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Health psychology interventions to improve adherence to maintenance therapies in asthma (Protocol)

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[Intervention Protocol]

Health psychology interventions to improve adherence to maintenance therapies in asthma

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ABSTRACT

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

Main objectives

- To determine the effectiveness of theory-based and non-theory based health psychology interventions for improving adherence to maintenance therapy in adults with asthma

Secondary objectives

- To compare the effectiveness of adherence interventions which are based on theory, as defined by the Theory Coding Scheme (TCS), to interventions which are not theory-based
- To identify and describe, using the TSC and Theoretical Domain Framework (TDF), the different health psychology theories which have been used in interventions to improve adherence to maintenance therapy in adults with asthma
- To evaluate the extent to which health psychology theory has been applied to the development of adherence interventions in asthma

BACKGROUND

Description of the condition

Asthma is a long-term inflammatory condition of the airways which results in variable symptoms and affects more than 300 million adults and children worldwide, with marked ethnic and racial variations in prevalence (Global Asthma Report 2014; Gorman 2009; Netuveli 2005). In the UK, it is estimated that nearly 30% of people will report symptoms suggestive of asthma at some point during their lives, which amounts to over 18 million individuals (Mukherjee 2016). The prevalence of asthma is likely still increasing across both high and lower income countries. The reason for the increasing prevalence is not fully understood, but is thought to be largely due to environmental factors (Global Asthma Report 2014).There has been a recent decline in healthcare utilisation in some settings, which may be a result of improved care (Anandan 2010; Asher 2006; Braman 2006). Asthma can cause shortness of breath, chest tightness and cough, and typically presents with wheezing. Many people with asthma experience intermittent worsening of their asthma symptoms, known as 'exacerbations', 'flare-ups' or 'attacks' (GINA 2016). Approximately 20% of people with asthma have at some point been admitted to hospital or have attended an emergency department for asthma treatment (Rodrigo 2004). Attacks can be triggered by common irritants and allergens such as pollution, tobacco smoke, pollen and house dust mites, as well as upper respiratory tract infections (CDC 2016). Most asthma-related deaths occur in middle-income and low-income countries. Poorly controlled asthma places a huge burden on individuals, their families and society (WHO 2013), a burden that has been increasing over the last 40 years (Braman 2006)

The mainstay of asthma treatment for most people with asthma is inhaled corticosteroids (ICS) (BTS/SIGN 2016; NICE 2017). ICS are also known as 'preventer' or 'controller' medications, and are used once or twice daily (depending on the preparation), even when the patient feels well, to treat inflammation and maintain control over asthma symptoms. In addition, people with asthma are prescribed short-acting beta-agonists (SABAs), often known as 'reliever' medications, to give short-term relief from acute worsening of symptoms (BTS/SIGN 2016; NICE 2017). Of note, inappropriate SABA use may be associated with increased morbidity and healthcare costs (FitzGerald 2017). Both types of drug are usually delivered directly to the patient's airways via an inhaler. ICS work by suppressing the multiple inflammatory cascades that are activated in the airways of a person with asthma. Inflammation leads to increased inflammatory swelling of the lining of the airways, mucus production and airway constriction, which cause the variable symptoms of asthma. Reduction in underlying inflammation through sustained use of ICS can result in symptom improvement and reduced asthma-related morbidity and mortality (Barnes 2003; Bårnes 2015). Commonly used ICS include budesonide, beclomethasone, fluticasone (propionate and furoate), mometasone and ciclesonide. These can be given alone or in combination with other controller medications such as inhaled long-acting beta$_2$-agonists (LABAs) or inhaled long-acting muscarinic antagonists (LAMAs); oral drugs such as leukotriene receptor antagonists (LTRAs) or theophylline; or injectable drugs such as omalizumab or mepolizumab (BNF; BTS/SIGN 2016; NICE 2017).

