPD Exacerbations (trial)
FVC	forced vital capacity
GAD	Generalized Anxiety Disorder scale
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GOLD GENE	GOLD Genetic Epidemiology of COPD study cohort
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HDI	Human Development Index
HFA	hydrofluoroalkane
ICD-10	International Classification of Diseases, Tenth Revision
ICS	inhaled corticosteroid
ICU	intensive care unit
IMP	individualized management plan
KQ	key question

Abbreviation	Definition
LABA	long-acting beta 2-agonist
LAMA	long-acting antimuscarinic agent
LLN	lower limit of normal
LOTT	Long-Term Oxygen Treatment Trial
LTOT	long-term oxygen therapy
MACCE	major adverse cardiac and cerebrovascular events
MDI	metered dose inhaler
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHS	U.S. Military Health System
mMRC	Modified Medical Research Council Dyspnea Scale
N/A	not applicable
NAM	National Academy of Medicine (formerly Institute of Medicine)
Neb	nebulized solution
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NNT	number needed to treat
OR	odds ratio
PaO_2	partial pressure of oxygen in arterial blood
PBD	pre-bronchodilator
PDE	phosphodiesterase
PEFR	peak expiratory flow rate
PFT	pulmonary function test
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting
pMDI	pressurized metered dose inhaler
Pre-/Post-BD	pre- or post-bronchodilator
QoL	quality of life
RCT	randomized controlled trial
REDUCE	Reduction in the Use of Corticosteroids in Exacerbated COPD (trial)
RR	risk ratio
RSV	respiratory syncytial virus
RZV	recombinant zoster vaccine
SABA	short-acting beta 2-agonist
SAC-TDI	Self-Administered Computerized Transition Dyspnea Index
SAMA	short-acting muscarinic antagonist
SAMHSA	Substance Abuse and Mental Health Services Administration
SaO_2	arterial oxygen saturation
SGRQ	St. George's Respiratory Questionnaire
SMI	soft mist inhaler
SR	systematic review
SSRI	selective serotonin reuptake inhibitor
TIC	trauma-informed care
UK	United Kingdom
U.S.	United States of America
USPSTF	U.S. Preventive Services Task Force
VA	U.S. Department of Veterans Affairs
VA ESP	VA Evidence Synthesis Program
VHA	U.S. Veterans Health Administration

Abbreviation	Definition
6MWD/6MWT	six-minute walking distance test or six-minute walk test

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