# Cochrane Airways Prepared protocol text

## Background

*[If the text is in regular font, you should not change it. However, you can modify it if you have good reason. If the text is italicised and in square brackets it is for guidance only and you should delete it before you submit your first protocol draft].*

*[Please refer to the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org; in RevMan 5: Help > Handbook) for guidelines on the development and completion of your protocol. See 'Guide to the contents of a Cochrane protocol or review' in Section 4.5 of the Handbook.*

*The Methodological Expectations of Cochrane Intervention Reviews (MECIR) project has specified conduct and reporting expectations for Cochrane protocols and reviews, and is designed to support authors and editorial bases to produce Cochrane reviews of the highest possible standard. Please click on the blue icon at the top right of this screen to see the MECIR guidance that is relevant to each section of the protocol. Cochrane Airways has devised this standard protocol text to capture the main standards for most intervention reviews. However, you may need to modify the text to fit your specific review questions; if so, do follow the guidance in the Handbook.*

*Before checking in your draft for editorial approval, please check that there are no 'Errors' and review the 'Warnings' on the Validation Report (File > Reports > Validation Report). In addition, make sure that your text follows the Cochrane Style Manual. When you are ready to submit your protocol for editorial approval, check it back into Archie - see the Quick Start Guide for authors for details.*

*If you have any questions about the development of your protocol, please email Emma Dennett at edennett@sgul.ac.uk].*

## Description of the condition

[See MECIR reporting standards R19 to R22. These are also summarised in the guidance screen to the right].

## Description of the intervention

## How the intervention might work

*[It is highly desirable for you to include any details of equity and how the intervention relates to specific populations, if this is relevant. Please document what is known about effect modifiers for the treatment].*

## Why it is important to do this review

## Objectives

# Methods

## Criteria for considering studies for this review

## Types of studies

We will include randomised controlled trials (RCTs). We will include studies reported in full text, those published as an abstract only and unpublished data.

*[You must include RCTs in your review, but if you want to include any additional study designs, you must justify your choice].*

## Types of participants

We will include [adults or children or both] with a diagnosis of [asthma/COPD/other]. We will exclude participants with the following co-morbidities/characteristics:

*[Predefine unambiguous criteria for participants. Define in advance how you will handle studies that include only a subset of relevant participants. Restrictions to study populations must be based on a sound rationale and described here. Define age cut-offs for adults/children/infants].*

## Types of interventions

We will include studies comparing [insert intervention] with [placebo/usual care/other]. We will include the following co-interventions provided they are not part of the randomised treatment:

*[Define in advance the eligible interventions and the interventions against which these can be compared in the included studies. Pay attention to active comparator interventions (e.g. a different variant of the same intervention, a different drug or a different kind of therapy). If you plan more than one comparison, define each one (e.g. steroids versus placebo; steroid versus steroid plus LABA)].*

## Types of outcome measures

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies.

*[You may not use reporting of outcomes in studies as an inclusion criterion unless you have a very good reason and provide a rationale within the protocol].*

### Primary outcomes

*[Define in advance which primary and secondary outcomes are of interest. Keep the total number of outcomes as small as possible. Choose outcomes that are relevant to stakeholders such as consumers, health professionals and policy makers. Avoid trivial outcomes and biochemical, interim and process outcomes, but consider the importance of resource-use outcomes. Consider mortality, exacerbations, quality of life, disease control, lung function, etc. Cochrane Airways suggest including around seven outcomes in total. Define in advance details of what are acceptable outcome measures (e.g. diagnostic criteria, scales or composite outcomes). Define in advance how you will select outcome measures when there are several possible measures (e.g. multiple definitions, assessors or scales) and time points of interest. Include a rationale to explain why you have chosen the primary and secondary outcomes listed].*

1. Serious adverse events.

## Secondary outcomes

1. Adverse events/side effects.

## Search methods for identification of studies

### Electronic searches

*[Contact Liz Stovold (estovold@sgul.ac.uk), the Cochrane Airways Information Specialist, to discuss your search terms before submitting your protocol for editorial approval].*

We will identify studies from searches of the following databases and trial registries:

Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies, all years to date;Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, all years to date;MEDLINE Ovid SP 1946 to date;Embase Ovid SP 1974 to date;US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

The proposed MEDLINE search strategy is listed in Appendix 1. This will be adapted for use in the other databases. The search strategy was developed by the Cochrane Airways Information Specialist in collaboration with the authors, and was peer-reviewed by another Cochrane Information Specialist using the PRESS checklist (McGowan 2016).

