Electronic monitoring and reminding devices for improving adherence to inhaled therapy in patients with asthma (Protocol)

Craven VE, Morton RW, Spencer S, Devadason SG, Everard ML

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# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Header</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Background</td>
<td>1</td>
</tr>
<tr>
<td>Objectives</td>
<td>3</td>
</tr>
<tr>
<td>Methods</td>
<td>3</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>7</td>
</tr>
<tr>
<td>References</td>
<td>7</td>
</tr>
<tr>
<td>Appendices</td>
<td>9</td>
</tr>
<tr>
<td>Contributions of Authors</td>
<td>11</td>
</tr>
<tr>
<td>Declarations of Interest</td>
<td>11</td>
</tr>
<tr>
<td>Sources of Support</td>
<td>11</td>
</tr>
</tbody>
</table>

Electronic monitoring and reminding devices for improving adherence to inhaled therapy in patients with asthma (Protocol)  

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**Electrical monitoring and reminding devices for improving adherence to inhaled therapy in patients with asthma**

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**ABSTRACT**

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy of electronic monitors, reminder devices or both, on adherence with regular inhaled medication regimes in people with asthma.

**BACKGROUND**

Description of the condition

Asthma is one of the most common chronic diseases in children and adults and can be a significant cause of disability, poor quality of life and health resources utilisation among those affected. Asthma is estimated to affect over 300 million people worldwide (WHO 2007). The International Study of Asthma and Allergy in Childhood found that the United Kingdom, Australia and New Zealand had among the highest worldwide prevalence, with 15% of children affected (Pearce 2007). Global prevalence rates in adults obtained from the cross-sectional World Health Survey (WHS) indicated that 18.2% of adults in the UK had a clinical diagnosis of asthma with a 4.3% prevalence globally (To 2012). The number of disability-adjusted life years (DALYs) lost to asthma worldwide has been estimated to be about 15 million per year and worldwide accounts for around 1% of all DALYs lost (GINA 2014). Developed economies spend 1 to 2% of their health-care budget on asthma, each patient costing between $300 and $1300 per year. The total economic burden exceeds this when indirect costs are taken into account (Braman 2006). In Europe, the loss of productivity and work impairment due to asthma is estimated as EURO9.8 billion per year (ERS 2015).

Poor adherence to maintenance inhaled corticosteroid therapy is a challenge for those treating patients with asthma, as parental reporting in children and self-reporting in adults have been shown to correlate poorly with actual use (Tashkin 1991; Bender 2000; Burgess 2011; Patel 2013). Prescription checks are also imprecise, merely representing the maximum that could have been taken. In one study of 115 adults with difficult to control asthma, 65% had sub-optimal adherence to inhaled treatment (defined as less than 80% usage) and this correlated with reduced forced expira-
tory volume in one second (FEV<sub>1</sub>) and higher sputum eosinophil counts (Murphy 2012). Poor adherence to asthma therapy in both children and adults is associated with a greater number of severe exacerbations (Ordonez 1998; Hermosa 2010; Jentzsch 2012), increased health care utilisation (Gamble 2011; McGrady 2013), reduced quality of life (Sullivan 2013), and increased mortality (Robertson 1992; Bergstrom 2008).

In a study of 182 adult patients with difficult-to-control asthma, 63 patients (35%) used over 50% of inhaled medications prescribed over a six-month period, with 45 of those patients subsequently admitting poor adherence when presented with prescription usage (Gamble 2009). Not identifying poor adherence can lead to potentially effective medications being considered ineffective or doses deemed inadequate which could lead to an unnecessary escalation of treatment in ‘difficult asthma’, a condition characterised by ongoing symptoms and/or exacerbations despite moderate to high dose inhaled steroids and add on therapy together with appropriate education and advice. It does not imply ‘severe disease’ though this may be one cause.

A qualitative study assessing the barriers to adherence found that a lack of motivation, social barriers and simply not remembering were common themes. Although children reported that parental prompts to take medication were ‘annoying’ they thought that they did improve their compliance with treatment (Penza-Clyve 2004). In a cohort of 250 children, parental reporting of their medication pattern and the feedback of pharmacy records of treatment usage produced a modest short term improvement in adherence but were no better than asthma education alone (Otsuki 2009).

