ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Drug Class Review: Inhaled corticosteroids (ICS) + long-acting beta-agonists (LABA) combination products for treatment of chronic obstructive pulmonary disease (COPD)

Comprehensive Research Plan: Systematic Review Unit

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Background:

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation in the lungs [1]. COPD is commonly assessed by clinical examination and spirometry. Important indicators considered in the diagnosis of COPD include age over 40 years and any of the following: 1) progressive and persistent dyspnea that worsens with exercise, 2) chronic cough, 3) chronic sputum production, 4) history of exposure to smoke from tobacco or cooking, occupational dusts and chemicals, and 5) family history of COPD [1].

COPD causes significant burden of illness, reduced quality of life, and premature death [2]. Symptoms include chronic cough, sputum production, and dyspnea [3]. The global prevalence of COPD has been estimated at 7.6% using data from a systematic review including 28 countries [4]. However, this is likely a conservative estimate, due to under-reporting and under-diagnosis. The prevalence and burden of COPD is rising due the greater proportion of elderly people in the population [1]. It is estimated that COPD will be the third-leading cause of death by 2020 [5].

The treatment of COPD usually involves reducing exposure (e.g., smoking cessation, occupation modifications), increasing exercise, and implementing appropriate pharmacologic therapy [1]. The most common drug classes are $beta_2$-agonists, anticholinergics, and methylxanthines. Inhaled corticosteroids (ICS) and systemic corticosteroids are often useful for acute exacerbations. The mode of administration may include inhaler, nebulizer, oral, or injection, depending on the type of medication.

According to the Global Initiative for COPD (GOLD), inhaled bronchodilators are recommended for patients with stable COPD [1]. Long-acting agents are preferred over short-acting agents [1]. ICS are recommended for those with severe airflow restrictions or who are experiencing frequent exacerbations. For these patients, combination therapy is recommended instead of increasing the dosage of the current therapy, as it might be more effective and safer [1].

There have been five Cochrane reviews that have examined the above agents for COPD. These include the following: 1) combination ICS and long-acting $beta_2$-agonist (LABA) versus tiotropium (a long-acting anticholinergic [LAMA]) [6], combination ICS and LABA and LAMA versus LAMA alone or ICS and LABA [7], 3) combined ICS and LABA in one inhaler versus LABA alone [8], 4) combined ICS and LABA in one inhaler versus ICS alone [9], and 5) combined

ICS and LABA in one inhaler versus placebo [10]. In the combination ICS and LABA versus tiotropium review, only 3 randomized clinical trials (RCTs) involving 1,528 patients were included after searching until November 2012 [6]. A meta-analysis was not conducted but the results from one RCT suggested that there were significantly more deaths for tiotropium alone (however this was affected by a high drop-out rate in the ICS and LABA combined group); more hospitalizations and pneumonia were observed in the fluticasone/salmeterol group [6]. There were no significant differences in hospitalizations due to exacerbation or exacerbations overall [6]. In the combination ICS and LABA and LAMA versus LAMA alone or combination ICS and LABA review, 3 RCTs were included (with 1,021 patients) [7]. There were no statistically significant differences in mortality, hospitalizations, and episodes of pneumonia or adverse events [7]. Combination therapy plus tiotropium was superior regarding quality of life, lung function, and forced expiratory volume. Meta-analysis was not conducted on exacerbations, due to significant heterogeneity [7]. In the review comparing combined ICS and LABA versus LABA alone, 14 RCTs were included (with 11,794 patients) after searching the literature until November 2011 [8]. The authors found that patients receiving ICS and LABA had higher quality of life, fewer exacerbations and less mortality compared with LABA alone [8]. However, there were more cases of pneumonia for combination ICS and LABA versus LABA alone. No significant differences were observed in hospitalizations [8]. In the review comparing ICS and LABA versus ICS alone, 15 RCTs were included (with 7,814 patients) after searching the literature until June 2013 [9]. The authors noted significantly fewer exacerbations for combination ICS and LABA versus ICS alone, yet there were no significant differences in hospitalizations or adverse events [9]. Finally, in the review comparing ICS and LABA versus placebo, 19 RCTs (with 10,400 patients) were included after searching the literature until June 2013 [10]. Combined therapy reduced exacerbations, mortality, symptoms, and increased health status and lung function [10]. However, combined therapy was associated with more pneumonia compared with placebo.

