Centers for Medicare and Medicaid Services: Drug Price Negotiations

Research Protocol

SEPTEMBER 18, 2024

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1. Background, Objectives, and Research Questions

1.1. Background

Under the Inflation Reduction Act (IRA), the Centers for Medicare and Medicaid Services (CMS) has initiated drug price negotiations on selected Medicare Part D drugs with participating drug manufacturers. In October 2023, the Institute for Clinical and Economic Review (ICER) published a special report on two of the 10 drugs selected for the first cycle of drug price negotiations, apixaban and rivaroxaban.[1] CMS recently released draft guidance for the second cycle, during which they will review up to 15 additional drugs, with drug price negotiations set to take effect in 2027. This ICER special report will focus on two drugs that are anticipated to be subject to price negotiations in this next cycle: a combination of fluticasone furoate and vilanterol (Breo Ellipta®, GSK) and a combination of fluticasone furoate, vilanterol, and umeclidinium (Trelegy Ellipta®, GSK), both as maintenance therapies for chronic obstructive pulmonary disorder (COPD).

COPD is a group of lung diseases characterized by progressive and persistent airflow obstruction in the lungs. It affects approximately 15.7 million people in the United States (US), with higher rates among non-Hispanic White individuals, American Indian/Alaska Native individuals, women, and adults older than 65.[2] COPD is the sixth leading cause of death among Americans and is the cause of over half-a-million hospitalizations, one million emergency department visits per year, and 16.4 million lost working days per year.[3-5] The total economic burden of COPD is estimated to be almost $50 billion per year, with $24 billion attributable to direct medical costs alone Pre-pandemic estimates were used, as experts indicated that the COVID-19 pandemic has temporarily impacted the most recent data.[4]

Patients with COPD experience shortness of breath, fatigue, wheezing, chest tightness, and cough. Symptom burden is high, with about half of COPD patients reporting near-daily symptoms and the majority reporting that symptoms have a moderate-to-great impact on everyday life.[6] In very severe COPD, patients may lose weight and/or develop right-sided heart failure. Women with COPD have been observed to be younger, smoke less, and have more dyspnea than men; women also account for a higher proportion of hospitalizations.[7,8] Lower socioeconomic status has been linked with greater disease progression.[9]

Diagnosis of COPD is based on symptoms and evidence of airflow obstruction, defined as a post-bronchodilator forced expiratory volume/forced vital capacity ratio (FEV_1/FVC) of <0.7.[10] Exacerbations are an important marker of disease, as they impact health-related quality of life, account for a large portion of COPD spending, and may accelerate disease progression.[11] The goals of pharmacologic therapy in COPD are to reduce symptoms and exacerbations. The Global Initiative

for Obstructive Lung Disease (GOLD) guidelines recommend dual therapy, either long-acting muscarinic antagonist (LAMA) combined with a long-acting beta-agonist (LABA) or inhaled corticosteroids (ICS) combined with a LABA, for patients who are not adequately controlled with single therapy (i.e., patients with persistent symptoms or exacerbations). Patients with COPD who continue to have exacerbations despite being on dual therapy or those with elevated eosinophil counts should be escalated to triple therapy: the combination of a LAMA, LABA, and ICS.[10] Dual therapies are consistently more effective than single therapies.[12-14] Triple therapies have demonstrated better outcomes for patients with severe COPD compared to dual therapies.[14-18] Literature suggests that there are no intraclass differences for dual therapies.[13] However, it remains uncertain whether variations exist in efficacy and safety among different triple therapy combinations.[19,20] Additionally, these dual or triple therapies often require multiple inhalations every day, sometimes administered by multiple inhalers, which can lead to poor adherence among patients with COPD.[21] Switching to once-daily therapy has been associated with improved adherence.[22,23]

Breo Ellipta® (GSK) and Trelegy Ellipta® (GSK) are both once-daily, fixed-dose inhalers indicated for COPD maintenance therapy. We will estimate the comparative therapeutic impact of Breo Ellipta and Trelegy Ellipta compared to their respective fixed-dose generic alternatives or open generic combinations in patients with moderate to severe COPD.

1.2 Objectives

This project will assess the comparative clinical effectiveness and economic impacts of Breo Ellipta and Trelegy Ellipta for the treatment of moderate to severe COPD. The assessment will systematically evaluate the existing evidence, taking uncertainty into account. This document presents the protocol for the systematic review of existing evidence. See the model analysis plan (expected posting: November 12, 2024) for details on the proposed methodology and model structure for the economic evaluation.

1.3 Research Questions

For the clinical evidence review, we will answer three separate research questions:

- **Research Question #1**: What is the net health benefit of Breo Ellipta versus generically available dual (ICS/LABA) therapy inhalers in patients with moderate to severe COPD?
- **Research Question #2**: What is the net health benefit of Trelegy Ellipta versus generically available triple therapy inhalers in patients with moderate to severe COPD with or without exacerbations?

In answering research question #2, we are also interested in understanding whether there are differences in efficacy and safety among different triple therapy combinations when they are taken consistently as directed. As such, we will also address this research question:

- **Research Question #3**: What is the comparative efficacy of triple therapy inhalers in patients with moderate to severe COPD when delivered with comparable treatment adherence?

1.4 PICOTS Criteria

In line with the three research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Populations, Interventions, and Comparators

Research Questions	Populations	Intervention	Comparators (generically available drugs based on CMS guidelines)
Research Question #1	Patients with moderate to severe COPD	Breo Ellipta (Fixed-dose combination of fluticasone furoate, ICS; and vilanterol trifenatate, LABA)	• Budesonide/formoterol fumarate [Fixed-dose ICS/LABA] • Fluticasone propionate/salmeterol xinafoate [Fixed-dose ICS/LABA]
Research Question #2	Patients with moderate to severe COPD with or without exacerbations	Trelegy Ellipta (Fixed-dose combination of fluticasone furoate, ICS; vilanterol, LABA; and umeclidinium, anticholinergic)	• Budesonide/formoterol fumarate in combination with tiotropium [open combination of ICS/LABA and LAMA] • Fluticasone propionate/salmeterol xinafoate in combination with tiotropium [open combination of ICS/LABA and LAMA] • Fluticasone furoate/vilanterol trifenatate in combination with tiotropium [open combination of ICS/LABA and LAMA]
Research Question #3	Patients with moderate to severe COPD	• All available fixed dose and open combinations of ICS/LABA/LAMA	

CMS: Centers for Medicare and Medicaid; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids, LABA: long-acting beta-agonists, LAMA: long-acting muscarinic antagonists

Outcomes

The outcomes of interest for research questions #1 and #2 are described below.

- Patient-Important Outcomes
    - Changes in dyspnea (e.g., transitional dyspnea index [TDI], Modified Medical Research Council Dyspnea Scale [mMRC])
    - Changes in functional capacity (e.g., 6-minute walk distance)
    - COPD-related hospitalization or emergency room visit
    - Use of rescue medication
    - Requirement for long-term continuous or intermittent oxygen use
    - Health-related quality of life (e.g., St. George's Respiratory Questionnaire [SGRQ])
    - Number of exacerbations (e.g., annual rate of moderate and severe exacerbations)
- Changes in lung function (e.g., changes in average or peak forced expiratory volume [FEV1])
- Adverse events (AEs) including but not limited to:
    - Serious AEs
    - Discontinuation due to AEs
    - Other AEs including but not limited to:
        - Mortality
        - Pneumonia
        - Cardiovascular outcomes (e.g., myocardial infarction, ischemic heart disease, stroke, hypertension)
        - Urinary tract risks, including urinary retention
- Adherence (e.g., Proportion of Days with full dose, proportion of doses received)
- Total discontinuation rate

The outcomes of interest for research question #3 are described below.

