International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

EXPERT OPINION

# Single-Inhaler Triple Therapy in Primary Care Across Europe: Expert Panel Consensus on the Consequences of Payer-Driven Access Rules and Call to Action

Fabiano Di Marco[1], Orjola Shahaj[2], Arschang Valipour[3], Bertrand Legrand[4], Claudio Jommi[5], Claudio Micheletto[6], Claus Franz Vogelmeier[7], Daryl Freeman[8], Janwillem WH Kocks[9], Luis Alves[10], Myriam Calle Rubio[11], Rudi Peché[12], Susanna Palkonen Snr[13], Tonya Winders[14], Nicolas Roche[15]

[1]Department of Health Sciences, Università Degli Studi Di Milano, Milan, Italy; [2]Aquarius Population Health, London, UK; [3]Department of Respiratory and Critical Care Medicine, the Karl-Landsteiner-Institute for Lung Research and Pulmonary Oncology, Vienna, Austria; [4]Lille University Hospital Centre, Lille University, Lille, France; [5]Department of Pharmaceutical Sciences, Università degli Studi Del Piemonte Orientale, Novara, Italy; [6]Respiratory Division, Università Di Verona, Verona, Italy; [7]Department of Pulmonology, University Hospital Marburg, Marburg, Germany; [8]Norfolk Community Health and Care, Norwich, UK; [9]Department of Pulmonology, University of Groningen, Groningen, the Netherlands; [10]EPIUnit Instituto de Saúde Pública, Universidade Do Porto, Porto, Portugal; [11]Pulmonology Department, Instituto de Investigación Sanitaria Del Hospital Clínico San Carlos (Idissc), Madrid, Spain; [12]Pulmonology Department, Charleroi, Belgium; [13]European Federation of Allergy and Airways Diseases Patients Associations (EFA), Brussels, Belgium; [14]Global Allergy & Airways Patient Platform, Vienna, Austria; [15]Respiratory Medicine, Paris Cité University, Paris, France

Correspondence: Orjola Shahaj, Aquarius Population Health, Unit 16 Tileyard Studios, London, N7 9AH, UK, Tel +44 207 993 2930, Email orjola.shahaj@aquariusph.com

**Background:** Chronic obstructive pulmonary disease (COPD) is a prevalent condition characterized by persistent airflow obstruction and respiratory symptoms. Single-Inhaler Triple Therapy (SITT) has been shown to improve patient adherence, reduce exacerbations, and lower healthcare resource utilization in patients who are not controlled despite being on dual therapy or Multiple-Inhaler Triple Therapy (MITT). Despite evidence supporting SITT, payer-driven access rules across Europe sometimes limit its use in primary care, creating barriers to optimal COPD management.

**Purpose:** Through expert consensus, the study seeks to generate a shared understanding of the unintended consequences of payer-driven access criteria for SITT in managing moderate-to-severe COPD in primary care.

**Methods:** A targeted literature review (TLR) was conducted to assess SITT initiation in primary care across Europe and examine the impact of access criteria. Semi-structured interviews were held with 14 experts from nine European countries, including clinicians, health economists, and patient advocacy representatives. A consensus generation workshop was conducted, where experts evaluated the findings and developed position statements to highlight the challenges posed by payer-driven access criteria.

**Results:** The TLR identified variability in access to SITT in Europe, with several countries restricting its initiation to specialists, thus limiting primary care physicians' (PCPs) ability to prescribe SITT. The expert panel generated seven consensus points stating that enabling PCPs to step up or switch eligible patients to SITT has the potential to support care continuity, enhance clinical autonomy for PCPs, reduce reliance on potentially less effective treatment options, improve patient and healthcare system outcomes, avoid unnecessary referrals to specialists, enable prompt initiation of guideline-directed medical therapy for COPD in primary care and reduce access inequalities.

**Conclusion:** Restrictions for SITT initiation in primary care may need to be revisited to mitigate their unintended health and cost consequences and improve equitable access to treatment. This should take into consideration each country's unique healthcare system.

**Keywords:** COPD, single-inhaler triple therapy, payer, access, reimbursement, primary care, expert consensus

Received: 30 October 2024
Accepted: 17 April 2025
Published: 22 May 2025

## Introduction

Chronic obstructive pulmonary disease (COPD), characterized by permanent airflow obstruction and respiratory symptoms, represents a widespread condition; recent estimates suggest that the global prevalence could be as high as 392 million people[1,2] while many cases remain undiagnosed. A review of community-based studies concludes that between 50%-70% of COPD worldwide may be undiagnosed.[3] In 2021, COPD caused 45.2 deaths per million population worldwide, making it the third leading cause of mortality (excluding COVID-19).[4] COPD patients typically suffer from reduced quality of life and increased susceptibility to comorbidities, especially cardiovascular disease.[5] The disease course for moderate-to-severe COPD is often marked by acute respiratory events (exacerbations) and hospitalizations.[6]

COPD, alongside other respiratory conditions, results in significant healthcare resource utilization (HCRU) and imposes a substantial burden on healthcare systems.[7–10] In the European Union (EU), respiratory diseases account for about 6% of the yearly healthcare budget, with COPD responsible for 56% of these costs, approximately 38.6 billion euros.[11] Exacerbations are frequently reported as the key driver of COPD's economic burden,[12] ranging from 45% to 70% of the total cost of managing the disease.[13] Moderate-to-severe COPD patients experience increased likelihood and severity of exacerbations,[14] contributing substantially to the disease burden and HCRU.[15]

COPD's optimal management aims to reduce symptoms and improve quality of life while preventing exacerbations, disease progression and mortality. It requires a multifaceted approach, including pharmacological and non-pharmacological interventions tailored to patients' needs[16,17] and collaborative efforts between primary and secondary care providers. Pharmacological treatment choices are guided by the patient's symptoms, exacerbation risk, existing comorbidities, treatment response, preference, and ability to use different drug delivery devices.[18] Adherence to guideline-directed medical therapy ensures that treatment plans consider all these elements and lead to better outcomes for patients and healthcare systems.[19]

The Global Initiative for Obstructive Lung Disease (GOLD) strategy document recommends the combination of a long-acting muscarinic antagonist (LAMA), long-acting β2-agonist (LABA) and an inhaled corticosteroid (ICS), referred to as "triple therapy", in moderate-to-severe COPD patients who are not adequately treated by dual therapy (LAMA/LABA). GOLD now also proposes first-line use of triple therapy in GOLD E patients (at risk of exacerbations) with > 300 blood eosinophils/μL.[17] Triple therapy can be administered as Multiple Inhaler Triple Therapy (MITT) or Single Inhaler Triple Therapy (SITT). The approved European Medicine Agency (EMA) indication for SITT is for patients who are not adequately controlled by dual therapy.[20–22]

Large randomized controlled trials (RCTs) comparing SITT to dual therapy (LABA/LAMA or ICS/LABA) demonstrated lower exacerbation rates and potentially decreased mortality for patients receiving SITT.[23,24] Reductions in COPD-related HCRU and costs have also been found,[25–28] mainly linked to the enhanced convenience and improved adherence that SITT offers compared to MITT.[29–33] Despite this evidence, access to SITT in primary care for moderate-to-severe COPD patients differs widely across Europe,[34] influenced, among other factors, by payer-driven access criteria.[35]

These criteria are typically intended to ensure prescription appropriateness and control costs.[35–37] On the other hand, they may affect the management of moderate-to-severe COPD patients in some primary care settings[35] because they restrict the range of treatment options that primary care providers (PCPs) can prescribe. However, no studies have described or quantified this impact so far.

This expert panel aims to generate a shared understanding of the potential consequences of payer-driven access criteria for SITT in primary care in various EU healthcare systems and assess whether there is a need to revisit these criteria. Through a comprehensive review of the available evidence and expert opinion (the authors), this statement provides key arguments highlighting the importance of ensuring equitable access to SITT for moderate-to-severe COPD patients across primary and secondary care settings.

## Materials and Methods

This study used three methods. First, a targeted literature review (TLR) was conducted to summarize the available evidence around SITT (clinical and economic impact compared to MITT and dual therapy) and how access to SITT in primary care varies across Europe. This was followed by in-depth semi-structured interviews to understand the views of various experts on how payer-driven access criteria that prevent PCPs from initiating SITT in eligible patients may affect

clinical practice, patients and healthcare systems. Lastly, a consensus generation workshop was run to develop a series of position statements that deliver evidence- and expert-backed arguments about the impact of payer-driven access criteria in primary care to inform policy recommendations.

## Targeted Literature Review (TLR)

Initial scoping searches were used to draft a series of hypotheses (potential arguments) and link them to relevant research questions for the TLR (see 1 Appendix). The research questions were then used to develop a PICO framework (see 2 Appendix) to guide pragmatic PubMed and Google Scholar searches. Manual searches of grey literature were conducted to identify information about payer-driven access criteria (eg, HTA and reimbursement policy documents, etc). Published articles and grey literature items were included based on their relevance to answering the research questions.

A refined structure of the hypotheses outlined in 3 Appendix was discussed with the experts; this was modified if there was insufficient evidence to back the arguments. Further amendments to the arguments were made based on the feedback provided by the experts (see section below on "Consensus generation activities").

Predetermined data extraction frameworks were used to sort the TLR evidence, and narrative synthesis was used to analyze the findings.