It's important to note that there is a planned Cochrane review that will focus on long-acting inhaled therapy (including LABA, anticholinergics, and ICS) for COPD [11]. The authors have published their protocol and are planning do to a network meta-analysis on this topic. However, we have no idea when these results will be made available as the protocol was only published earlier this

year.

In addition to the planned Cochrane review including a network meta-analysis [11], there have been a number of published network meta-analyses examining pharmacotherapy for COPD. Four of these will be described briefly here. Forty RCTs were included in a network meta-analysis examining all long-acting bronchodilators [12]. The literature was searched until July 2011. The authors concluded that indacaterol, glycopyrronium, and tiotropium were likely the most effective bronchodilators [12]. In a network meta-analysis of all long-acting muscarinic agents (LAMA), 21 studies were included (with 22,542 patients) after searching the literature until October 2012 [13]. It was found that the newest LAMA treatment (aclidinium) was likely similar to pre-existing agents (tiotropium and glycopyrronium) regarding lung function, quality of life, and dyspnea[13]. Another network meta-analysis of inhaled drugs for COPD included 35 RCTs (with 26,786 patients) after searching the literature until November 2007 [14]. The authors concluded that ICS and LABA combination therapy reduced exacerbations only in patients with low forced expiratory volume [14]. Finally, one network meta-analysis was funded by private industry (Merck, Dhome, and Nycomed) and examined RCTs greater than 24 weeks duration evaluating the effects of LABA (formoterol or salmeterol), LAMA (tiotropium), ICS (fluticasone or budesonide), PDE4 inhibitors (roflumilast), and combinations of these interventions [15]. The authors included 26 RCTs after searching the literature until 2010. They concluded that combination therapy is likely superior to single therapy regarding exacerbations [15].

In summary, evidence from previous reviews suggests that combination therapy is promising for patients with COPD. However, it is unclear which combinations are the most optimal or whether combination therapy is associated with more harm compared with single therapy. In order to examine this further, we are proposing to conduct a systematic review and network meta-analysis. Although previous network meta-analyses exist on this topic, none are up-to-date and none includes all of the agents of interest. For example, although one network meta-analysis examined LAMA, LABA, and ICS, it was **funded by private industry** and the authors restricted it to RCTs > 24 weeks duration and specific types of agents (i.e., **it was not a drug class systematic review**) [15].

Objectives:	To examine the comparative safety and efficacy of long-acting inhaled agents (ICS, LABA, LAMA) for patients with COPD.
Study Questions:	1) What is the comparative safety and efficacy of ICS and inhaled LABA versus ICS, inhaled LABA, inhaled LAMA, and placebo [in any combination] for adults with COPD? 2) Which intervention (or combination) is the most effective and safe for adults with COPD?
PICO Statement:	The population, intervention, comparator, and outcome (PICO) statement, including the study designs of interest, is as follows.
Study Population:	Adults with COPD. We will report the way that COPD was diagnosed across the included RCTs and conduct a sub-group analysis on this (please see the synthesis section below for further details). We will also consider sub-group analysis by severity of COPD, gender, and age (e.g., ≥65 years of age).
Intervention	Inclusion: inhaled LABA (formoerol, indacaterol, salmeterol), ICS (beclomethasone, budesonide, fluticasone, mometasone), and combination LABA and ICS in one inhaler (formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone) Exclusion: LABA (nebulizer and transdermal, e.g., arformoterol, tulobuterol, bambuterol), ICS (nebulizer), short-acting beta$_2$-agonists (all agents - oral, inhaler, nebulizer, injection), short-acting anticholinergics (all agents - inhaler and nebulizer), combination short-acting beta-agonist plus anticholinergic in one inhaler (all agents - inhaler and nebulizer), methylxanthines, systemic corticosteroids (oral), and phosphodiesterase-4 inhibitors (oral)
Comparator Groups	Eligible comparators are all inhaled long-acting agents (LABA, ICS, inhaled LAMA [aclidinium bromide, glycopyrronium bromide, tiotropium]) in any combination and placebo. Concomitant COPD medications will be included if both groups receive the same interventions.

