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Interventions to improve adherence to pharmacological therapy for chronic obstructive pulmonary disease (COPD) (Protocol)

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T A B L E   O F   C O N T E N T S

Interventions to improve adherence to pharmacological therapy for chronic obstructive pulmonary disease (COPD)

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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 determine the efficacy and safety of interventions intended to improve adherence to single or combined pharmacological treatments compared with usual care or interventions that are not intended to improve adherence in people with COPD.

B A C K G R O U N D

Description of the condition

It is predicted that chronic obstructive pulmonary disease (COPD) will be among the top causes of death by 2030 (WHO 2018). The Global Burden of Disease study has shown that COPD caused an estimated 3 million deaths (GBD 2015 Incidence and Prevalence Collaborators), and affected an estimated 174 million people worldwide (GBD 2015 Chronic Respiratory Disease Collaborators; GBD 2015 Incidence and Prevalence Collaborators). COPD represents 2.6% of the entire global burden of disease (GBD 2015 Incidence and Prevalence Collaborators); it is also on the increase, with more people suffering due to under-recognition, under-diagnosis, under-treatment (Quaderi 2018), and non-adherence (Humenberger 2018).

Chronic obstructive pulmonary disease is a progressive, chronic lung disease characterised by persistent respiratory symptoms and limited airflow due to airway or alveolar abnormalities (or both) resulting from significant exposure to noxious particles or gases. Causes include tobacco smoking, and environmental factors such as exposure to biomass fuel and air pollution (WHO 2017; COPD Foundation 2018). COPD diagnosis is based on symptoms including dyspnoea (shortness of breath), cough, or sputum production (or both), and is confirmed by means of spirometry demonstrating persistent airflow limitation, i.e. presence of post-bronchodilator forced expiratory volume in the first second (FEV1)/ forced vital capacity (FVC) of less than 70% (GOLD 2019). Disease severity is associated with frequency of exacerbations or "flare ups", and the presence of other co morbidities, such as cardiovascular disease, musculoskeletal impairment, or diabetes (Vestbo 2013; GOLD 2019).

It has been estimated that only 50% of people in developed countries with chronic disease adhere to treatment recommendations (WHO 2003). Although clinical studies have shown that adherence rates in COPD patients range from 70% to 90%, this is unlikely to be reflected in clinical practice (Wiśniewski 2014). One study showed that only 34% of COPD patients completely adhered to medication (Brandsetter 2017).

Despite optimisation of treatments, some patients with COPD continue to experience debilitating symptoms that can impact on their functional status and quality of life (e.g. increased exacerbations, hospitalisations, and risk of mortality). Adherence to medication is one of the most important factors that enables successful treatment of COPD (Duncan 2015). Benefits to clinical outcomes are often limited due to patients not taking medication as prescribed, which can also be costly for health services (WHO 2003; van Boven 2014; Chen 2017; Sulaiman 2017).

Description of the intervention

Pharmacological management of COPD often involves regular use of long-acting bronchodilators long-acting beta$_2$-adrenoceptor agonists (LABAs) or long-acting muscarinic receptor agonists (LAMAs), or both) and in selected patients inhaled corticosteroids (ICS) will be added. These maintenance inhalers are intended to improve lung function, reduce the risk of exacerbations, and improve quality of life. Most patients will also be prescribed a short-acting bronchodilator, such as a short-acting beta$_2$-adrenoceptor agonists (SABA), to manage acute symptoms such as breathlessness (Vogelmeier 2017). Maintenance inhalers can be given as monotherapy, which can be "stepped up" to dual or triple therapy if needed (e.g. ICS plus LABA, or ICS plus LABA plus LAMA) (Vogelmeier 2017). Other pharmacological treatments - such as oral glucocorticosteroids, phosphodiesterase-4 (PDE4) inhibitors, mucolytic agents and prophylactic antibiotics - may also be prescribed for specific indications. Oral glucocorticoids, for example, may be used in the short term for acute exacerbations, while prophylactic antibiotics and mucolytics may have a benefit in preventing flare-ups in patients who experience frequent exacerbations (Walters 2014; Herath 2018; Poole 2019).

