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Fixed-dose combination inhalers compared to long-acting bronchodilators for COPD: a network meta-analysis (Protocol)

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[Intervention Protocol]

Fixed-dose combination inhalers compared to long-acting bronchodilators for COPD: a network meta-analysis

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A B S T R A C T

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To compare the efficacy and safety of two different types of fixed-dose dual inhalers (i.e. LABA/LAMA vs ICS/LABA) as well as combination therapies versus LABA or LAMA monotherapy for patients with moderate to very severe COPD.

B A C K G R O U N D

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a globally prevalent illness, characterised by chronic airway inflammation leading to slow progression of airflow limitation (GOLD 2017). The inflammatory nature of the disease leads to variable degrees of small airway obstruction and destruction of lung parenchyma. COPD accounts for more than three million deaths annually and will likely become the third leading cause of death by 2030. This disease is due primarily to tobacco smoke in industrialised countries; air pollution and indoor biomass fuel consumption are the cause in low-income countries. The disease affects men and women equally (WHO 2016). Despite the worldwide prevalence of the disease, it remains largely under-recognised and underdiagnosed. COPD is a costly disease, with an estimated annual cost of USD 49.9 billion and an indirect cost estimated at approximately 41% of the total cost in the United States (Patel 2014). Clinically, the disease is characterised by chronic dyspnoea, productive cough and exposure to a risk factor. The post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) is required to be less than 0.7 for this diagnosis (GOLD 2017). The disease course usually is interrupted by episodes of acute exacerbation, the frequency of which contributes to overall morbidity and mortality (Suissa 2012).

Description of the intervention

Management of stable COPD

Once COPD has been diagnosed, the main goals of therapy include alleviation of symptoms and prevention of disease progression and acute exacerbations. Smoking cessation is one of the most important non-pharmacological interventions. Annual influenza

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vaccination is recommended for all patients with COPD. In observational studies, influenza vaccination was associated with fewer outpatient visits, hospitalisations and deaths (Trucchi 2015). Continuous oxygen therapy (> 15 hours/d) improves mortality among patients with chronic hypoxaemia and should be prescribed for all patients with severe resting hypoxaemia (partial pressure of oxygen dissolved in blood (PaO_2) $\leq$ 55 mmHg or peripheral capillary oxygen saturation (SpO_2) $\leq$ 88%) (Qaseem 2011). Pulmonary rehabilitation has been proven to improve exercise tolerance while reducing symptoms and exacerbations (McCarthy 2015; Rochester 2015). Inhaled medications, the mainstay of pharmacological therapies, are used to improve lung function, symptoms and quality of life, as well as to reduce acute exacerbations. Short-acting bronchodilators are given on an as-needed basis to provide immediate relief, and long-acting bronchodilators are used as maintenance therapy in patients with moderate to very severe disease (Decramer 2012). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends the addition of a longer-acting bronchodilator for symptomatic patients with moderate or more severe disease (GOLD 2017).

How the intervention might work

Combination bronchodilators

Fixed-dose dual inhalers include long-acting beta-adrenoceptor agonist/inhaled corticosteroid (LABA/ICS) and LABA/long-acting muscarinic antagonist (LAMA) combinations. An ICS has anti-inflammatory effects and may reduce airway inflammation as well as systemic inflammation, as evidenced by a reduction in C-reactive protein (Heidari 2012). ICSs and LABAs have synergistic effects when used in combination. Corticosteroids upregulate $beta_2$-receptors and $beta_2$-agonists and facilitate translocation of steroid receptors from the cytoplasm to the nucleus (Falk 2008). In vitro synergistic effects mentioned above may translate into clinical benefit. Clinical studies have suggested that a LABA/ICS combination significantly improved lung function, health status and rate of exacerbation compared with placebo, LABA alone or ICS alone (Nannini 2012).