All databases and trials registries will be searched from their inception to the present, and there will be no restriction on language or type of publication. Hand-searched conference abstracts and grey literature will be identified through the Cochrane Airways Trials Register and the CENTRAL database.

### 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 study information.

We will search on PubMed for errata or retractions from included studies published in full text, and report the date this was done within the review.

# Data collection and analysis

## Selection of studies

We plan to use Cochrane’s Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as an RCT or as Not an RCT; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs; and if appropriate, Cochrane Crowd (http://crowd.cochrane.org) – Cochrane’s citizen science platform where the Crowd help to identify and describe health evidence. More detailed information about the Screen4Me components can be found in the following publications: Marshall 2018, McDonald 2017, Noel-Storr 2018, Thomas 2017.

Following this initial assessment, two [or more] review authors (initials here) will screen the titles and abstracts of the remaining search results independently and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies and two [or more] review authors (initials here) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person/review author (initials here). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

## Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One [or more] review author (initials here) will extract the following study characteristics from included studies: [it is highly desirable, but not mandatory, for this process to be done in duplicate].

* Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study.
* Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
* Interventions: intervention, comparison, concomitant medications and excluded medications.
* Outcomes: primary and secondary outcomes specified and collected, and time points reported.
* Notes: funding for studies and notable conflicts of interest of trial authors.

Two [or more] review authors (initials here) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person/review author (initials here). One review author (initials here) will transfer data into the Review Manager file (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (initials here) will spot-check study characteristics for accuracy against the study report.

*[The contact person will have received a standard data collection form in the original email from the Managing Editor, which you may adapt for use in your specific review].*

## Assessment of risk of bias in included studies

*[Note: the following sections refer to individually randomised studies. If cluster-randomised or cross-over studies are included, you should use appropriate methods for assessing bias in these designs. See Handbook sections 16.3.2 and 16.4.3].*

Two [or more] review authors (insert initials here) will assess risk of bias independently for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (insert initials here). We will assess the 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 judge each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where 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). Where 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 the 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 justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

## Measures of treatment effect

We will analyse dichotomous data as odds ratios (OR) [if you wish to use risk ratio/risk difference you must provide a reason/justification] and continuous data as the mean difference (MD) or standardised mean difference (SMD). If data from rating scales are combined in a meta-analysis, we will ensure they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement).

We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).

Where multiple trial arms are reported in a single study, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will either combine the active arms or halve the control group to avoid double-counting.

If adjusted analyses are available (ANOVA or ANCOVA) we will use these as a preference in our meta-analyses. If both change from baseline and endpoint scores are available for continuous data, we will use [change from baseline unless there is low correlation between measurements in individuals]. If a study reports outcomes at multiple time points, we will use [complete as appropriate].

We will use intention-to-treat (ITT) or 'full analysis set' analyses where they are reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per protocol analyses [if you wish to favour completer or per protocol analyses in some cases, please justify].

## Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). However, if rate ratios are reported in a study, we will analyse them on this basis [or justify otherwise]. We will only meta-analyse data from cluster-RCTs if the available data have been adjusted (or can be adjusted), to account for the clustering.

*[If relevant to your review, you should describe how you will deal with other issues relating to the analysis of studies with non-standard designs here (e.g. cross-over studies, other considerations relating to cluster-randomised studies or the use of adjusted analyses within studies)].*

## Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

## Assessment of heterogeneity

We will use the I² statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity we will report it and explore the possible causes by prespecified subgroup analysis.

## Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small study and publication biases.

*[You may need to consult a statistician and the Handbook section 10.4 if you intend to explore possible publication bias].*

## Data synthesis

We will use a random-effects model and perform a sensitivity analysis with a fixed-effect model. [If you plan to deviate from this, justify your choice of model].