- Number of exacerbations
- Health-related quality of life
- Mortality
- Discontinuations due to AEs

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on all settings in the United States.

Study Design

For research questions #1 and #2, evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality, real-world observational studies will be included to inform evidence on long-term outcomes, low-frequency harms, and to validate our network meta-analysis results.

For research question #3, evidence will be abstracted from randomized controlled trials only.

2. Evidence Review Methods

2.1 Search Methods and Data Sources

The systematic literature review assessing the evidence on Breo Ellipta and Trelegy Ellipta for moderate to severe COPD will follow established best methods.[24,25] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[26] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials to identify relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 2.1. to 2.4. below. To ensure we have identified all relevant, high-quality observational studies in our search, we will also conduct a targeted search for data on dose frequency, adherence, long-term outcomes, and low-frequency adverse events for inhaler use in patients with COPD. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

For research question #3, we identified two network meta-analyses (NMAs) during our scoping phase that met our criteria. These NMAs provided indirect comparisons of available fixed-dose and open combinations of triple therapies, but their findings were inconsistent. Therefore, our goal is to update the triple therapy NMA in this assessment (research question #3), with a particular focus on the study by Lee et al., 2021 due to its methodological advantages.[20] We will identify RCTs of available fixed-dose and open combinations of triple therapies that meet our criteria from Lee et al. 2021 and search for new evidence on fixed-dose and open combinations by conducting an updated systematic literature search. In order to account for delays in indexing, we will overlap the search timeframe for fixed-dose and open combinations of triple therapies with that of the previous systematic review (Table 2.5. and 2.6.).

Table 2.1. Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews – Breo Ellipta (Research Question #1)

1	COPD	exp Pulmonary Disease, Chronic Obstructive/ OR ("Airflow Obstruction, Chronic" OR "Airflow Obstructions, Chronic" OR "chronic airflow obstruction" OR "chronic airway obstruction" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "chronic obstructive respiratory disease" OR "chronic pulmonary obstructive disease" OR "chronic pulmonary obstructive disorder" OR "Chronic Airflow Obstruction" OR "Chronic Airflow Obstructions" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Pulmonary Disease" OR "Chronic Obstructive Pulmonary Diseases" OR "COAD" OR "COPD" OR "lung chronic obstructive disease" OR "lung disease, chronic obstructive" OR "obstructive chronic lung disease" OR "obstructive chronic pulmonary disease" OR "obstructive lung disease, chronic" OR "pulmonary disease, chronic obstructive" OR "pulmonary disorder, chronic obstructive").ti,ab.
2	Breo Ellipta	("breo" OR "breo ellipta" OR "FF/VI" OR "fluticasone furoate plus vilanterol" OR "fluticasone furoate plus vilanterol trifenatate" OR "fluticasone furoate/vilanterol" OR "fluticasone furoate/vilanterol trifenatate" OR "GSK 2285997" OR "GSK 642444 (LABA)/GSK 685698 (ICS)" OR "GSK2285997" OR "GSK-2285997" OR "GSK642444 (LABA)/GSK685698 (ICS)" OR "GSK-642444 (LABA)/GSK-685698 (ICS)" OR "Horizon" OR "relovair" OR "relvar" OR "relvar ellipta" OR "revinty ellipta" OR "vilanterol plus fluticasone furoate" OR "vilanterol trifenatate plus fluticasone furoate" OR "vilanterol trifenatate/fluticasone furoate" OR "vilanterol/fluticasone furoate").ti,ab.
3	Generic ICS/LABA	("airbufo forspiro" or "alenia" or "assieme*" or "biresp spiromax" or "breyna" or "budamate" or "budased f" or "budelite f" or "buderap f" or "Budesonide Formoterol Drug Combination" or "Budesonide Formoterol Fumarate Drug Combination" or "budesonide plus formoterol*" or "budesonide, formoterol fumarate* " or "budesonide/formoterol*" or "budesonide-formoterol*" or "budevin f" or "budsocare f" or "bufar*" or "bufoler*" or "bufomix*" or "bufori easyhaler" or "Combination, Budesonide-Formoterol Drug" or "Drug Combination, Budesonide-Formoterol" or "duoresp spiromax" or "duori*" or "fixbufo easyhaler" or "flamboyant (drug)" or "fobuler" or "fobumix easyhaler" or "foracort*" or "foradil*" or "forarite" or "forb" or "formonide" or "formoterol fumarate dihydrate plus budesonide" or "formoterol fumarate dihydrate/budesonide" or "formoterol fumarate plus budesonide" or "formoterol fumarate/budesonide" or "formoterol plus budesonide" or "formoterol/budesonide" or "formoterol-budesonide" or "gardette*" or "gibiter*" or "ludonaze bf" or "orbufox*" or "orest*" or "pt 009" or "pt009" or "pulentia" or "pulmalio" or "pulmelia" or "pulmoresp" or "pulmoton" or "respimix easyhaler" or "rilast*" or "sinestic" or "Symbicort*" or "syn 010" or "syn010" or "vannair" or "vyaler spiromax" or "vylaer spiromax" or "weldinide f" or ("adoair" or "Advair* " or "Aerivio*" or "Airduo* " or "Airexar*" or "Airflusal*" or "anasma" or "apc 5000" or "apc5000" or "atmadisc" or "bropair spiromax" or "campona*" or "Combination, Fluticasone-Salmeterol" or "Drug Combination, Fluticasone-Salmeterol" or "Fluticasone - Salmeterol" or "Fluticasone Propionate-Salmeterol*" or "fluticasone propionate plus salmeterol* " or "Fluticasone Propionate Salmeterol*" or "Fluticasone Propionate, Salmeterol* " or "fluticasone propionate/salmeterol xinafoate" or "Fluticasone Salmeterol*" or "inaladuo" or "plusvent" or "salmeterol xinafoate plus fluticasone propionate" or "salmeterol xinafoate/fluticasone propionate" or "sas 40023" or "sas40023" or "seffalair spiromax" or "sereflo*" or "Seretide*" or "serflu" or "seroflo*" or "sirdupla" or "viani" or "wixela inhub")).ti,ab. OR

		((budesonide and ("formoterol fumarate" or formoterol)) or ((fluticasone or "fluticasone propionate") and (salmeterol or "salmeterol xinafoate"))).ti,ab.
4	Combination	1 AND (2 OR 3)
5	Animals	4 NOT (animals not (humans and animals)).sh.
6	Publication type	5 not (address or autobiography or bibliography or biography or comment or case report or congress or clinical trial, veterinary or collected work or consensus development conference or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or encyclopedia or "expression of concern" or festschrift or guideline or government publication or guideline or historical article or interactive tutorial or interview or lecture or legal case or legislation or letter or news or newspaper article or observational study, veterinary or patient education handout or periodical index or personal narrative or portrait or practice guideline or published erratum randomized controlled trial, veterinary or "retraction of publication" or video-audio media or webcast).pt.
7	English	limit 6 to English language
8	Duplicates	Remove duplicates from 7

Table 2.2. EMBASE Search Strategy – Breo Ellipta (Research Question #1)