Preclinical studies have suggested drug synergy between a $beta_2$-adrenoreceptor agonist and a muscarinic agonist. A possible mechanism for this synergism is that a muscarinic agonist causes less suppression of potassium channel opening, leading to relaxation of the airway smooth muscle, which further promotes $beta_2$-mediated smooth muscle relaxation by activating ion channels and other intracellular signalling pathways (Kume 2014). Clinical studies have demonstrated that LABA/LAMA combinations were superior to monotherapies with regard to lung function improvement and in a recent network meta-analysis (NMA) were associated with improved quality of life and symptom scores and reduced

COPD exacerbations as compared with LABA or LAMA alone (Oba 2016a).

Guidelines recommend a LABA/LAMA combination for patients whose symptoms are not well controlled with a single long-acting bronchodilator, and a LABA/LAMA or LABA/ICS combination for those with frequent exacerbations (i.e. two or more exacerbations per year or one hospitalisation per year for an exacerbation). A LABA/LAMA combination may be preferred to a LABA/ICS combination, as ICSs are associated with increased risk of pneumonia (GOLD 2017; Oba 2016b; Wedzicha 2016).

Why it is important to do this review

Data on the efficacy and safety of fixed-dose LABA/LAMA combinations are accumulating (Huisman 2015; Oba 2016a; Schlueter 2016). However, an important clinical question is how do the efficacy and safety of LABA/LAMA combinations compare with those of LABA/ICS combinations for patients with uncontrolled symptoms and/or frequent exacerbations. Additional clinical studies including several head-to-head trials comparing LABA/LAMA and LABA/ICS combinations (Donohue 2015; Singh 2015; Vogelmeier 2013; Vogelmeier 2015; Wedzicha 2016; Zhong 2015) have been published since an NMA comparing combination inhalers focused on studies up to December 2013 (Tricco 2015). Our review will update previous systematic reviews on fixed-dose combination inhalers and long-acting bronchodilators using the strength of an NMA.

OBJECTIVES

To compare the efficacy and safety of two different types of fixed-dose dual inhalers (i.e. LABA/LAMA vs ICS/LABA) as well as combination therapies versus LABA or LAMA monotherapy for patients with moderate to very severe COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) of at least 12 weeks' duration, published or unpublished. We will not consider cross-over trials.

Types of participants

We will include studies that recruited patients aged > 35 years with a diagnosis of COPD in accordance with American Thoracic Society-European Respiratory Society (ATS/ERS 2004), GOLD report (GOLD 2017) or equivalent criteria. Obstructive ventilatory defect should be at least moderate, with a baseline FEV_1 less than 80% of predicted. We will exclude studies that enrolled participants with a history of asthma or other respiratory disease.

Types of interventions

We will include studies comparing at least two of the following therapies.
- LAMA monotherapy (aclidinium, glycopyrronium, tiotropium, umeclidinium).
- LABA monotherapy (indacaterol, formoterol, olodaterol, salmeterol, vilanterol).
- Fixed-dose combination of LABA/ICS (formoterol/beclomethasone, formoterol/budesonide, formoterol/ciclesonide, formoterol/fluticasone, formoterol/mometasone, indacaterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone).
- Fixed-dose combination of LABA/LAMA (formoterol/aclidinium, indacaterol/glycopyrronium, indacaterol/tiotropium, olodaterol/tiotropium, vilanterol/umeclidinium).

We will allow the use of a short-acting bronchodilator, such as albuterol (salbutamol), and ipratropium as rescue treatment.

Types of outcome measures

Primary outcomes

- COPD exacerbation (moderate to severe and severe)

Secondary outcomes

- St George's Respiratory Questionnaire (SGRQ) score and decrease in SGRQ score ≥ 4 units (responder)
- Transition Dyspnea Index (TDI)
- Mortality
- Total serious adverse events (SAEs)
- Cardiac and COPD SAEs
- Dropout due to adverse event
- Trough FEV_1
- Pneumonia

We will use end-of-study data for dichotomous outcomes. For continuous outcomes, we will use end-of study data and data reported at three, six and 12 months, when available. Moderate exacerbation is defined as worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics; severe exacerbation is defined as rapid deterioration that requires hospitalisation.