Patients knowledge and understanding about medications as well as their physical and cognitive capabilities can affect medication adherence, that is the likelihood of medication being taken at the prescribed dose and frequency, and using the correct technique. Moreover, patients beliefs about medication can also influence their behaviours and, in turn, adherence. A report published by the WHO outlines three types of behaviour that can lead to non-adherence to ICS therapy, as follows (WHO 2003).

1. "Erratic non-adherence": missing doses because of forgetting, changing schedules or busy lifestyles. Patients understand their prescribed regimen but compliance is difficult, or they have not prioritised treatment management.

2. "Unwitting non-adherence": non-adherence due to not understanding the prescribed regimen, e.g. misunderstanding how many times an inhaler should be taken (leading to under-use or over-use), how to take it correctly, how the treatment works, or not understanding the importance of adhering to treatment.

3. "Intelligent non-adherence": patients may alter or stop taking treatment deliberately because they feel better or that they no longer need to take their medication. They may stop taking medication because of short-term (e.g. believing that they don't need to take their treatment) or long-term effects, bad taste, complexity and interference in their daily routine, or thinking that there is more harm than benefit of continuing medication. A range of interventions exist that can help people adhere to medication, for example, changes to medication (e.g. simplified drug regimens), and implementation of behavioural (e.g. cognitive behavioural therapy (CBT)) or educational interventions (e.g. discussion with a health professional, or written information) (Bryant 2013; Blackstock 2016). Adherence aids such as Dossette boxes or multi-compartment medication compliance aids (MCAs) could help those who have complex medication regimens (Furmedge 2018). Electronic inhaler monitoring devices or "smart" inhalers may provide automated medication reminders for patients at risk of forgetting to take their inhaler, or provide adherence feedback to the patient and healthcare professionals around which adherence discussions could take place. Other digital technologies aimed at aiding medication adherence are in development, such as mobile phone applications (Blakey 2018).

How the intervention might work

For an intervention to improve adherence to pharmacological treatment, its success is likely to be dependent on the type of intervention available, and type of non-adherence that it is intended to target. A simple intervention, for example, could remind patients to take their inhaler, whilst a complex intervention could provide education and support from a health professional to help change a patient's behaviour towards their medication.

Adherence to medication for medical disorders has been investigated in a previous Cochrane Review (Nieuwlaat 2014). Of the 182 randomised controlled trials (RCTs) included, overall, the authors reported that effects of interventions and measures of adherence were varied from study to study. Only a few RCTs on integrated, tailored or multi-component interventions that involved an individualised care plan, educational sessions about self-management, visits by a health professional or team of health professionals, and regular telephone consultations (from a specialist case manager nurse, for example) showed improvement in adherence and clinical outcomes, but even these interventions would be difficult to apply in a usual practice setting. (Nieuwlaat 2014).

Reasons for poor medication adherence in COPD are not well understood. Potentially these might include complex medication regimens which can lead to confusion and forgetting to take med-

ication, or a busy, unpredictable lifestyle could lead to deviation of prescribed regimen (Bryant 2013;WHO 2003). Other contributing factors can include inadequate education or knowledge about the disease process or comorbidities, side effects of treatment, patient acceptability and preference, cost of medication, and belief that there are more disadvantages of taking treatment than advantages (Restrepo 2008; Normansell 2017). Poor medication adherence may be explained by the "Ascertaining Barriers to Compliance (ABC)" taxonomy, which gives a description of the steps taken towards achieving medication adherence as prescribed (Vrijens 2016). The taxonomy is divided into three stages:

1. Initiation (when a patient takes the first dose as prescribed).
2. Implementation (the extent to which a patient's actual dosing corresponds to the prescribed regimen, from initiation until the last dose is taken).
3. Persistence (time elapsed from initiation to eventual treatment discontinuation).

Some reasons for poor adherence may act at several stages in the taxonomy and others predominantly affect a single stage. For example, not taking inhaled therapy (e.g. LABA, LAMA or ICS, combination of LABA and ICS as prescribed (under-use or over-use of inhalers)), or not using the right inhaler technique may affect implementation with little impact on initiation or persistence.(Vestbo 2009; van Boven 2014).