Despite the effectiveness of treatment with ICS for maintaining asthma control, many patients do not take ICS as prescribed, and are considered to have poor "adherence" to their treatment (Bårnes 2015), with average ICS adherence rates ranging from 30% to 70% (Gamble 2009; Morton 2014). In asthma, an adherence rate of at least 80% to ICS is associated with a reduced risk of asthma exacerbations (Williams 2011). Williams and colleagues also reported that the hazard ratio (HR) for an asthma exacerbation is reduced by 39% in those with more than 75% adherence compared to those with less than 25% adherence (HR 0.61; 95% confidence interval (CI) 0.41 to 0.90). The same study estimated that 24% of exacerbations were attributable to non-adherence to ICS (Williams 2011).

In those prescribed LABAs, adherence is closely linked to ICS adherence as current guidance suggests that they should not be prescribed separately in asthma, due to safety concerns (BTS/SIGN 2016). Adherence rates to oral medication such as LTRAs, while better than for ICS, are still sub-optimal (Carter 2003; Sherman 2001). The literature addressing adherence to injectable therapy is sparse, but most patients are reported to miss doses, especially when on a more frequent dosing regimen (Janson 2015). Given the prominence of ICS as the mainstay of maintenance treatment in asthma, much of the current literature focuses on improving adherence to ICS (Normansell 2017).

Adherence is defined by the World Health Organization (WHO) as "the degree to which use of medication by the patient corresponds with the prescribed regimen", and the "diversity and complexity of adherence behaviour" is recognised (WHO Report 2003). Non-adherence can be understood in terms of intent: "intentional non-adherence" describes an active decision by the patient not to take the treatment as prescribed, and "unintentional non-adherence" describes a more passive process in which the patient does not adhere to treatment due to circumstances not within their control, for example, a failure to understand the instructions or remember to take the medication (Gadkari 2012). Reasons for non-adherence to asthma therapies vary between and within individuals, over time, and according to how adherence is defined or measured (Barber 2004). Commonly cited factors associated with non-adherence include: treatment complexity; cost; administration route; patient beliefs about asthma or the treatment; lower socioeconomic status; inclusion in a minority ethnic group and fewer years of education (Bender 2005; Bårnes 2015; Clark 1999; Cochrane 1999; Horne 1999; Horne 2002). The difference in onset of action between the preventer and reliever medication may also act as a barrier to adherence; ICS can take two to three weeks to have an effect (Phillips 2004), rather than providing the im-

mediate symptom relief experienced with SABA therapies, which may diminish patient-perceived need for treatment with ICS, and encourage over-reliance with SABA medication (O'Byrne 2017). The use of combined ICS and LABA inhalers as both a maintenance and reliever treatment has proven useful, but this does not address other reasons for poor adherence. The National Review of Asthma deaths in 2014 confirmed non-adherence to preventer ICS is associated with increased risk of poor asthma control and should be continually monitored to prevent deaths due to asthma (NRAD 2014).

Description of the intervention

As adherence varies within and between individuals it may be best understood as a behaviour that is driven by a dynamic combination of both patient perception and practical factors, rather than as a stable characteristic that responds to a particular type of intervention over another (Barber 2004; Nunes 2009). By examining past adherence interventions using an approach that considers non-adherence as a behaviour, health psychology theories and models of behaviour change can be applied to understand which interventions work and why (Craig 2008; Craig 2013; Glanz 2010; Michie 2008; Stavri 2012). This is in line with current Medical Research Council (MRC) guidance for the development of complex interventions, which recommends the use of theory and models of behaviour change to evaluate the mechanisms behind interventions (Craig 2008; Craig 2013).

In the context of improving medication adherence, health psychology interventions target factors that are known to be associated with medication non-adherence and are deemed to be potentially modifiable to change. Research-evidenced health psychology theories underpin the development of interventions with planned assumptions about the outcomes under investigation. Health psychology theory can be used to understand interventions in different ways: to identify the factors that drive a particular health behaviour which could be targets for an intervention (such as treatment beliefs); to select behaviour change techniques to address the factors influencing the behaviour (such as the use of reminders and feedback); or to identify people who are most likely to benefit from the intervention (Webb 2010). Understanding the behavioural mechanisms which drive adherence helps to inform the future design of effective interventions; and finding out why an intervention does or does not work provides insights into the characteristics of effective versus less effective interventions (Craig 2008; Craig 2013).