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Information Specialist for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (see Appendix 1 for details). We will search all records in the CAGR using the search strategy detailed in Appendix 2. We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information. We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and will report within the review the date this was done.

Data collection and analysis

Selection of studies

Two review authors will independently screen studies by title and abstract to evaluate whether a study meets the inclusion and exclusion criteria. We will select studies that evaluate the clinical efficacy and safety of any of the following therapies in patients with COPD: LABA/LAMA, ICS/LABA, LABA and LAMA. We will resolve disagreements by involving a third review author. We will record the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and a 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

Two review authors will independently extract information on study design, study size, population, interventions (drug, dose, inhaler type, allowed comedications), severity of illness and end points of interest. We will gather information if a participant failed a long-acting bronchodilator before entry into clinical trials. We

will extract and verify data from each of the existing reviews, which will be cross-checked and verified by at least two review authors. We will resolve disagreements regarding values, inconsistencies and uncertainties by involving a third review author. Two review authors will independently extract outcome data from the included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a useable way. We will resolve disagreements by reaching consensus or by involving a third review author. One review author will transfer data into the Review Manager (RevMan 2014) file. We will double-check that data have been entered correctly by comparing data presented in the systematic review versus study reports. A second review author will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve disagreements by discussion or by consultation with another review author. We will assess risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We will grade each potential source of bias as high, low or unclear and will provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). When information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and will report deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

Network meta-analysis

When we find an insufficient number of clinical trials directly comparing all relevant treatment options, we can incorporate indirect comparisons to provide treatment effect estimates by comparing the relative effects of treatment against a common comparator, or by combining a variety of comparisons (variously referred to as mixed or multiple treatment comparisons, or NMAs) (Lu 2004). We will conduct NMAs using a Bayesian Markov chain Monte Carlo method and will use WinBUGS 1.4.3. for primary analyses. We will consider trials within separate analytical networks on the basis of risks of COPD complications. We will consider as high risk all trials that recruited patients with at least one COPD exacerbation in the 12 months before study entry. We will consider as low risk all trials that do not meet the above criteria. We will compare each pair of treatments by estimating an odds ratio (OR) or hazard ratio (HR) for dichotomous outcomes, and a difference in mean or median for continuous outcomes. We will use a normal likelihood with identity link for continuous outcomes (FEV_1, TDI and SGRQ) and a binomial likelihood with cloglog link for mortality, SAEs (total, cardiac and COPD), dropouts due to adverse events, SGRQ responders and pneumonia to allow for different study durations because a longer follow-up would likely make a difference in study results for these outcomes. We will use a shared parameter model for exacerbation outcomes, whereby data on the log hazard ratio (lnHR) are modelled with the assumption that continuous treatment differences (lnHR and standard error) have a normal likelihood. When lnHR data are not available, or when appropriate covariance matrices cannot be extracted for trials with more than two arms, we will model data on the number of participants with at least one exacerbation out of the total number of participants at a given time as lnHR by using a binomial likelihood with cloglog link. We will use HR data in preference to dichotomous data when available and will consider only HR for the first event. We will assess model fit by comparing residual deviance versus the number of data points, and by assessing the size of the between-study standard deviation (SD).

Direct pairwise meta-analysis

We will conduct pairwise meta-analyses considering only direct evidence. We will analyse dichotomous data as ORs and continuous data as mean differences or standardised mean differences (SMDs), along with their 95% confidence intervals (CIs). We will enter data presented as a scale with a consistent direction of effect. We will use a random-effects model as a primary analysis for all outcomes and a fixed-effect model as a sensitivity analysis. We will apply Haldane correction by adding 0.5 to each count when a data set contains zero in any cell, to make a calculation possible for the main effect of variance (Bhaumik 2012). We will undertake meta-

analyses only when this is meaningful (i.e. if treatments, participants and the underlying clinical question are similar enough for pooling to make sense). When multiple trial arms are reported in a single trial, we will include only the relevant arms.