Sources of clinical diversity are variations of medical problems, treatment regimens, and type of adherence intervention. There is currently no published evidence to determine which intervention would specifically help people with COPD to adhere to treatment (e.g. change in regimen, CBT, or information from a health professional). The most appropriate type of intervention and its effectiveness will likely depend on the reason for an individual's non-adherence.

Why it is important to do this review

As part of a programme of work funded to look at issues important to people with COPD, Cochrane Airways have discussed medication adherence with a COPD patient advisory group. The group highlighted what helps them to take medication (e.g. correct information about how to use their inhaler, or alarms to remind them to take their tablets) or what prevents them from taking medications (e.g. health professionals not giving the correct information about how to use an inhaler, difficulty in taking tablets, side-effects of inhalers, difficulty in taking too many medications, or forgetting to take their medication). Some of the patients in the patient advisory group said that they had become used to taking multiple medications, whereas some patients said that they only took medication, such as a nebuliser, in an emergency. It was evident from the discussion that although one method of adherence worked for one patient, it may not work for another patient. We intend to investigate what helps people with COPD to adhere to pharmacological treatments and whether adherence improves other health outcomes (e.g. quality of life). We will focus on investigating interventions to improve adherence to pharmacological treatments such as changes in treatment regimen, education, or cognitive behavioural therapy. Interventions intended to help patients to adhere to non-pharmacological treatments for COPD such as smoking cessation, pulmonary rehabilitation, oxygen therapy, and vaccinations will not be included in this review.

O B J E C T I V E S

To determine the efficacy and safety of interventions intended to improve adherence to single or combined pharmacological treatments compared with usual care or interventions that are not intended to improve adherence in people with COPD.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) only (parallel, cluster-randomised or cross-over designs). We will include studies reported in full text, those published as an abstract only and unpublished data. We will include studies from community and hospital settings.

Types of participants

We will include adults aged 35 years or over (NICE 2018) who have a diagnosis of chronic obstructive pulmonary disease (COPD) according to established criteria, e.g. Global Initiative for Obstructive Lung Disease (GOLD) staging (GOLD 2019), European Respiratory Society (ERS), or American Thoracic Society (ATS) criteria (Qaseem 2011). We will include adults with any co morbidities (e.g. diabetes), provided that the intervention is aimed at improving adherence to pharmacological treatment for COPD using at least one of the Types of interventions as outlined below.

We will exclude participants whose primary diagnosis is another respiratory condition such as asthma, bronchiectasis, and cystic fibrosis. We will include studies that include participants with "asthma-COPD overlap syndrome" but we will analyse outcomes in these participants separately if disaggregated data are available. We will also include trials in which the health professional is the target, who then delivers the intervention to COPD patients.

If we find trials in which only a subset of participants (at least 50%) have a diagnosis of COPD, we will include these participants, provided we can obtain disaggregated data from the trial authors.

Types of interventions

We will include trials in which the aim of the intervention is primarily to help improve adherence to pharmacological therapy. We will also include studies in which the primary aim of the intervention is to improve inhaler technique, and will report this as a separate comparison.

We will include the following intervention categories.

1. Changes to the pharmacological treatment itself, such as different medication formulations (e.g. using a combination inhaler or the same type of inhaler for all treatments rather than multiple different inhaler types, using tablets instead of inhalers or simplified drug regimens.

2. Adherence aids (e.g. Dosette box, alarm, reminder, keeping a list of all current medication).

3. Educational (e.g. discussion with healthcare professional, written information or pamphlets, access to health education information on the internet, pictorial or audiovisual material).

4. Behavioural or psychological interventions (e.g. cognitive behavioural therapy, counselling).

5. Communication or follow-up by health professional (e.g. by telephone, email, face-to-face, text-messaging).

6. Multi-component or tailored care package (provided that adherence is a key component of care or is one of the objectives of providing multi-component intervention to the patient).

7. Interventions that aim to improve inhaler technique (e.g. educational interventions, training tools; e.g. measured using a checklist).

We will compare the above interventions separately with any intervention that is not intended to improve either adherence or inhaler technique (e.g. usual care, active control, placebo or sham intervention).

Types of outcome measures

Primary outcomes

1. Adherence to pharmacotherapy[a,b] (all measures, as reported by trialists. We will consider the following order of preference of measures, e.g. electronic monitors, canister weights, prescription refills, self-report).