## In-Depth Semi-Structured Interviews

The semi-structured interviews were carried out by a team of two researchers (distinct from the expert panel) with a total of 14 experts: 11 clinicians involved in managing COPD (seven pulmonologists and four PCPs), one health economist, and two Patient Advocacy Group (PAG) representatives. The qualitative analysis followed the consolidated criteria for reporting qualitative research (CORE-Q) checklist.[38] Anonymized interview data were analyzed using reflexive thematic analysis.

### Participant Selection

A total of 15 potential participants (internationally recognized external experts whose clinical and research work includes COPD and inhaled therapy) were approached through an email invitation, and 14 agreed to participate in the study. The participants that were approached met one of the following criteria: 1) PCPs or respiratory specialists involved in the management of moderate-to-severe COPD patients working in any of the following countries at the time of the study: Austria, Belgium, England, France, Germany, Italy, Netherlands, Portugal or Spain; or 2) COPD PAG representatives with a global or European remit; or 3) health economist or policy expert with a deep understanding of payer rules for the pharmacological management of COPD in primary and secondary care.

Purposive sampling was used to identify experts from various European countries to provide a balanced comparison across healthcare systems that apply different rules to accessing SITT in primary and secondary care.

### Data Collection

Interviews took place between December 2023 and January 2024 online via Microsoft Teams®. All participants were provided with documentation outlining the nature and purpose of the study and how the data would be used, stored, and shared (the use of recordings and any future uses of the data). Participants provided informed written consent to participate, including consent to quote their words to substantiate the findings. All communications with the experts who participated in the study were managed online, including initial contact, scheduling, and conducting the interviews via emails and virtual meetings.

An example of an interview discussion guide is provided in 4 Appendix. Two interviewers were present in each call: a lead and a notetaker. Transcripts were not returned to participants for correction, but a summary of key findings was shared with all participants, and they were requested to corroborate the interpretation of interview data. All participants consented to receive follow-up emails with clarifying questions regarding the interview content.

### Data Analysis

A mix of deductive and inductive approaches was used. A predetermined coding framework derived from 1 Appendix guided the line-by-line coding in NVivo® to ensure that the interview data were organized in a similar structure as the TLR hypothesis. New codes were added to the framework wherever necessary (inductive component).

## Consensus Generation Activities

Following the individual interview process, the experts were invited to participate in a consensus-generation workshop that shaped agreement on the consensus arguments.

The experts received a pre-read prior to the workshop, which included the results of the TLR, themes from in-depth interviews, and an initial draft of the consensus arguments for validation (3 Appendix). Given the different nature of challenges in each country, the experts ranked the arguments and statements based on their applicability and relevance to each expert's country (5 Appendix).

A consensus generation workshop was then launched as a videoconference, with a moderator (distinct from the expert panel members) leading all the sessions. The experts were organized into four panels based on the status of payer-driven access criteria in their countries: a) PCPs face restrictions to prescribe SITT, b) no restrictions, c) restrictions lifted recently and d) experience from PAGs. Each expert was actively involved by asking questions about the impact of the payer-access criteria, focusing on identifying the key components of the "call to action" and optimal solutions.

The consensus arguments and their corresponding rankings of relevance were shared and discussed in the workshop. Group agreement was reached on (1) streamlining the arguments by removing those that did not apply to all countries and (2) refining the language for the arguments.

Finally, a written document including unanimously endorsed position statements and a summary of the evidence from the TLR and qualitative research were shared offline with the experts for their final approval, alongside a live version to provide comments. Similar to the workshop, an independent moderator (not part of the expert panel) facilitated the resolution of contradicting views through mutual agreement between the experts to reach full alignment.

# Ethics

No personal or patient-specific information was collected during the interviews and workshop discussions. Participants were asked questions regarding the healthcare services for COPD in their country. Therefore, the project was deemed a service evaluation, and no ethics approval or review was necessary. Any data collected before, during and after the interview was handled following the European Union's General Data Protection Regulation (GDPR) legislation.

# Results

## Targeted Literature Review

Only one published article described how access to triple therapy (focusing specifically on SITT) varies across Europe;[34] most of the evidence on the status of payer-driven access rules for SITT was informed by grey literature. Table 1 describes some of the payer-driven access criteria that affect the pharmacological management of COPD in primary care. In most European countries, these restrictions are not in place or have been lifted recently (France and Spain). However, in several others (eg, Austria, Bulgaria, Czech Republic, Greece, Hungary, Italy, Lithuania, and Romania), PCPs cannot initiate SITT because its initial prescription is limited to a respiratory specialist (or in some cases to other specialists such as internists).

**Table 1** Description of Some Payer-Driven Access Rules for Triple Therapy in Primary Care Across European Countries

| Country[a] | Access Rules for Triple Therapy (Including MITT and SITT)[b] in Primary Care | Other Access Rules Around the Pharmacological Management of COPD in Primary Care | Reference |
|---|---|---|---|
| **Austria** | Initiation limited to pulmonologists; PCPs can repeat | The initiation of dual therapy (ICS/LABA or LAMA/LABA) is also limited to specialist initiation | Osterreichische Sozialversicherung[39] |
| **Bulgaria** | Initiation limited to pulmonologists; PCPs can repeat | The initiation of all pharmacological treatment for COPD is limited to specialists; PCPs can repeat | National Health Insurance Fund[40] |

(*Continued*)

**Table 1** (Continued).

| Country[a] | Access Rules for Triple Therapy (Including MITT and SITT)[b] in Primary Care | Other Access Rules Around the Pharmacological Management of COPD in Primary Care | Reference |
|---|---|---|---|
| **Czech Republic** | Initiation and repeat prescriptions are limited to pulmonologists; PCPs cannot initiate or repeat prescriptions | The initiation of ICS/LABA (fixed-dose), LAMA/LABA (fixed-dose) and LAMA are limited to pulmonologist only; PCPs cannot initiate or repeat prescriptions; ICS and LABA separately are not limited to specialists | Database of registered and reimbursed products[41] |
| **Estonia** | Initiation limited to pulmonologists; PCPs can repeat | All treatment options for COPD need to be initiated by a specialist | Estonian Health Insurance Fund[42] |
| **Greece** | Pulmonologist initiation required for SITT, PCPs can repeat it | PCPs can initiate MITT; LAMA/LABA requires specialist initiation | Greece Ministry of Health[43] |
| **Hungary** | Initiation limited to pulmonologist initiation, PCPs can repeat | | Healthcare Professional Guideline On the diagnosis, treatment, and management of chronic obstructive pulmonary disease (COPD) - State Secretariat for Health[44] |
| **Italy** | Specialist initiation required for SITT, PCPs can repeat if a specialist-approved treatment plan is available | PCPs can initiate MITT | Agenzia Italiana del Farmaco; Nota 99[45] |
| **Lithuania** | Pulmonologist initiation for severe COPD | PCPs can initiate triple therapy for moderate COPD | *Expert opinion* |
| **Romania** | Pulmonologist initiation, PCPs can repeat | | *Expert opinion* |

**Notes**: [a]This list is informed by the desk research for this expert panel consensus, and it may not represent an exhaustive list of all countries that apply payer-driven access criteria in the EU; [b]Only rules that touch upon the initiation of MITT and SITT in primary care were scrutinized- other payer-driven access criteria affecting triple therapy (and the wider pharmacological management of COPD) are in place in these countries.
**Abbreviations**: MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy; PCP, primary care provider; COPD, Chronic Obstructive Pulmonary Disease; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta agonist; ICS, inhaled corticosteroid.

No published evidence was identified to describe the impact of payer-driven access criteria for SITT in primary care. There was good availability of evidence on the impact of using triple therapy (both SITT and MITT) on patients and healthcare systems. Appendix 6 provides details from 46 articles that compared SITT with dual therapies, six articles that compared prompt initiation of triple therapy (both SITT and MITT) after a COPD exacerbation to delayed treatment initiation, and 23 articles comparing SITT to MITT.

## Themes From Qualitative Analysis of Interview Data with the Experts

Following the in-depth interviews with 14 experts, we identified five themes: *1-Variations between countries; 2-Unintended consequences; 3-Specialist access; 4-Remaining challenges; and 5-Access inequalities for patients*. The detailed themes and subthemes are presented in Table 2.

The experts confirmed the TLR findings that while triple therapy is authorized in the EU as maintenance treatment for moderate-to-severe COPD patients who remain uncontrolled despite being on dual therapy, in some countries, it is subject to payer-driven access criteria that prevent its initiation in primary care. In these cases, either specialist initiation or approval of the therapeutic plan by a specialist is required. These restrictions may apply to MITT and SITT, but SITT seems disproportionally affected (in some countries, dual therapy initiation is also limited to specialist initiation only; see Table 1). The experts referred to cases where restrictions apply only to SITT while PCPs can initiate MITT (eg in Italy and Greece), posing logical inconsistencies and further complicating the treatment landscape.