This review aims to determine the effectiveness of theory-based adherence interventions, and to identify the characteristics of effective adherence interventions in asthma in terms of the health psychology theories and behaviour change techniques used in the intervention. The review will use published coding schemes and frameworks to identify the theories and techniques used in the intervention content, namely the Theory Coding Scheme (TCS) (Michie 2010), and the Theoretical Domain Framework (TDF) (Michie 2005). The TCS is a research tool which reliably describes the theoretical basis of interventions and the extent to which theory has been applied, thus allowing assessment of the different ways that interventions have used theory (Michie 2010). The TDF is a synthesis of 33 theories of behaviour and behaviour changes, grouped into 14 domains, and can be used to: identify influences on behaviours; design, implement, and evaluate interventions; and map behaviour change techniques used in interventions (Atkins 2017; Cane 2012).

How the intervention might work

There have been multiple adherence intervention studies conducted in the last decade. Most interventions appear to have limited effectiveness; and even among those that have demonstrated an effect, the effect size was small (Nieuwlaat 2014). A possible reason for the limited effectiveness is that the focus of previous interventions has been on sociodemographic barriers to adherence rather than on the behavioural aspects. Despite the large number of studies, no single sociodemographic factor, or group of factors, has consistently been shown to be predictive of adherence (DiMatteo 2004; Jackson 2010; Karamanidou 2008). There is much overlap between the sociodemographic categories. Furthermore, none of sociodemographic characteristics explain adherence as a health behaviour that is influenced by patient perceptions and beliefs. Current National Institute for Health and Care Excellence (NICE) guidelines recommend approaching non-adherence by focusing on perceptual and practical factors, where perceptual barriers are differentiated from practical barriers which influence adherence, as interventions to address these two types of barrier are likely to involve different techniques (Nunes 2009). There is a need for intervention content to focus on the perceptual barriers - understanding how patients interact with their treatment - rather than just on the individual patient themselves, without explicit acknowledgement of this complex interaction.

In line with this, several psychological theories - for example, the health belief model and the self-regulation theory - have been proposed and applied to explain adherence behaviour and to develop adherence interventions (Holmes 2014). These theories propose that patient adherence to treatment is driven by an underlying thought process, which is shaped by various perceptions, beliefs, and past experiences. It recognises adherence as a behaviour, and also recognises that behaviours are complex processes which require complex interventions. Complex interventions usually consist of several behaviour change techniques which influence the target behaviour. There is an increasing amount of literature supporting the use of theory in intervention development, showing that interventions which are informed by theory in their development are more effective than interventions which lack a theoretical basis (Conn 2017; Heath 2015; Holmes 2014; Marteau 2006; McCullough 2016; Michie 2007; Munro 2007; Noar 2007;

Painter 2008; Webb 2010). However, previous reviews have not explored the application of theory in adherence interventions in asthma, nor the extent to which theory has been applied, and what particular behaviour change techniques have been used. A recent systematic review evaluated adherence interventions in chronic respiratory conditions including asthma and the use of behaviour change theory (McCullough 2016), and it reported that use of theory was more common amongst effective interventions. However, it only reported on whether theory was used or not in the intervention, rather than the extent to which theory was used to guide the intervention development or how theory was applied (i.e. through what behaviour change techniques) and how this influenced intervention effectiveness.