2. Quality of life (measured using a validated scale such as the St. George's Respiratory Questionnaire (SGRQ) or COPD Assessment Test (CAT)).

3. Hospital service utilisation (e.g. hospital admissions going beyond emergency department). Depending on the data available, we will extract the number of participants who require hospitalisation, or the hospitalisation utilisation rate, or both (as defined by trialists).

Secondary outcomes

1. Exacerbations[c] (e.g. number of people with one or more exacerbation).

2. Self-efficacy (as a proxy for adherence, as reported by trialists).

3. All adverse events (AEs) (e.g. number of people with one or more AE).

4. Patient acceptability of intervention (as reported by trialists).

5. Inhaler technique (e.g. as reported by trialists, preferably using a validated scale or a validated videotaped scoring method (Rootmensen 2010)).

[a] Our understanding is that an observed improvement in adherence is likely to result in improved clinical outcomes. The The National Heart, Lung, and Blood Institute states that attempts to improve adherence should be judged by their clinical benefits (NHLBI 1982), and that only measuring adherence does not determine whether patient outcomes are improved or not. Equally, measuring patient outcomes does not determine whether the effects are observed as a result of adherence. We have therefore included adherence as our primary outcome, as well as quality-of-life and hospital service utilisation, since our aim is to assess whether improved adherence in turn improves clinical outcomes such as quality-of-life and hospital service utilisation. We have also considered exacerbations, self-efficacy, and adverse events as important outcomes.

[b] The adherence process consists of three phases: initiation (starting medication), implementation (taking medication daily), and persistence (duration of taking medication) (Vrijens 2016; De Geest 2018). It is expected that studies will measure different stages in the adherence taxonomy. Whilst we will include all adherence intervention studies, we anticipate the majority will measure the implementation stage.

[c] Moderate exacerbations are defined as worsening of respiratory status which requires treatment with antibiotics or systemic corticosteroids (or both); severe exacerbations are defined as requiring hospitalisation.

Reporting one or more of the outcomes listed here in the study is not an inclusion criterion for the review. We will extract data at all reported time points and will analyse data in the following groupings by time from baseline: < 3 months; $\geq$ 3 months but < 6 months; $\geq$ 6 months but < 12 months and $\geq$ 12 months.

Search methods for identification of studies

Electronic searches

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

1. Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies, all years to date;

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

The proposed CENTRAL 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 review authors.

All databases and trials registries will be searched from their inception to present, and there will be no restriction on language or type of publication. Handsearched 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:
1. known assessments, a service that matches records in the search results to records that have already been screened in Cochrane Crowd (Cochrane's citizen science platform where the Crowd help to identify and describe health evidence, crowd.cochrane.org) and labelled as 'RCT' or 'not an RCT';
2. the RCT classifier, a machine-learning model that distinguishes RCTs from non-RCTs; and
3. Cochrane Crowd, if appropriate.

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 three review authors (SJ, KP, RC) 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 three review authors (SJ, KP, RC) will independently screen them for inclusion,

recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion (SJ, KP, RC). 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 an Excel data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. Three review authors (SJ, KP, RC) will extract the following study characteristics from included studies.
1. 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, aim of the study (i.e. the primarily objective of the study is to improve adherence to pharmacotherapy).
2. Participants: number (N), mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention (we will use the classification list outlined in the Types of interventions section overall grouping of interventions. For multi-component interventions, we will extract all information on components of the intervention), comparison, concomitant medications and excluded medications, duration of intervention, method of delivery, and aim of the intervention (e.g. appropriate use of inhaler or to improve regularity of use).
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported. For adherence, we will record the type of non-adherence that is being targeted in studies.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Three review authors (SJ, KP, RC) 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 discussion (SJ, KP, RC). One review author (SJ) 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 (KP) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Three review authors (SJ, KP, RC) 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 any disagreements by discussion (SJ, KP, RC). We will assess the risk of bias according to the following domains:

1. Random sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcome assessment;
5. Incomplete outcome data;
6. Selective outcome reporting;
7. 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.

Measures of treatment effect

We will analyse dichotomous data (e.g. people having an event or not having an event) as odds ratios (ORs) 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, outcomes (e.g. measure of adherence), 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. treatment A versus placebo and treatment 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 the latest time point.