Outcome(s) of Interest	Efficacy outcomes: 1. Proportion of patients with exacerbations (primary outcome of interest) 2. Number of hospitalizations (overall and due to exacerbations) 3. Number of emergency room visits (overall and due to exacerbations) 4. Function (e.g., 6 minute walk test, paced shuttle walk test) 5. Forced expiratory volume (FEV) 6. Quality of life 7. Number of patients with ischemic heart disease 8. Dyspnea 9. Mortality (including cardiovascular-related mortality) Safety outcomes: 10. All harms 11. Serious harms 12. Withdrawals due to lack of efficacy 13. Treatment-related withdrawals 14. Fractures 15. Bone mineral density 16. Heart failure 17. Arrhythmia 18. Pneumonia 19. Cataracts 20. Oral thrush 21. Palpitations 22. Headache 23. Constipation 24. Dry mouth **Note:** this list may be truncated if we identify many studies for inclusion, as this is a rapid review.

Included Study Designs:	Randomized controlled trials *Time:* Studies of any duration will be included. *Other:* We will limit inclusion to English for the ODPRN report. We will note the RCTs written in languages other than English and consider including these prior to publishing our systematic review in full. Studies will be excluded if they are animal studies or if there is no quantitative data to abstract (e.g. letters, commentaries).
Methods	The figure in Appendix 1 displays the general approach that we use at the Li KaShing Knowledge Institute of St. Michael's Hospital to conduct a systematic review. *Protocol development* The Preferred Reporting Items for Systematic reviews and Meta-analysis for Protocols (PRISMA-P) Statement will guide review reporting of our protocol [16]. A draft protocol will be circulated to receive feedback from key stakeholders including the OPDRN, clinicianspharmacoepidemiologists, and systematic review methodologists. The final protocol will be registered with the prospective systematic review registry PROSPERO [17]. *Eligibility criteria* We use the Patients, Interventions, Comparators, Outcomes, Study designs and Time period (PICOST) framework (see above). The draft eligibility criteria can be found in Appendix 2. *Information sources and literature search* Comprehensive literature searches will be conducted by an experienced librarian (Becky Skidmore) in consultation with the team. We will search the MEDLINE, EMBASE, and Cochrane Library electronic databases from inception to January 2014. The preliminary MEDLINE search is presented in Appendix 3. The main (MEDLINE) search will be peer reviewed by another experienced librarian (Heather McDonald) using the Peer Review of Electronic Search Strategies (PRESS) checklist [18]. After this exercise, the MEDLINE search will be modified as necessary and the other databases will be searched in a similar manner. In order to identify unpublished and difficult to locate

material (also called grey literature), we will search conference abstracts (many of these are identified through the electronic searches), trial protocols (also often identified through the electronic searches), and trial registries (World Health Organization International Clinical Trials Registry Platform, which allows searching multiple trial registries simultaneously [19]). We will check the websites of manufacturers of the inhaled long-acting agents. We will contact authors of conference abstracts, trial protocols, and trial registries to determine whether the RCT has been published in full. If the RCT has not been published, we will request further information on the RCT methods to determine eligibility, as required. Unpublished data from conference abstracts fulfilling our eligibility criteria will be included only if the full publication or conference presentation is unobtainable. Literature saturation will be ensured by searching the reference lists of included studies and reference lists of relevant reviews [6-15].
The results from the literature search will be uploaded to Synthesi.SR, online software created by our team [20]. Our software will be used for screening the citations resulting from the electronic database, as well as all potentially relevant full-text articles.