## 'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes [List up to seven outcomes, including your primary outcomes, adverse events and all patient-important outcomes or those that are most important to guideline setters and people making decisions about healthcare]. We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

*[Cochrane Airways recommends that you create your 'Summary of findings' table as soon as possible AFTER you have conducted the 'Risk of bias' assessment and entered data into RevMan (RevMan 2014) but BEFORE you write up your results, discussion, abstract and conclusions. This will give you the opportunity to think about how the risk of bias in the studies contributing to each outcome, alongside other considerations listed above, affect the mean treatment effect and your confidence in it. At the point of completing your 'Summary of findings' table, we also encourage you to make contact with us to ask our Statistician to check your data before you finalise the review text and conclusions].*

## Subgroup analysis and investigation of heterogeneity

*[Please note that all subgroup/sensitivity analyses will need to be dichotomised and the splits specified (e.g. age (18 years and younger versus older than 18 years)) unless you have a reason not to, in which case please state the reason].*

We plan to carry out the following subgroup analyses:

We will use the following outcomes in subgroup analyses:

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014).

*[You would usually restrict subgroup analysis to the review’s primary outcomes].*

## Sensitivity analysis

We plan to carry out the following sensitivity analyses, removing the following from the primary outcome analyses:

1. We will compare the results from a fixed-effect model with the random-effects model.

## Acknowledgements

*[Acknowledge here people who helped you in writing the protocol. This includes if you are writing your review on host institution time, even if you have not specifically received a grant for the work].*

The Background and Methods sections of this protocol/review are based on a standard template used by Cochrane Airways.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Airways. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health. [Editorial base to remove paragraph if not programme grant funded]

## Contributions of authors

*J. Bloggs:*

*C. Darwin:*

*[Describe here the contribution of each author in the protocol and the planned contribution of each author for the full review].*

## Declarations of interest

*J. Bloggs: [describe conflict]*

*C. Darwin: none known*

*[The contact person should check that any relevant conflicts of interest reported in the electronic conflict of interest (COI) forms signed by your author team are consistent with what is reported here. If you think that you may have a potential conflict of interest please contact Cochrane Airways as soon as possible. See Cochrane's COI policy for more information].*

## Additional references

Cochrane Airways 2019

Cochrane Airways Trials Register. airways.cochrane.org/trials-register (accessed 7 May 2019).

GRADEpro GDT

GRADEpro GDT [Computer program]. Version accessed [authors please add date]. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015. Available at gradepro.org.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Marshall 2018

Marshall IJ, Noel-Storr AH, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying randomized controlled trials: an evaluation and practitioner’s guide. Research Synthesis Methods 2018;9(4):602-14.

McDonald 2017

McDonald S, Noel-Storr AH, Thomas J. Harnessing the efficiencies of machine learning and Cochrane Crowd to identify randomised trials for individual Cochrane reviews. In: Global Evidence Summit; 2017 September 13-16; Cape Town, South Africa. 2017.

McGowan 2016

McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. Journal of Clinical Epidemiology 2016;75:40-6. [DOI: 10.1016/j.jclinepi.2016.01.021]

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]

Noel-Storr 2018

Noel-Storr AH, Project Transform team. Cochrane Crowd: new ways of working together to produce health evidence. In: Evidence Live; 2018 June 18-20; Oxford, UK. 2018.

RevMan 2014

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

Surname Year

Author N, Author N, Author N, Author N, Author N, Author N, et al (include 'et al' after the sixth author). English title, with the first word with a capital and all other words in lower case (unless acronyms etc.). JAMA, BMJ, but otherwise include journals in the form of Annals of European Respiratory Journal; i.e. journal name in full with each word beginning with a capital Year;Number(Complete if available):1291-9 NOT 1291-1299 etc. *[Other: This is an example of how your references (journal only) should be entered. For other reference types, please refer to Cochrane Style Manual]*

Thomas 2017

Thomas J, Noel-Storr AH, Marshall I, Wallace B, McDonald S, Mavergames C, et al. Living systematic review network. Living systematic reviews: 2. Combining human and machine effort. In: Journal of Clinical Epidemiology. Vol. 91. 2017:31-7.