1	COPD	'chronic obstructive lung disease'/exp OR ('Airflow Obstruction, Chronic' OR 'Airflow Obstructions, Chronic' OR 'chronic airflow obstruction' OR 'chronic airway obstruction' OR 'chronic obstructive bronchopulmonary disease' OR 'chronic obstructive lung disease' OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive respiratory disease' OR 'chronic pulmonary obstructive disease' OR 'chronic pulmonary obstructive disorder' OR 'Chronic Airflow Obstruction' OR 'Chronic Airflow Obstructions' OR 'Chronic Obstructive Airway Disease' OR 'Chronic Obstructive Lung Disease' OR 'Chronic Obstructive Pulmonary Disease' OR 'Chronic Obstructive Pulmonary Diseases' OR 'COAD' OR 'COPD' OR 'lung chronic obstructive disease' OR 'lung disease, chronic obstructive' OR 'obstructive chronic lung disease' OR 'obstructive chronic pulmonary disease' OR 'obstructive lung disease, chronic' OR 'pulmonary disease, chronic obstructive' OR 'pulmonary disorder, chronic obstructive'):ti,ab
2	Breo Ellipta	('breo' OR 'breo ellipta' OR 'FF/VI' OR 'fluticasone furoate plus vilanterol' OR 'fluticasone furoate plus vilanterol trifenatate' OR 'fluticasone furoate/vilanterol' OR 'fluticasone furoate/vilanterol trifenatate' OR 'GSK 2285997' OR 'GSK 642444 (LABA)/GSK 685698 (ICS)' OR 'GSK2285997' OR 'GSK-2285997' OR 'GSK642444 (LABA)/GSK685698 (ICS)' OR 'GSK-642444 (LABA)/GSK-685698 (ICS)' OR 'Horizon' OR 'relovair' OR 'relvar' OR 'relvar ellipta' OR 'revinty ellipta' OR 'vilanterol plus fluticasone furoate' OR 'vilanterol trifenatate plus fluticasone furoate' OR 'vilanterol trifenatate/fluticasone furoate' OR 'vilanterol/fluticasone furoate'):ti,ab
3	Generic ICS/LABA	('airbufo forspiro' OR 'alenia' OR 'assieme*' OR 'biresp spiromax' OR 'breyna' OR 'budamate' OR 'budased f' OR 'budelite f' OR 'buderap f' OR 'Budesonide Formoterol Drug Combination' OR 'Budesonide Formoterol Fumarate Drug Combination' OR 'budesonide plus formoterol*' OR 'budesonide, formoterol fumarate*' OR 'budesonide/formoterol*' OR 'budesonide-formoterol*' OR 'budevin f' OR 'budsocare f' OR 'bufar*' OR 'bufoler*' OR 'bufomix*' OR 'bufori easyhaler' OR 'Combination, Budesonide-Formoterol Drug' OR 'Drug Combination, Budesonide-Formoterol' OR 'duoresp spiromax' OR 'duori*' OR 'fixbufo easyhaler' OR 'flamboyant (drug)' OR 'fobuler' OR 'fobumix easyhaler' OR 'foracort*' OR 'foradil*' OR 'forarite' OR 'forb' OR 'formonide' OR 'formoterol fumarate dihydrate plus budesonide' OR 'formoterol fumarate dihydrate/budesonide' OR 'formoterol fumarate plus budesonide' OR 'formoterol fumarate/budesonide' OR 'formoterol plus budesonide' OR 'formoterol/budesonide' OR 'formoterol-budesonide' OR 'gardette*' OR 'gibiter*' OR

		'ludonaze bf' OR 'orbufox*' OR 'orest*' OR 'pt 009' OR 'pt009' OR 'pulentia' OR 'pulmalio' OR 'pulmelia' OR 'pulmoresp' OR 'pulmoton' OR 'respimix easyhaler' OR 'rilast*' OR 'sinestic' OR 'Symbicort*' OR 'syn 010' OR 'syn010' OR 'vannair' OR 'vyaler spiromax' OR 'vylaer spiromax' OR 'weldinide f' OR 'adoair' OR 'Advair*' OR 'Aerivio*' OR 'Airduo*' OR 'Airexar*' OR 'Airflusal*' OR 'anasma' OR 'apc 5000' OR 'apc5000' OR 'atmadisc' OR 'bropair spiromax' OR 'campona*' OR 'Combination, Fluticasone-Salmeterol' OR 'Drug Combination, Fluticasone-Salmeterol' OR 'Fluticasone - Salmeterol' OR 'Fluticasone Propionate-Salmeterol*' OR 'fluticasone propionate plus salmeterol*' OR 'Fluticasone Propionate Salmeterol*' OR 'Fluticasone Propionate, Salmeterol*' OR 'fluticasone propionate/salmeterol xinafoate' OR 'Fluticasone Salmeterol*' OR 'inaladuo' OR 'plusvent' OR 'salmeterol xinafoate plus fluticasone propionate' OR 'salmeterol xinafoate/fluticasone propionate' OR 'sas 40023' OR 'sas40023' OR 'seffalair spiromax' OR 'sereflo*' OR 'Seretide*' OR 'serflu' OR 'seroflo*' OR 'sirdupla' OR 'viani' OR 'wixela inhub'):ti,ab OR ((budesonide AND ('formoterol fumarate' OR formoterol)) OR ((fluticasone OR 'fluticasone propionate') AND (salmeterol OR 'salmeterol xinafoate'))):ti,ab
4	Combination	#1 AND (#2 OR #3)
5	Animal	#4 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)
6	Publication type	#5 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'review'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)
7	English	#6 AND [english]/lim

Table 2.3 Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews – Trelegy Ellipta (Research Question #2)

1	COPD	exp Pulmonary Disease, Chronic Obstructive/ OR ("Airflow Obstruction, Chronic" OR "Airflow Obstructions, Chronic" OR "chronic airflow obstruction" OR "chronic airway obstruction" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "chronic obstructive respiratory disease" OR "chronic pulmonary obstructive disease" OR "chronic pulmonary obstructive disorder" OR "Chronic Airflow Obstruction" OR "Chronic Airflow Obstructions" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Pulmonary Disease" OR "Chronic Obstructive Pulmonary Diseases" OR "COAD" OR "COPD" OR "lung chronic obstructive disease" OR "lung disease, chronic obstructive" OR "obstructive chronic lung disease" OR "obstructive chronic pulmonary disease" OR "obstructive lung disease, chronic" OR "pulmonary disease, chronic obstructive" OR "pulmonary disorder, chronic obstructive").ti,ab.
2	Trelegy Ellipta	("elebrato ellipta" OR "fluticasone furoate plus umeclidinium bromide plus vilanterol trifenatate" OR "fluticasone furoate plus vilanterol plus umeclidinium" OR "fluticasone furoate plus vilanterol trifenatate plus umeclidinium bromide" OR "fluticasone furoate/umeclidinium bromide/vilanterol trifenatate" OR "fluticasone furoate/umeclidinium/vilanterol" OR "fluticasone furoate/vilanterol trifenatate/umeclidinium bromide" OR "fluticasone furoate/vilanterol/umeclidinium" OR "gsk 2834425" OR "gsk2834425" OR "temybric ellipta" OR "trelegy ellipta" OR "umeclidinium bromide plus fluticasone furoate plus vilanterol trifenatate" OR "umeclidinium bromide plus vilanterol trifenatate plus fluticasone furoate" OR "umeclidinium bromide/fluticasone furoate/vilanterol trifenatate" OR "umeclidinium bromide/vilanterol trifenatate/fluticasone furoate" OR "umeclidinium plus fluticasone furoate plus vilanterol" OR "umeclidinium plus vilanterol plus fluticasone furoate" OR