Why it is important to do this review

Most of the existing literature focuses on adherence to ICS. Suboptimal adherence leads to poorer clinical outcomes and increased health service utilisation. Although difficult to quantify, studies report that up to, and possibly in excess of, 50% of participants are non-adherent to their prescribed ICS (Bårnes 2015; Bender 2004; Mahkinova 2015; Murphy 2012; Rand 1994; Williams 2003). Failure to take appropriate medication was found to be a potentially avoidable factor contributing to approximately one-third of asthma deaths in the UK over the course of a year (NRAD 2014). Mahkinova and colleagues demonstrated that patients who are adherent to their preventer medication make fewer claims for oral corticosteroid prescriptions, reflecting a lower rate of exacerbation (Mahkinova 2015). An association has also been identified between hospitalisations and emergency department visits and non-adherence to ICS (Williams 2003). Murphy and colleagues found that non-adherence was an independent predictor of the need for ventilation therapy in acute severe asthma, as well as lower forced expiratory volume in one second (FEV_1) and higher sputum eosinophils, markers of poorly controlled asthma and ongoing inflammation (Murphy 2012). Another study identified an association between poorer asthma control and lower adherence rates (Lasmar 2009). A 2015 review of ICS adherence in asthma found that 24% of exacerbations and 60% of asthma-related hospitalisations could be attributed to poor adherence (Bårnes 2015). In addition, it is well recognised that uncontrolled asthma places a greater financial burden on an economy than that of controlled asthma (Barnes 1996; Global Asthma Report 2014).

This systematic review, which focuses on adherence to ICS only, builds on a previously published Cochrane Review which included all types of adherence interventions in asthma (Normansell 2017). The review reported that adherence education, electronic trackers or reminders and simplified regimens resulted in better adherence than in control groups. Although the review provided important information about which intervention type may potentially be more effective than others, it did not examine whether these differences in effectiveness were due to the incorporation of health psychology theory in those particular modes of intervention (e.g. adherence education may have been health psychology theory-based, or may have only focused on education or practical barriers). This review will give insight into which theories have been used, how often they have been incorporated in the development of adherence interventions, and their potential effectiveness compared to usual care. We will explore through subgroup analysis whether theory-based interventions are more or less effective than interventions that are not theory-based. Further, this review is being performed as a part of a wider programme of adherence research in asthma, linked with the Asthma UK Centre for Applied Research (AUKCAR). The review will provide important background to the development and design of the adherence interventions used in the future.

OBJECTIVES

Main objectives

- To determine the effectiveness of theory-based and non-theory based health psychology interventions for improving adherence to maintenance therapy in adults with asthma

Secondary objectives

- To compare the effectiveness of adherence interventions which are based on theory, as defined by the Theory Coding Scheme (TCS), to interventions which are not theory-based
- To identify and describe, using the TSC and Theoretical Domain Framework (TDF), the different health psychology theories which have been used in interventions to improve adherence to maintenance therapy in adults with asthma
- To evaluate the extent to which health psychology theory has been applied to the development of adherence interventions in asthma

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include cluster-randomised trials, providing the data have been or can be adjusted for clustering. If we identify relevant cross-over trials we will include only the first period due to the likely carry-over effects of the intervention. We will include studies reported

in full text, those published as an abstract only, and unpublished data.

Types of participants

We will include studies of adults (aged 18 years or more) with a diagnosis of asthma according to international or national guidelines, or as diagnosed by a healthcare professional, and currently prescribed one or more maintenance asthma therapies. We will exclude participants with other respiratory comorbidities such as chronic obstructive pulmonary disease (COPD) or bronchiectasis. We will include studies where only a subset of participants meet the inclusion criteria, providing disaggregated data can be obtained.