We will not include multi-component or tailored care package interventions in meta-analyses due to difficulty in determining the effects of a specific intervention on adherence to pharmacotherapy. 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.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of people admitted to hospital, rather than number of admissions per person). However, if rate ratios are reported in a study, we will analyse them on this basis. 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. For cross-over RCTs we will only include data in the meta-analysis from the first part of the study as we cannot exclude a carry-over effect.

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 I^2 statistic to measure heterogeneity among the studies in each analysis using the following criteria:
- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

If we identify substantial heterogeneity we will report it and explore the possible causes using prespecified subgroup analysis. If we find considerably high unexplained heterogeneity, we will not pool the data, but we will report narratively.

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.

Data synthesis

We will use a random-effects model and perform a sensitivity analysis with a fixed-effect model.

'Summary of findings' table

We will create separate 'Summary of findings' tables, one for each of the comparisons, using the following outcomes: adherence, hospitalisations, health-related quality of life, and adverse events. 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 GDT software (GRADEpro GDT). We will justify all decisions to downgrade the quality of evidence using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

1. COPD severity (moderate or severe);

2. Cognitive impairment (cognitive impairment versus no cognitive impairment);

3. Duration of intervention (less than 12 months versus 12 months or longer);

4. Who the intervention is delivered to (participant/career versus health professional); and

5. Treatment comparison (e.g. usual care, active control, placebo or sham intervention).

We will use the following outcomes in subgroup analyses:

1. adherence;

2. hospitalisations;

3. health-related quality of life; and

4. adverse events.

We will use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

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

1. Subjective measures for adherence to therapy (e.g. self-report);

2. Trials that do not show improvement of adherence;

3. Removing studies which recruited only patients, or a sub-set of patients, with asthma-COPD overlap syndrome (ACOS); and

4. Studies that are judged as having a high risk of selection bias.

We will also compare the results from a fixed-effect model with those using a random-effects model.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Database search strategies

Database: CENTRAL/Cochrane Airways Register of Trials

Platform: Cochrane Register of Studies (CRS)

#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 MeSH DESCRIPTOR Patient Compliance Explode All
#8 MeSH DESCRIPTOR Patient Acceptance of Health Care Explode All
#9 MeSH DESCRIPTOR Patient Dropouts
#10 adhere* or nonadhere* or non-adhere*
#11 complian* or noncomplian* or non-complian*
#12 refusal or refuse*:ti,ab,kw
#13 concord*:ti,ab,kw
#14 conform*:ti,ab,kw
#15 accept*:ti,ab,kw
#16 comply*:ti,ab,kw
#17 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 #6 AND #17

CONTRIBUTIONS OF AUTHORS

SJ, RC and KP drafted the background and methods of the protocol. For the full review, SJ, KP and RC will perform sifting of search results, data extraction, 'Risk of bias' assessment and write-up. Both RC and KP will provide clinical input in the discussion of the results.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor): edited the protocol; advised on methodology; approved the protocol prior to publication.
Chris Cates (Co-ordinating Editor): checked the planned methods.
Han Ni: edited the review; advised on content.
Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on content; edited the protocol.
Emma Jackson (Assistant Managing Editor): conducted peer review; edited the references.
Elizabeth Stovold (Information Specialist): designed the search strategy.

DECLARATIONS OF INTEREST

SJ: is employed full-time as a systematic reviewer by a National Institute for Health Research (NIHR) Programme Grant to complete work on this review.

RC: retired in 2018 as a general practitioner and has given lectures to primary care staff funded by GSK, BI, AZ, and Chiesi in the last 36 months.

KP: is a senior clinical lecturer in paediatric medicine at Great Ormond Street Hospital, has acted as a consultant on an advisory board for Respiri for development of a symptom monitoring device for asthma, and has given a lecture paid by GSK. KP has also attended a Novartis severe asthma consultation to develop educational material.

AC: is a COPD patient and is part of the patient advisory group for the current NIHR Programme Grant. He has given advice on the development of the protocol, and will provide further advice in the reviewing process.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

Cochrane Programme Grant 16/114/21: NHS priorities in the management of chronic respiratory disease
This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to the Airways Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health.