		"umeclidinium/fluticasone furoate/vilanterol" OR "umeclidinium/vilanterol/fluticasone furoate" OR "vilanterol plus fluticasone furoate plus umeclidinium" OR "vilanterol plus umeclidinium plus fluticasone furoate" OR "vilanterol trifenatate plus fluticasone furoate plus umeclidinium bromide" OR "vilanterol trifenatate plus umeclidinium bromide plus fluticasone furoate" OR "vilanterol trifenatate/fluticasone furoate/umeclidinium bromide" OR "vilanterol trifenatate/umeclidinium bromide/fluticasone furoate" OR "vilanterol/fluticasone furoate/umeclidinium" OR "vilanterol/umeclidinium/fluticasone furoate" OR "fluticasone furoate plus umeclidinium plus vilanterol").ti,ab.
3	Generic Triple Therapy	((tiotropium or "tiotropium bromide" or Spiriva*) and ((budesonide and (formoterol or "formoterol fumarate" or eformoterol or arformoterol)) or ("adoair" or "Advair*" or "Aerivio*" or "Airduo*" or "Airexar*" or "Airflusal*" or anasma or "apc 5000" or apc5000 or atmadisc or "bropair spiromax" or campona* or "Combination, Fluticasone-Salmeterol" or "Drug Combination, Fluticasone-Salmeterol" or "Fluticasone - Salmeterol" or "Fluticasone Propionate-Salmeterol*" or "fluticasone propionate plus salmeterol*" or "Fluticasone Propionate Salmeterol*" or "Fluticasone Propionate, Salmeterol*" or "fluticasone propionate/salmeterol xinafoate" or "Fluticasone Salmeterol*" or inaladuo or plusvent or "salmeterol xinafoate plus fluticasone propionate" or "salmeterol xinafoate/fluticasone propionate" or "sas 40023" or sas40023 or "seffalair spiromax" or "sereflo*" or "Seretide*" or serflu or "seroflo*" or sirdupla or viani or "wixela inhub") or (("fluticasone" or "fluticasone propionate") and ("salmeterol" or "salmeterol xinafoate")) or ("airbufo forspiro" or "alenia" or "assieme*" or "biresp spiromax" or "breyna" or "budamate" or "budased f" or "budelite f" or "buderap f" or "Budesonide Formoterol Drug Combination" or "Budesonide Formoterol Fumarate Drug Combination" or "budesonide plus formoterol*" or "budesonide, formoterol fumarate*" or "budesonide/formoterol*" or "budesonide-formoterol*" or "budevin f" or "budsocare f" or "bufar*" or "bufoler*" or "bufomix*" or "bufori easyhaler" or "Combination, Budesonide-Formoterol Drug" or "Drug Combination, Budesonide-Formoterol" or "duoresp spiromax" or "duori*" or "fixbufo easyhaler" or "flamboyant (drug)" or "fobuler" or "fobumix easyhaler" or "foracort*" or "foradil*" or "forarite" or "forb" or "formonide" or "formoterol fumarate dihydrate plus budesonide" or "formoterol fumarate dihydrate/budesonide" or "formoterol fumarate plus budesonide" or "formoterol fumarate/budesonide" or "formoterol plus budesonide" or "formoterol/budesonide" or "formoterol-budesonide" or "gardette*" or "gibiter*" or "ludonaze bf" or "orbufox*" or "orest*" or "pt 009" or "pt009" or "pulentia" or "pulmalio" or "pulmelia" or "pulmoresp" or "pulmoton" or "respimix easyhaler" or "rilast*" or "sinestic" or "Symbicort*" or "syn 010" or "syn010" or "vannair" or "vyaler spiromax" or "vylaer spiromax" or "weldinide f") or ((fluticasone or "fluticasone furoate") and (vilanterol or "vilanterol trifenatate")) or ("breo" or "breo ellipta" or "fluticasone furoate plus vilanterol trifenatate" or "fluticasone furoate/vilanterol" or "fluticasone furoate/vilanterol trifenatate" or "relovair" or "relvar" or "relvar ellipta" or "revinty ellipta" or "vilanterol plus fluticasone furoate" or "vilanterol trifenatate plus fluticasone furoate" or "vilanterol trifenatate/fluticasone furoate" or "vilanterol/fluticasone furoate" or "fluticasone furoate plus vilanterol"))).ti,ab.
6	Combination	1 AND (2 OR 3)
7	Animals	6 NOT (animals not (humans and animals)).sh.
8	Publication type	5 not (address or autobiography or bibliography or biography or comment or case report or congress or clinical trial, veterinary or collected work or consensus development conference or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or encyclopedia or "expression of concern" or festschrift or guideline or government publication or

		guideline or historical article or interactive tutorial or interview or lecture or legal case or legislation or letter or news or newspaper article or observational study, veterinary or patient education handout or periodical index or personal narrative or portrait or practice guideline or published erratum randomized controlled trial, veterinary or "retraction of publication" or video-audio media or webcast).pt.
9	English	limit 8 to English language
10	Duplicates	Remove duplicates from 9

Table 2.4. EMBASE Search Strategy – Trelegy Ellipta (Research Question #2)

1	COPD	'chronic obstructive lung disease'/exp OR ('Airflow Obstruction, Chronic' OR 'Airflow Obstructions, Chronic' OR 'chronic airflow obstruction' OR 'chronic airway obstruction' OR 'chronic obstructive bronchopulmonary disease' OR 'chronic obstructive lung disease' OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive respiratory disease' OR 'chronic pulmonary obstructive disease' OR 'chronic pulmonary obstructive disorder' OR 'Chronic Airflow Obstruction' OR 'Chronic Airflow Obstructions' OR 'Chronic Obstructive Airway Disease' OR 'Chronic Obstructive Lung Disease' OR 'Chronic Obstructive Pulmonary Disease' OR 'Chronic Obstructive Pulmonary Diseases' OR 'COAD' OR 'COPD' OR 'lung chronic obstructive disease' OR 'lung disease, chronic obstructive' OR 'obstructive chronic lung disease' OR 'obstructive chronic pulmonary disease' OR 'obstructive lung disease, chronic' OR 'pulmonary disease, chronic obstructive' OR 'pulmonary disorder, chronic obstructive'):ti,ab
2	Trelegy Ellipta	('elebrato ellipta' OR 'fluticasone furoate plus umeclidinium bromide plus vilanterol trifenatate' OR 'fluticasone furoate plus vilanterol plus umeclidinium' OR 'fluticasone furoate plus vilanterol trifenatate plus umeclidinium bromide' OR 'fluticasone furoate/umeclidinium bromide/vilanterol trifenatate' OR 'fluticasone furoate/umeclidinium/vilanterol' OR 'fluticasone furoate/vilanterol trifenatate/umeclidinium bromide' OR 'fluticasone furoate/vilanterol/umeclidinium' OR 'gsk 2834425' OR 'gsk2834425' OR 'temybric ellipta' OR 'trelegy ellipta' OR 'umeclidinium bromide plus fluticasone furoate plus vilanterol trifenatate' OR 'umeclidinium bromide plus vilanterol trifenatate plus fluticasone furoate' OR 'umeclidinium bromide/fluticasone furoate/vilanterol trifenatate' OR 'umeclidinium bromide/vilanterol trifenatate/fluticasone furoate' OR 'umeclidinium plus fluticasone furoate plus vilanterol' OR 'umeclidinium plus vilanterol plus fluticasone furoate' OR 'umeclidinium/fluticasone furoate/vilanterol' OR 'umeclidinium/vilanterol/fluticasone furoate' OR 'vilanterol plus fluticasone furoate plus umeclidinium' OR 'vilanterol plus umeclidinium plus fluticasone furoate' OR 'vilanterol trifenatate plus fluticasone furoate plus umeclidinium bromide' OR 'vilanterol trifenatate plus umeclidinium bromide plus fluticasone furoate' OR 'vilanterol trifenatate/fluticasone furoate/umeclidinium bromide' OR 'vilanterol trifenatate/umeclidinium bromide/fluticasone furoate' OR 'vilanterol/fluticasone furoate/umeclidinium' OR 'vilanterol/umeclidinium/fluticasone furoate' OR 'fluticasone furoate plus umeclidinium plus vilanterol'):ti,ab
3	Generic Triple Therapy	(tiotropium:ti,ab OR 'tiotropium bromide':ti,ab OR spiriva*:ti,ab) AND (budesonide:ti,ab AND (formoterol:ti,ab OR 'formoterol fumarate':ti,ab OR eformoterol:ti,ab OR arformoterol:ti,ab) OR 'adoair':ti,ab OR 'advair*':ti,ab OR 'aerivio*':ti,ab OR 'airduo*':ti,ab OR 'airexar*':ti,ab OR 'airflusal*':ti,ab OR anasma:ti,ab OR 'apc 5000':ti,ab OR apc5000:ti,ab OR atmadisc:ti,ab OR 'bropair spiromax':ti,ab OR campona*:ti,ab OR 'fluticasone - salmeterol':ti,ab OR 'fluticasone propionate-salmeterol*':ti,ab OR 'fluticasone propionate plus salmeterol*':ti,ab OR 'fluticasone propionate/salmeterol xinafoate':ti,ab OR 'fluticasone salmeterol*':ti,ab OR inaladuo:ti,ab OR plusvent:ti,ab OR 'salmeterol xinafoate plus fluticasone