Types of interventions

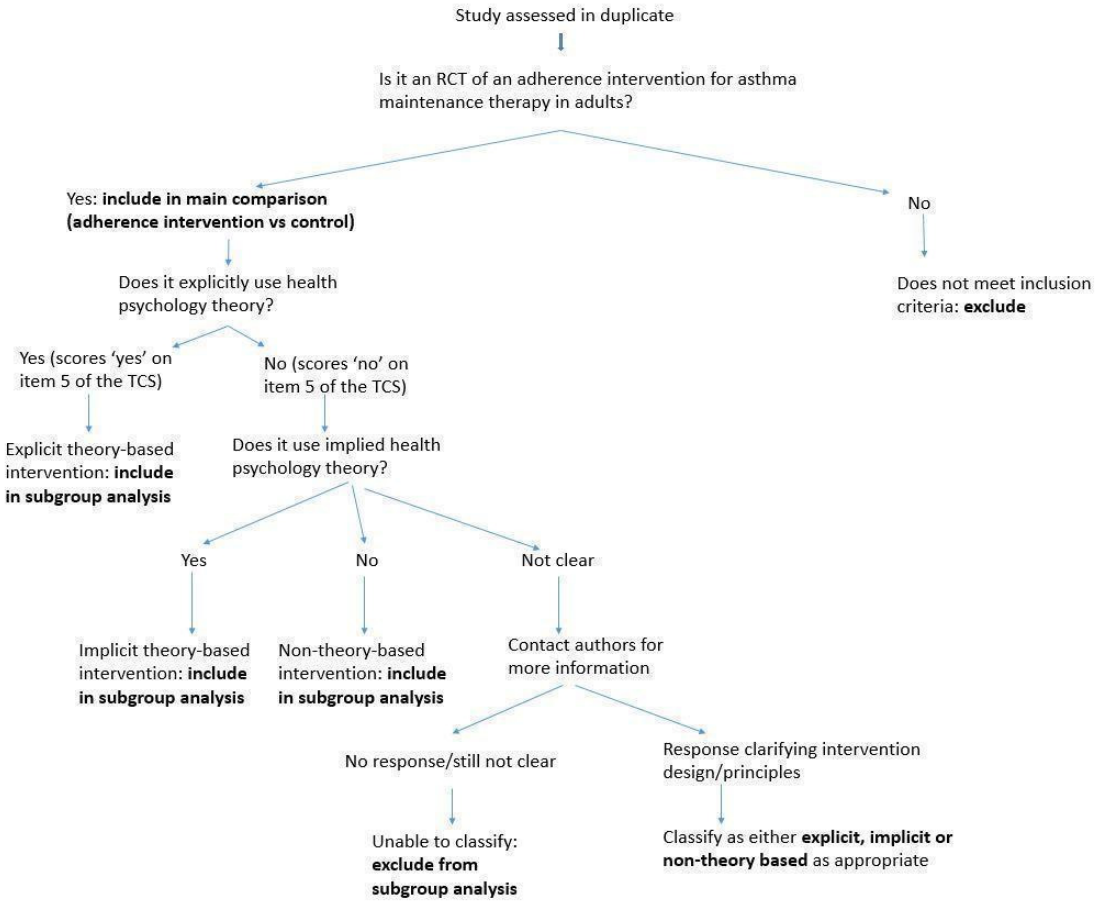
We will include studies which examine any intervention with either a primary or secondary aim of improving adherence to asthma maintenance therapy, compared with usual care or a different intervention not specifically aimed at improving adherence.

We will include any intervention which aims to improve adherence to asthma maintenance therapy. As one of our secondary aims is to compare interventions which are based on theory versus those that are not, we will therefore include both interventions with theory-based components (either identified explicitly or implied), and interventions without such components.

We will later classify the interventions used in the studies as either: explicit theory (i.e. the authors have defined a priori that their intervention will be based on a recognised named theory), implied theory (no particular theory expressed in the methods by the authors but a clear use of theory can be deduced from the study description), combined (i.e. theory plus non-theory components), or no theory components.

Where interventions have not been described in sufficient detail to determine whether they were based on explicit or implied theory, or a combination, then we will contact the authors of the studies to obtain further information. In the case of non-response after initial contact, study authors will be followed up twice (once every two weeks). After that, on the grounds that it will not be possible to accurately classify the study, we will exclude the study from the subgroup analysis investigating the impact of theory. See Figure 1 for a flow diagram describing the decision process.

Figure 1. Flow diagram for study selection and inclusion in main subgroup analysis



Interventions may be delivered to the participant by any healthcare professional or trained peer. We will exclude interventions delivered to a healthcare professional. Interventions may be delivered face-to-face or virtually, and can be delivered either to individuals or groups.