Unit of analysis issues

We will analyse dichotomous data by using number of participants (rather than events) as the unit of analysis to avoid multiple counting of data from the same participant.

Dealing with missing data

We will request additional data from manufacturers through clinicalstudydatarequest.com and/or from the responsible author of the included study to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study is identified as an abstract only). When this is not possible, and when the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by performing a sensitivity analysis.

Assessment of heterogeneity

Assessment of similarity of participants, interventions and trial methods

We will assess similarity of participants, interventions, potential effect modifiers and trial methods in all studies and across pairwise comparisons to ensure low heterogeneity and consistency in the NMA. We will formulate a table to assess similarity of participant characteristics in class pairwise comparisons (e.g. LABA/LAMA vs LABA/ICS, LABA/LAMA vs LABA.). The initial editorial review had questioned the similarity of patient populations across clinical trials owing to the presence of potential effect modifiers. After a preliminary search of clinical studies and review of inclusion/exclusion criteria, participant characteristics and trial methods, we decided to divide the study populations into those with and those without a history of COPD exacerbations, which we viewed as a potential effect modifier. This is consistent with the GOLD 2017 update (GOLD 2017), which recommends treatment options based on exacerbation history. Otherwise, the distribution of participant and study characteristics appeared sufficiently similar in different sets of RCTs that go into an indirect comparison. We will consider confounding by difference in the distribution of effect modifiers when carrying out subgroup comparisons between trials. If effect modifiers are clearly different (treatment-by-covariate interactions) between clinical trials with a formal analysis, we will emphasise results derived by direct comparison and will downgrade NMA estimates as providing a lower level of evidence or as probably biased.

Assessment of heterogeneity and statistical consistency

We will assess heterogeneity by comparing a between-trials SD versus the size of relative treatment effects, using log-scale for OR and HR. We will assess consistency by comparing the model fit and between-study heterogeneity from NMA models versus those from an unrelated effects (inconsistency) model (Dias 2013a; Dias 2013b). We will use this test to determine the presence and area of inconsistency. We will qualitatively compare the results from direct pairwise meta-analysis versus NMA estimates to check for broad agreement. If we identify substantial inconsistency, we will explore factors, including participant and design characteristics, that may contribute to inconsistency. We will comment on these characteristics and will restrict our analysis to a subset of studies for which the evidence may be more comparable. For the pairwise meta-analysis, we will test heterogeneity among studies with $I^2 > 30\%$ indicating substantial heterogeneity (Higgins 2003). We will use optimal information size calculations as an objective measure of imprecision for grading evidence, with an α of 0.05 and a β of 0.80 (Guyatt 2011a). We will address heterogeneity through direct comparison based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (Guyatt 2011b).

Assessment of reporting biases

We will minimise reporting bias from unpublished studies or selective outcome reporting by using a broad search strategy and by checking references of included studies and relevant systematic reviews. For each outcome, we will estimate and present the proportion of studies contributing data to the NMA. For the pairwise meta-analysis, we will assess small study and publication bias through visual inspection of a funnel plot and performance of the Egger test (Egger 1997) if more than 10 studies are being pooled. We will assume the presence of small study bias when the number of participants is fewer than 50 per study, 1000 per pooled analysis or 100 per arm when no more than 10 studies can be pooled (Dechartres 2013; Nüesch 2010). We will assume a selective reporting bias if a clinical trial is not registered (Mathieu 2009).