		propionate':ti,ab OR 'sas 40023':ti,ab OR sas40023:ti,ab OR 'seffalair spiromax':ti,ab OR 'sereflo*':ti,ab OR 'seretide*':ti,ab OR serflu:ti,ab OR 'seroflo*':ti,ab OR sirdupla:ti,ab OR viani:ti,ab OR 'wixela inhub':ti,ab OR ('fluticasone':ti,ab AND ('salmeterol':ti,ab OR 'salmeterol xinafoate':ti,ab)) OR 'airbufo forspiro':ti,ab OR 'alenia':ti,ab OR 'assieme*':ti,ab OR 'biresp spiromax':ti,ab OR 'breyna':ti,ab OR 'budamate':ti,ab OR 'budased f':ti,ab OR 'budelite f':ti,ab OR 'buderap f':ti,ab OR 'budesonide formoterol drug combination':ti,ab OR 'budesonide plus formoterol*':ti,ab OR 'budesonide/formoterol*':ti,ab OR 'budesonide-formoterol*':ti,ab OR 'bufomix*':ti,ab OR 'duoresp spiromax':ti,ab OR 'symbicort*':ti,ab OR 'vannair':ti,ab OR 'vyaler spiromax':ti,ab OR 'vylaer spiromax':ti,ab OR 'weldinide f':ti,ab OR ((fluticasone:ti,ab OR 'fluticasone furoate':ti,ab) AND (vilanterol:ti,ab OR 'vilanterol trifenatate':ti,ab)) OR 'breo':ti,ab OR 'breo ellipta':ti,ab OR 'fluticasone furoate plus vilanterol trifenatate':ti,ab OR 'relvar ellipta':ti,ab OR 'vilanterol/fluticasone furoate':ti,ab)
6	Combination	#1 AND (#2 OR #3)
5	Animal	#4 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)
6	Publication type	#5 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'review'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)
7	English	#6 AND [english]/lim

Table 2.5. Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials – Triple Therapy NMA (Research Question #3)

1	COPD patients	exp Pulmonary Disease, Chronic Obstructive/ or ("Airflow Obstruction, Chronic" or "Airflow Obstructions, Chronic" or "chronic airflow obstruction" or "chronic airway obstruction" or "chronic obstructive bronchopulmonary disease" or "chronic obstructive lung disease" or "chronic obstructive pulmonary disease" or "chronic obstructive respiratory disease" or "chronic pulmonary obstructive disease" or "chronic pulmonary obstructive disorder" or "Chronic Airflow Obstruction" or "Chronic Airflow Obstructions" or "Chronic Obstructive Airway Disease" or "Chronic Obstructive Lung Disease" or "Chronic Obstructive Pulmonary Disease" or "Chronic Obstructive Pulmonary Diseases" or "COAD" or "COPD" or "lung chronic obstructive disease" or "lung disease, chronic obstructive" or "obstructive chronic lung disease" or "obstructive chronic pulmonary disease" or "obstructive lung disease, chronic" or "pulmonary disease, chronic obstructive" or "pulmonary disorder, chronic obstructive").ti,ab.
2	LABA (General)	exp "adrenergic beta-2 receptor agonists"/ or ("long-acting OR long acting OR ultra-long acting OR ultra-long-acting" and ("B agonist*" or "B-agonist*" or "B2 agonist*" or "B2-agonist*" or "B-2 agonist*" or "B(2) agonist*" or "B(2)-agonist*" or "B adrenergic agonist*" or "B-adrenergic agonist*" or "B2 adrenergic agonist*" or "B2-adrenergic agonist*" or "B-2 adrenergic agonist*" or "B-2-adrenergic agonist*" or "B2 adrenergic agonist*" or "B2-adrenergic agonist*" or "B-2 adrenergic agonist*" or "B-2-adrenergic agonist*" or "B(2) adrenergic agonist*" or "B(2)-adrenergic agonist*" or "B adrenoceptor agonist*" or "B-adrenoceptor agonist*" or "B2 adrenoceptor agonist*" or "B2-adrenoceptor agonist*" or "B-2 adrenoceptor agonist*" or "B-2-adrenoceptor agonist*" or "B2 adrenoceptor agonist*" or "B2-adrenoceptor agonist*" or "B-2 adrenoceptor agonist*" or "B-2-adrenoceptor agonist*" or "B(2) adrenoceptor agonist*" or "B(2)-adrenoceptor agonist*" or "beta agonist*" or "beta-agonist*" or "beta2 agonist*" or "beta2-agonist*" or "beta-2 agonist*" or "beta-2-agonist*" or "beta(2) agonist*" or "beta(2)-agonist*" or "beta adrenergic agonist*" or "beta-adrenergic agonist*" or "beta2 adrenergic agonist*" or "beta2-adrenergic agonist*" or "beta-2 adrenergic agonist*" or "beta-2-adrenergic agonist*" or "beta(2) adrenergic