Study selection process

To ensure reliability, a training exercise will be conducted prior to commencing screening. Using the inclusion and exclusion criteria, a random sample of 25 titles and abstracts (also called citations) from the literature search will be screened by all team members. Inter-rater agreement for study inclusion will be calculated using percent agreement and if it is >90% across the team, we will proceed to the next stage. If poor agreement is found, the inclusion and exclusion criteria will be revised. Screening will only commence when the percent agreement is >90%. Two reviewers will screen citations for inclusion, independently (Level 1 screening). They will then independently review the full-text of potentially relevant articles to determine inclusion using the same inclusion and exclusion criteria (Level 2 screening). Conflicts will be resolved by discussion or the involvement of a third reviewer.

Data items and data abstraction process

We will abstract data on study characteristics (e.g., year of conduct [if not reported, we will use the year of publication], sample size, setting [e.g., hospital, community, multi-center, single center], country of study conduct [if not

reported, we will use the country of origin of the first author], duration of treatment, duration of follow-up, intervention and comparator dosage, monotherapy, combination therapy), participant characteristics (e.g., number of patients, age mean and standard deviation, severity of COPD, how COPD was diagnosed), and the definitions of outcomes (e.g., exacerbations [e.g., number of patients with at least 1 exacerbation], hospitalizations [overall or due to exacerbations], function [e.g., 6-minute walk test, paced shuttle test], quality of life [e.g., St George respiratory questionnaire], serious adverse events [e.g., a harm resulting in hospitalization], arrhythmia [e.g., tachycardia, bradycardia]). This is particularly important for exacerbations, as the way that the trialists define this can result in biased estimates of treatment effect [21]. Finally, we will abstract the outcome results (e.g. number of patients with exacerbations, number of patients hospitalized) for the longest duration of follow-up only, as this is the most conservative approach. The data will be extracted and stored in Excel. The draft data abstraction form can be found in Appendix 4. We will create a "cheat sheet" that will accompany reviewers while they are performing data abstraction. This will allow them to navigate the Excel file and result in greater inter-rater reliability. Furthermore, we will conduct a calibration exercise of the data abstraction form and cheat sheet amongst the team. This will entail the entire team conducting data abstraction on a random sample of 10 articles. Data abstraction will only commence when high agreement is achieved (e.g., only minor disagreements/recording errors noted across the team). The data abstraction form and cheat sheet will be revised, if low agreement is observed.

Since this systematic review is being completed in a short time-frame, only the outcome data will be abstracted in duplicate. Discrepancies will be resolved by discussion or the involvement of a third reviewer. Details relating to the study characteristics and patient characteristics will only be abstracted by one person for the ODPRN report. This will subsequently be conducted in duplicate prior to publication.

We suspect that multiple study publications may report data from the same study group (i.e., companion reports). When this occurs, the report with the most complete follow-up data will be included and used to abstract data. The other report(s) will provide supplementary data only. We also anticipate that studies may report a variety of time-points and where appropriate we will use subgroup analysis to explore this; if 2 studies from the same cohort of patients are reported, the outcome at the oldest age point will be included. We will

contact the study authors for further information when the data are not clearly reported. Finally, we will search for errata and retractions for all of the included studies to ensure that the outcome data used in the analysis are correct.

Risk of bias appraisal process

We will appraise the included RCTs using the Cochrane Risk of Bias Tool [22]. This will be conducted by one reviewer for the ODPRN report. This will subsequently be conducted in duplicate prior to publication. We will also assess the studies using a modified McHarm tool [23] for the publication and not for the ODPRN report, due to time constraints. Publication bias will be assessed using funnel plots [24].

Synthesis of included studies

We will first describe our systematic review results, reporting study characteristics, patient characteristics, risk of bias results, and frequencies of outcomes across the included studies. Prior to considering meta-analysis, we will assess for statistical, clinical, and methodological heterogeneity. If extensive statistical (e.g., a statistically significant Q statistic [$p<0.1$] for heterogeneity or an I^2 statistic greater than 75%[26]), clinical, or methodological heterogeneity[26] is observed we will conduct meta-regression analysis, if feasible depending on the number of eligible studies. The total number of covariates will be constrained so that it is equal to 1/10 the number of studies [27], due to issues with multiple testing in systematic reviews [26]. Meta-regression analysis will explore the influence of a few important factors, such as effect sizes and duration of follow-up. Both meta-analysis and meta-regression will be analyzed in the R software [28]. The relative risk will be calculated for dichotomous values and the mean difference will be calculated for continuous variables. The standardized mean difference will be used to pool studies that use different scales for the same outcomes (e.g., quality of life). We anticipate that some of the included studies will not report all relevant data (e.g., standard deviations or standard errors). To include these studies in our analysis, the missing data will be imputed using the median standard deviations reported across the included RCTs or using those from similar RCTs [29].