Providing feedback of peak flow rates in children has been shown to increase the perception of lung function and the adherence to inhaled corticosteroids in a paediatric cohort (Feldman 2012); in adults, monitoring inhaler usage in chronic obstructive pulmonary disease in adults was shown to increase usage four months later (Nides 1993).

Adherence is a complex behavioural process and there is no single mechanism for changing adherence behaviour. Evidence suggests that education alone may not be sufficient to bring about a sustained change in adherence behaviour in asthma (Gibson 2002). Technology now exists to monitor inhaler usage in a non-intrusive and reliable manner rather than to rely on patient feedback as a measure of compliance. They have opened up the possibility of addressing the ‘simply not remembering’ aspect of poor adherence whilst also acting as a potential source of motivation knowing that usage is being observed and may be fed back. The cost-benefits of using electronic monitors or reminding facilities to improve adherence to asthma medication is currently unclear, but they have the potential to improve asthma control through more efficient disease management.

**Description of the intervention**

Short message service (SMS) messaging (i.e., text messaging) reminders have been shown to be effective at increasing asthma medication usage in a cohort of adults who received a daily reminder on their phone (Strandbygaard 2010). The difference in adherence rate between this group and the controls was 17.8%, measured by dose counting on the inhaler, although no difference in lung function was seen after 12 weeks (Strandbygaard 2010). A Cochrane systematic review addressed the use of feedback from mobile phone applications (“apps”) based upon self-reporting of symptoms and lung function results from two studies (Marcano Belisario 2013). This represents a downstream intervention from our intended study and they found insufficient evidence to advise on such self-management programmes.

Electronic monitors and reminding facilities are two ways in which adherence can be targeted. Electronic monitoring devices, initially termed “nebuliser chronologs”, were first described in asthma clinical practice in the 1980s (Spector 1986). They were prone to technical problems (Gong 1988; Nides 1993), but since then have been more successfully used to monitor treatment usage (Gibson 1995; Foster 2012; Patel 2013). They make it possible to record medication usage and patterns of treatment. This can be of particular interest around the time of contact with health professionals when there may be a transient increase in adherence or episodes of ‘dose dumping’ in which there may be multiple actuations of inhalers to give the impression of longer term good adherence (Nides 1993).

Electronic reminding facilities, as with the monitors, can also be integrated into inhalers and have been used with some success in the treatment of other disorders such as glaucoma (Laster 1996), schizophrenia (Ruskin 2003), and in optimising tooth brushing techniques (McCracken 2004). They usually combine an audio alarm with a visual cue. The alarm sounds at designated times, serving to remind the user to take their medication, and continues at intervals until the dose is taken. The visual cue shows the patient whether they have delivered their medication during the designated period. Poor technique or willful avoidance of a medication is not monitored.

**How the intervention might work**

Electronic monitoring and clinician feedback enables the issue of adherence to be discussed in an open and objective manner. For some patients, this awareness that treatment is being monitored will lead to increased adherence, the so-called Hawthorne effect. Barriers to adherence are both intentional for example the patient disagrees with diagnosis, has no concerns about their symptoms or has concerns about the effects of inhaled steroids; or non-intentional in that they are practical adherence barriers such as forgetting. Monitoring feedback and regular reinforced education will address intentional barriers, and reminders will address non-intentional (Horne 2002). In a cohort of 15 children aged 7 to 12 years old, a home intervention programme of asthma education.
and electronic monitoring and feedback of inhaler usage showed that initially 28.6% used their asthma medications as prescribed, increasing to 54.1% after a 4 week study period (Bartlett 2002). The electronic reminders serve to prompt the user to use their inhalers, an intervention perceived to increase adherence in children (Penza-Clyve 2004), and reportedly increase short term adherence in adults (Strandbygaard 2010). We are interested in whether electronic monitoring and/or reminding devices can improve adherence to regular inhaled therapy in asthma thus benefiting disease control as well as empowering the patient to better manage their own condition through the implementation of an effective self management aid.

Why it is important to do this review

Asthma is highly prevalent and optimising adherence to its treatment may improve disease control (Ordonez 1998), improve quality of life (Sullivan 2013), reduce mortality (Robertson 1992), and have marked economic benefits by potentially curbing the unnecessary escalation of treatment and decreasing hospitalisation rates in adults and children (Williams 2004; McGrady 2013).