		agonist*" or "beta(2)-adrenergic agonist*" or "beta adrenoceptor agonist*" or "beta-adrenoceptor agonist*" or "beta2 adrenoceptor agonist*" or "beta2-adrenoceptor agonist*" or "beta-2 adrenoceptor agonist*" or "beta-2-adrenoceptor agonist*" or "beta(2) adrenoceptor agonist*" or "beta(2)-adrenoceptor agonist*")).ti,ab. or ("LABA" or "LABAs" or "ultra-LABA" or "ultra-LABAs").ti,ab.
3	LABA (Individual drugs)	exp "Formoterol Fumarate"/ or exp "Salmeterol Xinafoate"/ or ("formoterol" or "formoterol-fumarate" or "eformoterol" or "Atimos" or "EFO" or "Fluir" or "Foradil" or "Foradile" or "Formoair" or "Oxis" or "Perforomist" or "Tempus" or "indacaterol" or "indacaterol" or "Indacaterol-maleate" or "arcapta" or "hirobriz" or "onbrez" or "onbrize" or "oslif" or "olodaterol" or "olodaterol" or "Striverdi" or "Salmeterol" or "Salmeterolum" or "Salmeterol-xinafoate" or "Aeromax" or "Astmerole" or "Arial" or "Neovent" or "Qitai" or "Serevent" or "Vertine" or "vilanterol" or "Vilanterol-trifenatate" or "vilanterol").ti,ab.
4	LAMA (General)	exp "Muscarinic Antagonists"/ or exp "Cholinergic Antagonists"/ or ((("long-acting" or "long acting" or "ultra-long acting" or "ultra-long-acting") and (muscarinic antagonist* or muscarinic receptor antagonist* or antimuscarinic agent* or anti-muscarinic agent* or muscarinic blocker* or muscarinic receptor blocker* or Cholinergic antagonist* or Cholinergic receptor antagonist* or anticholinergic agent* or anti-cholinergic agent* or cholinergic blocker* or cholinergic receptor blocker* or cholinolytic agent*)) or "LAMA" or "LAMAs" or "ultra-LAMA" or "ultra-LAMAs").ti,ab.
5	LAMA (Individual drugs)	exp "Glycopyrrolate"/ or exp "tiotropium bromide"/ or ("aclidinium bromide" or "aclidinium" or "aclidinium-bromide" or "Tudorza" or "Eklira" or "Bretaris" or "Glycopyrrolate" or "glycopyrronium" or "Glycopyrronium-bromide" or "Seebri" or "tiotropium" or "Tiotropium-bromide" or "Spiriva" or "Tiova" or "Umeclidinium" or "Umeclidinium-bromide" or "Incruse").ti,ab.
6	ICS (General)	(Inhal*.ti,ab. and ((exp Steroids/ or exp "Adrenal Cortex Hormones"/) and (exp "Bronchodilator Agents"/ or exp "Anti-Asthmatic Agents"/))) or (corticosteroid* or cortico-steroid* or glucocorticoid* or steroid* or ICS).ti,ab.
7	ICS (Individual drugs)	exp "Beclomethasone"/ or exp "Budesonide"/ or exp "Fluticasone"/ or exp "Mometasone Furoate"/ or exp "Triamcinolone"/ or exp "Triamcinolone Acetonide"/ or ("beclomethasone 17-monopropionate" or "beclomethasone" or "beclometasone" or "Beclomethasone-17-monopropionate" or "Beclometasone-17-monopropionate" or "Beclomethasone-dipropionate" or "Beclometasone-dipropionate" or "Beclomethasone-dipropionate-monohydrate" or "AeroBec" or "Aerovent" or "Asmabec" or "Beclate" or "Beclazone" or "Becloforte" or "Beclomet" or "Beclovent" or "Beconase" or "Becotide" or "Bekotid" or "Clenil" or "Qvar" or "Respocort" or "Vanceril" or "Vancenase" or "Ventolair" or "Budesonide" or "Aeronide" or "Aerovent" or "B Cort" or "Benita" or "Budecort" or "Budeson" or "Budiair" or "Giona" or "Horacort" or "Miflonide" or "Noex" or "Novopulmon" or "Numark" or "Pulmicort" or "Rhinocort" or "ciclesonide" or "ciclesonide M1" or "ciclesonide" or "Alvesco" or "Flunisolide" or "Flunisolide" or "Aerobid" or "Aerospan" or "Pulmilide" or "fluticasone propionate-17-carboxylic acid" or "fluticasone furoate" or "Fluticason" or "Fluticasone" or "Fluticasone-propionate" or "Fluticasone-furoate" or "Allegro" or "Arnuity" or "Dalman" or "Flixotide" or "Flutica" or "Flutide" or "Flutivate" or "Flovent" or "Mometason" or "Mometasone" or "Mometasone-furoate" or "Mometasone-furoate-monohydrate" or "Asmanex" or "Elocom" or "Elocon" or "Ecural" or "Mometasona" or "Novasone" or "Triamcinolone" or "Aristocort" or "Azmacort" or "Kenacort" or "Kenalog" or "Tricort" or "Trilone" or "Volon").ti,ab.
8	ICS/LABA/LAMA (Mixed drugs)	(Trimbow or "Trelegy" or "FF/UMEC/VI" or "Triohale" or "fluticasone furoate/umeclidinium/vilanterol" or "Closed Triple" or "Elebrato Ellipta" or "Temybric Ellipta" or "triple therapy" or "BGF" or "BGF MDI" or "budesonide + formoterol fumarate + glycopyrronium" or "budesonide/formoterol fumarate/glycopyrronium" or

		"BUD/GLY/FOR" or "BUD/FOR/GLY" or "Trixeo Aerosphere" or "Riltrava Aerosphere").ti,ab.
9	Combination	1 and (((2 or 7) and (3 or 4) and (5 or 6)) or 8)
10	Animals	9 NOT ((animals not (humans and animals)).sh.)
11	English	limit 10 to english language
12	Publication Type	11 not ("clinical trial, veterinary" or "collected work " or "comment" or "congress " or "consensus development conference " or "consensus development conference, nih " or "video-audio media " or "webcast" or "technical report " or "corrected and republished article OR dataset OR dictionary OR directory OR duplicate publication OR editorial OR electronic supplementary materials OR evaluation study OR lecture OR legal case OR legislation OR letter OR meta analysis OR expression of concern " or "festschrift " or "government publication " or "guideline " or "historical article " or "interactive tutorial " or "interview " or "introductory journal article " or "patient education handout " or "news " or "retracted publication " or "newspaper article " or "observational study, veterinary " or "retraction of publication OR review " or "scientific integrity review OR systematic review " or "randomized controlled trial, veterinary " or "periodical index " or "personal narrative " or "portrait " or "practice guideline " or "pragmatic clinical trial " or "preprint " or "published erratum ").pt.
13	RCT	12 and ((groups or trial or randomly).ti,ab. or drug therapy.sh. or placebo.ti,ab. or randomized.ti,ab. or controlled clinical trial.pt. or randomized controlled trial.pt.)
14	Date Limit	limit 13 to yr="2020 -Current"
15	Duplicates	Remove duplicates from 14

Table 2.6. EMBASE Search Strategy – Triple Therapy NMA (Research Question #3)

1	COPD	'chronic obstructive lung disease'/exp OR 'airflow obstruction, chronic':ti,ab OR 'airflow obstructions, chronic':ti,ab OR 'chronic airway obstruction':ti,ab OR 'chronic obstructive bronchopulmonary disease':ti,ab OR 'chronic obstructive respiratory disease':ti,ab OR 'chronic pulmonary obstructive disease':ti,ab OR 'chronic pulmonary obstructive disorder':ti,ab OR 'chronic airflow obstruction':ti,ab OR 'chronic airflow obstructions':ti,ab OR 'chronic obstructive airway disease':ti,ab OR 'chronic obstructive lung disease':ti,ab OR 'chronic obstructive pulmonary disease':ti,ab OR 'chronic obstructive pulmonary diseases':ti,ab OR 'coad':ti,ab OR 'copd':ti,ab OR 'lung chronic obstructive disease':ti,ab OR 'lung disease, chronic obstructive':ti,ab OR 'obstructive chronic lung disease':ti,ab OR 'obstructive chronic pulmonary disease':ti,ab OR 'obstructive lung disease, chronic':ti,ab OR 'pulmonary disease, chronic obstructive':ti,ab OR 'pulmonary disorder, chronic obstructive':ti,ab
2	LABA (General)	'beta 2 adrenergic receptor stimulating agent'/exp OR (('long-acting':ab,ti OR 'long acting':ab,ti OR 'ultra-long acting':ab,ti OR 'ultra-long-acting':ab,ti) AND ('β agonist*':ab,ti OR 'β-agonist*':ab,ti OR 'β2 agonist*':ab,ti OR 'β2-agonist*':ab,ti OR 'β-2 agonist*':ab,ti OR 'β-2-agonist*':ab,ti OR 'b2 agonist*':ab,ti OR 'b2-agonist*':ab,ti OR 'b-2 agonist*':ab,ti OR 'b-2-agonist*':ab,ti OR 'β(2) agonist*':ab,ti OR 'β(2)-agonist*':ab,ti OR 'β adrenergic agonist*':ab,ti OR 'β-adrenergic agonist*':ab,ti OR 'β2 adrenergic agonist*':ab,ti OR 'β2-adrenergic agonist*':ab,ti OR 'β-2 adrenergic agonist*':ab,ti OR 'β-2-adrenergic agonist*':ab,ti OR 'b2 adrenergic agonist*':ab,ti OR 'b2-adrenergic agonist*':ab,ti OR 'b-2 adrenergic agonist*':ab,ti OR 'b-2-adrenergic agonist*':ab,ti OR 'β(2) adrenergic agonist*':ab,ti OR 'β(2)-adrenergic agonist*':ab,ti OR 'β adrenoceptor agonist*':ab,ti OR 'β-adrenoceptor agonist*':ab,ti OR 'β2 adrenoceptor agonist*':ab,ti OR 'β2-adrenoceptor agonist*':ab,ti OR 'β-2 adrenoceptor agonist*':ab,ti OR 'β-2-adrenoceptor agonist*':ab,ti OR 'b2 adrenoceptor agonist*':ab,ti OR 'b2-adrenoceptor agonist*':ab,ti OR 'b-2 adrenoceptor agonist*':ab,ti OR 'b-2-adrenoceptor agonist*':ab,ti