**Table 2** Themes and Subthemes From Analyzing 14 Interview Transcript With Experts Across Nine Countries: Austria, Belgium, England, France, Germany, Italy, Netherlands, Portugal and Spain

| Theme | Interpretation | Subthemes |
|---|---|---|
| 1. Variations between countries | Variations in access criteria about TT that affect the clinical management of moderate-severe COPD patients in primary care | 1.1 The initiation of TT in primary care is to some extent determined by the presence or lack of payer-driven access rules<br><br>1.2 There is variation in how limiting or strict these criteria are, but they usually limit PCPs ability to initiate treatment with TT<br><br>1.3 In some settings, PCPs can prescribe MITT but not SITT, posing logical inconsistencies in access-rules<br><br>1.4 Payer-driven access criteria about TT may be linked to other requirements that aim to improve the clinical management of COPD patients, such as spirometry results<br><br>1.5 The criteria are often in place to ensure the appropriateness of prescriptions or contain costs |
| 1. Unintended consequences | Payer-driven access criteria around the pharmacological management of COPD may have unintended consequences | 2.1 Reduced autonomy of primary care physicians when they cannot prescribe the full range of available treatment options for their COPD patients<br><br>2.2 Payer-driven access criteria perpetuate a lack of awareness among PCPs about the availability of better treatment options (ie, SITT versus MITT)<br><br>2.3 Access criteria contribute to interrupted care journey for COPD patients who struggle with access to specialists<br><br>2.4 Increased barriers to timely access to guideline-directed medical therapy may lead to suboptimal outcomes, resulting in higher costs in the long-term<br><br>2.5 Some payers have changed some access criteria when sufficient evidence of the unintended consequences is provided (France, Spain) |


https://doi.org/10.2147/COPD.S503726

| | | |
|---|---|---|
| 1. Specialist access | The impact of the access criteria on the utilization of triple therapy depends on the organization of the healthcare systems regarding specialist access | 3.1 Areas with reduced access to specialists (eg, rural) may be disproportionately affected by the payer-driven access criteria for TT<br><br>3.2 Where no referral to access specialists is required, the impact of the access criteria may be smaller<br><br>3.3 The long waiting times to see a specialist in some settings might further worsen the barriers patients face in accessing TT |
| 1. Remaining challenges | The lack of payer-driven access criteria for SITT does not always mean optimal management of COPD patients in primary care | 4.1 Insufficient awareness among PCPs about the availability of more cost-effective treatment options (ie, SITT versus MITT)<br><br>4.2 The availability and quality of spirometry to diagnose and assess the severity of COPD remain pervasive issues across European countries<br><br>4.3 The prescription appropriateness of TT among PCPs can be further improved by education and training |
| 1. Access inequalities for patients | Patients see access criteria for SITT as a driver of inequality, especially when treatment initiation depends heavily on having good access to specialists | 5.1 Timely access to effective pharmacological options is more important to patients than which physician provides the treatment<br><br>5.2 Treatment optimization at the first point of call following an exacerbation is essential for COPD patients, who are often discharged to see their PCPs |

**Abbreviations**: TT, triple therapy; SITT, Single-inhaler triple therapy; MITT, multiple-inhaler triple therapy; PCPs, primary care providers; COPD, chronic obstructive pulmonary disease.


https://doi.org/10.2147/COPD.S503726

The experts perceived several potential unintended consequences arising from payer-driven access criteria for SITT in primary care, including reduced PCP autonomy, perpetuation of lack of awareness about SITT, interruption of patient care journeys, and possibly suboptimal outcomes leading to higher long-term costs. The experts explained that the extent of these unintended consequences is influenced by the organization of the healthcare system, particularly regarding specialist access. They suggested that areas with limited specialist access may be disproportionately affected, whereas in healthcare systems where no referral to specialists is required (eg, Austria), some of the unintended consequences may be mitigated by direct access to specialists.

However, even in countries with no payer-driven access criteria for SITT, experts identified ongoing obstacles to optimal COPD management in primary care. These included their perceptions of insufficient PCP awareness about SITT, limited availability of quality spirometry, and the need for improved prescription appropriateness through education.

According to the PAG representatives, patients view payer-driven access criteria as drivers of inequality, especially when treatment initiation depends heavily on specialist access. They reported that patients prioritize timely access to effective treatment options at the first and most convenient point of contact with the healthcare system.

Finally, the experts highlighted the complex interplay between payer-driven access criteria for the pharmacological management of COPD, healthcare system organization, and the need for continuity of care for COPD patients. They suggested the need for potential policy initiatives to reduce avoidable barriers to guideline-directed medical therapy in primary care.

## Results From Consensus Generation Activities

After considering the TLR evidence, qualitative evidence from the interviews, and the workshop discussions (see Appendix 4 for the experts' ranking of the initial hypothesis), seven position statements were endorsed by all the 14 experts in the panel (Figure 1).

# Discussion

The findings from the in-depth interviews and the consensus generation activities showed that the views of the experts in this panel were aligned; payer-driven access criteria can have unintended consequences on the clinical practice when managing COPD patients in primary care. The lack of peer-reviewed publications that quantify this impact can be a barrier to providing payers with sufficient evidence for revisiting the criteria. However, the position statements provided by the expert panel could serve as a valid indication that the payer-driven access criteria in primary care represent an avoidable barrier to the continuum of care for COPD patients in countries where they are applicable.

This discussion further elaborates on each statement to showcase the rationale behind each statement and provide further interpretation in light of available evidence on SITT.

The position statements are shaped by the experts' views and their interpretation of the available evidence. The expert's previous experience with inhaled therapy for COPD and, more specifically, with SITT may introduce an unavoidable selection bias that must be considered when interpreting each statement.

## Position Statement 1

There is an unmet need for appropriate pharmacological management among COPD patients who remain inadequately treated by dual therapy or MITT in primary care, adding to COPD's clinical and economic burden.

A significant proportion of moderate-to-severe COPD patients in primary care who are eligible for SITT remain inadequately controlled with dual therapy or MITT.[35,46–55] The persistence of symptoms and exacerbations despite being on treatment highlights potential issues with current COPD management strategies in primary care.[46] Among other reasons (eg, issues related to medication adherence and the severity of individual cases), inappropriate therapy selection[53,55,56] and a lack of treatment adjustments[57] based on patient-specific disease progression are important contributors.

It is worth emphasizing that the nature of the unmet need in primary care may be different for patients on LAMA/LABA dual therapy from those treated with MITT, given that patients on MITT already have an ICS in their regimen and the poor symptom control may be attributable to issues with persistence and adherence[58] (further explored in Position Statement 2).

Patients who do not respond to dual therapy often experience a lower quality of life, marked by increased dyspnoea, fatigue, and limited physical activity.[26,28,46] Frequent exacerbations, which are common in this population, lead to

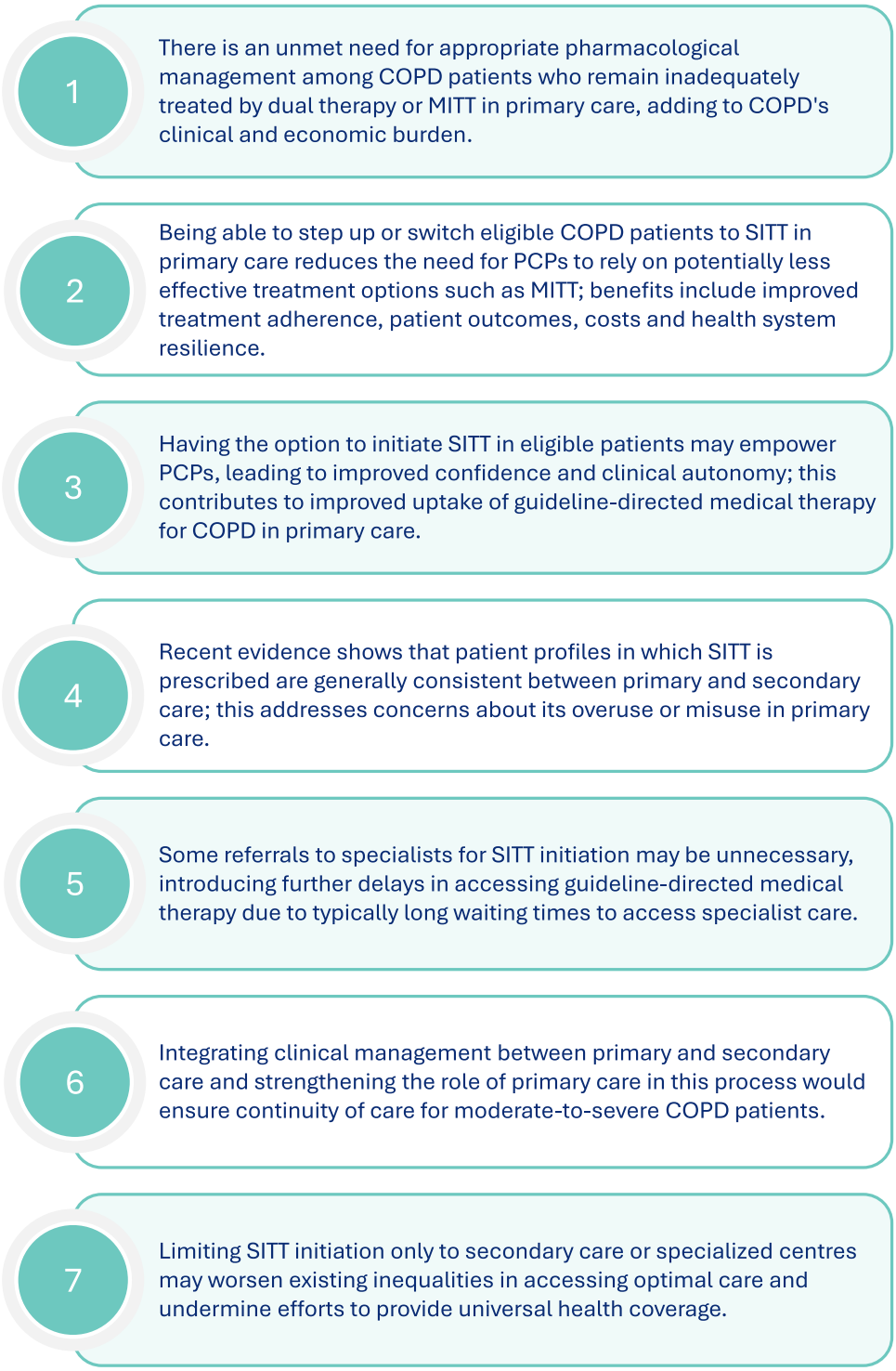


**Figure 1** Final position statements (seven) emerging from the expert consensus panel on the need to revisit payer-drive access rules that prevent primary care physicians from prescribing single-inhaler triple therapy to moderate-to-severe COPD patients that meet clinical criteria according to the guidelines.