Digital adherence interventions, such as short message service (SMS) interventions or electronic adherence monitors which do not use health psychology theory will be included in a linked review (Chan 2018, review in development).

Types of outcome measures

The main objective will be evaluated by our primary and secondary outcomes. The secondary objectives will be evaluated by subgroup analysis and by using descriptive statistics and narratives summaries (e.g. percentages, counts and summary tables).

Primary outcomes

1. Adherence to asthma maintenance therapy (as reported by trialists)
2. Asthma control (measured using a validated tool such as the Asthma Control Test (Nathan 2004) or Asthma Control Questionnaire (Juniper 1993), or other validated instrument)
3. Exacerbations requiring at least oral corticosteroid treatment

We have chosen primary outcomes to reflect those important to patients, practitioners and policy makers, and in keeping with the published literature (Reddel 2009).

Secondary outcomes

1. Unscheduled visits to a healthcare provider (primary care visits, emergency department visits and hospitalisations will be analysed separately where possible)

2. Days absent from work

3. Quality of life (measured using a validated tool such as the Asthma Quality of Life Questionnaire (Juniper 1993), or as reported by trialists)

4. Adverse events

5. Rescue medication use (e.g. change in puffs per day of short-acting beta-agonist (SABA), or change in SABA prescription frequency).

6. Narrative summary of reported cost-effectiveness

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 subgroup outcomes by the following time points for meta-analysis: < 3 months, ≥ 3 to < 6 months, ≥ 6 to < 12 months and ≥ 12 months. If studies report post-intervention follow-up, we will extract this information and present it narratively. If multiple measures of adherence are used, we will include the most objective measure in the review.

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org);

2. weekly searches of MEDLINE Ovid SP 1946 to date;

3. weekly searches of Embase Ovid SP 1974 to date;

4. monthly searches of PsycINFO Ovid SP 1967 to date;

5. monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1937 to date;

6. monthly searches of AMED EBSCO (Allied and Complementary Medicine);

7. handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings, are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We will search the following trials registries:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)

2. WHO International Clinical Trials Registry Platform (www.who.int/trialsearch)

We will search the Cochrane Airways Trials Register and additional sources from inception to present, with 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 for errata or retractions from included studies published in full text on PubMed and report the date this was done within the review.

Data collection and analysis

Selection of studies

Using the Rayyan application (an online reference screening tool; Elmagarmid 2014), four review authors (RN, AC, KK, CK) will screen the titles and abstracts of the 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 review authors (RN, AC) 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 (RH). 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 the meeting inclusion criteria. Four review authors (RN, AC, KK, CK) 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.

2. Participants: number, mean age, age range, gender, socioeconomic data (e.g. income, education levels, deprivation index etc., where available) severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.

3. Interventions: intervention target (primary and secondary), implementer, type of health psychology theory used*, explicitly stated theory versus no explicit theory stated, complex (i.e. comprising several interacting components (Campbell 2000)) or non-complex, comparison, concomitant medications and excluded medications. We will use the Theory Coding Scheme (TCS) and Theoretical Domain Framework (TDF)* to record the way in which each study has applied theory to their

intervention. We will use the TIDIER checklist to report intervention components (Hoffmann 2014).

4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.

5. Notes: funding for studies and notable conflicts of interest of trial authors.

Four review authors (RN, AC, KK, CK) will undertake duplicate data extraction 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 (RH). Two review authors (RN, AC) 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.

*The TCS can be used to code how theory has been used in the design of the adherence intervention. These items can identify whether theory was used to select recipients of the intervention, and to design and tailor the intervention. The items can be summed to provide a 'use of theory' score - previous literature has based this score on items 1 to 11 as these relate to the intervention design - which can help quantify the extent that theory was used in an intervention. Item 5 of the coding scheme highlights whether theory was used to develop the intervention techniques. Previous literature has coded interventions as having a 'theoretical basis' if this item 5 was checked. Two reviewers can apply the TCS independently; discrepancies can be resolved by consensus discussion with a third independent author (Webb 2010). We will use the 14 domains of the TDF to further explore and describe intervention components.