OBJECTIVES

To assess the efficacy of electronic monitors, reminder devices or both, on adherence with regular inhaled medication regimes in people with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We will include published and unpublished randomised controlled trials (RCTs), including cross-over studies, that evaluated interventions to improve adherence with inhaled asthma medication.

Types of participants

We will include any patients using regular inhaled corticosteroids and other preventer medications that fulfil any of the internationally-recognised diagnostic guidelines by the American Thoracic Society, European Respiratory Society and Global Initiative for Asthma. We will not apply age or gender limitations and will only consider studies that excluded patients with significant co-morbidities.

Types of interventions

We will only include trials involving objective electronic monitoring of compliance of all inhalers. We will consider the following interventions and comparators.

1. Electronic monitors with health professional feedback of inhaler usage versus monitoring without feedback.
2. Electronic monitors with ongoing feedback from the device versus monitoring without feedback.
3. Electronic reminders and monitors without health professional feedback versus monitoring only without feedback.
4. Electronic reminders and monitors with health professional feedback versus monitoring without feedback.
5. Electronic monitors and/or reminders with health professional feedback versus an alternative intervention for inhaler adherence e.g. education programmes, written information, follow up support, medication training.
6. Electronic monitors and/or reminders with health professional feedback versus monitoring without feedback.

Types of outcome measures

Primary outcomes

1. Inhaler adherence, e.g. proportion taking prescribed medication
2. Health-related quality of life (using clinically validated measurement tools)
3. Number of asthma exacerbations as defined by hospital admissions or treatment with oral corticosteroids and antibiotics or both

Secondary outcomes

1. Lung function measurement: FEV₁, peak expiratory flow rate
2. Asthma control (measured using clinically validated questionnaires)
3. Days of missed school or work
5. Adverse events/side effects, barriers to effectiveness

Reporting one of more of these outcomes in the trial is not an inclusion criterion for the review. We will assess all outcome measures at six months from the start of the study (if data is available) and at the end of the study.

Search methods for identification of studies

Electronic searches
We will identify trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We will search all records in the CAGR using the search strategy in Appendix 2. We will also conduct a search of ClinicalTrials.gov (https://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

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

Data collection and analysis

Selection of studies
Two review authors (VEC and RM) will independently screen study titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as ‘retrieve’ (eligible or potentially eligible/unclear) or ‘do not retrieve’. We will retrieve the full-text study reports/publication and two review authors (VEC, and RM) will independently screen the full-text articles and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third author (SGD). We will grade each potential source of bias as high, low or unclear for our judgment in the 'Risk of bias' table. We will consider blinding separately for different study types and for each of the domains listed. We will consider blinding separately for different outcomes which has been piloted on at least one study in the review. Two review authors (VEC and RM) will extract study characteristics from included studies.

We will extract the following study characteristics.

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 of participants, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (VEC and RM) will independently extract outcome data from included studies. We will note in the ‘Characteristics of included studies’ table if outcome data was not reported in a usable way. We will resolve disagreements by consensus or by involving a third author (SGD). One review author (VEC) will transfer data into the Cochrane Collaboration statistical software, Review Manager 2014. We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (RM) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies
Two review authors (MLE and SS) 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 or by involving a third author (SGD). 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.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment 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 report any deviations form it in the ‘Differences between protocol and review’ section of the systematic review.

Measures of treatment effect

Continuous data

For continuous data, we will estimate effects of the intervention using mean difference (MDs) and corresponding 95% confidence intervals (CIs). If standard deviations are not reported but other measures of population variance, such as standard errors, CIs, P values or t values are reported, we will calculate these according to guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Binary data

For dichotomous data, we will use risk ratios (RRs) with 95% CIs.

Multiple outcome measures

Where different scales are used to measure the same outcome, we will use standardised mean differences (SMDs) and their 95% CIs. If studies use different measures of effect, we will analyse and report these separately. We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

Cross-over trials

We will use data from only the first part of the study in order to minimise potential bias from carry-over effects.

Cluster-randomised trials

We will analyse cluster-randomised trials in accordance with methods described in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using the average cluster size and an estimate of the intra class correlation coefficient (ICC) to adjust sample sizes to effect size. Where the study ICC is not available we will use external ICC estimates. We will combine single RCTs with cluster RCTs if the designs and interventions are considered sufficiently similar and the effect of the intervention is unlikely to be influenced by the method of randomisation.