a further decline in lung function, increased hospital admissions, increased cardiopulmonary risk, and a greater risk of mortality.[59–62] The physical and psychological distress associated with uncontrolled symptoms significantly impacts patients' overall well-being and ability to perform daily activities.[46,59]

From an economic perspective, inadequately managed COPD places a burden on healthcare systems; frequent exacerbations, hospitalizations, and cardiovascular events associated with poorly controlled COPD result in high direct medical costs.[61–64]


https://doi.org/10.2147/COPD.S503726

Policymakers, payers, and healthcare providers must understand this unmet need and revisit any policies or access rules that further complicate the care pathway to optimized treatment for COPD patients who remain uncontrolled on dual therapy or MITT in primary care.

## Position Statement 2

Being able to step up or switch eligible COPD patients to SITT in primary care reduces the need for PCPs to rely on potentially less effective treatment options such as MITT; benefits include improved treatment adherence, patient outcomes, costs and health system resilience.

In the management of COPD, the availability of SITT can influence the choice of treatment strategies for healthcare providers; when PCPs lack access to initiate SITT, it impacts their prescribing patterns and attitudes towards managing moderate-to-severe COPD patients.[35,36,65] This limitation often forces PCPs to rely on MITT (in countries where they can initiate it), which involves the use of multiple inhalers.[35] This can lead to increased complexity in managing medication regimens for patients and decreased treatment adherence.[30] Prescribing MITT instead of SITT can adversely affect patient-reported outcomes; compared to MITT, SITT is preferred by patients and associated with higher quality of life.[29,66] The impact of prescribing MITT instead of SITT also extends to clinical outcomes. Studies have demonstrated that SITT can lead to better symptom control, reduce the rate of exacerbations, and potentially lower mortality compared to MITT.[31,32,67,68]

The effectiveness of COPD treatment regimens relies significantly on patient adherence and proper inhaler technique. Current evidence suggests that treatment adherence rates are notably higher with SITT compared to MITT,[30,32,69,70] supporting a stronger case for the preferential use of SITT in clinical practice for patients who are eligible for triple therapy. This is primarily due to SITT's simplified regimen, which involves only one inhaler instead of the multiple devices required in MITT. This is easier for patients to manage and reduces the likelihood of missing doses, a common issue involving multiple inhalers.[71] Moreover, the potential for inhaler usage errors is markedly reduced with SITT.[66] The complexity of handling multiple inhalers may lead to incorrect use,[30,72] which can significantly undermine the effectiveness of the therapy.

Lastly, the economic implications of prescribing SITT versus MITT are significant. SITT is cost-saving compared to MITT due to higher adherence rates, decreased exacerbations, and hospital visits.[32,33] This reduces direct healthcare costs associated with treating exacerbations and decreases the overall healthcare resource utilization.[32,73] Patients also benefit from switching to SITT as this reduces out-of-pocket payments due to prescription charges (patients that are prescribed MITT pay more than one prescription charge); in the UK, the prescription charge is £9.99 per medicine[74]).

Enabling step-up or switching to SITT for COPD patients who remain poorly controlled despite receiving dual therapy or MITT can improve prescribing patterns for PCPs, enhance patient-reported and clinical outcomes, and lead to cost savings when managing COPD. Healthcare policies must align to support the use of the most effective and efficient therapies in primary care.

## Position Statement 3

Having the option to initiate SITT in eligible patients may empower PCPs, leading to improved confidence and clinical autonomy; this contributes to improved uptake of guideline-directed medical therapy for COPD in primary care.

Primary care settings play a pivotal role in managing COPD,[75] including regularly reviewing patient conditions, modifying treatment plans, and making necessary specialist referrals.[76] PCPs' active engagement in these areas is crucial for timely adjustments to treatment as the disease progresses. When PCPs are restricted from initiating treatment options like SITT, their ability to provide optimal care is limited. This impacts PCPs' clinical autonomy, diminishing their ability to make independent, informed decisions regarding the pharmacological management of moderate-to-severe COPD patients. Such constraints can also affect the interest and engagement in managing these patients altogether, leading to therapeutic inertia marked by clinical and economic consequences.[46,77] Moreover, the restrictions can lead to frustration and dissatisfaction among PCPs, further complicating the management landscape of COPD.

However, all clinicians should recognize the negative consequences of inappropriate prescribing of ICS[78] and ensure the step-up to SITT is done in line with clinical guidelines and treatment indications. Education of PCPs and improved awareness of guidelines will have an impact on prescribing.

Enabling PCPs to initiate the full range of the necessary treatment options in primary care, alongside improved training and education around SITT, could mitigate some of the therapeutic inertia and the associated burden; a balanced view of benefits and risks is essential to ensure the step-up to SITT leads to improved outcomes.

## Position Statement 4

Recent evidence shows that patient profiles in which SITT is prescribed are generally consistent between primary and secondary care; this addresses concerns about its overuse or misuse in primary care.

One of the reasons why payers sometimes impose access rules on SITT is concerns about prescription appropriateness, particularly in primary care settings compared to secondary care.[34] These concerns stem from assumptions that PCPs might not have the same specialized expertise as their secondary care counterparts, potentially leading to inappropriate prescribing. However, although relatively limited, the available evidence indicates that the characteristics of the patients for whom SITT is prescribed are the same, irrespective of whether PCPs or specialists in secondary care initiate the treatment.[70,79–81] This evidence supports the argument for equitable access to SITT across different care settings, ensuring that all patients who meet the clinical criteria can benefit from this treatment option at the earliest point of interacting with the healthcare system without unnecessary restrictions.

However, even when there are no restrictions in place, there is insufficient awareness among PCPs about the availability of more convenient and effective treatment options such as SITT compared to MITT.[82] Moreover, the diagnosis and assessment of COPD severity are often hindered by the availability and quality of spirometry,[36,65,83,84] which can lead to delays in diagnosis or misclassification of disease severity,[85] affecting the initiation of any COPD treatment, including SITT. Programmes to improve access to and use of spirometry are needed to overcome this challenge. They should be linked to targeted education and training in primary care settings to improve the appropriateness of treatment prescriptions for COPD.[86]

## Position Statement 5

Some referrals to specialists for SITT initiation may be unnecessary, introducing further delays in accessing guideline-directed medical therapy due to typically long waiting times to access specialist care.

PCPs are central in COPD management,[75] including making decisions about when to escalate treatment and refer to a specialist. When PCPs have access to all available treatment options, they are more likely to assume greater responsibilities in managing COPD patients in primary care.[35,87,88] If they cannot provide the necessary treatment option, they might default to referring patients to specialists. Some of these referrals could be unnecessary or contribute to increased waiting times before COPD care is provided,[65] leading to inefficiencies in patient pathways.[89]

This is particularly relevant in countries where a PCP referral is requested to see a specialist. The waiting time to see a specialist for COPD varies widely,[90] and it is determined by various factors, but the experts in this panel reported that it ranges from a few weeks to up to 12 months. The clinical outcomes of delayed access to SITT are significant; prolonged periods without optimal treatment can lead to increased rates of exacerbations,[91–93] and poor symptom control.[94] As a correlate, delays in receiving the most effective treatment can lead to increased HCRU, including more frequent hospital admissions, emergency visits, and a general escalation in healthcare costs associated with managing acute exacerbations and complications of inadequately treated moderate-to-severe COPD.[58,93,95–97]

Streamlining the patient pathway to SITT by removing unnecessary barriers where possible could result in more efficient use of healthcare resources.

## Position Statement 6

Integrating clinical management between primary and secondary care and strengthening the role of primary care in this process would improve continuity of care for moderate-to-severe COPD patients.

COPD is a highly prevalent disease,[98] and integrated clinical management between primary and secondary care is crucial for maintaining continuity of care throughout the healthcare system, particularly for patients with moderate-to-severe COPD.[99] Strengthening the role of primary care in this integrated model is expected to enhance the patient experience by ensuring that the care journey is responsive to the patient's needs at various stages of their treatment.[100–102]

Collaboration and integration between primary care and specialists are crucial for limiting therapeutic inertia in COPD, especially in patients with inadequate pharmacological treatment regimens.[103] Furthermore, such models contribute to better overall health outcomes and have been shown to be cost-effective.[104–107]

PCPs are well-positioned to manage patients with comorbidities, as they can integrate and coordinate information from different specialities.[88] This is particularly beneficial in COPD management, where comorbid conditions such as cardiovascular disease, diabetes, and anxiety frequently coexist and can complicate treatment protocols.[88,108] Primary care physicians' holistic view of their patients' health allows for more comprehensive management for moderate-to-severe COPD patients.[109]

Enhancing the role and autonomy of primary care and improving collaboration, communication and integration with secondary care is essential for ensuring continuity of care for moderate-to-severe COPD patients.[35,110,111]

## Position Statement 7

Limiting SITT initiation only to secondary care or specialized centres may worsen existing inequalities in accessing optimal care and undermine efforts to provide universal health coverage.