Assessment of risk of bias in included studies

Two review authors (AC, KK) 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 (RN). 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.

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 (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; we will only combine studies in which the participants, interventions, comparator and outcomes are similar enough for a pooled effect estimate 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. intervention A versus usual care and intervention B versus usual care) 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 reported time point.

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 participants admitted to hospital, rather than number of admissions per participant). However, if rate ratios are reported in a study, we will analyse them on this basis. We plan to include relevant cluster-randomised trials, but will only include data from such trials in the meta-analyses if the available data have been adjusted (or can be adjusted), to account for the clustering. Based on recommendations from the

Cochrane Handbook, we will adjust cluster-randomised data by inflating standard errors using a design effect (DE) calculated with an intracluster correlation coefficient (ICC).

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. If we identify substantial heterogeneity we will report it and explore the possible causes by prespecified subgroup analysis. Furthermore, to aid interpretation of the pooled estimates, we will construct a summary table outlining the key features of the included studies to allow easy comparison between trials contributing data to the review. We will explore possible clinical heterogeneity narratively in the discussion.

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 a 'Summary of findings' table using the following outcomes at longest follow up point: adherence to asthma maintenance therapy; asthma control; exacerbations requiring at least oral corticosteroid treatment; unscheduled visits to a healthcare provider; days absent from work; 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 the 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 use footnotes to document our justification of all decisions to downgrade our assessments of the quality of evidence, 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. Inteventions which specify the use of theory explicitly to design their intervention (score of "yes" at item 5 of TCS) versus implied theory (score of "no" at item 5 of TSC, but theory use implied) versus those interventions with no evidence of use of theory
2. Interventions using only theory versus those using both theory and non-theory components
3. Interventions using theory throughout entire intervention versus those using theory for one component of the intervention
4. Type of adherence measure used (e.g. subjective versus objective measures)
5. Type of asthma maintenance therapy targeted by adherence intervention (inhaled/nebulised versus oral versus injectable)
6. Baseline treatment of participants (inhaled corticosteroids (ICS) alone versus ICS/long-acting $beta_2$-agonists in a combination inhaler)
7. Method of randomisation (cluster versus patient level)

We will use the following outcomes in subgroup analyses.

1. Adherence to asthma maintenance therapy
2. Asthma control
3. Exacerbations requiring at least oral corticosteroid treatment

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, for the primary outcomes.

1. Exclusion of unpublished data
2. Exclusion of trials with high risk of selection bias
3. Exclusion of trials with mixed participant samples (e.g. where asthma patient data were extracted from a trial with asthma and COPD patients)
4. Run the main analysis with more and less conservative estimates of the ICC (to assess the impact of cluster-randomisation)

We will 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. Sources and search methods for the Cochrane Airways Trials Register

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

MEDLINE search strategy used to identify studies from the Cochrane Airways Trials Register

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised 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 studies in other electronic databases.

Appendix 2. Search strategy to identify relevant studies from the Cochrane Airways Trials Register (via Cochrane Register of Studies (CRS))

Search line	Search terms	Notes
#1	AST:MISC1	MISC1 is field in the record where the reference has been coded for condition, in this case, asthma
#2	MeSH DESCRIPTOR Asthma Explode All	Index term has been exploded to include all narrow terms to asthma
#3	asthma*:ti,ab	Text word search in title & abstract fields
#4	#1 or #2 or #3	Combines all population terms

(*Continued*)

#5	MESH DESCRIPTOR Treatment Adherence and Compliance EXPLODE ALL	Index term has been exploded to include all narrower terms
#6	adhere* or nonadhere* or non-adhere*:ti,ab,kw	text word search in title, abstract & keyword fields
#7	complian* or noncomplian* or non-complian*:ti,ab,kw	text word search in title, abstract & keyword fields
#8	refusal or refuse*:ti,ab,kw	text word search in title, abstract & keyword fields
#9	concord*:ti,ab,kw	text word search in title, abstract & keyword fields
#10	conform*:ti,ab,kw	text word search in title, abstract & keyword fields
#11	accept*:ti,ab,kw	text word search in title, abstract & keyword fields
#12	comply*:ti,ab,kw	text word search in title, abstract & keyword fields
#13	{OR #5-#12}	Combines all adherence terms
#14	#4 AND #13	Combines the population and adherence terms

CONTRIBUTIONS OF AUTHORS

Rebecca Normansell: draft protocol, develop search strategy, obtain full-text reports, carry out and interpret analyses, draft final review.