		OR 'β(2) adrenoceptor agonist*':ab,ti OR 'β(2)-adrenoceptor agonist*':ab,ti OR 'beta agonist*':ab,ti OR 'beta-agonist*':ab,ti OR 'beta2 agonist*':ab,ti OR 'beta2-agonist*':ab,ti OR 'beta-2 agonist*':ab,ti OR 'beta-2-agonist*':ab,ti OR 'beta(2) agonist*':ab,ti OR 'beta(2)-agonist*':ab,ti OR 'beta adrenergic agonist*':ab,ti OR 'beta-adrenergic agonist*':ab,ti OR 'beta2 adrenergic agonist*':ab,ti OR 'beta2-adrenergic agonist*':ab,ti OR 'beta-2 adrenergic agonist*':ab,ti OR 'beta-2-adrenergic agonist*':ab,ti OR 'beta(2) adrenergic agonist*':ab,ti OR 'beta(2)-adrenergic agonist*':ab,ti OR 'beta adrenoceptor agonist*':ab,ti OR 'beta-adrenoceptor agonist*':ab,ti OR 'beta2 adrenoceptor agonist*':ab,ti OR 'beta2-adrenoceptor agonist*':ab,ti OR 'beta-2 adrenoceptor agonist*':ab,ti OR 'beta-2-adrenoceptor agonist*':ab,ti OR 'beta(2) adrenoceptor agonist*':ab,ti OR 'beta(2)-adrenoceptor agonist*':ab,ti)) OR 'laba':ab,ti OR 'labas':ab,ti OR 'ultra-laba':ab,ti OR 'ultra-labas':ab,ti
3	LABA (Individual drugs)	'formoterol fumarate'/exp OR 'formoterol':ab,ti OR 'formoterol-fumarate':ab,ti OR 'eformoterol':ab,ti OR 'atimos':ab,ti OR 'efo':ab,ti OR 'fluir':ab,ti OR 'foradil':ab,ti OR 'foradile':ab,ti OR 'formoair':ab,ti OR 'oxis':ab,ti OR 'perforomist':ab,ti OR 'tempus':ab,ti OR 'indacaterol'/exp OR 'indacaterol':ab,ti OR 'indacaterol-maleate':ab,ti OR 'arcapta':ab,ti OR 'hirobriz':ab,ti OR 'onbrez':ab,ti OR 'onbrize':ab,ti OR 'oslif':ab,ti OR 'olodaterol'/exp OR 'olodaterol':ab,ti OR 'striverdi':ab,ti OR 'salmeterol xinafoate'/exp OR 'salmeterol':ab,ti OR 'salmeterolum':ab,ti OR 'salmeterol-xinafoate':ab,ti OR 'aeromax':ab,ti OR 'astmerole':ab,ti OR 'arial':ab,ti OR 'neovent':ab,ti OR 'qitai':ab,ti OR 'serevent':ab,ti OR 'vertine':ab,ti OR 'vilanterol'/exp OR 'vilanterol-trifenatate':ab,ti OR 'vilanterol':ab,ti
4	LAMA (General)	'cholinergic receptor blocking agent'/exp OR 'muscarinic receptor blocking agent'/exp OR (('long-acting':ab,ti OR 'long acting':ab,ti OR 'ultra-long acting':ab,ti OR 'ultra-long-acting':ab,ti) AND ('muscarinic antagonist*':ab,ti OR 'muscarinic receptor antagonist*':ab,ti OR 'antimuscarinic agent*':ab,ti OR 'anti-muscarinic agent*':ab,ti OR 'muscarinic blocker*':ab,ti OR 'muscarinic receptor blocker*':ab,ti OR 'cholinergic antagonist*':ab,ti OR 'cholinergic receptor antagonist*':ab,ti OR 'anticholinergic agent*':ab,ti OR 'anti-cholinergic agent*':ab,ti OR 'cholinergic blocker*':ab,ti OR 'cholinergic receptor blocker*':ab,ti OR 'cholinolytic agent*':ab,ti)) OR 'lama':ab,ti OR 'lamas':ab,ti OR 'ultra-lama':ab,ti OR 'ultra-lamas':ab,ti
5	LAMA (Individual drugs)	'aclidinium bromide'/exp OR 'aclidinium':ab,ti OR 'aclidinium-bromide':ab,ti OR 'tudorza':ab,ti OR 'eklira':ab,ti OR 'bretaris':ab,ti OR 'glycopyrrolate'/exp OR 'glycopyrronium'/exp OR 'glycopyrrolate':ab,ti OR 'glycopyrronium':ab,ti OR 'glycopyrronium-bromide':ab,ti OR 'seebri':ab,ti OR 'tiotropium bromide'/exp OR 'tiotropium':ab,ti OR 'tiotropium-bromide':ab,ti OR 'spiriva':ab,ti OR 'tiova':ab,ti OR 'umeclidinium':ab,ti OR 'umeclidinium-bromide':ab,ti OR 'incruse':ab,ti
6	ICS (General)	'inhal*':ab,ti AND ('glucocorticoid'/exp OR 'corticosteroid':ab,ti OR 'cortico-steroid':ab,ti OR 'glucocorticoid*':ab,ti OR 'steroid*':ab,ti) OR 'ics':ab,ti
7	ICS (Individual drugs)	'beclomethasone'/exp OR 'beclometasone'/exp OR 'beclometasone dipropionate'/exp OR 'beclomethasone':ab,ti OR 'beclometasone':ab,ti OR 'beclomethasone-17-monopropionate':ab,ti OR 'beclometasone-17-monopropionate':ab,ti OR 'beclomethasone-dipropionate':ab,ti OR 'beclometasone-dipropionate':ab,ti OR 'beclomethasone-dipropionate-monohydrate':ab,ti OR 'aerobec':ab,ti OR 'asmabec':ab,ti OR 'beclate':ab,ti OR 'beclazone':ab,ti OR 'becloforte':ab,ti OR 'beclomet':ab,ti OR 'beclovent':ab,ti OR 'beconase':ab,ti OR 'becotide':ab,ti OR 'bekotid':ab,ti OR 'clenil':ab,ti OR 'qvar':ab,ti OR 'respocort':ab,ti OR 'vanceril':ab,ti OR 'vancenase':ab,ti OR 'ventolair':ab,ti OR 'budesonide'/exp OR 'budesonide':ab,ti OR 'aeronide':ab,ti OR 'aerovent':ab,ti OR 'b cort':ab,ti OR 'benita':ab,ti OR 'budecort':ab,ti OR 'budeson':ab,ti OR 'budiair':ab,ti OR 'giona':ab,ti OR 'horacort':ab,ti OR 'miflonide':ab,ti OR 'noex':ab,ti OR 'novopulmon':ab,ti OR 'numark':ab,ti OR 'pulmicort':ab,ti OR 'rhinocort':ab,ti OR 'ciclesonide'/exp OR 'ciclesonide':ab,ti OR