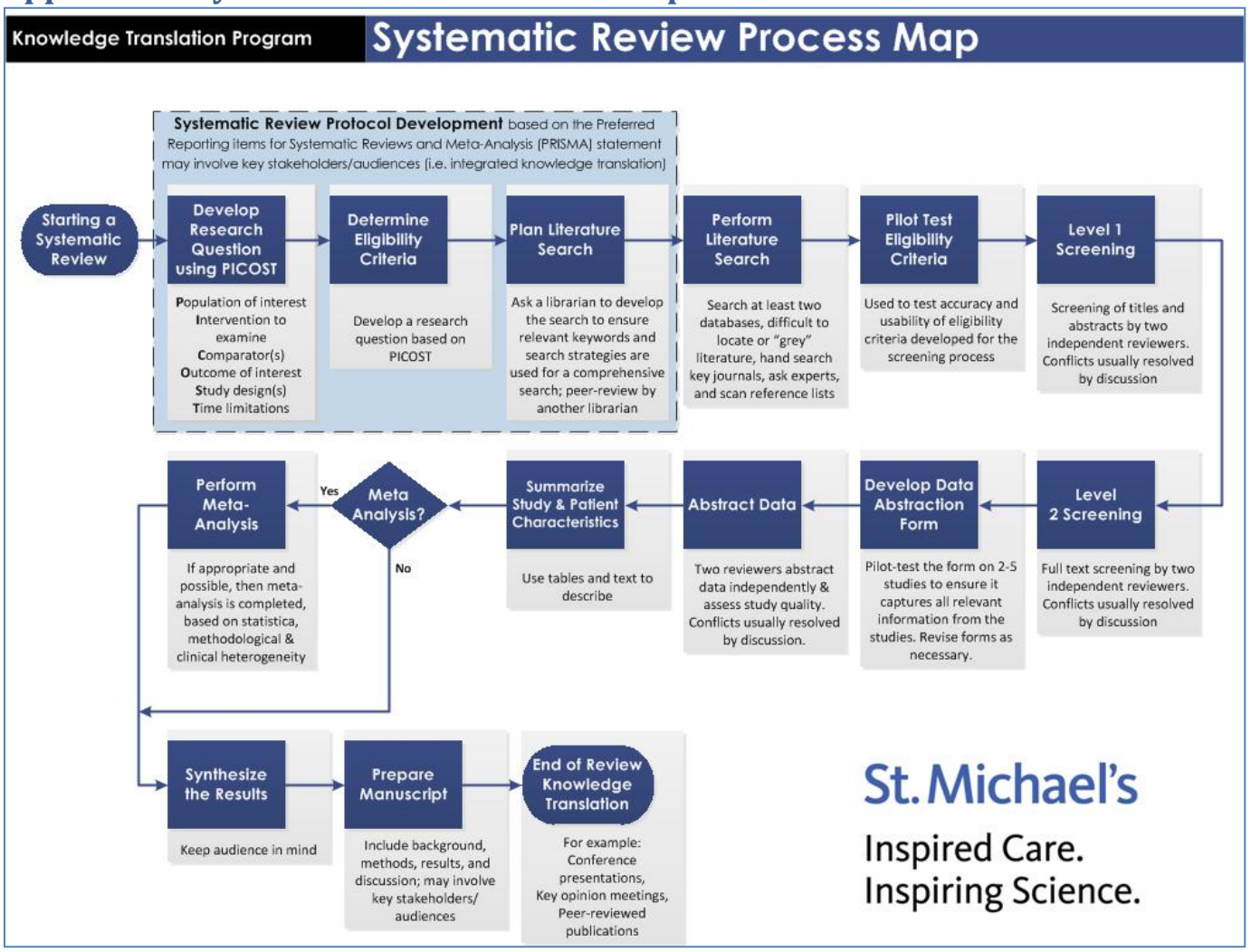
We will explore the effects of subgroups on outcomes to establish the robustness of findings. We will limit the number of subgroup analysis, due to