Access to specialist care for COPD varies between and within countries,[112,113] often reflecting broader healthcare resource distribution and infrastructure differences.[36] In some areas, access to specialists may be limited and requires travel time, which places a burden on patients who need regular and specialized COPD management.[36,114]

Geographic and socioeconomic factors significantly influence the unequal access to quality care for COPD patients.[113,115] Those living in remote or economically disadvantaged areas are less likely to have timely access to specialist care, including access to treatment such as SITT.[36] This uneven access landscape can lead to disparities in health outcomes.[116,117]

The timing and appropriateness of pharmacological interventions play a critical role in managing moderate-to-severe COPD,[91,92] often outweighing the importance of who initiates the treatment (PCP or specialist).[38,46] For example, treatment optimization at the first point of call following an exacerbation is vital for COPD patients. When access to specialists is limited, PCPs become crucial in ensuring the continuity of care. They carry out critical tasks such as adjusting and optimizing treatment plans based on the current clinical status and recent exacerbations.[76]

Considering all the above, payer-driven access criteria may inadvertently affect the equity and continuity of care for moderate-to-severe COPD patients; health policies must promote equitable access to COPD treatments across all levels of care, ensuring that all patients, regardless of their geographical location or economic status, can receive the best possible care for their condition.

# Conclusion

Payers need to consider reassessing the criteria that limit PCPs' ability to initiate SITT in countries where they are still applicable to mitigate the unintended consequences that may affect patient outcomes, healthcare system efficiency, costs and equitable access to care. This reassessment should be done in line with considerations about the unique features of each country's healthcare system and the available evidence that demonstrates the impact.

# Acknowledgment

Yuchen Hsu and Emma Crawford supported the main authors with the narrative synthesis of the targeted literature review.

# Author Contributions

All authors made a significant contribution to the work reported. All coauthors drafted, revised or critically reviewed the article; agreed on the journal to which the article will be submitted; gave final approval of the version to be published; and agreed to take responsibility and be accountable for the article's contents.

# Funding

Aquarius Population Health was funded by AstraZeneca to carry out this research. The study design, data collection, data analysis and interpretation of results were carried out independently by the authors. AstraZeneca reviewed the manuscript

for medical and scientific accuracy. The authors confirm they had full access to all the data in this study and take complete responsibility for the integrity and accuracy of the analysis.

## Disclosure

FDM has received honoraria for lectures at national and international meetings, served as a consultant, and received financial support for research funds and fees from AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Chiesi Farmaceutici, Guidotti/Malesci, GLAXOSMITHKLINE., and fees (advisory boards, consultation, education, presentations) from Austral, Biosency, MSD., AstraZeneca, Chiesi, Menarini, Nuvaira, Neopharmed Gentili, Novartis, Sanofi, and Zambon. OS declare no conflicting interests in relation to this work. AV has received honoraria for lectures at national and international meetings and served as a consultant for Astra Zeneca, Boehringer Ingelheim, Chiesi, GLAXOSMITHKLINE, Menarini, Sanofi, and Zentiva. CJ reports serving as an advisory board member and a paid speaker for Amgen, AstraZeneca, BMS, CSL, Behring, Gilead, Incyte, MSD, Roche, Sanofi, and Takeda. Outside the submitted work CJ has carried out research projects in the last 3 years funded by AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Biogen, B.M.S., Boehringer Ingelheim, Daiichi Sankyo, Egualia, Gilead, Incyte, Janssen Cilag, Lundbeck, MSD, Novartis, Roche, Pfizer, Sandoz, Sanofi, Takeda, and Teva. BL reports personal fees from ASTRA ZENECA, GSK, and CHIESI. CM received fees as a speaker from AstraZeneca, GLAXOSMITHKLINE, Sanofi, Chiesi, Menarini, Guidotti, Novartis, Zambon, and Boehringer. GP has received lecture and consultancy fees from Alfasigma, AstraZeneca, Chiesi, GlaxoSmithKline, Guidotti-Malesci, Menarini, Mundipharma, Novartis, Sanofi, and Zambon. CFV has given presentations at symposia and/or served on scientific advisory boards sponsored by Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, CSL, Behring, Grifols, GLAXOSMITHKLINE, Insmed, MedUpdate, Menarini, Novartis, Nuvaira, Roche, and Sanofi. *DF* has received honoraria for lectures from AstraZeneca, GLAXOSMITHKLINE, and Chiesi, provided funded consultant support to AstraZeneca and received support for local healthcare projects from AstraZeneca. JWHK reports grants, personal fees and non-financial support from AstraZeneca, grants, personal fees and non-financial support from Boehringer Ingelheim, grants and personal fees from Chiesi, grants, personal fees and non-financial support from GLAXOSMITHKLINE, non-financial support from Mundi Pharma, grants and personal fees from Teva, personal fees from MSD, personal fees from COVIS Pharma, personal fees from ALK-Abello, grants from Valneva outside the submitted work; and JWHK holds <5% shares of Lothar Medtec GmbH and 72.5% of shares in the General Practitioners Research Institute. LA has served as an advisor or consultant for AstraZeneca, GlaxoSmithKline, and Merck Sharp & Dohme; served as a speaker or a member of a speakers bureau for AstraZeneca, GlaxoSmithKline, BIAL, Viatris, and Novartis Pharmaceuticals Corporation. He is also a member of the Education Subcommittee of the International Primary Care Respiratory Group and a member of the GRESP, the Portuguese Primary Care Study Group for Respiratory Diseases. MCR has received speaker fees from AstraZeneca, Boehringer Ingelheim, Bial, Chiesi, CSL, Behring, GlaxoSmithKline, Menarini, Novartis, Pulmox, Zambón and Grifols, and consulting fees from GlaxoSmithKline and Bial. RP has received consulting fees from AstraZeneca, Chiesi, GlaxoSmithKline, MSD and Sanofi and has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, Chiesi and GlaxoSmithKline. SP reports grants from AbbVie, AstraZeneca, Aimmune, Boehringer Ingelheim, Chiesi, DBV Technologies, OM Pharma, GlaxoSmithKline, Novartis, Pfizer, Regeneron, Roche, and Sanofi. SP reports employment at the European Federation of Allergy and Airways Diseases Patients Associations (EFA). EFA receives unrestricted grants from corporate entities, as mentioned above. SP serves as EFA representative in the following advisory groups of these entities: AstraZeneca (COPD Advisory Committee, Global Respiratory Taskforce), GlaxoSmithKline (Health Advisory Board), Novartis (European Patient Advisory Group and Steering Committee of European Patient Innovation Summit), and Sanofi (Severe Asthma Working Group). TW received paid speaker and advisor fees for AstraZeneca, GSK, Merck/MSD, Novartis, and Sanofi Regeneron outside the submitted work. NR reported receiving grant funding from Boehringer Ingelheim, Novartis AG, Pfizer Inc, and GlaxoSmithKline and personal fees from Boehringer Ingelheim, Novartis AG, Pfizer Inc, GlaxoSmithKline, Austral Pharma, Biosency, MSD, AstraZeneca, Chiesi Farmaceutici SpA, Menarini Group, Nuvaira, Sanofi SA, and Zambon outside the submitted work. The authors report no other conflicts of interest in this work.