Data synthesis

We will consider all regimen doses as individual treatments. If the network structure allows, we will consider a class-model meta-analysis as the primary analysis (as used in Kew 2014). We will estimate the probability that each class ranks at one of the four possible positions. For NMAs, we will compare fixed-effect and random-effects models using the Deviance Information Criterion (DIC). We will use the model with lower values on the DIC. When two models have a similar DIC (i.e. within 3 units of each other), we will choose a model on the basis of heterogeneity in the pairwise comparison. We will use a random-effects model if we detect heterogeneity and a fixed-effect model otherwise (Spiegelhalter 2002). We will report all results for the NMA as posterior medians

or means with corresponding 95% credible intervals. For pairwise meta-analyses, we will use a random-effects model, and for sensitivity analysis, we will use a fixed-effect model.

Summary of findings table

We will use the GRADE system to assess the quality of evidence as it relates to studies that contribute data to the pairwise meta-analyses. We will create a 'Summary of findings' table using the following outcomes: mortality, COPD exacerbations (moderate to severe and severe), pneumonia, SGRQ responder, TDI and change from baseline in SGRQ. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to studies that contribute data to meta-analyses for pre-specified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and will use GRADEpro GDT 2016 software. We will justify all decisions to downgrade or upgrade the quality of studies by using footnotes, and we will make comments to aid the reader's understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We plan to perform subgroup analyses based on baseline disease severity, treatment duration, smoking status, type of each arm (intraclass comparison), dose of ICS component for pneumonia and publication status, provided that treatments could be compared indirectly with those in other trial comparisons through one or more common comparators (i.e. the networks remained 'connected'). If we detect substantial heterogeneity in the NMA, we will explore potential sources of heterogeneity by fitting covariates (i.e. FEV_1 at baseline, treatment duration, publication status (published vs unpublished and publication year), smoking status,

comorbidity, etc.) in a meta-regression analysis and conducting a subgroup analysis based on inhaler strength (analyse all doses separately). We will use the formal test for subgroup interactions provided in Review Manager (RevMan 2014).

Sensitivity analysis

We will perform sensitivity analyses while excluding studies at high risk of bias from the overall analysis (provided that the networks remain connected) and will analyse studies of different duration separately. We will use a model not used in the primary analysis (fixed-effect or random-effects) as a sensitivity analysis for both NMAs and pairwise meta-analyses. For the NMA, we will explore bias adjustment methods based on risk of bias of each study for blinding and allocation concealment components, on their own or in combination (subject to network structure) (Dias 2010).

ACKNOWLEDGEMENTS

REFERENCES

Additional references

ATS/ERS 2004
Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *European Respiratory Journal* 2004;**23**(6):932–46.

Bhaumik 2012
Bhaumik DK, Amatya A, Normand SL, Greenhouse J, Kaizar E, Neelon B, et al. Meta-analysis of rare binary adverse event data. *Journal of the American Statistical Association* 2012;**107**:555–67. [PUBMED: 23734068]

Dechartres 2013
Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-

epidemiological study. *British Medical Journal* 2013;**346**:f2304.

Decramer 2012
Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *Lancet* 2012;**379**:1341–51.

Dias 2010
Dias S, Welton NJ, Marinho VCC, Salanti G, Higgins JPT, Ades AE. Estimation and adjustment of bias in randomized evidence by using mixed treatment comparison meta-analysis. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 2010;**173**:613–29.

Dias 2013a
Dias S, Welton NJ, Marinho VCC Salanti G, Higgins JPT, Ades AE. Evidence synthesis for decision making 2: a

generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Medical Decision Making* 2013;**33**:607–17.

Dias 2013b

Dias S Welton NJ Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Medical Decision Making* 2013;**33**:641–56. [PUBMED: 23804508]

Donohue 2015

Donohue JF, Worsley S, Zhu CQ, Hardaker L, Church A. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respiratory Medicine* 2015;**109**(7):870–81.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal (Clinical Research Ed.)* 1997;**315**(7109): 629–34.