Multiple arm trials

Where trials have more than two arms and the variance of the difference between the comparisons of interest are not reported, we will calculate this from the variances of all the trial arms. Where a study includes multiple treatment arms, where relevant, we will combine groups to create a single pair-wise comparison. Where studies only report differences between treatment groups, as opposed to the mean effects for each group, we will analyse data using the generic inverse variance function.

Dealing with missing data

We will use an intention-to-treat approach and missing data will be imputed. Where applicable, all authors will be contacted for missing data. We will note differential dropout between study groups and reasons for withdrawal. Missing data will be described in the risk of bias table and its influence on study outcomes discussed in the text. If there are enough trials, we will use sensitivity analyses to determine the resistance of our results to the effects of missing data.

Assessment of heterogeneity

It is likely that there will be considerable heterogeneity between studies in terms of the precise nature of the intervention, the study design and the outcomes. Variability may be a consequence of clinical variation in the population, or the intervention, differences in study quality, or random differences.

We will assess potential sources of variability as follows.

- Clinical variability: we will compare the distribution of participants, interventions and outcomes across the included studies and discuss and agree potential clinical heterogeneity by consensus.
- Methodological variability: we will compare study designs and study quality using the risk of bias criteria as outlined above (Assessment of risk of bias in included studies).
- Statistical heterogeneity: we will analyse heterogeneity in terms of age (preschool child (2-5 years), child (6 to 12 years), adolescent (13-18 years), adult (19 years and older)) and severity of asthma (defined by the Global Initiative for Asthma) (GINA 2014). Where variability in the effects of interventions is greater than expected by chance alone, we will evaluate statistical significance using the Chi² test (P ≤ 0.10 for statistical significance). However, this test may be unreliable with few/small studies or large numbers of studies. Therefore we will also quantify the magnitude of heterogeneity using the I² statistic with the following interpretation
thresholds, based on recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011):

- 0 to 30%: might not be important;
- 31 to 50%: moderate heterogeneity;
- 51 to 75%: substantial heterogeneity;
- 76 to 100%: considerable heterogeneity.

Where data is synthesised using a random-effects model, we will use the between-study variance ($\chi^2$) to calculate the distribution (standard deviation) of effects across studies, as an index of heterogeneity. It is possible for all studies to show large consistent effects in the face of significant heterogeneity, therefore the importance of heterogeneity will be discussed according to the strength of evidence ($\chi^2$ and I² statistics) and the strength of effects (magnitude and consistency).

Assessment of reporting biases

If there are more than 10 studies, we will explore reporting biases and the effects of small studies using Egger’s method to test for asymmetry in funnel plots (Egger 1997).

Data synthesis

According to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), for dichotomous outcomes we will sum sample sizes and events across groups and for continuous outcomes, we will combine means and standard deviations. We will synthesis and report intervention comparisons separately according to the type of data (dichotomous or continuous). Where end of study point estimates and change from baseline are reported, we will also analyse these separately.

If there is sufficient data, we will examine the combined effects of interventions by pooling data using meta-analysis. Studies will be included in meta-analyses only when the study designs, interventions and outcomes are similar. Where important heterogeneity is identified we will report the outcomes narratively in the text. It is likely that studies will be heterogeneous therefore we will use meta-analysis with a random-effects model. However, where there are few studies or the effects of interventions are not randomly distributed across studies, e.g. publication bias, random-effects estimates may be biased. It is likely that this review will include a small number of low-powered studies, where meta-analysis conducted using a fixed-effect model would give more reliable estimates. To resolve the uncertainty over model choice we will only pool data using meta-analysis when studies appear sufficiently heterogeneous and we will compare pooled data estimates from both random-effects and fixed-effect models in the text. We will report the mean effect estimate and its CI for both models, noting that the CI for the random-effects model is not an estimate of heterogeneity (Assessment of heterogeneity). We will perform the analyses using Review Manager 2014.

Summary of findings

We will create a ‘Summary of findings’ table using the following outcomes:

- inhaler adherence;
- health-related quality of life using clinically validated measurement tools;
- number of asthma exacerbations as defined by hospital admissions;
- lung function measurement ($FEV_1$);
- days of missed school or work;
- cost of interventions (cost-benefit, cost-effectiveness);
- adverse events.