## References


1. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. *Lancet Respir Med*. 2022;10(5):447–458. doi:10.1016/S2213-2600(21)00511-7
2. Ho T, Cusack RP, Chaudhary N, Satia I, Kurmi OP. Under- and over-diagnosis of COPD: a global perspective. *Breathe*. 2019;15(1):24–35. doi:10.1183/20734735.0346-2018
3. Diab N, Gershon AS, Sin DD, et al. Underdiagnosis and overdiagnosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;198(9):1130–1139. doi:10.1164/rccm.201804-0621CI
4. Naghavi M, Ong KL, Aali A, et al. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the global burden of disease study 2021. *Lancet*. 2024;403(10440):2100–2132. doi:10.1016/S0140-6736(24)00367-2
5. Polman R, Hurst JR, Uysal OF, Mandal S, Linz D, Simons S. Cardiovascular disease and risk in COPD: a state of the art review. *Expert Rev Cardiovasc Ther*. 2024;22(4–5):177–191. doi:10.1080/14779072.2024.2333786
6. Dos Santos NC, Miravitlles M, Camelier AA, de Almeida VDC, Maciel RRBT, Camelier FWR. Prevalence and impact of comorbidities in individuals with chronic obstructive pulmonary disease: a systematic review. *Tuberc Respir Dis*. 2022;85(3):205–220. doi:10.4046/trd.2021.0179
7. Hurst JR, Siddiqui MK, Singh B, Varghese P, Holmgren U, de Nigris E. A systematic literature review of the humanistic burden of COPD. *Int J Chron Obstruct Pulmon Dis*. 2021;16:1303–1314. doi:10.2147/COPD.S296696
8. Rehman AU, Hassali MAA, Muhammad SA, Harun SN, Shah S, Abbas S. The economic burden of chronic obstructive pulmonary disease (COPD) in Europe: results from a systematic review of the literature. *Eur J Health Econ*. 2020;21(2):181–194. doi:10.1007/s10198-019-01119-1
9. Pollack M, Daniels K, Tave A, et al. Health care resource utilization and costs following acute exacerbation of COPD and associated cardiovascular events in a large us claims database: the exacos-cv study. *CHEST*. 2023;164(4):A4966–A4968. doi:10.1016/j.chest.2023.07.3217
10. Parsekar K, Kossack N, Hernández I, et al. Healthcare resource utilization and costs in patients experiencing severe cardiac events following a COPD exacerbation: results from EXACOS-CV studies in Spain, Germany, the Netherlands and Canada. *Value in Health*. 2023;26(12):S508–S509. doi:10.1016/j.jval.2023.09.2743
11. Forum of International Respiratory Societies. The global impact of respiratory disease. European Respiratory Society; 2021. Available from: https://firsnet.org/images/publications/FIRS_Master_09202021.pdf. Accessed October 29, 2024.
12. Stafyla E, Geitona M, Kerenidi T, Economou A, Daniil Z, Gourgoulianis KI. The annual direct costs of stable COPD in Greece. *Int J Chron Obstruct Pulmon Dis*. 2018;13:309–315. doi:10.2147/COPD.S148051
13. Agarwal D. COPD generates substantial cost for health systems. *Lancet Glob Health*. 2023;11(8):e1138–e1139. doi:10.1016/S2214-109X(23)00304-2
14. Whittaker H, Rubino A, Müllerová H, et al. Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. *Int J Chron Obstruct Pulmon Dis*. 2022;17:427–437. doi:10.2147/COPD.S346591
15. Wallace AE, Kaila S, Bayer V, et al. Health care resource utilization and exacerbation rates in patients with COPD stratified by disease severity in a commercially insured population. *J Manag Care Spec Pharm*. 2019;25(2):205–217. doi:10.18553/jmcp.2019.25.2.205
16. Bhutani M, Price DB, Winders TA, et al. Quality standard position statements for health system policy changes in diagnosis and management of COPD: a global perspective. *Adv Ther*. 2022;39(6):2302–2322. doi:10.1007/s12325-022-02137-x
17. 2024 GOLD report. global initiative for chronic obstructive lung disease - GOLD. Available from: https://goldcopd.org/2024-gold-report/. Accessed February 16, 2024.
18. Global Initiative for Chronic Obstructive Lung Disease. 2024 GOLD report. global initiative for chronic obstructive lung disease - GOLD. Available from: https://goldcopd.org/2024-gold-report/. Accessed April 15, 2024.
19. Mannino DM, Yu T-C, Huanxue Zhou MS, Keiko Higuchi MPH. Effects of GOLD-adherent prescribing on COPD symptom burden, exacerbations, and health care utilization in a real-world setting. *Chronic Obstr Pulm Dis COPD Found*. 2015;2(3):223–235.
20. Trelegy Ellipta | European Medicines Agency (EMA). Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/trelegy-ellipta. Accessed September 30, 2024.
21. Trimbow | European Medicines Agency (EMA). Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/trimbow. Accessed September 30, 2024.
22. Trixeo Aerosphere | European Medicines Agency (EMA). Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/trixeo-aerosphere. Accessed September 30, 2024.
23. Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med*. 2018;378(18):1671–1680. doi:10.1056/NEJMoa1713901
24. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35–48. doi:10.1056/NEJMoa1916046
25. Rogliani P, Ora J, Cavalli F, Cazzola M, Calzetta L. Comparing the efficacy and safety profile of triple fixed-dose combinations in COPD: a Meta-analysis and IBiS score. *J Clin Med*. 2022;11(15):4491. doi:10.3390/jcm11154491
26. Tabberer M, Lomas DA, Birk R, et al. Once-daily triple therapy in patients with COPD: patient-reported symptoms and quality of life. *Adv Ther*. 2018;35(1):56–71. doi:10.1007/s12325-017-0650-4
27. Johnston K, Shephard C, Friesen M, Azzalini C, Penz E. Cost-effectiveness of triple therapy with budesonide/glycopyrronium/formoterol fumarate dihydrate compared with dual therapy for the treatment of chronic obstructive pulmonary disease (COPD) in Canada. *Can J Respir Crit Care Sleep Med*. 2024;8(1):4–16. doi:10.1080/24745332.2023.2289890
28. Bourdin A, Molinari N, Ferguson GT, et al. Efficacy and safety of budesonide/glycopyrronium/formoterol fumarate versus other triple combinations in COPD: a systematic literature review and network meta-analysis. *Adv Ther*. 2021;38(6):3089–3112. doi:10.1007/s12325-021-01703-z
29. Zhang L, Wang X, Zhang Y, Chen W. Efficacy and safety of single inhaler triple therapy versus separate triple therapy in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Clin Ther*. 2022;44(6):859–873. doi:10.1016/j.clinthera.2022.04.004

30. Brusselle G, Himpe U, Fievez P, et al. Evolving to a single inhaler extrafine LABA/LAMA/ICS – inhalation technique and adherence at the heart of COPD patient care (TRIVOLVE). *Respir Med*. 2023;218:107368. doi:10.1016/j.rmed.2023.107368
31. Pollack M, Rapsomaniki E, Anzueto A, et al. Reduced risk of mortality for COPD patients associated with initiation of treatment with single inhaler triple therapy (budesonide/glycopyrrolate/formoterol) versus multiple inhaler triple therapy in the United States: the MAZI Study. Available from: https://www.abstractsonline.com/pp8/#!/11007/presentation/12727. Accessed April 25, 2024.
32. Alcázar-Navarrete B, Jamart L, Sánchez-Covisa J, Juárez M, Graefenhain R, Sicras-Mainar A. Clinical characteristics, treatment persistence, and outcomes among patients with COPD treated with single- or multiple-inhaler triple therapy: a retrospective analysis in Spain. *CHEST*. 2022;162(5):1017–1029. doi:10.1016/j.chest.2022.06.033
33. Halpin DMG, Kendall R, Shukla S, et al. Cost-effectiveness of single- versus multiple-inhaler triple therapy in a UK COPD population: the INTREPID trial. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2745–2755. doi:10.2147/COPD.S370577
34. Cook J, Bloom C, Lewis J, Marjenberg Z, Platz JH, Langham S. Impact of health technology assessment on prescribing patterns of inhaled fixed-dose combination triple therapy in chronic obstructive pulmonary disease. *J Mark Access Health Policy*. 2021;9(1):1929757. doi:10.1080/20016689.2021.1929757
35. Di Marco F, Shahaj O, Valipour A, et al. Variations in the pharmacological management of COPD due to payer-driven access criteria for triple therapy: pan-European cross-expertise qualitative insights. 2024. Available from: https://www.ipcrg.org/24157. Accessed June 7, 2024.
36. Shahaj O, Meiwald A, Sudhir KP, et al. Mapping the common barriers to optimal COPD care in high and middle-income countries: qualitative perspectives from clinicians. *Int J Chron Obstruct Pulmon Dis*. 2024;19:1207–1223. doi:10.2147/COPD.S449659
37. Park Y, Raza S, George A, Agrawal R, Ko J. The effect of formulary restrictions on patient and payer outcomes: a systematic literature review. *J Manag Care Spec Pharm*. 2017;23(8):893–901. doi:10.18553/jmcp.2017.23.8.893
38. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care J Int Soc Qual Health Care*. 2007;19(6):349–357. doi:10.1093/intqhc/mzm042
39. Infotool for the reimbursement code. the portal of the Austrian social insurance. Available from: https://www.sozialversicherung.at/oeko/views/index.xhtml. Accessed January 22, 2025.
40. Заболявания по специалности (Diseases by specialty). Национална здравноосигурителна каса (НЗОК) (National Health Insurance Fund) Bulgarian. Available from: https://www.nhif.bg/bg/medical_requirements/definitions. Accessed September 30, 2024.
41. Přehled léčiv (Overview of Medicines). SÚKL (State Institute for Drug Control). Available from: https://prehledy.sukl.cz/prehled_leciv.html#/. Accessed January 22, 2025.
42. Ulevaatliktabel (overview table). Tervisekassa (Estonian Health Insurance Fund). Available from: https://www.tervisekassa.ee/sites/default/files/ulevaatliktabel_01.08.2024.xls. Accessed September 30, 2024.
43. Αναθεώρηση Καταλόγου Αποζημιούμενων Φαρμάκων του άρθρου 251 του ν. 4512/2018, όπως τροποποιήθηκε με το άρθρο 24 του ν. 4633/2019 (Revision of the List of Reimbursed Medicines of article 251 of law 4512/2018, as amended by article 24 of law 4633/2019). Greek. Υπουργείο Υγείας. Available from: https://www.moh.gov.gr/articles/times-farmakwn/epitroph-aksiologhshs-kai-apozhmiwshs-farmakwn/12470-anathewrhsh-katalogoy-apozhmioymenwn-farmakwn-toy-arthroy-251-toy-n-4512-2018-opws-tropopoihthhke-me-to-arthro-24-toy-n-4633-2019. Accessed September 11, 2024.
44. Egészségügyi szakmai irányelv A krónikus obstruktív tüdőbetegség (chronic obstructive pulmonary disease – COPD) diagnosztikájáról, kezeléséről és gondozásáról (Healthcare Professional Guideline On the diagnosis, treatment, and management of chronic obstructive pulmonary disease [COPD]). Hungarian. Available from: https://kollegium.aeek.hu/Download/Download/3617. Accessed April 21, 2025.
45. Nota 99 | agenzia Italiana del Farmaco (Italian Medicines Agency). Italian. Available from: https://www.aifa.gov.it/nota-99. Accessed September 11, 2024.
46. Chen S, Small M, Lindner L, Xu X. Symptomatic burden of COPD for patients receiving dual or triple therapy. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1365–1376. doi:10.2147/COPD.S163717
47. Buhl R, Greulich T, Azabdaftari D, et al. Clinical burden of disease in COPD patients on double and triple therapy – a retrospective, longitudinal German claims study. *Eur Respir J*. 2024;64(suppl 68). doi:10.1183/13993003.congress-2024.PA3009
48. Wu P, Qun JY, Si FL, et al. Pharmaceutical treatment status of patients with COPD in the community based on medical Internet of Things: a real-world study. *Npj Prim Care Respir Med*. 2024;34(1):1–10. doi:10.1038/s41533-024-00371-0
49. Ingebrigtsen TS, Marott JL, Vestbo J, et al. Characteristics of undertreatment in COPD in the general population. *Chest*. 2013;144(6):1811–1818. doi:10.1378/chest.13-0453
50. Mannino DM, Yu TC, Zhou H, Higuchi K. Effects of GOLD-adherent prescribing on COPD symptom burden, exacerbations, and health care utilization in a real-world setting. *Chronic Obstr Pulm Dis Miami Fla*. 2015;2(3):223–235. doi:10.15326/jcopdf.2.3.2014.0151
51. Thomas M, Radwan A, Stonham C, Marshall S. COPD exacerbation frequency, pharmacotherapy and resource use: an observational study in UK primary care. *COPD*. 2014;11(3):300–309. doi:10.3109/15412555.2013.841671
52. Barrecheguren M, Monteagudo M, Ferrer J, et al. Treatment patterns in COPD patients newly diagnosed in primary care. A population-based study. *Respir Med*. 2016;111:47–53. doi:10.1016/j.rmed.2015.12.004
53. Herth FJF, Vogelmeier CF, Trudzinski FC, et al. Unmet needs in patients with COPD in Germany: a retrospective, cross-sectional study. *ERJ Open Res*. 00976–2024. doi:10.1183/23120541.00976-2024.
54. Brusselle G, Price D, Gruffydd-Jones K, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. *Int J Chron Obstruct Pulmon Dis*. 2015;10:2207–2217. doi:10.2147/COPD.S91694
55. Bourbeau J, Sebaldt RJ, Day A, et al. Practice patterns in the management of chronic obstructive pulmonary disease in primary practice: the cage study. *Can Respir J*. 2008;15:13–19. doi:10.1155/2008/173904
56. Giacomelli IL, Steidle LJM, Moreira FF, Meyer IV, Souza RG, Pincelli MP. Hospitalized patients with COPD: analysis of prior treatment. *J Bras Pneumol*. 2014;40(3):229–237. doi:10.1590/S1806-37132014000300005
57. Sandelowsky H, Janson C, Wiklund F, Telg G, de F Licht S, Ställberg B. Lack of COPD-related follow-up visits and pharmacological treatment in Swedish primary and secondary care. *Int J Chron Obstruct Pulmon Dis*. 2022;17:1769–1780. doi:10.2147/COPD.S372266
58. Lee CH, Kim MS, Yeo SH, et al. Treatment patterns and cost of exacerbations in patients with chronic obstructive pulmonary disease using multiple inhaler triple therapy in South Korea. *Respir Res*. 2022;23(1):231. doi:10.1186/s12931-022-02136-0