Falk 2008

Falk JA, Minai OA, Mosenifar Z. Inhaled and systemic corticosteroids in chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society* 2008;**5**(4): 506–12.

GOLD 2017

The Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). http://goldcopd.org (accessed 17 December 2016).

GRADEpro GDT 2016 [Computer program]

Brozek J, Oxman A, Schünemann H. GRADEpro GDT. Version accessed 7 July 2016. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Guyatt 2011a

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence - imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283–93.

Guyatt 2011b

Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *Journal of Clinical Epidemiology* 2011;**64**(4):380–2.

Heidari 2012

Heidari B. The importance of C-reactive protein and other inflammatory markers in patients with chronic obstructive pulmonary disease. *Caspian Journal of Internal Medicine* 2012;**3**(2):428–35.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *British Medical Journal* 2003;**327**(7414):557–60.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Huisman 2015

Huisman EL, Cockle SM, Ismaila AS, Karabis A, Punekar YS. Comparative efficacy of combination bronchodilator therapies in COPD: a network meta-analysis. *International Journal of Chronic Obstructive Pulmonary Disease* 2015 Sep; **10**:1863–81.

Kew 2014

Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2014 Mar;**26**(3):CD010844.

Kume 2014

Kume H, Imbe S, Nishiyama O, Iwanaga T, Higashimoto Y, Tohda Y. Involvement of regulation of KCa channels via Gi, Gs in the synergistic action between anticholinergic agents and β2-adrenergic receptor agonists in airway smooth muscle. *American Journal of Respiratory and Critical Care Medicine* 2014;**189**:A5589.

Lu 2004

Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine* 2004;**23**(20):3105–24.

Mathieu 2009

Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. *JAMA* 2009;**302**(9): 977–84.

McCarthy 2015

McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015 Feb;**23**(2):CD003793.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7): e1000097. [DOI: 10.1371/journal.pmed.1000097]

Nannini 2012

Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012 Sep; **12**(9):CD006829.

Nüesch 2010

Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010;**341**:c3515.

Oba 2016a

Oba Y, Sarva ST, Dias S. Efficacy and safety of long-acting beta-agonist/long-acting muscarinic antagonist combinations in COPD: a network meta-analysis. *Thorax* 2016;**71**(1):15–25.

Oba 2016b

Oba Y, Chandran A, Devasahayam J. Long-acting muscarinic antagonist versus inhaled corticosteroid when added to long-acting *β*-agonist for COPD: a meta-analysis. *COPD* 2016;**13**(6):677–85.

Patel 2014

Patel JG, Nagar SP, Dalal AA. Indirect costs in chronic obstructive pulmonary disease: a review of the economic burden on employers and individuals in the United States. *International Journal of Chronic Obstructive Pulmonary Disease* 2014;**9**:289–300.

Qaseem 2011

Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Annals of Internal Medicine* 2011;**155**(3):179–91.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rochester 2015

Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al. ATS/ERS Task Force on Policy in Pulmonary Rehabilitation. An Official American Thoracic Society/European Respiratory Society Policy Statement. Enhancing implementation, use, and delivery of pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine* 2015;**192**(11):1373–86.

Schlueter 2016

Schlueter M, Gonzalez-Rojas N, Baldwin M, Groenke L, Voss F, Reason T. Comparative efficacy of fixed-dose combinations of long-acting muscarinic antagonists and long-acting *β*2-agonists: a systematic review and network meta-analysis. *Therapeutic Advances in Respiratory Disease* 2016;**10**(2):89–104.

Singh 2015

Singh D, Worsley S, Zhu CQ, Hardaker L, Church A. Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial. *BMC Pulmonary Medicine* 2015;**15**:91.

Spiegelhalter 2002

Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society. Series B (Statistical Methodology)* 2002;**64**(4):583–39.

Suissa 2012

Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012;**67**(11):957–63.

Tricco 2015

Tricco AC, Strifler L, Veroniki AA, Yazdi F, Khan PA, Scott A, et al. Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis. *BMJ Open* 2015;**5**(10):e009183.