issues with multiple testing in systematic reviews [26]. Subgroups that we will explore include the diagnosis of COPD (e.g., according to the GOLD criteria [1] versus all others), severity of COPD (e.g., moderate-severe versus all others), gender, and definitions of outcomes (exacerbations in particular [21]).

Network meta-analysis will be conducted to derive the combined outcome effect size between each 2 comparisons, as well as rank the safety among all available interventions [30]. The placebo group will be used as a reference in the network meta-analysis. To facilitate the practicality of treatment comparisons, median rankings will be used as point estimates of intervention safety. We will use the NODE XL program to present the network meta-analysis results [31]. Network meta-analysis will be conducted in WinBUGS [32], a Bayesian software program used to build complex statistical models using Markov Chain Monte Carlo simulation.

This will be conducted using a burn-in sample of 50000, followed by 100000 samples for inference. Convergence of the Markov chain Monte Carlo simulation will assessed with the Gelman-Rubin-Brooks plot and diagnostic test [33]. Default prior distributions (in all cases non-informative) will be adopted for all parameters in the model. Statistical significance will be expressed by 95% credible intervals that will be established using the 2.5 and 97.5 percentiles obtained via Markov Chain Monte Carlo simulation. We will interpret the 95% credible interval in a similar manner as confidence intervals are interpreted when they are derived using standard meta-analysis. The consistency of the results between direct versus indirect evidence will be compared using the node-splitting method [34].

Appendix 1: Systematic Review Process Map



Appendix 2: Draft Eligibility Criteria

Level 1 screening:

1. Does this study include adult patients diagnosed with COPD? i. YES _____ ii. NO _____ iii. UNCLEAR _____
2. Is this a randomized clinical trial? i. YES _____ ii. NO _____ iii. UNCLEAR _____
3. Does this study examine ANY of the following agents: inhaled LABA (e.g., formoterol, indacaterol, salmeterol), ICS (e.g., beclomethasone, budesonide, fluticasone), combination LABA and ICS in one inhaler (e.g., formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone), and inhaled LAMA (adidinium bromide, glycoyrronium bromide, tiotropium) [in any combination]? i. YES _____ ii. NO _____ iii. UNCLEAR _____
4. Does this study compare a relevant intervention to ANY of the following agents: inhaled LABA (e.g., formoterol, indacaterol, salmeterol), ICS (e.g., beclomethasone, budesonide, fluticasone), combination LABA and ICS in one inhaler (e.g., formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone), inhaled LAMA (adidinium bromide, glycoyrronium bromide, tiotropium), and placebo [in any combination]? i. YES _____ ii. NO _____ iii. UNCLEAR _____
5. This study likely fulfills our eligibility criteria but is: i. Not written in English _____ (note: will not fully exclude from the review) ii. A conference abstract (need to contact authors) _____ iii. A trial protocol (need to contact authors) _____ iv. A relevant systematic review (need to scan references) _____

Level 2 screening:

1. Does this study include adult patients diagnosed with COPD? YES _____ NO _____ UNCLEAR _____
2. Is this a randomized clinical trial? YES _____ NO _____ UNCLEAR _____
3. Does this study examine ANY of the following agents: inhaled LABA (e.g., formoterol, indacaterol, salmeterol), ICS (e.g., beclomethasone, budesonide, fluticasone), combination LABA and ICS in one inhaler (e.g., formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone), and inhaled LAMA (adidinium bromide, glycoyrronium bromide, tiotropium) [in any combination]? YES _____ NO _____ UNCLEAR _____
4. Does this study compare a relevant intervention to ANY of the following agents: inhaled LABA (e.g., formoerol, arformoterol, indacaterol, salmeterol, tulobuterol), ICS (e.g., beclomethasone, budesonide, fluticasone), combination LABA and ICS in one inhaler (e.g., formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone), inhaled LAMA (adidinium bromide, glycoyrronium bromide, tiotropium), and placebo [in any combination]? YES _____ NO _____ UNCLEAR _____
5. Does this study report on ANY of the following outcomes: proportion of patients with exacerbations, number of hospitalizations (overall and due to exacerbations), number of emergency room visits (overall and due to exacerbations), function, forced expiratory volume, quality of life, number of patients with pneumonia, number of patients with ischemic heart disease, mortality, harms (including all harms, serious harms, withdrawals due to lack of efficacy, treatment-related withdrawals, and the following specific harms: fractures, bone mineral density, heart failure, arrhythmia, cataracts, oral thrush, palpitations, headache, constipation, and dry mouth). YES _____ NO _____ UNCLEAR _____

6. This study likely fulfills our eligibility criteria but:

   Is not written in English _____ (note: will not fully exclude from the review)

   Is a conference abstract (need to contact authors) _____

   Is a trial protocol (need to contact authors) _____

   Is a relevant systematic review (need to scan references) _____

   Does not contain abstractable data (need to contact authors) _____

Note: If you answer NO to any of these questions, the citation/study will be excluded. All other citations/studies will be included. We will keep track of reviews that have potentially relevant material and will scan their reference lists to ensure all studies have been captured.

Appendix 3: Draft MEDLINE search

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Search Strategy:

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1 exp Pulmonary Disease, Chronic Obstructive/

2 exp Emphysema/ or exp Pulmonary Emphysema/

3 ((chronic adj2 obstructi*) and (pulmonary or airway* or air way* or lung$1 or airflow* or air flow*)).tw.

4 (COPD or COAD).tw.

5 (chronic adj2 bronchitis).tw.

6 emphysema*.tw.

7 or/1-6

8 Formoterol*.tw,rn.

9 (BD 40A or HSDB 7287 or Oxis or UNII-5ZZ84GCW8B).tw.

10 (eformoterol or Foradil).tw.

11 73573-87-2.rn.

12 Indacaterol.tw,rn.

13 (Arcapta or Onbrez or QAB 149 or QAB149 or UNII-8OR09251MQ).tw.

14 312753-06-3.rn.

15 Salmeterol*.tw,rn.

16 (Aeromax or Astmerole or "GR 33343 X" or "GR 33343X" or HSDB 7315 or SN408D or UNII-2I4BC502BT).tw.

17 89365-50-4.rn.

18 Salmeterolxinafoate.tw,rn.

19 (Arial or Asmerole or Beglan or Betamican or Dilamax or Inaspir or Salmetedur or Serevent or Ultrabeta or UNII-6EW8Q962A5).tw.

20 94749-08-3.rn.

21 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-agonist* or betaagonist* or beta-adrenergic* or adrenergic beta-receptor* or beta-receptor agonist* or beta-adrenoceptor agonist*)).tw.

22 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-2-agonist* or beta-2agonist* or beta-2-adrenergic* or adrenergic beta-2-receptor* or beta-2-receptor agonist* or beta-2-adrenoceptor agonist*)).tw.

23 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-

acting) and (beta2-agonist* or beta2agonist* or beta2-adrenergic* or adrenergic beta2-receptor* or beta2-receptor agonist* or beta2- adrenoceptor agonist*)).tw.

24 ((longacting or long-acting) and ("beta(2)-agonist*" or "beta(2)agonist*" or "beta(2)-adrenergic*" or "adrenergic beta(2)-receptor*" or "beta(2)-receptor agonist*" or "beta(2)-adrenoceptor agonist*")).tw.

25 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (B2-agonist* or B2-adrenergic* or adrenergic B2-receptor* or B2-receptor agonist* or B2-adrenoceptor agonist*)).tw.

26 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (B-2-agonist* or B-2-adrenergic* or adrenergic B-2-receptor* or B-2-receptor agonist* or B-2-adrenoceptor agonist*)).tw.

27 (LABA or LABAs or Ultra-LABA* or UltraLABA*).tw.

28 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and bronchodilator*).tw.