59. Hurst JR, Skolnik N, Hansen GJ, et al. Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life. *Eur J Intern Med*. 2020;73:1–6. doi:10.1016/j.ejim.2019.12.014
60. Machado A, Barusso M, De Brandt J, et al. Impact of acute exacerbations of COPD on patients' health status beyond pulmonary function: a scoping review. *Pulmonology*. 2023;29(6):518–534. doi:10.1016/j.pulmoe.2022.04.004
61. Halpin DM, Miravitlles M, Metzdorf N, Celli B. Impact and prevention of severe exacerbations of COPD: a review of the evidence. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2891–2908. doi:10.2147/COPD.S139470
62. Adams EJ, van Doornewaard A, Ma Y, et al. Estimating the health and economic impact of improved management in prevalent chronic obstructive pulmonary disease populations in England, Germany, Canada, and Japan: a modelling study. *Int J Chron Obstruct Pulmon Dis*. 2023;18:2127–2146. doi:10.2147/COPD.S416988
63. Iheanacho I, Zhang S, King D, Rizzo M, Ismaila AS. Economic burden of chronic obstructive pulmonary disease (COPD): a systematic literature review. *Int J Chron Obstruct Pulmon Dis*. 2020;15:439–460. doi:10.2147/COPD.S234942
64. Gutiérrez Villegas C, Paz-Zulueta M, Herrero-Montes M, Parás-Bravo P, Madrazo Pérez M. Cost analysis of chronic obstructive pulmonary disease (COPD): a systematic review. *Health Econ Rev*. 2021;11(1):31. doi:10.1186/s13561-021-00329-9
65. Meiwald A, Gara-Adams R, Rowlandson A, et al. Qualitative validation of COPD evidenced care pathways in Japan, Canada, England, and Germany: common barriers to optimal COPD care. *Int J Chron Obstruct Pulmon Dis*. 2022;17:1507–1521. doi:10.2147/COPD.S360983
66. van der Palen J, van Beurden WM, Dawson CM, et al. A randomized, open-label, single-visit crossover study simulating triple-drug delivery with Ellipta compared with dual inhaler combinations in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2515–2523. doi:10.2147/COPD.S169060
67. Lin L, Liu C, Cheng W, et al. Comparison of treatment persistence, adherence, and risk of exacerbation in patients with COPD treated with single-inhaler versus multiple-inhaler triple therapy: a prospective observational study in China. *Front Pharmacol*. 2023;14. doi:10.3389/fphar.2023.1147985
68. Halpin DMG, Worsley S, Ismaila AS, et al. INTREPID: single- versus multiple-inhaler triple therapy for COPD in usual clinical practice. *ERJ Open Res*. 2021;7(2):00950–02020. doi:10.1183/23120541.00950-2020
69. Halpin DMG, Rothnie KJ, Banks V, et al. Comparative adherence and persistence of single- and multiple-inhaler triple therapies among patients with chronic obstructive pulmonary disease in an English real-world primary care setting. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2417–2429. doi:10.2147/COPD.S370540
70. Deslee G, Fabry-Vendrand C, Poccardi N, et al. Use and persistence of single and multiple inhaler triple therapy prescribed for patients with COPD in France: a retrospective study on THIN database (OPTI study). *BMJ Open Respir Res*. 2023;10(1). doi:10.1136/bmjresp-2022-001585
71. Mannino D, Bogart M, Wu B, et al. Adherence and persistence to once-daily single-inhaler versus multiple-inhaler triple therapy among patients with chronic obstructive pulmonary disease in the USA: a real-world study. *Respir Med*. 2022;197:106807. doi:10.1016/j.rmed.2022.106807
72. Bosnic-Anticevich S, Chrystyn H, Costello RW, et al. The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes. *Int J Chron Obstruct Pulmon Dis*. 2017;12:59. doi:10.2147/COPD.S117196
73. Hanania NA, Bunner SH, Bengtson LGS, Ismaila AS, Bogart M. COPD exacerbations, costs, and health care resource utilization before and after initiation of fluticasone furoate/umeclidinium/vilanterol in routine care in the USA. *Int J Chron Obstruct Pulmon Dis*. 2023;18:407–418. doi:10.2147/COPD.S378867
74. NHS prescription charges from 1 May 2024. GOV.UK. Available from: https://www.gov.uk/government/news/nhs-prescription-charges-from-1-may-2024. Accessed February 19, 2025.
75. Cho EE, Mecredy GC, Wong HH, Stanbrook MB, Gershon AS. Which physicians are taking care of people with COPD? *CHEST*. 2019;155(4):771–777. doi:10.1016/j.chest.2018.12.018
76. Gruffydd-Jones K, Haughney J, Jones R, Loveridge C, Pinnock H. Quick guide to the diagnosis and management of COPD in primary care | primary care respiratory society. 2016. Available from: https://www.pcrs-uk.org/resource/current/quick-guide-diagnosis-and-management-copd-primary-care. Accessed June 10, 2024.
77. Sethi S, Wright A, Hartgers-Gubbels ES, et al. Costs and clinical consequences of compliance with COPD GOLD recommendations or national guidelines compared with current clinical practice in Belgium, Germany, Sweden, and the United States. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2149–2160. doi:10.2147/COPD.S371440
78. White P, Thornton H, Pinnock H, Georgopoulou S, Booth HP. Overtreatment of COPD with inhaled corticosteroids--implications for safety and costs: cross-sectional observational study. *PLoS One*. 2013;8(10):e75221. doi:10.1371/journal.pone.0075221
79. Price D, West D, Brusselle G, et al. Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. *Int J Chron Obstruct Pulmon Dis*. 2014;9:889–904. doi:10.2147/COPD.S62750
80. Di Marco F, Santus P, Terraneo S, et al. Characteristics of newly diagnosed COPD patients treated with triple inhaled therapy by general practitioners: a real world Italian study. *NPJ Prim Care Respir Med*. 2017;27(1):51. doi:10.1038/s41533-017-0051-9
81. Vetrano DL, Zucchelli A, Bianchini E, et al. Triple inhaled therapy in COPD patients: determinants of prescription in primary care. *Respir Med*. 2019;154:12–17. doi:10.1016/j.rmed.2019.05.022
82. Perera B, Barton C, Osadnik C. General practice management of COPD patients following acute exacerbations: a qualitative study. *Br J Gen Pract*. 2023;73(728):e186–e195. doi:10.3399/BJGP.2022.0342
83. van de Hei SJ, Flokstra-de Blok BMJ, Baretta HJ, et al. Quality of spirometry and related diagnosis in primary care with a focus on clinical use. *Npj Prim Care Respir Med*. 2020;30(1):1–7. doi:10.1038/s41533-020-0177-z
84. Heinmüller S, Schaubroeck E, Frank L, et al. The quality of COPD care in German general practice—A cross-sectional study. *Chron Respir Dis*. 2020;17:1479973120964814. doi:10.1177/1479973120964814
85. Athlin Å, Lisspers K, Hasselgren M, et al. Diagnostic spirometry in COPD is increasing, a comparison of two Swedish cohorts. *Npj Prim Care Respir Med*. 2023;33(1):1–7. doi:10.1038/s41533-023-00345-8
86. Vachon B, Giasson G, Gaboury I, et al. Challenges and strategies for improving COPD primary care services in Quebec: results of the experience of the COMPAS+ quality improvement collaborative. *Int J Chron Obstruct Pulmon Dis*. 2022;17:259–272. doi:10.2147/COPD.S341905
87. Glaab T, Banik N, Rutschmann OT, Wencker M. National survey of guideline-compliant COPD management among pneumologists and primary care physicians. *COPD J Chronic Obstr Pulm Dis*. 2006;3(3):141–148. doi:10.1080/15412550600829299