Trucchi 2015

Trucchi C, Paganino C, Orsi A, De Florentiis D, Ansaldi F. Influenza vaccination in the elderly: why are the overall benefits still hotly debated?. *Journal of Preventive Medicine and Hygiene* 2015;**56**(1):E37–43.

Vogelmeier 2013

Vogelmeier CF, Bateman ED, Pallante J, Alagappan VK, D'Andrea P, Chen H, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respiratory Medicine* 2013;**1**(1):51–60.

Vogelmeier 2015

Vogelmeier C, Paggiaro PL, Dorca J, Sliwinski P, Mallet M, Kirsten A, et al. Efficacy of aclidinium/formoterol fixed-dose combination versus salmeterol/fluticasone in COPD. *European Respiratory Journal* 2015;**46**(suppl 59):PA2960.

Wedzicha 2016

Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *New England Journal of Medicine* 2016;**374**(23):2222–34.

WHO 2016

World Health Organization. Chronic obstructive pulmonary disease. Burden of COPD. http://www.who.int/respiratory/copd/burden/en/ (accessed 17 December 2016).

WinBUGS 1.4.3. [Computer program]

Medical Research Council (MRC). WinBUGS. Version 1.4.3. UK: Medical Research Council (MRC), August 6, 2007.

Zhong 2015

Zhong N, Wang C, Zhou X, Zhang N, Humphries M, Wang L, et al. LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease* 2015;**10**:1015–26.

* Indicates the major publication for the study

A P P E N D I C E S

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema$.mp.
4. (chronic$ adj3 bronchiti$).mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 2. Search strategy to identify relevant trials from the CAGR

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 mometasone* AND formoterol*
#8 fluticasone* AND salmeterol*
#9 budesonide* AND formoterol*
#10 beclomethasone* AND formoterol*
#11 fluticasone* AND formoterol*
#12 Flutiform or Fostair or Simplyone
#13 fluticasone* AND vilanterol*
#14 mometasone* AND indacaterol*
#15 formoterol* and ciclesonide*
#16 QMF149
#17 GW685698 AND GW642444
#18 steroid* OR corticosteroid* or ICS
#19 (long-acting* or long NEXT acting*) NEAR beta*
#20 #18 AND #19
#21 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #20
#21 formoterol* AND aclidinium*
#22 indacaterol* AND glycopyrronium*
#23 indacaterol* AND tiotropium*
#24 olodaterol* AND tiotropium*

#25 vilanterol* AND umeclidinium*
#26 QVA149
#27 Ultibro or Stiolto or Duaklir Genuair
#28 Muscarinic* Next Antagonist*
#29 #19 AND #28
#30 #21 or # 22 or #23 or #24 or #25 or #26 or #27 or # 29
#31 combin* NEAR inhaler*
#32 FDC:ti,ab
#33 #21 or #30 or #31 or #32
#34 #6 AND #33
[In search line #4, MISC1 denotes the field in which the reference has been coded for condition, in this case, COPD]

CONTRIBUTIONS OF AUTHORS

Yuji Oba and Mario Fadila wrote this protocol, with feedback and methodological support provided by Edna Keeney and Sofia Dias. All review authors approved the final version of the document.

For the review, Yuji Oba and Mario Fadila will extract data, assess methodological quality of included trials, perform pairwise and network meta-analyses and prepare tables and figures. Edna Keeney and Sofia Dias will supervise the NMAs and will formulate and run a model with WinBUGS as necessary. All review authors will contribute to writing of the full review.

DECLARATIONS OF INTEREST

Y Oba, M Fadila, E Keeney: none known.

S Dias: Pfizer Portugal, Novartis and Boehringer Ingelheim have paid fees to the University of Bristol for seminars. S Dias is a coapplicant on a grant by which Pfizer is partially sponsoring a researcher (not herself).

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