We will use the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), using the GRADEpro (GRADEproGDT) software (http://www.guidelinedevelopment.org/). We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid reader’s understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis

Where comparison group sample sizes permit, we will perform the following subgroup analyses on each intervention comparison.

1. Intervention complexity: single - as stated in intervention comparisons; complex - where the reminder/monitoring device is part of a multi-component intervention.
2. Age group 1: children (18 years or younger), adults (19 years or older).
3. Age group 2: preschool child (2 to 5 years), child (6 to 12 years), adolescent (13 to 18 years).
4. Severity of asthma, as defined by the Global Initiative for Asthma (GINA 2014).
5. Follow-up duration: short term defined as less than one month and long term meaning one year or more.

Investigation of heterogeneity

If there are sufficient numbers of studies we will manage potential sources of heterogeneity as follows.

- Check data integrity, including measures of effect and units of analysis.
- Explore the impact of subgroups e.g. small versus large studies.
• Exclude outliers, where there is a clear reason for exclusion. We will inspect the graph and iteratively remove outlying studies to determine whether homogeneity is restored.

Decisions will be fully discussed and reported in the review.

**Sensitivity analysis**

Where there are sufficient number of included studies we will perform sensitivity analyses as follows.

• Missing data: comparing results including and excluding studies containing outcomes with missing data.

• Risk of bias: comparing results including and excluding studies at high risk of bias on random sequence generation and blinding of participants.

**ACKNOWLEDGEMENTS**

This protocol has been written with input from all the authors.

Chris Cates was the Editor for this review and commented critically on the review.

The background and methods section of this protocol/review is based on a standard template used by Cochrane Airways Group.

**REFERENCES**

Bartlett 2002


Bender 2000


Bergstrom 2008


Braman 2006


Burgess 2011


Egger 1997


ERS 2015


Feldman 2012


Foster 2012


Gamble 2009


Gamble 2011


Gibson 1995


Gibson 2002


GINA 2014


Gong 1988

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**WHO 2007**

**Williams 2004**

* Indicates the major publication for the study

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**APPENDICES**

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

**Electronic sources**

<table>
<thead>
<tr>
<th>Database</th>
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<td>Weekly</td>
</tr>
<tr>
<td>Embase (Ovid)</td>
<td>Weekly</td>
</tr>
<tr>
<td>PsycINFO (Ovid)</td>
<td>Monthly</td>
</tr>
<tr>
<td>CINAHL (EBSCO)</td>
<td>Monthly</td>
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<tr>
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<td>Monthly</td>
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**Handsearching of core respiratory conference abstracts**
<table>
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<tr>
<td>American Academy of Allergy, Asthma and Immunology</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>American Thoracic Society</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>Asia Pacific Society of Respirology</td>
<td>2004 onwards</td>
</tr>
<tr>
<td>British Thoracic Society Winter Meeting</td>
<td>2000 onwards</td>
</tr>
<tr>
<td>Chest Meeting</td>
<td>2003 onwards</td>
</tr>
<tr>
<td>International Primary Care Respiratory Group Congress</td>
<td>2002 onwards</td>
</tr>
<tr>
<td>Thoracic Society of Australia and New Zealand</td>
<td>1999 onwards</td>
</tr>
</tbody>
</table>

**MEDLINE search strategy used to identify trials for the CAGR**

**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.
Appendix 2. Search strategy for Cochrane Airways Group Register

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 adher*
#6 (electronic* or medication*) near3 (monitor* or reminder*)
#7 MeSH DESCRIPTOR Medication Adherence
#8 data* NEAR3 log*
#9 #5 or #6 or #7 or #8
#10 #4 and #9

[Note: in search line #1, MISC1 denotes the field in which the record is coded for condition, in this case, asthma]

CONTRIBUTIONS OF AUTHORS

This protocol has been written by Vanessa Craven and subsequently reviewed and edited following comments from Robert Morton, Sally Spencer, Sunalene Devadason and Mark Everard.

DECLARATIONS OF INTEREST

Dr Devadason has received research grants and travel expenses from Philips Respironics (USA) and Pari GmBh (Germany) relating to research studies performed in her research institution.

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Internal sources

- The authors declare that no funding was received for this systematic review, Other.

External sources

- The authors declare that no funding was received for this systematic review, Other.