88. Laue J, Melbye H, Halvorsen PA, et al. How do general practitioners implement decision-making regarding COPD patients with exacerbations? An international focus group study. *Int J Chron Obstruct Pulmon Dis*. 2016;11:3109–3119. doi:10.2147/COPD.S118856
89. Greenwood-Lee J, Jewett L, Woodhouse L, Marshall DA. A categorization of problems and solutions to improve patient referrals from primary to specialty care. *BMC Health Serv Res*. 2018;18(1):986. doi:10.1186/s12913-018-3745-y
90. Martin S, Siciliani L, Smith P. Socioeconomic inequalities in waiting times for primary care across ten OECD countries. *Soc Sci Med*. 2020;263:113230. doi:10.1016/j.socscimed.2020.113230
91. Wilkinson TMA, Donaldson GC, Hurst JR, Seemungal TAR, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;169(12):1298–1303. doi:10.1164/rccm.200310-1443OC
92. Decramer M, Cooper CB. Treatment of COPD: the sooner the better? *Thorax*. 2010;65(9):837–841. doi:10.1136/thx.2009.133355
93. Calabria S, Ronconi G, Dondi L, et al. EPH200 healthcare resource consumption of patients with chronic obstructive pulmonary disease treated with triple and dual therapy and experiencing an acute exacerbation. *Value Health*. 2023;26(12):S239. doi:10.1016/j.jval.2023.09.1241
94. Ismaila AS, Rothnie KJ, Wood RP, et al. Benefit of prompt initiation of single-inhaler fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) in patients with COPD in England following an exacerbation: a retrospective cohort study. *Respir Res*. 2023;24(1):229. doi:10.1186/s12931-023-02523-1
95. Mainar AS, Huerta A, Artieda RN, Monsó E, Landis SH, Ismaila AS. Economic impact of delaying initiation with multiple-inhaler maintenance triple therapy in Spanish patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2121–2129. doi:10.2147/COPD.S211854
96. Tkacz J, Evans KA, Touchette DR, et al. PRIMUS - prompt initiation of maintenance therapy in the US: a real-world analysis of clinical and economic outcomes among patients initiating triple therapy following a COPD exacerbation. *Int J Chron Obstruct Pulmon Dis*. 2022;17:329–342. doi:10.2147/COPD.S347735
97. Bogart M, Glassberg MB, Reinsch T, Stanford RH. Impact of prompt versus delayed initiation of triple therapy post COPD exacerbation in a US-managed care setting. *Respir Med*. 2018;145:138–144. doi:10.1016/j.rmed.2018.10.013
98. World Health Organization. Chronic obstructive pulmonary disease (COPD). Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-copd. Accessed June 6, 2024.
99. Licskai C, Sands T, Ong M, Paolatto L, Nicoletti I. Using a knowledge translation framework to implement asthma clinical practice guidelines in primary care. *Int J Qual Health Care*. 2012;24(5):538–546. doi:10.1093/intqhc/mzs043
100. Hussey AJ, Wing K, Ferrone M, Licskai CJ. Integrated disease management for chronic obstructive pulmonary disease in primary care, from the controlled trial to clinical program: a cohort study. *Int J Chron Obstruct Pulmon Dis*. 2021;16:3449–3464. doi:10.2147/COPD.S338851
101. Waibel S, Vargas I, Aller MB, Gusmão R, Henao D, Vázquez ML. The performance of integrated health care networks in continuity of care: a qualitative multiple case study of COPD patients. *Int J Integr Care*. 2015;15(3):e029. doi:10.5334/ijic.1527
102. Wu CX, Hwang CH, Tan WS, et al. Effectiveness of a chronic obstructive pulmonary disease integrated care pathway in a regional health system: a propensity score matched cohort study. *BMJ Open*. 2018;8(3):e019425. doi:10.1136/bmjopen-2017-019425
103. Patel K, Pye A, Edgar RG, et al. Cluster randomized controlled trial of specialist-led integrated COPD care (INTEGR COPD). *Thorax*. 2024;79(3):209–218. doi:10.1136/thorax-2023-220435
104. Bollmeier SG, Hartmann AP. Management of chronic obstructive pulmonary disease: a review focusing on exacerbations. *Am J Health Syst Pharm*. 2020;77(4):259–268. doi:10.1093/ajhp/zxz306
105. Licskai C, Hussey A, Rowley V, et al. Quantifying sustained health system benefits of primary care-based integrated disease management for COPD: a 6-year interrupted time series study. *Thorax*. 2024;79(8):725–734. doi:10.1136/thorax-2023-221211
106. Ferrone M, Masciantonio MG, Malus N, et al. The impact of integrated disease management in high-risk COPD patients in primary care. *NPJ Prim Care Respir Med*. 2019;29(1):8. doi:10.1038/s41533-019-0119-9
107. Scarffe AD, Licskai CJ, Ferrone M, Brand K, Thavorn K, Coyle D. Cost-effectiveness of integrated disease management for high risk, exacerbation prone, patients with chronic obstructive pulmonary disease in a primary care setting. *Cost Eff Resour Alloc*. 2022;20(1):39. doi:10.1186/s12962-022-00377-w
108. Fabbri LM, Celli BR, Agustí A, et al. COPD and multimorbidity: recognizing and addressing a syndemic occurrence. *Lancet Respir Med*. 2023;11(11):1020–1034. doi:10.1016/S2213-2600(23)00261-8
109. Sandelowsky H, Weinreich UM, Aarli BB, et al. COPD – do the right thing. *BMC Fam Pract*. 2021;22(1):244. doi:10.1186/s12875-021-01583-w
110. Kayyali R, Odeh B, Frerichs I, et al. COPD care delivery pathways in five European Union countries: mapping and health care professionals' perceptions. *Int J Chron Obstruct Pulmon Dis*. 2016;11(1):2831–2838. doi:10.2147/COPD.S104136
111. Tranmer J, Rotter T, O'Donnell D, et al. Determining the influence of the primary and specialist network of care on patient and system outcomes among patients with a new diagnosis of chronic obstructive pulmonary disease (COPD). *BMC Health Serv Res*. 2022;22(1):1210. doi:10.1186/s12913-022-08588-w
112. Croft JB, Lu H, Zhang X, Holt JB. Geographic accessibility of pulmonologists for adults with COPD: United States, 2013. *CHEST*. 2016;150(3):544–553. doi:10.1016/j.chest.2016.05.014
113. Shatto JA, Stickland MK, Soril LJJ. Variations in COPD health care access and outcomes: a rapid review. *Chronic Obstr Pulm Dis J COPD Found*. 2024;11(2):229–246. doi:10.15326/jcopdf.2023.0441
114. Sav A, Thomas ST, Cardona M, Michaleff ZA, Dobler CC. Treatment burden discussion in clinical encounters: priorities of COPD patients, carers and physicians. *Int J Chron Obstruct Pulmon Dis*. 2022;17:1929–1942. doi:10.2147/COPD.S366412
115. Polverino F, Bhutani M, Zabert G, et al. Access to treatment for chronic obstructive pulmonary disease (COPD) in the Americas: a call for action. *Ann Am Thorac Soc*. 2024;21(11):1463–1470. doi:10.1513/AnnalsATS.202404-386FR
116. Tøttenborg SS, Lange P, Johnsen SP, Nielsen H, Ingebrigtsen TS, Thomsen RW. Socioeconomic inequalities in adherence to inhaled maintenance medications and clinical prognosis of COPD. *Respir Med*. 2016;119:160–167. doi:10.1016/j.rmed.2016.09.007
117. Gaffney AW, Hawks L, White AC, et al. Health care disparities across the urban-rural divide: a national study of individuals with COPD. *J Rural Health off J Am Rural Health Assoc Natl Rural Health Care Assoc*. 2022;38(1):207–216. doi:10.1111/jrh.12525