29 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (betamimetic* or beta-mimetic*)).tw.

30 exp Adrenergic beta-Agonists/ or Bronchodilator Agents/

31 (longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting).tw.

32 30 and 31

33 or/21-29,32

34 Administration, Inhalation/

35 exp Aerosols/

36 (inhal* or aerosol*).tw.

37 or/34-36)

38 33 and 37

39 or/8-20,38

40 Beclomethasone/

41 (Aerobec or AeroBec Forte or Aldecin or Apo-Beclomethasone or Ascocortonyl or AsmabecClickhaler).tw.

42 (Beclamet or Beclazone or BecloAsma or Beclo AZU or Beclocort or Becloforte or Beclomet or Beclometason* or Beclomethasone or Beclorhinol or Becloturmant or Beclovent or Becodisk* or Beconase or Becotide or BemedrexEasyhaler or Bronchocort).tw.

43 (Ecobec or Filair or Junik or Nasobec Aqueous or Prolair or Propaderm or Qvar or Respocort or Sanasthmax or Sanasthmyl or Vancenase or Vanceril or Ventolair or Viarin).tw.

44 (BMJ 5800 or EINECS 224-585-9 or UNII-KGZ1SLC28Z).tw.

45 4419-39-0.rn.

46 Budesonide/

47 (Budesonide or Micronyl or Preferid or Pulmicort or Respules or Rhinocort or "S 1320" or Spirocort or Uceris or UNII-Q3OKS62Q6X).tw.

48 51333-22-3.rn.

49 Fluticasone.tw,rn.

50 (Cutivate or Flixonase or Flixotide or Flonase or Flovent or Fluticason* or HSDB 7740 or UNII-CUT2W21N7U).tw.

51 Glucocorticoids/

52 glucocorticoid*.tw.

53 Adrenal Cortex Hormones/

54 (corticoid* or corticosteroid* or cortico-steroid*).tw.

55 ((adrenal cortex or adrenal cortical) adj3 hormon*).tw.

56 ((adrenal cortex or adrenal cortical) adj3 steroid*).tw.

57 or/51-56

58 57 and 37

59 or/40-50,58

60 (Fluticasone adj3 salmeterol).tw,rn.

61 (Adoair or Advair or Foxair or "Quikhale SF" or Seretide or Viani).tw.

62 (formoterol adj3 mometasone).tw,rn.

63 (Zenhale or Dulera).tw.

64 (formoterol adj3 budesonide).tw,rn.

65 (Rilast or Symbicord or Symbicort or Vannair).tw.

66 (vilanterol adj3 fluticasone).tw,rn.

67 Breo Ellipta.tw.

68 or/60-67

69 tiotropium.tw,rn.

70 (BA 679 BR or BA 679BR or Spiriva or tiotropium or UNII-0EB439235F or UNII-XX112XZP0J).tw.

71 aclidiniumbromide.tw,rn.

72 (LAS 34273 or LAS W-330 or BretarisGenuair or EkliraGenuair or TudorzaPressair or UNII-UQW7UF9N91).tw.

73 glycoyrroniumbromide.tw,rn.

74 (erythro-glycopyrronium bromide or UNII-9SFK0PX55W).tw.

75 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (anticholinergic* or anti-cholinergic* or cholinolytic* or cholinergic-blocking or antimuscarinic* or anti-muscarinic* or ((cholinergic or acetylcholine or muscarinic) adj3 antagonist*))).tw.

76 (LAMA or LAMAs or Ultra-LAMA* or UltraLAMA*).tw.

77 Muscarinic Antagonists/ or Cholinergic Antagonists/
78 77 and 31
79 75 or 76 or 78
80 79 and 37
81 or/69-74,80
82 39 or 59 or 68 or 81
83 7 and 82
84 randomized controlled trial.pt.
85 controlled clinical trial.pt.
86 randomized.ab.
87 placebo.ab.
88 clinical trials as topic/
89 randomly.ab.
90 trial.ti.
91 or/84-90
92 83 and 91
93 exp Animals/ not (exp Animals/ and Humans/)
94 92 not 93