Amy Chan: draft protocol, screen search, obtain full-text reports, carry out and interpret analyses, draft final review

Caroline Katzer: draft protocol, screen search, obtain full-text reports, interpret analyses, draft final review.

Kayleigh M Kew: draft protocol, interpret analyses, draft final review.

Marissa Mes: draft protocol, obtain full-text reports, interpret analysis, draft final review.

Chris J Newby: draft protocol, carry out and interpret analyses, draft final review.

Anoop Chauhan: draft protocol, draft final review.

Stephanie JC Taylor: draft protocol, develop search strategy, interpret analyses, draft final review.

Hilary Pinnock: draft protocol, draft final review.

Aziz Sheikh: draft protocol, draft final review.

Vari Wileman: draft protocol, interpret analyses, draft final review.

DECLARATIONS OF INTEREST

Rebecca Normansell: I am Joint Co-ordinating Editor of Cochrane Airways, employed by an NIHR grant, and a qualified general practitioner.

Amy Chan: I have received consultancy fees from Janssen-Cilag, speaker fees from Novartis, and travel grants from Maurice Phyllis Paykel Trust and Max Health for activities outside this submitted work. I am also a freelance consultant for Spoonful of Sugar Limited, a University College London spin-out behaviour change consultancy company.

Caroline Katzer: I am funded by the NIHR Collaboration for Leadership in Applied Health Research and Care North Thames. I am also a freelance consultant for Spoonful of Sugar Limited, a University College London spin-out behaviour change consultancy company.

Kayleigh M Kew: I was a paid researcher on a National Institute for Health Research (NIHR) Cochrane Programme Grant until December 2016. The grant was awarded to the Cochrane Airways review group at St George's, University of London, where I continued as an honorary research assistant until April 2017. Part of the work underpinning this review was undertaken during the course of the grant.

Marissa A Mes: I am completing a PhD that is fully funded by the National Institute of Health Research Collaboration for Leadership in Applied Health Research and Care (NIHR CLAHRC) North Thames. My PhD is based at the University College London School of Pharmacy, and is affiliated with the Asthma UK Centre for Applied Research (AUKCAR). I have completed freelance work for Spoonful of Sugar Limited, a University College London spin-out behaviour change consultancy company

Chris J Newby: I am a co-applicant on a NIHR programme grant.

Anoop Chauhan: I have a clinical and academic interest in severe asthma, and have been Chief Investigator on many asthma trials evaluating new technologies and treatment effects. Adherence measurements are an important part of this work. I have also received research grants, consultancy fees and honoraria for educational meetings from Novartis, Boehringer Ingelheim, Pfizer, TEVA, Astra Zeneca and Airsonett.

Stephanie JC Taylor: I have no known conflicts of interest.

Hilary Pinnock: I have an academic interest in self-management of asthma (including adherence); I chair the Evidence Review Group on Self-management (including adherence) for the BTS/SIGN British Asthma Guideline. My university receives funding from Asthma UK for the Asthma UK Centre for Applied Research, and had a recent grant from the NIHR Programme Grants for Applied Research investigating implementation of asthma self-management. I regularly speak on the subject of asthma self-management (including adherence) at educational meetings, sometimes receiving an honorarium. Boehringer Ingelheim (who do not have a specific interest in self-management or adherence) paid for my accommodation in London for the ERS 2016.

Aziz Sheikh: I am Director of the Asthma UK Centre for Applied Research.

Vari Wileman: I am employed by the North London NIHR CLAHRC.

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