		'alvesco':ab,ti OR 'flunisolide':ab,ti OR 'flunisolide'/exp OR 'aerobid':ab,ti OR 'aerospan':ab,ti OR 'pulmilide':ab,ti OR 'fluticasone'/exp OR 'fluticasone furoate'/exp OR 'fluticason':ab,ti OR 'fluticasone':ab,ti OR 'fluticasone-propionate':ab,ti OR 'fluticasone-furoate':ab,ti OR 'allegro':ab,ti OR 'arnuity':ab,ti OR 'dalman':ab,ti OR 'flixotide':ab,ti OR 'flutica':ab,ti OR 'flutide':ab,ti OR 'flutivate':ab,ti OR 'flovent':ab,ti OR 'mometasone furoate'/exp OR 'mometason':ab,ti OR 'mometasone':ab,ti OR 'mometasone-furoate':ab,ti OR 'mometasone-furoate-monohydrate':ab,ti OR 'asmanex':ab,ti OR 'elocom':ab,ti OR 'elocon':ab,ti OR 'ecural':ab,ti OR 'mometasona':ab,ti OR 'novasone':ab,ti OR 'triamcinolone'/exp OR 'triamcinolone acetonide'/exp OR 'triamcinolone':ab,ti OR 'aristocort':ab,ti OR 'azmacort':ab,ti OR 'kenacort':ab,ti OR 'kenalog':ab,ti OR 'tricort':ab,ti OR 'trilone':ab,ti OR 'volon':ab,ti
8	ICS/LABA/LAMA (Mixed drugs)	trimbow:ti,ab OR 'trelegy':ti,ab OR 'ff/umec/vi':ti,ab OR 'triohale':ti,ab OR 'fluticasone furoate/umeclidinium/vilanterol':ti,ab OR 'closed triple':ti,ab OR 'elebrato ellipta':ti,ab OR 'temybric ellipta':ti,ab OR 'triple therapy':ti,ab OR 'bgf':ti,ab OR 'bgf mdi':ti,ab OR 'budesonide + formoterol fumarate + glycopyrronium':ti,ab OR 'budesonide/formoterol fumarate/glycopyrronium':ti,ab OR 'bud/gly/for':ti,ab OR 'bud/for/gly':ti,ab OR 'trixeo aerosphere':ti,ab OR 'riltrava aerosphere':ti,ab
9	Combination	#1 AND ((#2 or #3) and (#4 or #5) and (#6 or #7) or #8)
10	Human	#9 NOT 'animal'/exp NOT ('human'/exp AND 'animal'/exp)
11	English	#10 AND [english]/lim
12	Publication type	#11 NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)
13	RCT	#12 AND ('double blind procedure'/exp OR 'double blind procedure':ab,ti OR 'randomized controlled trial'/exp OR 'randomized controlled trial':ab,ti OR 'single blind procedure'/exp OR 'single blind procedure':ab,ti OR 'random*':ab,ti OR 'factorial*':ab,ti OR 'placebo*':ab,ti OR ('doubl*':ab,ti AND 'blind*':ab,ti) OR ('singl*':ab,ti AND 'blind*':ab,ti) OR 'assign*':ab,ti OR 'allocat*':ab,ti OR 'volunteer*':ab,ti)
13	Date Limit	#12 AND [31-12-2019]/sd NOT [29-08-2024]/sd

2.2 Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using Nested Knowledge; a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

For research question #3, we plan to include double-blinded RCTs with comparable treatment adherence across all arms to ensure that adherence is not a confounding factor in the analysis.

2.3 Data Extraction Strategy

Data will be extracted into Microsoft Excel. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.

2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

2.4 Risk of Bias

We will examine the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[27,28] Risk of bias will be assessed by study outcome for each of the following domains: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers will independently assess these domains. Any disagreements will be resolved through discussion or by consulting a third reviewer.

2.5 Subgroup Credibility

We will examine the credibility of subgroup analyses (aka effect modification analyses) determined to be clinically important for the review using criteria published in the Instrument for the Credibility of Effect Modification ANalyses (ICEMAN) tool (Version 1.1).[29] The credibility of each effect modifier will be assessed by outcome of interest, time point of interest, and effect measure. One reviewer will independently assess the credibility of the subgroup analyses and a second reviewer will validate the ratings.

2.6 Clinical Trial Diversity

We will evaluate the demographic diversity for each clinical trial in this review using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[30] Three demographic categories will be evaluated: race and ethnicity, sex, and age. Representation for each demographic category will be evaluated relative to the disease prevalence, using the metric “Participant to Disease-prevalence Representation Ratio” (PDRR). Each article will receive a rating of “Good”, “Fair”, or “Poor” for the

three demographic categories. One reviewer will use the extracted and validated data from the trials to calculate the ratings. A second reviewer will validate the ratings.

2.7 Publication Bias

We will search the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include “chronic obstructive pulmonary disorder”, "COPD", "Trelegy Ellipta", and "Breo Ellipta". We will select studies that would have met our inclusion criteria and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

2.8 Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains three components: (1) a summary of the evidence base, (2) synthesis of outcome results, and (3) heterogeneity and subgroups.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

In addition, for each outcome of interest, we will evaluate the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessments. If studies are sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, we will conduct restricted maximum likelihood random or fixed effect pairwise meta-analyses or network meta-analyses (NMA) where feasible.

An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)).[31,32] NMA would be conducted under a Bayesian framework. For continuous outcomes (e.g., annual rate of moderate and severe exacerbations), the NMA model corresponds to a generalized linear model with identity link. For binary outcomes (e.g., mortality outcomes), the NMA model corresponds to a generalized linear model with a logit link. For all analyses, we will include random effects on the treatment parameters, and the amount of between-study variance (i.e., heterogeneity) will be assumed constant across all treatment comparisons. We will use noninformative prior distributions for all model parameters. We will initially discard the first 40,000 iterations as "burn-in" and base inferences on an additional 40,000 iterations using three chains. Convergence of chains will be assessed with the Gelman-Rubin statistic and visually using trace plots. If the chains do not converge, an additional 10,000 iterations will be run, sequentially, until convergence.

Furthermore, for any network where there are "loops" in evidence, we will empirically compare the direct and indirect estimates to assess if the NMA consistency assumption is violated using a node-splitting approach.[33] If there is evidence of inconsistency, the results will be presented for the direct and indirect evidence separately. If there is no evidence of inconsistency, we will present the pooled results.

All NMAs will be conducted using RStudio and/or IndiRect NMA platform (CRG-EVERSANA, 2020™). Results for all comparisons will be presented with point estimates and 95% credible intervals. We will also present results graphically for each intervention versus generically available comparators listed above.

Heterogeneity and Subgroups

To explore heterogeneity across studies, we will examine if there are differences in the distribution of key characteristics across studies. For this project, key characteristics include those with disabilities, those with end-stage renal disease (ESRD), those with terminal illness, pediatric population, and Medicare-aged population (≥65 years). If studies differ with respect to these characteristics, subgroup analyses or meta-regressions may be performed where sufficient data exist.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Page et al. 2021.[26]

Section and Topic	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.

Section and Topic	#	Checklist Item
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.

Section and Topic	#	Checklist Item
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

Appendix B. Data Extraction Summary Table Shell

Author & Year of Publication (Trial)	Study Design	Interventions (n) & Dosing Schedule	Inclusion & Exclusion Criteria	Patient Characteristics	Outcomes

Table Footnotes